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What is the potential of p53 isoforms as a predictive biomarker in the treatment of cancer

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Abstract

Introduction:
For decades, p53 was researched as a single protein with alterations described as mutants. The discovery of 12 human p53 isoforms expressed from 9 transcripts changed this perception, eloquently explaining the numerous roles p53 plays, including apoptosis, senescence and regeneration.

Area covered:
Here we summarise the p53 isoforms and their relevance to cancer to establish an understanding and theorise on potential applications of the isoforms in clinical practice.

Expert commentary:

Pertaining to the different expression of isoforms in different tumours, it is concluded that the clinical use of isoforms as prognostic and predictive biomarkers will be different depending on the cell type, the tissue origin of the tumours, the position of the TP53 mutation and the driver-oncogene.

Keywords – *Apoptosis, biomarker, cancer, p53, p53 isoforms, tumour*

For decades, p53 was researched as a single protein with alterations described as mutants. The discovery of 12 human p53 isoforms expressed from 9 transcripts changed this perception, eloquently explaining the numerous roles p53 plays, including apoptosis, senescence and regeneration. Here we summarise the p53 isoforms and their relevance to cancer to establish an understanding and theorise on potential applications of the isoforms in clinical practice. Pertaining to the different expression of isoforms in different tumours, it is concluded that the clinical use of isoforms as prognostic and predictive biomarkers will be different depending on the cell type and tissue origin of the tumours.

1- *Introduction to p53 and the concept of isoforms*

The protein 53 (p53; canonical p53), initially discovered in 1979 and often termed the "Guardian of the Genome" for its role in regulating cell division and arresting the formation of tumours, is no exception to the concept of *"One gene, many proteins."* Like most genes within the human genome, the *TP53* gene is subject to "alternative splicing, alternative initiation of translation, and alternative promoter usage," **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1177/1947601911408893", "ISBN" : "1947-6027 (Electronic)\\r1947-6019 (Linking)", "ISSN" : "1947-6019", "PMID" : "21779513", "abstract" : "Normal function of the p53 pathway is ubiquitously lost in cancers either through mutation or inactivating interaction with viral or cellular proteins. However, it is difficult in clinical studies to link p53 mutation status to cancer treatment and clinical outcome, suggesting that the p53 pathway is not fully understood. We have recently reported that the human p53 gene expresses not only 1 but 12 different p53 proteins (isoforms) due to alternative splicing, alternative initiation of translation, and alternative promoter usage. p53 isoform proteins thus contain distinct protein domains. They are expressed in normal human tissues but are abnormally expressed in a wide range of cancer types. We have recently reported that p53 isoform expression is associated with breast cancer prognosis, suggesting that they play a role in carcinogenesis. Indeed, the cellular response to damages can be switched from cell cycle arrest to apoptosis by only manipulating p53 isoform expression. This may provide an explanation to the hitherto inconsistent relationship between p53 mutation, treatment response, and outcome in breast cancer. However, the molecular mechanism is still unknown. Recent reports suggest that it involves modulation of gene expression in a p53-dependent and -independent manner. In this review, we summarize our current knowledge about the biological activities of p53 isoforms and propose a molecular mechanism conciliating our current knowledge on p53 and integrating p63 and p73 isoforms in the p53 pathway.", "author" : [{ "dropping-particle" : "", "family" : "Khoury", "given" : "M. P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bourdon", "given" : "J.-C.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Genes & Cancer", "id" : "ITEM-1", "issue" : "4", "issued" : { "date-parts" : [["2011"]] }, "page" : "453-465", "title" : "p53 Isoforms: An Intracellular Microprocessor?", "type" : "article-journal", "volume" : "2" }, "uris" : ["http://www.mendeley.com/documents/?uuid=9d530c4a-b7e0-4241-a1b4-7a5bc16f78ad"] }], "mendeley" : { "formattedCitation" : "(1)", "plainTextFormattedCitation" : "(1)", "previouslyFormattedCitation" : "(1)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}** a process resulting in at least 12 different p53 protein isoforms being differentially expressed from 9 mRNA transcripts. This is an important notion to grasp; neatly explaining the extensive role that p53 plays in maintaining cell integrity and tissue function. Moreover p53 is subject to various post-translational modifications (phosphorylation, acetylation, methylation, ubiquitination,...). Different types of p53-activating stimuli may elicit different types of modification (2).

1.1 The Gene

Human *TP53* has the cytogenetic location 17p13.1. This alludes to chromosome 17, with (p) referencing the short arm of said chromosome, on position 13.1 , according to human reference genome *GRCh38* (3).The gene itself is highly conserved and is composed of 11 exons –with a large intron between exon 1 and exon 2. To a molecular level, the gene spans 19,148 base pairs on chromosome 17, from base pairs 7,661,779 to 7,687,550. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "URL" : "https://ghr.nlm.nih.gov/gene/TP53#", "accessed" : { "date-parts" : [["2017", "7", "5"]] }, "container-title" : "Genetic Home Referencing", "id" : "ITEM-1", "issued" : { "date-parts" : [["2015"]] }, "title" : "TP53 Gene", "type" : "webpage" }, "uris" : ["http://www.mendeley.com/documents/?uuid=fb5bf47c-7d79-46cc-b45a-d294289e6350"] }], "mendeley" : { "formattedCitation" : "(2)", "plainTextFormattedCitation" : "(2)", "previouslyFormattedCitation" : "(2)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**

1.2 Structure of full-length p53 protein (p53, FLp53; canonical p53; p53α)

Full-length p53 protein structurally spans 393 amino acids and is loosely divided into 7 functional domains [Figure 1] **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1101/cshperspect.a026039", "ISSN" : "21571422", "PMID" : "26801896", "abstract" : "It is poorly understood how a single protein, p53, can be responsive to so many stress signals and orchestrates very diverse cell responses to maintain/restore cell/tissue functions. The uncovering that TP53 gene physiologically expresses, in a tissue-dependent manner, several p53 splice variants (isoforms) provides an explanation to its pleiotropic biological activities. Here, we summarize a decade of research on p53 isoforms. The clinical studies and the diverse cellular and animal models of p53 isoforms (zebrafish, Drosophila, and mouse) lead us to realize that a p53-mediated cell response is, in fact, the sum of the intrinsic activities of the coexpressed p53 isoforms and that unbalancing expression of different p53 isoforms leads to cancer, premature aging, (neuro)degenerative diseases, inflammation, embryo malformations, or defects in tissue regeneration. Cracking the p53 isoforms' code is, thus, a necessary step to improve cancer treatment. It also opens new exciting perspectives in tissue regeneration.", "author" : [{ "dropping-particle" : "", "family" : "Joruiz", "given" : "Sebastien M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bourdon", "given" : "Jean Christophe", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Cold Spring Harbor Perspectives in Medicine", "id" : "ITEM-1", "issue" : "8", "issued" : { "date-parts" : [["2016"]] }, "title" : "P53 isoforms: Key regulators of the cell fate decision", "type" : "article-journal", "volume" : "6" }, "uris" : ["http://www.mendeley.com/documents/?uuid=3fcefb35-42f2-4b37-b4d0-eea9a44802c3"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.1101/cshperspect.a000927", "ISBN" : "1943-0264", "ISSN" : "19430264", "PMID" : "20300206", "abstract" : "p53 is a transcription factor with a key role in the maintenance of genetic stability and therefore preventing cancer formation. It belongs to a family of genes composed of p53, p63, and p73. The p63 and p73 genes have a dual gene structure with an internal promoter in intron-3 and together with alternative splicing, can express 6 and 29 mRNA variants, respectively. Such a complex expression pattern had not been previously described for the p53 gene, which was not consistent with our understanding of the evolution of the p53 gene family. Consequently, we revisited the human p53 gene structure and established that it encodes nine different p53 protein isoforms because of alternative splicing, alternative promoter usage, and alternative initiation sites of translation. Therefore, the human p53 gene family (p53, p63, and p73) has a dual gene structure. We determined that the dual gene structure is conserved in Drosophila and in zebrafish p53 genes. The conservation through evolution of the dual gene structure suggests that the p53 isoforms play an important role in p53 tumor-suppressor activity. We and others have established that the p53 isoforms can regulate cell-fate outcome in response to stress, by modulating p53 transcriptional activity in a promoter and stress-dependent manner. We have also shown that the p53 isoforms are abnormally expressed in several types of human cancers, suggesting that they play an important role in cancer formation. The determination of p53 isoforms' expression may help to link clinical outcome to p53 status and to improve cancer patient treatment.", "author" : [{ "dropping-particle" : "", "family" : "Khoury", "given" : "Marie P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bourdon", "given" : "Jean Christophe", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Cold Spring Harbor perspectives in biology", "id" : "ITEM-2", "issue" : "3", "issued" : { "date-parts" : [["2010"]] }, "title" : "The isoforms of the p53 protein.", "type" : "article", "volume" : "2" }, "uris" : ["http://www.mendeley.com/documents/?uuid=f4bbbf5c-e510-461e-9f38-7cb50a53d2e3"] }, { "id" : "ITEM-3", "itemData" : { "DOI" : "10.1074/jbc.M005676200", "ISBN" : "0021-9258", "ISSN" : "00219258", "PMID" : "10982799", "abstract" : "The p53 protein contains several functional domains necessary for inducing cell cycle arrest and apoptosis. The C-terminal basic domain within residues 364-393 and the proline-rich domain within residues 64-91 are required for apoptotic activity. In addition, activation domain 2 within residues 43-63 is necessary for apoptotic activity when the N-terminal activation domain 1 within residues 1-42 is deleted (DeltaAD1) or mutated (AD1(-)). Here we have discovered that an activation domain 2 mutation at residues 53-54 (AD2(-)) abrogates the apoptotic activity but has no significant effect on cell cycle arrest. We have also found that p53-(DeltaAD2), which lacks activation domain 2, is inert in inducing apoptosis. p53-(AD2(-)DeltaBD), which is defective in activation domain 2 and lacks the C-terminal basic domain, p53-(DeltaAD2DeltaBD), which lacks both activation domain 2 and the C-terminal basic domain, and p53-(DeltaPRDDeltaBD), which lacks both the proline-rich domain and the C-terminal basic domain, are also inert in inducing apoptosis. All four mutants are still capable of inducing cell cycle arrest, albeit to a lesser extent than wild-type p53. Interestingly, we have found that deletion of the N-terminal activation domain 1 alleviates the requirement of the C-terminal basic domain for apoptotic activity. Thus, we have generated a small but potent p53-(DeltaAD1DeltaBD) molecule. Furthermore, we have determined that at least two of the three domains (activation domain 1, activation domain 2, and the proline-rich domain), are required for inducing cell cycle arrest. Taken together, our results suggest that activation domain 2 and the proline-rich domain form an activation domain for inducing pro-apoptotic genes or inhibiting anti-apoptotic genes. The C-terminal basic domain is required for maintaining this activation domain competent for transactivation or transrepression.", "author" : [{ "dropping-particle" : "", "family" : "Zhu", "given" : "Jianhui", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Zhang", "given" : "Shunzhen", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Jiang", "given" : "Jieyuan", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Chen", "given" : "Xinbin", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Journal of Biological Chemistry", "id" :

"ITEM-3", "issue" : "51", "issued" : { "date-parts" : [["2000"]] }, "page" : "39927-39934", "title" : "Definition of the p53 functional domains necessary for inducing apoptosis", "type" : "article-journal", "volume" : "275" }, "uris" : ["http://www.mendeley.com/documents/?uuid=02990603-fc1b-4d6b-b4e5-98ce02e502e5"] }], "mendeley" : { "formattedCitation" : "(3\u20135)", "plainTextFormattedCitation" : "(3\u20135)", "previouslyFormattedCitation" : "(3\u20135)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**:

1. *Transactivation Domain 1 (TAD1; AD1)*
2. *Transactivation Domain 2 (TAD2)*

   Initially, it was thought that only one TA domain existed within FLp53; however further investigation revealed the presence of two transactivation subdomains – TAD1 existing between amino acid 1 – 42 and TAD2, a subdomain existing between 43 and 63. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1074/jbc.273.21.13030", "ISBN" : "0021-9258 (Print)\\r0021-9258 (Linking)", "ISSN" : "00219258", "PMID" : "9582339", "abstract" : "The ability of p53 to induce apoptosis requires its sequence-specific DNA binding activity; however, the transactivation-deficient p53(Gln22-Ser23) can still induce apoptosis. Previously, we have shown that the region between residues 23 and 97 in p53 is necessary for such activity. In an effort to more precisely map a domain necessary for apoptosis within the N terminus, we found that deletion of the N-terminal 23 amino acids compromises, but does not abolish, p53 induction of apoptosis. Surprisingly, p53(Delta1-42), which lacks the N-terminal 42 amino acids and the previously defined activation domain, retains the ability to induce apoptosis to an even higher level than wild-type p53. A more extensive deletion, which eliminates the N-terminal 63 amino acids, renders p53 completely inert in mediating apoptosis. In addition, we found that both p53(Delta1-42) and p53(Gln22-Ser23) can activate a subset of cellular p53 targets. Furthermore, we showed that residues 53 and 54 are critical for the apoptotic and transcriptional activities of both p53(Delta1-42) and p53(Gln22-Ser23). Taken together, these data suggest that within residues 43-63 lie an apoptotic domain as well as another transcriptional activation domain. We therefore postulate that the apoptotic activity in p53(Gln22-Ser23) and p53(Delta1-42) is still transcription-dependent.", "author" : [{ "dropping-particle" : "", "family" : "Zhu", "given" : "Jianhui", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Zhou", "given" : "Wenjing", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Jiang", "given" : "Jieyuan", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Chen", "given" : "Xinbin", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Journal of Biological Chemistry", "id" : "ITEM-1", "issue" : "21", "issued" : { "date-parts" : [["1998"]] }, "page" : "13030-13036", "title" : "Identification of a novel p53 functional domain that is necessary for mediating apoptosis", "type" : "article-journal", "volume" : "273" }, "uris" : ["http://www.mendeley.com/documents/?uuid=dfd2f8f2-e561-4b4f-a0bb-101b5ef7bb78"] }, { "id" : "ITEM-2", "itemData" : { "DOI" :

"10.1038/sj.onc.1201244", "ISBN" : "0950-9232 (Print)", "ISSN" : "0950-9232", "PMID" : "9266967", "abstract" : "The ability of p53 to function as a tumor suppressor is linked to its function as a transcriptional activator, since p53 mutants that do not transactivate are unable to suppress tumor cell growth. Previous studies identified an activation domain in the amino terminal 40 residues of the protein, a region that binds to several general transcription factors and to some oncogene products. For example, mdm-2, a cellular oncoprotein, binds to this region and represses p53 transactivation. Here we describe a new activation domain within the amino terminus of p53 that maps between amino acids 40-83, and whose residues trp-53 and phe-54 are critical for function both in yeast and in mammalian cells. In vivo studies in yeast show that the new activation subdomain, unlike the previously described, is mdm-2 independent. Both p53 activation subdomains (1-40 and 40-83) require the yeast adaptor complex ADA2/ADA3/GCN5 for transcriptional activation. Moreover, since activation by p53 requires GCN5's enzymatic histone acetyltransferase domain, p53 may regulate gene expression by influencing chromatin modification.", "author" : [{ "dropping-particle" : "", "family" : "Candau", "given" : "R", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Scolnick", "given" : "D M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Darpino", "given" : "P", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Ying", "given" : "C Y", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Halazonetis", "given" : "T D", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Berger", "given" : "S L", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Oncogene", "id" : "ITEM-2", "issue" : "7", "issued" : { "date-parts" : [["1997"]] }, "page" : "807-16", "title" : "Two tandem and independent sub-activation domains in the amino terminus of p53 require the adaptor complex for activity.", "type" : "article-journal", "volume" : "15" }, "uris" : ["http://www.mendeley.com/documents/?uuid=bba2810e-06d0-4579-ba6a-aa5e22bb5e7a"] }], "mendeley" : { "formattedCitation" : "(6,7)", "plainTextFormattedCitation" : "(6,7)", "previouslyFormattedCitation" : "(6,7)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}** TAD1 plays a central role in controlling the transcription of several genes; an example being the ability to interact with TBP (TATA-Binding protein) in order to activate transcription. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1074/jbc.270.42.25014", "ISBN" : "0021-9258 (Print) 0021-9258 (Linking)", "ISSN" : "00219258", "PMID" : "7559631", "abstract" : "Tumor suppressor protein p53 is a potent transcriptional activator and regulates cell growth negatively. To characterize the transcriptional activation domain (TAD) of p53, various point mutants were constructed in the context of Gal4 DNA binding domain and tested for their transactivation ability. Our results demonstrated that the positionally conserved hydrophobic residues shared with herpes simplex virus VP16 and other transactivators are essential for transactivation. Also, the negatively charged residues and proline residues are necessary for full activity, but not essential for the activity of p53 TAD. Deletion analyses showed that p53 TAD can be divided into two subdomains, amino acids 1-40 and 43-73. An in vitro glutathione S-transferase pull-down assay establishes a linear correlation between p53 TAD-mediated transactivation in vivo and the binding activity of p53 TAD to TATA-binding protein (TBP) in vitro. Mutations that diminish the transactivation ability of Gal4-p53 TAD also impair the binding activity to TBP severely. Our results suggest that at least TBP is a direct target for p53 TAD and that the binding strength of TAD to TBP (TFIID) is an important parameter controlling activity of p53 TAD. In addition, circular dichroism spectroscopy has shown that p53 TAD peptide lacks any regular secondary structure in solution and that there is no significant difference between the spectra of the wild type TAD and that of the transactivation deficient mutant type.", "author" : [{ "dropping-particle" : "", "family" : "Chang", "given" : "J.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kim", "given" : "D. H.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Seung Woo Lee", "given" : "", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kwan Yong Choi", "given" : "", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Young Chul Sung", "given" : "", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Journal of Biological Chemistry", "id" : "ITEM-1", "issue" : "42", "issued" : { "date-parts" : [["1995"]] }, "page" : "25014-25019", "title" : "Transactivation ability of p53 transcriptional activation domain is directly related to the binding affinity to TATA-binding protein", "type" : "article-journal", "volume" : "270" }, "uris" : ["http://www.mendeley.com/documents/?uuid=bf129568-5df0-4f70-bf95-0715ccc5d617"] }], "mendeley" : { "formattedCitation" : "(8)", "plainTextFormattedCitation" : "(8)", "previouslyFormattedCitation" : "(8)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }} The function of TAD2 is hypothesised to be more pro apoptotic in nature – in the words of Zhu et al, it “regulates a subset of cellular p53 targets that are responsible for apoptosis.” {ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1074/jbc.273.21.13030", "ISBN" : "0021-9258 (Print)\\r0021-9258 (Linking)", "ISSN" : "00219258", "PMID" : "9582339", "abstract" : "The ability of p53 to induce apoptosis requires its sequence-specific DNA binding activity; however, the transactivation-deficient p53(Gln22-Ser23) can still induce apoptosis. 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We therefore postulate that the apoptotic activity in p53(Gln22-Ser23) and p53(Delta1-42) is still transcription-dependent.", "author" : [{ "dropping-particle" : "", "family" : "Zhu", "given" : "Jianhui", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Zhou", "given" : "Wenjing", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Jiang", "given" : "Jieyuan", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Chen", "given" : "Xinbin", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Journal of Biological Chemistry", "id" : "ITEM-1", "issue" : "21", "issued" : { "date-parts" : [["1998"]] }, "page" : "13030-13036", "title" : "Identification of a novel p53 functional domain that is necessary for mediating apoptosis", "type" : "article-journal", "volume" : "273" }, "uris" : ["http://www.mendeley.com/documents/?uuid=dfd2f8f2-e561-4b4f-a0bb-101b5ef7bb78"] }], "mendeley" : { "formattedCitation" : "(6)", "plainTextFormattedCitation" : "(6)", "previouslyFormattedCitation" : "(6)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**

3. *Proline Domain (PRD)*

The proline domain extends 27 amino acids, from residue 64 to residue 91. The domain is essential in inhibiting transcription – Venot et al. describes how mutated FLp53 lacking the proline domain does not inhibit transcription as effectively as WT FLp53. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1093/emboj/17.16.4668", "ISBN" : "0261-4189 (Print)", "ISSN" : "02614189", "PMID" : "9707426", "abstract" : "Wild-type p53 is a tumor suppressor gene which can activate or repress transcription, as well as induce apoptosis. The human p53 proline-rich domain localized between amino acids 64 and 92 has been reported to be necessary for efficient growth suppression. This study shows that this property mainly results from impaired apoptotic activity. Although deletion of the proline-rich domain does not affect transactivation of several promoters, such as WAF1, MDM2 and BAX, it does alter transcriptional repression, reactive oxygen species production and sequence-specific transactivation of the PIG3 gene, and these are activities which affect apoptosis. Whereas gel retardation assays revealed that this domain did not alter in vitro the specific binding to the p53-responsive element of PIG3, this domain plays a critical role in transactivation from a synthetic promoter containing this element. To explain this discrepancy, evidence is given for a proline-rich domain-mediated cellular activation of p53 DNA binding.", "author" : [{ "dropping-particle" : "", "family" : "Venot", "given" : "Corinne", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Maratrat", "given" : "Michel", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Dureuil", "given" : "Christine", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Conseiller", "given" : "Emmanuel", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bracco", "given" : "Laurent", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Debussche", "given" : "Laurent", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "EMBO Journal", "id" : "ITEM-1", "issue" : "16", "issued" : { "date-parts" : [["1998"]] }, "page" : "4668-4679", "title" : "The requirement for the p53 proline-rich functional domain for mediation of apoptosis is correlated with specific PIG3 gene transactivation and with transcriptional repression", "type" : "article-journal", "volume" : "17" }, "uris" : ["http://www.mendeley.com/documents/?uuid=d3924930-d5dd-4de4-ab4e-6496f8f13b33"] }], "mendeley" : { "formattedCitation" : "(9)", "plainTextFormattedCitation" : "(9)", "previouslyFormattedCitation" : "(9)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}** Other functions include being an important domain in the regulation of apoptosis. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1074/jbc.M005676200", "ISBN" : "0021-9258", "ISSN" : "00219258", "PMID" : "10982799", "abstract" : "The p53 protein contains several functional domains necessary for inducing cell cycle arrest and apoptosis. The C-terminal basic domain within residues 364-393 and the proline-rich domain within residues 64-91 are required for apoptotic activity. In addition, activation domain 2 within residues 43-63 is necessary for apoptotic activity when the N-terminal activation domain 1 within residues 1-42 is deleted (DeltaAD1) or mutated (AD1(-)). Here we have discovered that an activation domain 2 mutation at residues 53-54 (AD2(-)) abrogates the apoptotic activity but has no significant effect on cell cycle arrest. We have also found that p53-(DeltaAD2), which lacks activation domain 2, is inert in inducing apoptosis. p53-(AD2(-)DeltaBD), which is defective in activation domain 2 and lacks the C-terminal basic domain, p53-(DeltaAD2DeltaBD), which lacks both activation domain 2 and the C-terminal basic domain, and p53-(DeltaPRDDeltaBD), which lacks both the proline-rich domain and the C-terminal basic domain, are also inert in inducing apoptosis. All four mutants are still capable of inducing cell cycle arrest, albeit to a lesser extent than wild-type p53. Interestingly, we have found that deletion of the N-terminal activation domain 1 alleviates the requirement of the C-terminal basic domain for apoptotic activity. Thus, we have generated a small but potent p53-(DeltaAD1DeltaBD) molecule. Furthermore, we have determined that at least two of the three domains (activation domain 1, activation domain 2, and the proline-rich domain), are required for inducing cell cycle arrest. Taken together, our results suggest that activation domain 2 and the proline-rich domain form an activation domain for inducing pro-apoptotic genes or inhibiting anti-apoptotic genes. The C-terminal basic domain is required for maintaining this activation domain competent for transactivation or transrepression.", "author" : [{ "dropping-particle" : "", "family" : "Zhu", "given" : "Jianhui", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Zhang", "given" : "Shunzhen", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Jiang", "given" : "Jieyuan", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Chen", "given" : "Xinbin", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Journal of Biological Chemistry", "id" : "ITEM-1", "issue" : "51", "issued" : { "date-parts" : [["2000"]] }, "page" : "39927-39934", "title" : "Definition of the p53 functional domains necessary for inducing apoptosis", "type" : "article-journal", "volume" : "275" }, "uris" : ["http://www.mendeley.com/documents/?uuid=02990603-fc1b-4d6b-b4e5-98ce02e502e5"] }], "mendeley" : { "formattedCitation" : "(5)", "plainTextFormattedCitation" : "(5)", "previouslyFormattedCitation" : "(5)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**

4. *DNA Binding Domain (DBD)*

The DBD is located within the central region of the p53 protein, loosely between amino acids 102 and 292. Structurally, the DBD consists of “two anti – parallel β sheets that have four and five β strands,” **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1126/science.8023157", "ISBN" : "0036-8075 (Print)\\r0036-8075 (Linking)", "ISSN" : "0036-8075", "PMID" : "8023157", "abstract" : "Mutations in the p53 tumor suppressor are the most frequently observed genetic alterations in human cancer. The majority of the mutations occur in the core domain which contains the sequence-specific DNA binding activity of the p53 protein (residues 102-292), and they result in loss of DNA binding. The crystal structure of a complex containing the core domain of human p53 and a DNA binding site has been determined at 2.2 angstroms resolution and refined to a crystallographic R factor of 20.5 percent. The core domain structure consists of a beta sandwich that serves as a scaffold for two large loops and a loop-sheet-helix motif. The two loops, which are held together in part by a tetrahedrally coordinated zinc atom, and the loop-sheet-helix motif form the DNA binding surface of p53. Residues from the loop-sheet-helix motif interact in the major groove of the DNA, while an arginine from one of the two large loops interacts in the minor groove. The loops and the loop-sheet-helix motif consist of the conserved regions of the core domain and contain the majority of the p53 mutations identified in tumors. The structure supports the hypothesis that DNA binding is critical for the biological activity of p53, and provides a framework for understanding how mutations inactivate it.", "author" : [{ "dropping-particle" : "", "family" : "Cho", "given" : "Y", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Gorina", "given" : "S", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Jeffrey", "given" : "P D", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Pavletich", "given" : "N P", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Science (New York, N.Y.)", "id" : "ITEM-1", "issue" : "5170", "issued" : { "date-parts" : [["1994"]] }, "page" : "346-355", "title" : "Crystal structure of a p53 tumor suppressor-DNA complex: understanding tumorigenic mutations.", "type" : "article-journal", "volume" : "265" }, "uris" : ["http://www.mendeley.com/documents/?uuid=ef6e1eef-b0f0-4161-bf37-7cd8b78e8bd5"] }], "mendeley" : { "formattedCitation" : "(10)", "plainTextFormattedCitation" : "(10)", "previouslyFormattedCitation" : "(10)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}** which supports three α - helical loops. Between loops L2 and L3 lies a zinc atom, stabilising the structure of this domain. Discovered through the ability of the DBD to withstand proteolysis **{**ADDIN

CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1101/gad.7.12b.2556", "ISBN" : "0890-9369 (Print)\\r0890-9369 (Linking)", "ISSN" : "08909369", "PMID" : "8276238", "abstract" : "Mutations in the p53 tumor suppressor gene are the most commonly observed genetic alterations in human cancer. The majority of these mutations occur in the conserved central portion of the gene, but there has been little information about the function of this region. Using proteolytic digestion of the 393-amino-acid human p53 protein, we have identified a 191-amino-acid protease-resistant fragment (residues 102-292) that corresponds to the central portion of p53, and we show that this core fragment is the sequence-specific DNA-binding domain of the protein. DNA binding is inhibited by metal chelating agents, and we find that the core domain contains zinc. Proteolytic digests also reveal a 53-amino-acid carboxy-terminal domain which we show to be the tetramerization domain of p53.", "author" : [{ "dropping-particle" : "", "family" : "Pavletich", "given" : "Nikola P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Chambers", "given" : "Kristen A.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Pabo", "given" : "Carl O.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Genes and Development", "id" : "ITEM-1", "issue" : "12 PART B", "issued" : { "date-parts" : [["1993"]] }, "page" : "2556-2564", "title" : "The DNA-binding domain of p53 contains the four conserved regions and the major mutation hot spots", "type" : "article-journal", "volume" : "7" }, "uris" : ["http://www.mendeley.com/documents/?uuid=3c40ad6a-15d4-4426-8089-8159f6818ff1"] }], "mendeley" : { "formattedCitation" : "(11)", "plainTextFormattedCitation" : "(11)", "previouslyFormattedCitation" : "(11)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**, the DBD is of great interest as it represents the region of p53 in which 80 – 90% of mutations occur. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1126/science.8023157", "ISBN" : "0036-8075 (Print)\\r0036-8075 (Linking)", "ISSN" : "0036-8075", "PMID" : "8023157", "abstract" : "Mutations in the p53 tumor suppressor are the most frequently observed genetic alterations in human cancer. The majority of the mutations occur in the core domain which contains the sequence-specific DNA binding activity of the p53 protein (residues 102-292), and they result in loss of DNA binding. The crystal structure of a complex containing the core domain of human p53 and a DNA binding site has been determined at 2.2 angstroms resolution and refined to a crystallographic R factor of 20.5 percent. The core domain structure consists of a beta sandwich that serves as a scaffold for two large loops and a loop-sheet-helix motif. The two loops, which are held together in part by a tetrahedrally coordinated zinc atom, and the loop-sheet-helix motif form the DNA binding surface of p53. Residues from the loop-sheet-helix motif interact in the major groove of the DNA, while an arginine from one of the two large loops interacts in the minor groove. The loops and the loop-sheet-helix motif consist of the conserved regions of the core domain and contain the majority of the p53 mutations identified in tumors. The structure supports the hypothesis that DNA binding is critical for the biological activity of p53, and provides a framework for understanding how mutations inactivate it.", "author" : [{ "dropping-particle" : "", "family" : "Cho", "given" : "Y", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Gorina", "given" : "S", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Jeffrey", "given" : "P D", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Pavletich", "given" : "N P", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Science (New York, N.Y.)", "id" : "ITEM-1", "issue" : "5170", "issued" : { "date-parts" : [["1994"]] }, "page" : "346-355", "title" : "Crystal structure of a p53 tumor suppressor-DNA complex: understanding tumorigenic mutations.", "type" : "article-journal", "volume" : "265" }, "uris" : ["http://www.mendeley.com/documents/?uuid=ef6e1eef-b0f0-4161-bf37-7cd8b78e8bd5"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.1101/cshperspect.a001008", "ISBN" : "1943-0264 (Electronic)", "ISSN" : "19430264", "PMID" : "20182602", "abstract" : "Somatic mutations in the TP53 gene are one of the most frequent alterations in human cancers, and germline mutations are the underlying cause of Li-Fraumeni syndrome, which predisposes to a wide spectrum of early-onset cancers. Most mutations are single-base substitutions distributed throughout the coding sequence. Their diverse types and positions may inform on the nature of mutagenic mechanisms involved in cancer etiology. TP53 mutations are also potential prognostic and predictive markers, as well as targets for pharmacological intervention. All mutations found in human cancers are compiled in the IARC TP53 Database (http://www-p53.iarc.fr/). A human TP53 knockin mouse model (Hupki mouse) provides an experimental model to study mutagenesis in the context of a human TP53 sequence. Here, we summarize current knowledge on TP53 gene variations observed in human cancers and populations, and current clinical applications derived from this knowledge.", "author" : [{ "dropping-particle" : "", "family" : "Olivier", "given" : "Magali", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Hollstein", "given" : "Monica", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Hainaut", "given" : "Pierre", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Cold Spring Harbor perspectives in biology", "id" : "ITEM-2", "issue" : "1", "issued" : { "date-parts" : [["2010"]] }, "title" : "TP53 mutations in human cancers: origins, consequences, and clinical use.", "type" : "article", "volume" : "2" }, "uris" : ["http://www.mendeley.com/documents/?uuid=8bdad104-c46c-4d45-9bcf-80780b24d218"] }], "mendeley" : { "formattedCitation" : "(10,12)", "plainTextFormattedCitation" : "(10,12)", "previouslyFormattedCitation" : "(10,12)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**

5. *Nuclear localisation signalling region (NLS)*

The NLS is responsible for directing the movement of p53 into the nucleus. Three regions exist but NLS 1, the primary NLS, is found between amino acids 313 and 322. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1128/MCB.10.12.6565", "ISBN" : "0270-7306 (Print)", "ISSN" : "0270-7306", "PMID" : "2247074", "abstract" : "The basic carboxy terminus of p53 plays an important role in directing the protein into the nuclear compartment. The C terminus of the p53 molecule contains a cluster of several nuclear localization signals (NLSs) that mediate the migration of the protein into the cell nucleus. NLSI, the most active domain, is highly conserved in genetically diverged species and shares perfect homology with consensus NLS sequences found in other nuclear proteins. The other two NLSs, II and III, appear to be less effective and less conserved. Although nuclear localization is dictated primarily by the NLSs inherent in the primary amino acid sequence, the actual nuclear homing can be modified by interactions with other proteins expressed in the cell. Comparison between wild-type p53 and naturally occurring mutant p53 showed that both protein categories could migrate into the nucleus of rat primary embryonic fibroblasts by essentially similar mechanisms. Nuclear localization of both proteins was totally dependent on the existence of functional NLS domains. In COS cells, however, we found that NLS-deprived wild-type p53 molecules could migrate into the nucleus by complexing with another nuclear protein, simian virus 40 large-T antigen. Wild-type and mutant p53 proteins differentially complexed with viral or cellular proteins, which may significantly affect the ultimate compartmentalization of p53 in the cell; this finding suggests that the actual subcellular compartmentalization of proteins may differ in various cell type milieux and may largely be affected by the ability of these proteins to complex with other proteins expressed in the cell. Experiments designed to test the physiological significance of p53 subcellular localization indicated that nuclear localization of mutant p53 is essential for this protein to enhance the process of malignant transformation of partially transformed cells, suggesting that p53 functions within the cell nucleus.", "author" : [{ "dropping-particle" : "", "family" : "Shaulsky", "given" : "G", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Goldfinger", "given" : "N", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Ben-Ze'ev", "given" : "A", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Rotter", "given" : "V", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Molecular and Cellular Biology", "id" : "ITEM-1", "issue" : "12", "issued" : { "date-parts" : [["1990"]] }, "page" : "6565-6577", "title" : "Nuclear accumulation of p53 protein is mediated by several nuclear localization signals and plays a role in tumorigenesis.", "type" : "article-journal", "volume" : "10" }, "uris" : ["http://www.mendeley.com/documents/?uuid=a30c7b6f-de8c-44cd-af41-80407c051ae3"] }], "mendeley" : { "formattedCitation" : "(13)", "plainTextFormattedCitation" : "(13)", "previouslyFormattedCitation" : "(13)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**

6. *Tetramerization Domain/Oligomerization domain (TD/OD)*

The TD/OD is credited with p53's capacity to form a tetramer. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1073/pnas.90.8.3319", "ISBN" : "0027-8424 (Print)", "ISSN" : "0027-8424", "PMID" : "8475074", "abstract" : "We have analyzed the size and structure of native immunopurified human p53 protein. By using a combination of chemical crosslinking, gel filtration chromatography, and zonal velocity gradient centrifugation, we have determined that the predominant form of p53 in such preparations is a tetramer. The behavior of purified p53 in gels and sucrose gradients implies that the protein has an extended shape. Wild-type p53 has been shown to bind specifically to sites in cellular and viral DNA. We show in this study by Southwestern ligand blotting and by analysis of DNA-bound crosslinked p53 that p53 monomers, dimers, and tetramers can bind directly to DNA.", "author" : [{ "dropping-particle" : "", "family" : "Friedman", "given" : "P N", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Chen", "given" : "X", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bargonetti", "given" : "J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Prives", "given" : "C", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Proceedings of the National Academy of Sciences of the United States of America", "id" : "ITEM-1", "issue" : "8", "issued" : { "date-parts" : [["1993"]] }, "page" : "3319-3323", "title" : "The p53 protein is an unusually shaped tetramer that binds directly to DNA.", "type" : "article-journal", "volume" : "90" }, "uris" : ["http://www.mendeley.com/documents/?uuid=eea710ca-e465-45d8-85d8-be8c9c92da16"] }], "mendeley" : { "formattedCitation" : "(14)", "plainTextFormattedCitation" : "(14)", "previouslyFormattedCitation" : "(14)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}** p53 mutants lacking the TD are still able to bind p53 response element on DNA; however it is estimated to be 10 – 100 times lower when compared to WT FLp53 **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1073/pnas.92.19.8591", "ISBN" : "0027-8424 (Print) 0027-8424 (Linking)", "ISSN" : "0027-8424", "PMID" : "7567980", "abstract" : "Recent structural studies of the minimal core DNA-binding domain of p53 (p53DBD) complexed to a single consensus pentamer sequence and of the isolated p53 tet-ramerization domain have provided valuable insights into their functions, but many questions about their interacting roles and synergism remain unanswered. To better under-stand these relationships, we have examined the binding of the p53DBD to two biologically important full-response elements (the WAFI and ribosomal gene cluster sites) by using DNA circularization and analytical ultracentrifugation. We show that the p53DBD binds DNA strongly and cooperatively with p53DBD to DNA binding stoichiometries of 4:1. For the WAFI element, the mean apparent Kd is (8.3 + 1.4) x 10-8 M, and no intermediate species of lower stoichiometries can be de-tected. We show further that complex formation induces an axial bend of at least 60\u00b0 in both response elements. These results, taken collectively, demonstrate that p53DBD pos-sesses the ability to direct the formation of a tight nucleopro-tein complex having the same 4:1 DNA-binding stoichiometry as wild-type p53 which is accompanied by a substantial confor-mational change in the response-element DNA. This suggests that the p53DBD may play a role in the tetramerization function of p53. A possible role in this regard is proposed.", "author" : [{ "dropping-particle" : "", "family" : "Balagurumoorthy", "given" : "Pichumani", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Sakamotot", "given" : "Hiroshi", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, {

"dropping-particle" : "", "family" : "Lewist", "given" : "Marc S", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Zambranot", "given" : "Nicola", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Clore", "given" : "G Marius", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Gronenborn", "given" : "Angela M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Appellat", "given" : "Errore", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Harrington", "given" : "Rodney E", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Biochemistry", "id" : "ITEM-1", "issued" : { "date-parts" : [["1995"]] }, "page" : "8591-8595", "title" : "Four p53 DNA-binding domain peptides bind natural p53-response elements and bend the DNA (cooperative DNA binding/DNA bending/cyclization)", "type" : "article-journal", "volume" : "92" }, "uris" : ["http://www.mendeley.com/documents/?uuid=39b6dd5a-fcf3-4422-8b85-a1a72b5f1dfa"] }], "mendeley" : { "formattedCitation" : "(15)", "plainTextFormattedCitation" : "(15)", "previouslyFormattedCitation" : "(15)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**, demonstrating the importance of this domain to DNA binding. This is achieved by correcting the orientation of the p53 protein, and mediating the twisting of DNA to allow for a precise 'fit' per say. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1073/pnas.96.5.1875", "ISBN" : "0027-8424 (Print)\\n0027-8424 (Linking)", "ISSN" : "0027-8424", "PMID" : "10051562", "abstract" : "DNA binding activity of p53 is crucial for its tumor suppressor function. Our recent studies have shown that four molecules of the DNA binding domain of human p53 (p53DBD) bind the response elements with high cooperativity and bend the DNA. By using A-tract phasing experiments, we find significant differences between the bending and twisting of DNA by p53DBD and by full-length human wild-type (wt) p53. Our data show that four subunits of p53DBD bend the DNA by 32-36 degrees, whereas wt p53 bends it by 51-57 degrees. The directionality of bending is consistent with major groove bends at the two pentamer junctions in the consensus DNA response element. More sophisticated phasing analyses also demonstrate that p53DBD and wt p53 overtwist the DNA response element by approximately 35 degrees and approximately 70 degrees, respectively. These results are in accord with molecular modeling studies of the tetrameric complex. Within the constraints imposed by the protein subunits, the DNA can assume a range of conformations resulting from correlated changes in bend and twist angles such that the p53-DNA tetrameric complex is stabilized by DNA overtwisting and bending toward the major groove at the CATG tetramers. This bending is consistent with the inherent sequence-dependent anisotropy of the duplex. Overall, the four p53 moieties are placed laterally in a staggered array on the external side of the DNA loop and have numerous interprotein interactions that increase the stability and cooperativity of binding. The novel architecture of the p53 tetrameric complex has important functional implications including possible p53 interactions with chromatin.", "author" : [{ "dropping-particle" : "", "family" : "Nagaich", "given" : "A. K.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Zhurkin", "given" : "V. B.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Durell", "given" : "S. R.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Jernigan", "given" : "R. L.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Appella", "given" : "E.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Harrington", "given" : "R. E.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Proceedings of the National Academy of Sciences of the United States of America", "id" : "ITEM-1", "issue" : "5", "issued" : { "date-parts" : [["1999"]] }, "page" : "1875-80", "title" : "p53-induced DNA bending and twisting: p53 tetramer binds on the outer side of a DNA loop and increases DNA twisting.", "type" : "article-journal", "volume" : "96" }, "uris" : ["http://www.mendeley.com/documents/?uuid=4bb38809-64a4-49d4-bf13-c2713ec6acbf"] }], "mendeley" : { "formattedCitation" : "(16)", "plainTextFormattedCitation" : "(16)", "previouslyFormattedCitation" : "(16)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}** Notably, very few mutations occur upon the TD, which is located between residues 326 – 355. (18)

7. *α-Regulatory Domain / DNA Damage Recognition Domain (α)*

The α-regulatory domain is a basic region located between amino acids 363 and 393, which is heavily modified by post-translational modification, integrating multiple cell signals and regulating p53 transcriptional activity and promoter specificity. (4; 19)

Figure 1 A to scale representation of the human p53 domains; the transactivation domains (TAD-1/TAD-2), the proline rich domain (PRD), the DNA binding domain (DBD), the nuclear localisation signal (NLS), the tetramerisation/oligomerisation domain (TD/OD) and the α regulatory domain (α). Numerical checkpoints denote the final amino acid of each domain.

1.3 Generalised Functions of the p53 protein

Certain regions of *TP53* are known to be highly conserved across species; a concept eloquently encapsulating the vital functions p53 pathway plays within other species as well as humans. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1101/cshperspect.a001198", "ISBN" : "1943-0264", "ISSN" : "19430264", "PMID" :

"20516129", "abstract" : "A common ancestor to the three p53 family members of human genes p53, p63, and p73 is first detected in the evolution of modern-day sea anemones, in which both structurally and functionally it acts to protect the germ line from genomic instabilities in response to stresses. This p63/p73 common ancestor gene is found in almost all invertebrates and first duplicates to produce a p53 gene and a p63/p73 ancestor in cartilaginous fish. Bony fish contain all three genes, p53, p63, and p73, and the functions of these three transcription factors diversify in the higher vertebrates. Thus, this gene family has preserved its structural features and functional activities for over one billion years of evolution.", "author" : [{ "dropping-particle" : "", "family" : "Belyi", "given" : "Vladimir A.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Ak", "given" : "Prashanth", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Markert", "given" : "Elke", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Wang", "given" : "Haijian", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Hu", "given" : "Wenwei", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Puzio-Kuter", "given" : "Anna", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Levine", "given" : "Arnold J.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Cold Spring Harbor perspectives in biology", "id" : "ITEM-1", "issue" : "6", "issued" : { "date-parts" : [["2010"]] }, "title" : "The origins and evolution of the p53 family of genes.", "type" : "article", "volume" : "2" }, "uris" : ["http://www.mendeley.com/documents/?uuid=ddf23079-f266-4e23-a5bd-df8ae0c6e6ba"] }], "mendeley" : { "formattedCitation" : "(19)", "plainTextFormattedCitation" : "(19)", "previouslyFormattedCitation" : "(19)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}** The p53 pathway is involved in multiple biological processes, responding to a diverse number of stress signals consequentially leading to different cell outcomes, many of which are tumour suppressive. [Summarised in Figure 2]

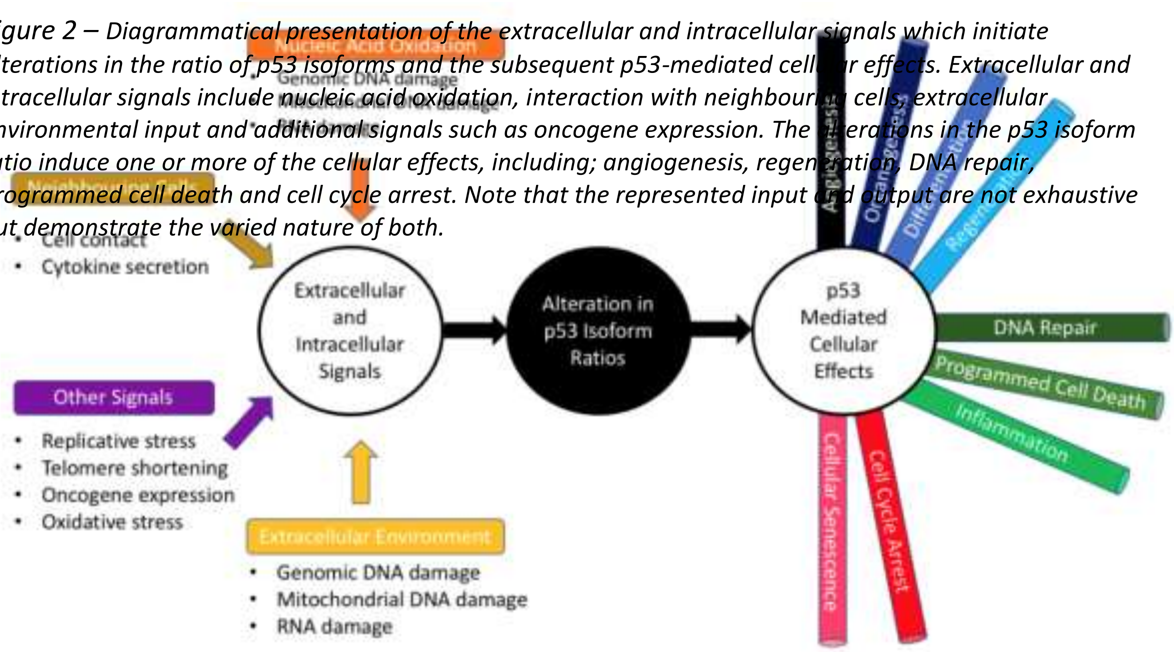

Figure 2 – Diagrammatical presentation of the extracellular and intracellular signals which initiate alterations in the ratio of p53 isoforms and the subsequent p53-mediated cellular effects. Extracellular and intracellular signals include nucleic acid oxidation, interaction with neighbouring cells, extracellular environmental input and additional signals such as oncogene expression. The alterations in the p53 isoform ratio induce one or more of the cellular effects, including; angiogenesis, regeneration, DNA repair, programmed cell death and cell cycle arrest. Note that the represented input and output are not exhaustive but demonstrate the varied nature of both.

Canonical p53 protein has been estimated to interact directly with more than 250 proteins, exemplifying the diverse roles and functions it fulfils (21). It is estimated that more than 10% of all human genes are regulated by p53 pathway (22,23). It is therefore important to mention that only a few are explored in this review.

a- Cell Cycle Arrest in Response to DNA Damage

In the absence of DNA damage, canonical p53 protein is tagged for degradation by MDM2 (a p53-specific E3 ubiquitin ligase) or its homolog MDMX (24), regulating p53 activities. Upon DNA damage, MDM2 is phosphorylated, reducing its affinity for FLp53. Thus, several MDM2 inhibitors have been evaluated as potential novel anticancer drugs (25). FLp53 is stabilized and retained in the nucleus in response to cellular stress. The stabilization of FLp53 is dependent on a variety of proteins, including damage sensors such as ATM and poly-(ADP-ribose)-polymerase 1 (26-29), as well as on different p53 isoforms (1, 5).

Canonical p53 can arrest the cell cycle at the G1 / S checkpoint in the presence of unrepaired DNA damage; a delay crucial in aiding repair mechanisms. {ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1016/S0092-8674(00)81871-1", "ISBN" : "0092-8674", "ISSN" : "00928674", "PMID" : "9039259", "abstract" : "The p53 gene and its protein product have become the center of intensive study ever since it became clear that slightly more than 50% of human cancers contain mutations in this gene. An extensive database catalogs these mutations in more than 50 different cell and tissue types, although some types of cancers never appear to select for p53 mutations. The nature of these genetic changes in cancer cells is most commonly a missense mutation in one allele, producing a faulty protein that is then observed at high concentrations in these cells, followed by a reduction to homozygosity. More rarely, deletions or chain-termination mutations in the p53 gene indicate that the null phenotype predisposes to cancer, as has been observed in mice with a homozygous p53 null mutation. There have been some suggestions that the missense mutant producing a faulty p53 protein could contribute a \"gain of function\" phenotype, but this remains to be substantiated by additional experimentation.", "author" : [{ "dropping-particle" : "", "family" : "Levine", "given" : "Arnold J.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Cell", "id" : "ITEM-1", "issue" : "3", "issued" : { "date-parts" : [["1997"]] }, "page" : "323-331", "title" : "p53, the cellular gatekeeper for growth and division", "type" : "article", "volume" : "88" }, "uris" : ["http://www.mendeley.com/documents/?uuid=d78a4add-e8a1-4230-bbcc-20596bfe4dcc"] }], "mendeley" : { "formattedCitation" : "(20)", "plainTextFormattedCitation" : "(20)", "previouslyFormattedCitation" : "(20)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }} This can be achieved via the transcription of many genes under the control of p53; one being $p21^{WAF1/CIP1}$ - a CDK inhibitor. CDK (cyclin dependent kinase) complexes govern the progression of the cell cycle from G1 to S stage and the transition from G2 to the mitotic stage of the cell cycle. By inhibiting CDK, $p21^{WAF1/CIP1}$ arrests the cell cycle at the G1 checkpoint). {ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "https://doi.org/10.1016/S0014-5793(01)02114-7", "abstract" : "The ability to self-replicate is a fundamental feature of life, reflected at the cellular level by a highly regulated process initiated in G1 phase via commitment to a round of DNA replication and cell division. Here we briefly highlight recent advances in understanding the molecular pathways which govern the decision of mammalian somatic cells to enter S phase, and the so-called cell cycle checkpoints which guard the G1/S transition and S phase progression against potentially deleterious effects of genotoxic stress. Particular emphasis is put on the emerging parallel yet cooperative pathways of retinoblastoma protein (pRB)\u2013E2F and Myc, their convergence to control the activity of the cyclin-dependent kinase 2 (Cdk2) at the G1/S boundary, as well as the two waves of checkpoint responses at G1/S: the rapid pathway(s) leading to Cdc25A degradation, and the delayed p53\u2013p21 cascade, both silencing the Cdk2 activity upon DNA damage.", "author" : [{ "dropping-particle" : "", "family" : "Bartek", "given" : "Jiri", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lukas", "given" : "Jiri", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "FEBS Letters", "id" : "ITEM-1", "issue" : "3", "issued" : { "date-parts" : [["2001"]] }, "page" : "117-122", "title" : "Pathways governing G1/S transition and their response to DNA damage", "type" : "article-journal", "volume" : "490" }, "uris" : ["http://www.mendeley.com/documents/?uuid=d298725c-8aa7-45e9-af13-9b1c72c6f082"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.1038/35042675", "ISBN" : "0028-0836", "ISSN" : "0028-0836", "PMID" : "11099028", "abstract" : "The p53 tumour-suppressor gene integrates numerous signals that control cell life and death. As when a highly connected node in the Internet breaks down, the disruption of p53 has severe consequences. Tumour-suppressor genes are needed to keep cells under control. Just as a car's brakes regulate its speed, properly functioning tumour-suppressor genes act as brakes to the cycle of cell growth, DNA replication and division into two new cells.", "author" : [{ "dropping-particle" : "", "family" : "Vogelstein", "given" : "B", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lane", "given" : "D", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Levine", "given" : "A J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Nature", "id" : "ITEM-2", "issue" : "6810", "issued" : { "date-parts" : [["2000"]] }, "page" : "307-310", "title" : "Surfing the p53 network.", "type" : "article-journal", "volume" : "408" }, "uris" : ["http://www.mendeley.com/documents/?uuid=5badd26d-4c2b-419f-b730-1794d85cfc1f"] }], "mendeley" : { "formattedCitation" : "(21,22)", "plainTextFormattedCitation" : "(21,22)", "previouslyFormattedCitation" : "(21,22)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**.

p53 pathway also maintains control over the transition to G2 / M stage, through inhibition of the *CDC2* gene product– Cdk1. In short, the kinase activity of the Cdk1/Cyclin B1 complex is required for G2 / M progression. p53 pathway can control entry into mitosis by inhibiting expression of *CDC2* and/or Cyclin B and by inducing expression of p53 target genes such as 14-3-3σ. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1038/sj.onc.1204252", "ISSN" : "0950-9232", "author" : [{ "dropping-particle" : "", "family" : "Taylor", "given" : "William R", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Stark", "given" : "George R", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Oncogene", "id" : "ITEM-1", "issue" : "15", "issued" : { "date-parts" : [["2001", "4", "5"]] }, "page" : "1803-1815", "publisher" : "Nature Publishing Group", "title" : "Regulation of the G2/M transition by p53", "type" : "article-journal", "volume" : "20" }, "uris" : ["http://www.mendeley.com/documents/?uuid=5047fdb7-ed34-3d21-b7fe-8cba3c87d2bc"] }], "mendeley" : { "formattedCitation" : "(23)", "plainTextFormattedCitation" : "(23)", "previouslyFormattedCitation" : "(23)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**

<u>b. Cellular Senescence</u>

Cellular senescence occurs when cells do not progress through the cell cycle (G0), hence resulting in the permanent arresting of DNA replication, even if conditions permit its continuity. This state can be induced by p53 pathway in response to a varying number of signals, including telomere erosion during replication **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1038/345458a0", "ISBN" : "doi:10.1038/345458a0", "ISSN" : "0028-0836", "PMID" : "2342578", "abstract" : "The terminus of a DNA helix has been called its Achilles' heel. Thus to prevent possible incomplete replication and instability of the termini of linear DNA, eukaryotic chromosomes end in characteristic repetitive DNA sequences within specialized structures called telomeres. In immortal cells, loss of telomeric DNA due to degradation or incomplete replication is apparently balanced by telomere elongation, which may involve de novo synthesis of additional repeats by novel DNA polymerase called telomerase. Such a polymerase has been recently detected in HeLa cells. It has been proposed that the finite doubling capacity of normal mammalian cells is due to a loss of telomeric DNA and eventual deletion of essential sequences. In yeast, the est1 mutation causes gradual loss of telomeric DNA and eventual cell death mimicking senescence in higher eukaryotic cells. Here, we show that the amount and length of telomeric DNA in human fibroblasts does in fact decrease as a function of serial passage during ageing in vitro and possibly in vivo. It is not known whether this loss of DNA has a causal role in senescence.", "author" : [{ "dropping-particle" : "", "family" : "Harley", "given" : "Calvin B", "non-dropping-particle" : "", "parse-

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accumulation of ROS and DNA damage.
Studies have also revealed the expression of oncogenes can stimulate senescence – an example being the overproduction of pro – proliferative proteins such as E2F -1, RAF, MOS and BRAF.

The p53 pathway for mobilising senescence is reliant on p21; the protein is recruited by FLp53 when DNA damage signals in particular are received. A deficiency of p21 results in the failure of a cell to initiate cell cycle arrest in response to radiation **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1038/377552a0", "ISBN" : "0028-0836 (Print)\\n0028-0836 (Linking)", "ISSN" : "0028-0836", "PMID" : "7566157", "abstract" : "The protein p21 is a dual inhibitor of cyclin-dependent kinases and proliferating-cell nuclear antigen (PCNA), both of which are required for passage through the cell cycle. The p21 gene is under the transcriptional control of p53 (ref. 5), suggesting that p21 might promote p53-dependent cell cycle arrest or apoptosis. p21 has also been implicated in cell senescence and in cell-cycle withdrawal upon terminal differentiation. Here we investigate the role of p21 in these processes using chimaeric mice composed partly of p21-/- and partly of p21+/+ cells. Immunohistochemical studies of the p21+/+ and p21-/- components of adult small intestine indicated that deletion of p21 has no detectable effect on the migration-associated differentiation of the four principal intestinal epithelial cell lineages or on p53-dependent apoptosis following irradiation. However, p21-/- mouse embryo fibroblasts are impaired in their ability to undergo G1 arrest following DNA damage.", "author" : [{ "dropping-particle" : "", "family" : "Brugarolas", "given" : "J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Chandrasekaran", "given" : "C", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Gordon", "given" : "J I", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Beach", "given" : "D", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Jacks", "given" : "T", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Hannon", "given" : "G J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Nature", "id" : "ITEM-1", "issue" : "6549", "issued" : { "date-parts" : [["1995"]] }, "page" : "552-557", "title" : "Radiation-induced cell cycle arrest compromised by p21 deficiency.", "type" : "article", "volume" : "377" }, "uris" : ["http://www.mendeley.com/documents/?uuid=c0e407c7-2242-4fa9-af40-c7d9a043c835"] }], "mendeley" : { "formattedCitation" : "(25)", "plainTextFormattedCitation" : "(25)", "previouslyFormattedCitation" : "(25)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**,

indicating its importance in inducing cellular senescence. {ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1038/nrm2233", "ISBN" : "doi:10.1038/nrm2233", "ISSN" : "1471-0072", "PMID" : "17667954", "abstract" : "Cells continually experience stress and damage from exogenous and endogenous sources, and their responses range from complete recovery to cell death. Proliferating cells can initiate an additional response by adopting a state of permanent cell-cycle arrest that is termed cellular senescence. Understanding the causes and consequences of cellular senescence has provided novel insights into how cells react to stress, especially genotoxic stress, and how this cellular response can affect complex organismal processes such as the development of cancer and ageing.", "author" : [{ "dropping-particle" : "", "family" : "Campisi", "given" : "Judith", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "d'Adda di Fagagna", "given" : "Fabrizio", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Nature reviews. Molecular cell biology", "id" : "ITEM-1", "issue" : "9", "issued" : { "date-parts" : [["2007"]] }, "page" : "729-740", "title" : "Cellular senescence: when bad things happen to good cells.", "type" : "article-journal", "volume" : "8" }, "uris" : ["http://www.mendeley.com/documents/?uuid=92c4627c-4428-4229-a1d7-9e5b32ed7d90"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.1038/onc.2012.640", "ISBN" : "1476-5594 (Electronic)\\r0950-9232 (Linking)", "ISSN" : "1476-5594", "PMID" : "23416979", "abstract" : "p53 functions as a transcription factor involved in cell-cycle control, DNA repair, apoptosis and cellular stress responses. However, besides inducing cell growth arrest and apoptosis, p53 activation also modulates cellular senescence and organismal aging. Senescence is an irreversible cell-cycle arrest that has a crucial role both in aging and as a robust physiological antitumor response, which counteracts oncogenic insults. Therefore, via the regulation of senescence, p53 contributes to tumor growth suppression, in a manner strictly dependent by its expression and cellular context. In this review, we focus on the recent advances on the contribution of p53 to cellular senescence and its implication for cancer therapy, and we will discuss p53's impact on animal lifespan. Moreover, we describe p53-mediated regulation of several physiological pathways that could mediate its role in both senescence and aging.", "author" : [{ "dropping-particle" : "", "family" : "Rufini", "given" : "a", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Tucci", "given" : "P", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Celardo", "given" : "I", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Melino", "given" : "G", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Oncogene", "id" : "ITEM-2", "issue" : "43", "issued" : { "date-parts" : [["2013"]] }, "page" : "5129-43", "title" : "Senescence and aging: the critical roles of p53.", "type" : "article-journal", "volume" : "32" }, "uris" : ["http://www.mendeley.com/documents/?uuid=be82a691-37f4-418b-88da-d2554ebf99dc"] }], "mendeley" : { "formattedCitation" : "(26,27)", "plainTextFormattedCitation" : "(26,27)", "previouslyFormattedCitation" : "(26,27)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }}

c. Apoptosis

Upon DNA damage, the cell can also undergo apoptosis. Whether the cell elects for apoptosis or cell cycle arrest is contingent on several factors, including the cell type and the form of cellular stress experienced. The two most studied apoptotic signalling pathways are regulated by p53 pathway: the intrinsic mitochondrial pathway and the extrinsic death receptor pathway. {ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1039/b905129p", "ISBN" : "1539-6509", "ISSN" : "1944-7930", "PMID" : "20193641", "abstract" : "The dynamic and multiple functions of p53, together with its involvement in the most common non-infectious diseases, underscore the need to elucidate the complexity of the p53 regulatory networks. Pathological conditions such as cancer, neurodegeneration, ischemia, cholestasis, and atherosclerosis are all strongly associated with deregulated levels of apoptosis in which p53 dysfunction has a prominent role. We will highlight recent developments of p53-induced apoptosis in human diseases, with a focus on modulation of liver cell apoptosis. In addition, we will discuss controversies arising from widespread p53 activation as a therapeutic approach to cancer. Recent studies have provided relevant and unprecedented information about mechanistic antiapoptotic functions of the endogenous bile acid, ursodeoxycholic acid (UDCA), suggesting that the finely tuned, complex control of p53 by Mdm-2 (mouse double minute-2, an oncoprotein) is a key step in UDCA modulation of p53-triggered apoptosis. We will also review recent therapeutic strategies and clinical applications of targeted agents, their safety, and efficacy, with particular emphasis on potential benefits of UDCA.", "author" : [{ "dropping-particle" : "", "family" : "Amaral", "given" : "Joana D", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Xavier", "given" : "Joana M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Steer", "given" : "Clifford J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Rodrigues", "given" : "Cec\u00edlia M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Discovery medicine", "id" : "ITEM-1", "issue" : "45", "issued" : { "date-parts" : [["2010"]] }, "page" : "145-152", "title" : "The role of p53 in apoptosis.", "type" : "article-journal", "volume" : "9" }, "uris" : ["http://www.mendeley.com/documents/?uuid=41c60312-be58-4990-97d3-e7fab9cf64c6"] }], "mendeley" : { "formattedCitation" : "(28)", "plainTextFormattedCitation" : "(28)", "previouslyFormattedCitation" : "(28)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }}

a. *Intrinsic Mitochondrial Pathway*

This pathway involves the transcription of pro – apoptotic genes, chiefly of the Bcl-2 family of proteins (including BAX, PUMA and NOX). Bcl-2 proteins control the release of cytochrome C from the mitochondria {ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1016/S0092-8674(02)01036-X", "ISBN" : "0092-8674 (Print)\\n0092-8674 (Linking)", "ISSN" : "00928674", "PMID" : "12419244", "abstract" : "Bcl-2 family proteins regulate the release of proteins like cytochrome c from mitochondria during apoptosis. We used cell-free systems and ultimately a vesicular reconstitution from defined molecules to show that outer membrane permeabilization by Bcl-2 family proteins requires neither the mitochondrial matrix, the inner membrane, nor other proteins. Bid, or its BH3-domain peptide, activated monomeric Bax to produce membrane openings that allowed the passage of very large (2 megadalton) dextran molecules, explaining the translocation of large mitochondrial proteins during apoptosis. This process required cardiolipin and was inhibited by antiapoptotic Bcl-xL. We conclude that mitochondrial protein release in apoptosis can be mediated by supramolecular openings in the outer mitochondrial membrane, promoted by BH3/Bax/lipid interaction and directly inhibited by Bcl-xL.", "author" : [{ "dropping-particle" : "", "family" : "Kuwana", "given" : "Tomomi", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Mackey", "given" : "Mason R.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Perkins", "given" : "Guy", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Ellisman", "given" : "Mark H.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Latterich", "given" : "Martin", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Schneiter", "given" : "Roger", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Green", "given" : "Douglas R.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Newmeyer", "given" : "Donald D.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Cell", "id" : "ITEM-1", "issue" : "3", "issued" : { "date-parts" : [["2002"]] }, "page" : "331-342", "title" : "Bid, Bax, and lipids cooperate to form supramolecular openings in the outer mitochondrial membrane", "type" : "article-journal", "volume" : "111" }, "uris" : ["http://www.mendeley.com/documents/?uuid=785a0229-8e71-4f0b-87fb-4057d6df6112"] }], "mendeley" : { "formattedCitation" : "(29)", "plainTextFormattedCitation" : "(29)", "previouslyFormattedCitation" : "(29)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**, which in turn activates caspase – 9 and a sequential caspase cascade that results in the destruction of the cell. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1016/S0092-8674(00)80434-1", "ISSN" : "00928674", "author" : [{ "dropping-particle" : "", "family" : "Li", "given" : "Peng", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Nijhawan", "given" : "Deepak", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Budihardjo", "given" : "Imawati", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Srinivasula", "given" : "Srinivasa M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Ahmad", "given" : "Manzoor", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Alnemri", "given" : "Emad S", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Wang", "given" : "Xiaodong", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Cell", "id" : "ITEM-1", "issue" : "4", "issued" : { "date-parts" : [["1997", "11"]] }, "page" : "479-489", "title" : "Cytochrome c and dATP-Dependent Formation of Apaf-1/Caspase-9 Complex Initiates an Apoptotic Protease Cascade", "type" : "article-journal", "volume" : "91" }, "uris" : ["http://www.mendeley.com/documents/?uuid=c2bee90e-24cc-3cff-87eb-2b4abc36c0bd"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.1242/jcs.00739", "ISBN" : "0021-9533 (Print)\\r0021-9533 (Linking)", "ISSN" : "0021-9533", "PMID" : "12972501", "abstract" : "Exposure to cellular stress can trigger the p53 tumor suppressor, a sequence-specific transcription factor, to induce cell growth arrest or apoptosis. The choice between these cellular responses is influenced by many factors, including the type of cell and stress, and the action of p53 co-activators. p53 stimulates a wide network of signals that act through two major apoptotic pathways. The extrinsic, death receptor pathway triggers the activation of a caspase cascade, and the intrinsic, mitochondrial pathway shifts the balance in the Bcl-2 family towards the pro-apoptotic members, promoting the formation of the apoptosome, and consequently caspase-mediated apoptosis. The impact of these two apoptotic pathways may be enhanced when they converge through Bid, which is a p53 target. The majority of these apoptotic effects are mediated through the induction of specific apoptotic target genes. However, p53 can also promote apoptosis by a transcription-independent mechanism under certain conditions. Thus, a multitude of mechanisms are employed by p53 to ensure efficient induction of apoptosis in a stage-, tissue- and stress-signal-specific manner. Manipulation of the apoptotic functions of p53 constitutes an attractive target for cancer therapy.", "author" : [{ "dropping-particle" : "", "family" : "Haupt", "given" : "Susan", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Berger", "given" : "Michael", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Goldberg", "given" : "Zehavit", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Haupt", "given" : "Ygal", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Journal of cell science", "id" : "ITEM-2", "issue" : "Pt 20", "issued" : { "date-parts" : [["2003"]] }, "page" : "4077-85", "title" : "Apoptosis - the p53 network.", "type" : "article-journal", "volume" : "116" }, "uris" : ["http://www.mendeley.com/documents/?uuid=8ec1ee91-ede7-4fdd-8db0-00797104a582"] }], "mendeley" : { "formattedCitation" : "(30,31)", "plainTextFormattedCitation" : "(30,31)", "previouslyFormattedCitation" : "(30,31)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**

b. *Extrinsic Death Receptor Pathway*

p53 pathway can also stimulate the apoptotic pathway through the activation of genes encoding three proteins in particular: Fas, DR5 (Trail) and PERP.
Fas, when bound to FasL (its ligand), prompts the release of caspases **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1126/science.7533326", "ISBN" : "0036-8075 (Print)\\n0036-8075 (Linking)", "ISSN" : "0036-8075", "PMID" : "7533326", "abstract" : "Fas ligand (FasL), a cell surface molecule belonging to the tumor necrosis factor family, binds to its receptor Fas, thus inducing apoptosis of Fas-bearing cells. Various cells express Fas, whereas FasL is expressed predominantly in activated T cells. In the immune system, Fas and FasL are involved in down-regulation of immune reactions as well as in T cell-mediated cytotoxicity. Malfunction of the Fas system causes lymphoproliferative disorders and accelerates autoimmune diseases, whereas its exacerbation may cause tissue destruction.", "author" : [{ "dropping-particle" : "", "family" : "Nagata",

"given" : "S", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Golstein", "given" : "P", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Science (New York, N.Y.)", "id" : "ITEM-1", "issue" : "5203", "issued" : { "date-parts" : [["1995"]] }, "page" : "1449-1456", "title" : "The Fas death factor.", "type" : "article-journal", "volume" : "267" }, "uris" : ["http://www.mendeley.com/documents/?uuid=396ec846-2dba-4ca5-9165-c62d7af88a45"] }], "mendeley" : { "formattedCitation" : "(32)", "plainTextFormattedCitation" : "(32)", "previouslyFormattedCitation" : "(32)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}** leading to the degradation of the cell. The expression of Fas often occurs in response to gamma radiation. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1038/sj.onc.1203366", "ISSN" : "09509232", "PMID" : "10698510", "abstract" : "The mechanisms by which the p53 tumour suppressor protein would, in vivo, co-ordinate the adaptive response to genotoxic stress is poorly understood. p53 has been shown to transactivate several genes that could be involved in two main cellular responses, growth arrest and apoptosis. To get further insight into the tissue-specific regulation of p53 transcriptional activity, we performed an extensive study looking at the expression of four well characterized p53-responsive genes, before and after gamma-irradiation in p53 wild-type (p53+/+) and p53-deficient (p53-/-) mice. The waf1, bax, fas and mdm2 genes were chosen for their different potential roles in the cellular response to stress. Our data demonstrate the strict p53-dependence of mRNA up-regulation for bax, fas and mdm2 in irradiated tissues and confirm such findings for waf1. They further highlight complex levels of regulatory mechanisms that could lead, in vivo, to selective transcriptional activation of genes by p53. In addition, our results provide arguments for the involvement of p53 in the basal mRNA expression of the four genes in some organs. Finally, in situ expression of Bax and p21Waf-1 protein suggests, at least in lymphoid organs, a direct correlation between selective p53-target gene expression and a particular response of a cell to ionising radiation.", "author" : [{ "dropping-particle" : "", "family" : "Bouvard", "given" : "V\u00e9ronique", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Zaitchouk", "given" : "Tatiana", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Vacher", "given" : "Monique", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Duthu", "given" : "Arlette", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Canivet", "given" : "Martine", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Choisy-Rossi", "given" : "Caroline", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Nieruchalski", "given" : "Myriam", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "May", "given" : "Evelyne", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Oncogene", "id" : "ITEM-1", "issue" : "5", "issued" : { "date-parts" : [["2000", "2", "17"]] }, "page" : "649-660", "title" : "Tissue and cell-specific expression of the p53-target genes: bax, fas, mdm2 and waf1/p21, before and following ionising irradiation in mice", "type" : "article-journal", "volume" : "19" }, "uris" : ["http://www.mendeley.com/documents/?uuid=a6aa6051-a569-3632-8c72-74ad48f1e822"] }], "mendeley" : { "formattedCitation" : "(33)", "plainTextFormattedCitation" : "(33)", "previouslyFormattedCitation" : "(33)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }} DR5 promotes cell death through the activation of caspase – 8, leading to a similar cascade. PERP is suggested to be directly associated with p53, possibly cooperating with activated E2F-1 which contributes to apoptosis. {ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1242/jcs.00739", "ISBN" : "0021-9533 (Print)\\r0021-9533 (Linking)", "ISSN" : "0021-9533", "PMID" : "12972501", "abstract" : "Exposure to cellular stress can trigger the p53 tumor suppressor, a sequence-specific transcription factor, to induce cell growth arrest or apoptosis. The choice between these cellular responses is influenced by many factors, including the type of cell and stress, and the action of p53 co-activators. p53 stimulates a wide network of signals that act through two major apoptotic pathways. The extrinsic, death receptor pathway triggers the activation of a caspase cascade, and the intrinsic, mitochondrial pathway shifts the balance in the Bcl-2 family towards the pro-apoptotic members, promoting the formation of the apoptosome, and consequently caspase-mediated apoptosis. The impact of these two apoptotic pathways may be enhanced when they converge through Bid, which is a p53 target. The majority of these apoptotic effects are mediated through the induction of specific apoptotic target genes. However, p53 can also promote apoptosis by a transcription-independent mechanism under certain conditions. Thus, a multitude of mechanisms are employed by p53 to ensure efficient induction of apoptosis in a stage-, tissue- and stress-signal-specific manner. Manipulation of the apoptotic functions of p53 constitutes an attractive target for cancer therapy.", "author" : [{ "dropping-particle" : "", "family" : "Haupt", "given" : "Susan", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Berger", "given" : "Michael", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Goldberg", "given" : "Zehavit", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Haupt", "given" : "Ygal", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Journal of cell science", "id" : "ITEM-1", "issue" : "Pt 20", "issued" : { "date-parts" : [["2003"]] }, "page" : "4077-85", "title" : "Apoptosis - the p53 network.", "type" : "article-journal", "volume" : "116" }, "uris" : ["http://www.mendeley.com/documents/?uuid=8ec1ee91-ede7-4fdd-8db0-00797104a582"] }], "mendeley" : { "formattedCitation" : "(31)", "plainTextFormattedCitation" : "(31)", "previouslyFormattedCitation" : "(31)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }}

It is presently understood that the p53-mediated acute response to DNA damage is only part of p53-mediated tumour suppression (46). p53 carries out 'baseline surveillance' of the integrity of the genome along with its acute-phase functions. The control at baseline involves transient fluctuations in p53 levels that are not sufficient to activate apoptosis or cellular senescence, but instead target the detection and repair of the lesion. p53 also plays a role in innate and adaptive immune responses, including anticancer immunity. (47)

2- The p53 Isoforms

As mentioned, the p53 isoforms arise as a result of "alternative splicing [of introns], alternative initiation of translation and alternative promoter usage". **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1177/1947601911408893", "ISBN" : "1947-6027 (Electronic)\\r1947-6019 (Linking)", "ISSN" : "1947-6019", "PMID" : "21779513", "abstract" : "Normal function of the p53 pathway is ubiquitously lost in cancers either through mutation or inactivating interaction with viral or cellular proteins. However, it is difficult in clinical studies to link p53 mutation status to cancer treatment and clinical outcome, suggesting that the p53 pathway is not fully understood. We have recently reported that the human p53 gene expresses not only 1 but 12 different p53 proteins (isoforms) due to alternative splicing, alternative initiation of translation, and alternative promoter usage. p53 isoform proteins thus contain distinct protein domains. They are expressed in normal human tissues but are abnormally expressed in a wide range of cancer types. We have recently reported that p53 isoform expression is associated with breast cancer prognosis, suggesting that they play a role in carcinogenesis. Indeed, the cellular response to damages can be switched from cell cycle arrest to apoptosis by only manipulating p53 isoform expression. This may provide an explanation to the hitherto inconsistent relationship between p53 mutation, treatment response, and outcome in breast cancer. However, the molecular mechanism is still unknown. Recent reports suggest that it involves modulation of gene expression in a p53-dependent and -independent manner. In this review, we summarize our current knowledge about the biological activities of p53 isoforms and propose a molecular mechanism conciliating our current knowledge on p53 and integrating p63 and p73 isoforms in the p53 pathway.", "author" : [{ "dropping-particle" : "", "family" : "Khoury", "given" : "M. P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bourdon", "given" : "J.-C.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Genes & Cancer", "id" : "ITEM-1", "issue" : "4", "issued" : { "date-parts" : [["2011"]] }, "page" : "453-465", "title" : "p53 Isoforms: An Intracellular Microprocessor?", "type" : "article-journal", "volume" : "2" }, "uris" : ["http://www.mendeley.com/documents/?uuid=9d530c4a-b7e0-4241-a1b4-7a5bc16f78ad"] }], "mendeley" : { "formattedCitation" : "(1)", "plainTextFormattedCitation" : "(1)", "previouslyFormattedCitation" : "(1)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**
Initially, three human p53 isoforms were described prior to the discovery of further isoforms in 2005 by Bourdon *et al* **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1101/gad.1339905", "ISBN" : "2514458412", "ISSN" : "08909369", "PMID" : "16131611", "abstract" : "The recently discovered p53-related genes, p73 and p63, express multiple splice variants and N-terminally truncated forms initiated from an alternative promoter in intron 3. To date, no alternative promoter and multiple splice variants have been described for the p53 gene. In this study, we show that p53 has a gene structure similar to the p73 and p63 genes. The human p53 gene contains an alternative promoter and transcribes multiple splice variants. We show that p53 variants are expressed in normal human tissue in a tissue-dependent manner. We determine that the alternative

promoter is conserved through evolution from Drosophila to man, suggesting that the p53 family gene structure plays an essential role in the multiple activities of the p53 family members. Consistent with this hypothesis, p53 variants are differentially expressed in human breast tumors compared with normal breast tissue. We establish that p53beta can bind differentially to promoters and can enhance p53 target gene expression in a promoter-dependent manner, while Delta133p53 is dominant-negative toward full-length p53, inhibiting p53-mediated apoptosis. The differential expression of the p53 isoforms in human tumors may explain the difficulties in linking p53 status to the biological properties and drug sensitivity of human cancer.", "author" : [{ "dropping-particle" : "", "family" : "Bourdon", "given" : "Jean Christophe", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Fernandes", "given" : "Kenneth", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Murray-Zmijewski", "given" : "Fiona", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Liu", "given" : "Geng", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Diot", "given" : "Alexandra", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Xirodimas", "given" : "Dimitris P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Saville", "given" : "Mark K.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lane", "given" : "David P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Genes and Development", "id" : "ITEM-1", "issue" : "18", "issued" : { "date-parts" : [["2005"]] }, "page" : "2122-2137", "title" : "p53 isoforms can regulate p53 transcriptional activity", "type" : "article-journal", "volume" : "19" }, "uris" : ["http://www.mendeley.com/documents/?uuid=87bfab4c-0377-4811-b35f-c1e089298fe3"] }], "mendeley" : { "formattedCitation" : "(34)", "plainTextFormattedCitation" : "(34)", "previouslyFormattedCitation" : "(34)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}** and in 2010 by Marcel *et al*. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1016/j.febslet.2010.10.005", "ISBN" : "1873-3468 (Electronic)\\r0014-5793 (Linking)", "ISSN" : "00145793", "PMID" : "20937277", "abstract" : "p53 gene expresses several protein isoforms modulating p53-mediated responses through regulation of gene expression. Here, we identify a novel p53 isoform, \u0394160p53, lacking the first 159 residues. By knockdown experiments and site-directed mutagenesis, we show that \u0394160p53 is encoded by \u0394133p53 transcript using ATG160 as translational initiation site. This hypothesis is supported by endogenous expression of \u0394160p53 in U2OS, T47D and K562 cells, the latter ones carrying a premature stop codon that impairs p53 and \u0394133p53 protein expression but not the one of \u0394160p53. Overall, these results show that the \u0394133p53 transcript generates two different p53 isoforms, \u0394133p53 and \u0394160p53. \u00a9 2010 Federation of European Biochemical Societies.", "author" : [{ "dropping-particle" : "", "family" : "Marcel", "given" : "Virginie", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Perrier", "given" : "St\u00e9phane", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Aoubala", "given" : "Mustapha", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Ageorges", "given" : "Sylvain", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Groves", "given" : "Michael J.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Diot", "given" : "Alexandra", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Fernandes", "given" : "Kenneth", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Tauro", "given" : "Sudhir", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bourdon", "given" : "Jean Christophe", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "FEBS Letters", "id" : "ITEM-1", "issue" : "21", "issued" : { "date-parts" : [["2010"]] }, "page" : "4463-4468", "title" : "\u0394160p53 is a novel N-terminal p53 isoform encoded by \u0394133p53 transcript", "type" : "article-journal", "volume" : "584" }, "uris" : ["http://www.mendeley.com/documents/?uuid=25cb923a-cb50-419c-b1af-dbe54c5e2949"] }], "mendeley" : { "formattedCitation" : "(35)", "plainTextFormattedCitation" : "(35)", "previouslyFormattedCitation" : "(35)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**. These encompassed the full length p53 protein (p53α; canonical p53), p53i9 (p53β) as reported by Flaman *et al* **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "ISBN" : "0950-9232 (Print)", "ISSN" : "0950-9232 (Print)", "PMID" : "8632903", "abstract" : "Alternative splicing affecting the p53 carboxy-terminus has previously been described in mouse but not in normal human cells. We report here the detection in normal human lymphocytes of an alternatively spliced form of human p53 mRNA containing an additional 133 bp exon derived from intron 9. This splice variant encodes a truncated protein of 341 amino-acids including 10 new amino-acids derived from the novel exon. The truncated protein, which lacks part of the p53 tetramerization domain, fails to bind DNA in vitro and has a transcriptional defect in vivo in both yeast and mammalian cells. 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"10.1038/sj.onc.1205874", "ISBN" : "0950-9232 (Print)\\n0950-9232 (Linking)", "ISSN" : "0950-9232", "PMID" : "12360399", "abstract" : "The tumor suppressor protein p53 is ubiquitously expressed as a major isoform of 53 kD, but several forms of lower molecular weight have been observed. Here, we describe a new isoform, DeltaN-p53, produced by internal initiation of translation at codon 40 and lacking the N-terminal first transactivation domain. This isoform has impaired transcriptional activation capacity, and does not complex with the p53 regulatory protein Mdm2. Furthermore, DeltaN-p53 oligomerizes with full-length p53 (FL-p53) and negatively regulates its transcriptional and growth-suppressive activities. Consistent with the lack of Mdm2 binding, DeltaN-p53 does not accumulate in response to DNA-damage, suggesting that this isoform is not involved in the response to genotoxic stress. However, in serum-starved cells expressing wild-type p53, DeltaN-p53 becomes the predominant p53 form during the synchronous progression into S phase after serum stimulation. These results suggest that DeltaN-p53 may play a role as a transient, negative regulator of p53 during cell cycle progression.", "author" : [{ "dropping-particle" : "", "family" : "Courtois", "given" : "St\u00e9phanie", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Verhaegh", "given" : "Gerald", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "North", "given" : "Sophie", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Luciani", "given" : "Maria-Gloria", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lassus", "given" : "Patrice", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Hibner", "given" : "Ula", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Oren", "given" : "Moshe", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Hainaut", "given" : "Pierre", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Oncogene", "id" : "ITEM-1", "issue" : "44", "issued" : { "date-parts" : [["2002"]] }, "page" : "6722-6728", "title" : "\u0394N-p53, a natural isoform of p53 lacking the first transactivation domain, counteracts growth suppression by wild-type p53", "type" : "article-journal", "volume" : "21" }, "uris" : ["http://www.mendeley.com/documents/?uuid=c9cf92e6-91bc-4ae8-9662-6d1c61a82804"] }], "mendeley" : { "formattedCitation" : "(37)", "plainTextFormattedCitation" : "(37)", "previouslyFormattedCitation" : "(37)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**. To date, the 12 isoforms expressed are classified as follows [Figure 3A; Figure 3B, Figure 3C]:

- p53α
- p53β
- p53γ

- Δ40p53α
- Δ40p53β
- Δ40p53γ

- Δ133p53α
- Δ133p53β
- Δ133p53γ

- Δ160p53α
- Δ160p53β
- Δ160p53γ

2.1 p53α, p53β and p53γ

The p53α isoform refers to the canonical p53 protein (also named FLp53). It was discovered in 1979, as a protein associating with the T antigen from the SV40 virus. (52,53). It is transcribed from P1 (proximal promoter 1) and translated from the canonically spliced mRNA transcript (i) using the ATG1 as translation initiation site. {ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1101/gad.1339905", "ISBN" : "2514458412", "ISSN" : "08909369", "PMID" : "16131611", "abstract" : "The recently discovered p53-related genes, p73 and p63, express multiple splice variants and N-terminally truncated forms initiated from an alternative promoter in intron 3. To date, no alternative promoter and multiple splice variants have been described for the p53 gene. In this study, we show that p53 has a gene structure similar to the p73 and p63 genes. The human p53 gene contains an alternative promoter and transcribes multiple splice variants. 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P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bourdon", "given" : "J.-C.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Genes & Cancer", "id" : "ITEM-2", "issue" : "4", "issued" : { "date-parts" : [["2011"]] }, "page" : "453-465", "title" : "p53 Isoforms: An Intracellular Microprocessor?", "type" : "article-journal", "volume" : "2" }, "uris" : ["http://www.mendeley.com/documents/?uuid=9d530c4a-b7e0-4241-a1b4-7a5bc16f78ad"] }], "mendeley" : { "formattedCitation" : "(1,34)", "plainTextFormattedCitation" : "(1,34)", "previouslyFormattedCitation" : "(1,34)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**

p53β was initially described as p53i9 **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "ISBN" : "0950-9232 (Print)", "ISSN" : "0950-9232 (Print)", "PMID" : "8632903", "abstract" : "Alternative splicing affecting the p53 carboxy-terminus has previously been described in mouse but not in normal human cells. We report here the detection in normal human lymphocytes of an alternatively spliced form of human p53 mRNA containing an additional 133 bp exon derived from intron 9. This splice variant encodes a truncated protein of 341 amino-acids including 10 new amino-acids derived from the novel exon. The truncated protein, which lacks part of the p53 tetramerization domain, fails to bind DNA in vitro and has a transcriptional defect in vivo in both yeast and mammalian cells. Quantitative RT-PCR experiments suggest that the alternatively spliced form is only present in significant amounts in quiescent cells. 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It is produced through the alternative splicing of exon 9b (contained within intron 9) which contains a stop codon, resulting in mRNA transcript (ii). Translation of mRNA transcript (ii) results in a protein devoid of the canonical tetramerization domain and the α - domain; but ending with 10 different amino acids –*DQTSFQKENC.* **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1101/gad.1339905", "ISBN" : "2514458412", "ISSN" : "08909369", "PMID" : "16131611", "abstract" : "The recently discovered p53-related genes, p73 and p63, express multiple splice variants and N-terminally truncated forms initiated from an alternative promoter in intron 3. To date, no alternative promoter and multiple splice variants have been described for the p53 gene. In this study, we show that p53 has a gene structure similar to the p73 and p63 genes. The human p53 gene contains an alternative promoter and transcribes multiple splice variants. 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p53γ is similarly devoid of the canonical tetramerization domain and the α - domain, ending instead with 15 additional 5 amino acids – *MLLDLRWCYFLINSS*. This is achieved through a different, alternative splicing of intron 9 - exon 9γ (contained within intron 9), generating mRNA transcript (iii), as well as being transcribed from P1 (proximal promoter 1).
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Exons 9β and 9γ are both referred to as "cryptic exons" due to their presence within intron 9. Both contain stop codons, resulting in exons 10 and 11 being non-coding in β and γ mRNA variants of p53. This explains why p53 is said to have 11 "canonical" exons and 13 functional exons in total. All the above mRNA variants are transcribed from P1 (proximal promoter 1).
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2.2 Δ40p53α, Δ40p53β, Δ40p53γ

The Δ40p53 isoforms are produced by three distinct mechanisms; by initiation of translation at codon 40, by alternative splicing (retention) of intron 2, which contains several stop codons or by proteolytic cleavage (54). This results in proteins lacking the first 39 amino acids which are thus devoid of the first transactivation domain (TAD1). **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1101/gad.1339905", "ISBN" : "2514458412", "ISSN" : "08909369", "PMID" : "16131611", "abstract" : "The recently discovered p53-related genes, p73 and p63, express multiple splice variants and N-terminally truncated forms initiated from an alternative promoter in intron 3. To date, no alternative promoter and multiple splice variants have been described for the p53 gene. In this study, we show that p53 has a gene structure similar to the p73 and p63 genes. The human p53 gene contains an alternative promoter and transcribes multiple splice variants. 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Δ40p53α (also termed p47 or ΔNp53) retains the second transactivation domain; the rest of the transcript mirrors p53α. The isoform yields not only from the translation of the fourth mRNA transcript (iv), but also from mRNA transcript (i) due to the occurrence of an internal ribosomal entry site (IRES) {ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1038/sj.embor.7400623", "ISBN" : "1469-221X (Print)\\r1469-221X (Linking)", "ISSN" : "1469-221X", "PMID" : "16440000", "abstract" : "The p53 tumour suppressor protein has a crucial role in cell\u2010cycle arrest and apoptosis. Previous reports show that the p53 messenger RNA is translated to produce an amino\u2010terminal\u2010deleted isoform (\u0394N\u2010p53) from an internal initiation codon, which acts as a dominant\u2010negative inhibitor of full\u2010length p53. Here, we show that two internal ribosome entry sites (IRESs) mediate the translation of both full\u2010length and \u0394N\u2010p53 isoforms. The IRES directing the translation of full\u2010length p53 is in the 5\u2032\u2010untranslated region of the mRNA, whereas the IRES mediating the translation of \u0394N\u2010p53 extends into the protein\u2010coding region. The two IRESs show distinct cell\u2010cycle phase\u2010dependent activity, with the IRES for full\u2010length p53 being active at the G2\u2013M transition and the IRES for \u0394N\u2010p53 showing highest activity at the G1\u2013S transition. These results indicate a novel translational control of p53 gene expression and activity.", "author" : [{ "dropping-particle" : "", "family" : "Ray", "given" : "Partho Sarothi", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Grover", "given" : "Richa", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Das", "given" : "Saumitra", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Barraille", "given" : "P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Chinestra", "given" : "P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bayard", "given" : "F.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Faye", "given" : "JC.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bunz", "given" : "F.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Dutriaux", "given" : "A.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lengauer", "given" : "C.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Waldman", "given" : "T.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Zhou", "given" : "S.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Brown", "given" : "JP.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Sedivy", "given" : "JM.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kinzler", "given" : "KW.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Vogelstein", "given" : "B.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Cornelis", "given" : "S.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bruynooghe", "given" : "Y.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Denecker", "given" : "G.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "Van", "family" : "Huffel", "given" : "S.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Tinton", "given" : "S.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Beyaert", "given" :

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alternative promoter in intron 3. To date, no alternative promoter and multiple splice variants have been described for the p53 gene. In this study, we show that p53 has a gene structure similar to the p73 and p63 genes. The human p53 gene contains an alternative promoter and transcribes multiple splice variants. We show that p53 variants are expressed in normal human tissue in a tissue-dependent manner. We determine that the alternative promoter is conserved through evolution from Drosophila to man, suggesting that the p53 family gene structure plays an essential role in the multiple activities of the p53 family members. Consistent with this hypothesis, p53 variants are differentially expressed in human breast tumors compared with normal breast tissue. We establish that p53beta can bind differentially to promoters and can enhance p53 target gene expression in a promoter-dependent manner, while Delta133p53 is dominant-negative toward full-length p53, inhibiting p53-mediated apoptosis. The differential expression of the p53 isoforms in human tumors may explain the difficulties in linking p53 status to the biological properties and drug sensitivity of human cancer.", "author" : [{ "dropping-particle" : "", "family" : "Bourdon", "given" : "Jean Christophe", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Fernandes", "given" : "Kenneth", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Murray-Zmijewski", "given" : "Fiona", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Liu", "given" : "Geng", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Diot", "given" : "Alexandra", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Xirodimas", "given" : "Dimitris P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Saville", "given" : "Mark K.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lane", "given" : "David P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Genes and Development", "id" : "ITEM-2", "issue" : "18", "issued" : { "date-parts" : [["2005"]] }, "page" : "2122-2137", "title" : "p53 isoforms can regulate p53 transcriptional activity", "type" : "article-journal", "volume" : "19" }, "uris" : ["http://www.mendeley.com/documents/?uuid=87bfab4c-0377-4811-b35f-c1e089298fe3"] }, { "id" : "ITEM-3", "itemData" : { "DOI" : "10.1177/1947601911408893", "ISBN" : "1947-6027 (Electronic)\\r1947-6019 (Linking)", "ISSN" : "1947-6019", "PMID" : "21779513", "abstract" : "Normal function of the p53 pathway is ubiquitously lost in cancers either through mutation or inactivating interaction with viral or cellular proteins. However, it is difficult in clinical studies to link p53 mutation status to cancer treatment and clinical outcome, suggesting that the p53 pathway is not fully understood. We have recently reported that the human p53 gene expresses not only 1 but 12 different p53 proteins (isoforms) due to alternative splicing, alternative initiation of translation, and alternative promoter usage. p53 isoform proteins thus contain distinct protein domains. They are expressed in normal human tissues but are abnormally expressed in a wide range of cancer types. We have recently reported that p53 isoform expression is associated with breast cancer prognosis, suggesting that they play a role in carcinogenesis. Indeed, the cellular response to damages can be switched from cell cycle arrest to apoptosis by only manipulating p53 isoform expression. This may provide an explanation to the hitherto inconsistent relationship between p53 mutation, treatment response, and outcome in breast cancer. However, the molecular mechanism is still unknown. Recent reports suggest that it involves modulation of gene expression in a p53-dependent and -independent manner. In this review, we summarize our current knowledge about the biological activities of p53 isoforms and propose a molecular mechanism conciliating our current knowledge on p53 and integrating p63 and p73 isoforms in the p53 pathway.", "author" : [{ "dropping-particle" : "", "family" : "Khoury", "given" : "M. 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Likewise, Δ40p53β is also clipped of the first 40 amino acids; however, being a β isoform it lacks the canonical tetramerization domain and the α - domain as well; instead concluding with 10 amino acids – *DQTSFQKENC.* This is due to the presence of exon 9β. This results in the transcription of Δ40p53β from mRNA transcript (v), but similar to the Δ40p53α isoform, an IRES also allows the translation of Δ40p53β from mRNA transcript (ii). **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1038/sj.embor.7400623", "ISBN" : "1469-221X (Print)\\r1469-221X (Linking)", "ISSN" : "1469-221X", "PMID" : "16440000", "abstract" : "The p53 tumour suppressor protein has a crucial role in cell\u2010cycle arrest and apoptosis. Previous reports show that the p53 messenger RNA is translated to produce an amino\u2010terminal\u2010deleted isoform (\u0394N\u2010p53) from an internal initiation codon, which acts as a dominant\u2010negative inhibitor of full\u2010length p53. Here, we show that two internal ribosome entry sites (IRESs) mediate the translation of both full\u2010length and \u0394N\u2010p53 isoforms. The IRES directing the translation of full\u2010length p53 is in the 5\u2032\u2010untranslated region of the mRNA, whereas the IRES mediating the translation of \u0394N\u2010p53 extends into the protein\u2010coding region. The two IRESs show distinct cell\u2010cycle phase\u2010dependent activity, with the IRES for full\u2010length p53 being active at the G2\u2013M transition and the IRES for \u0394N\u2010p53 showing highest activity at the G1\u2013S transition. These results indicate a novel translational control of p53 gene expression and activity.", "author" : [{ "dropping-particle" : "", "family" : "Ray", "given" : "Partho Sarothi", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Grover", "given" : "Richa", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Das", "given" : "Saumitra", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Barraille", "given" : "P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Chinestra", "given" : "P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bayard", "given" : "F.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Faye", "given" : "JC.", 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related genes, p73 and p63, express multiple splice variants and N-terminally truncated forms initiated from an alternative promoter in intron 3. To date, no alternative promoter and multiple splice variants have been described for the p53 gene. In this study, we show that p53 has a gene structure similar to the p73 and p63 genes. The human p53 gene contains an alternative promoter and transcribes multiple splice variants. We show that p53 variants are expressed in normal human tissue in a tissue-dependent manner. We determine that the alternative promoter is conserved through evolution from Drosophila to man, suggesting that the p53 family gene structure plays an essential role in the multiple activities of the p53 family members. Consistent with this hypothesis, p53 variants are differentially expressed in human breast tumors compared with normal breast tissue. We establish that p53beta can bind differentially to promoters and can enhance p53 target gene expression in a promoter-dependent manner, while Delta133p53 is dominant-negative toward full-length p53, inhibiting p53-mediated apoptosis. The differential expression of the p53 isoforms in human tumors may explain the difficulties in linking p53 status to the biological properties and drug sensitivity of human cancer.", "author" : [{ "dropping-particle" : "", "family" : "Bourdon", "given" : "Jean Christophe", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Fernandes", "given" : "Kenneth", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Murray-Zmijewski", "given" : "Fiona", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Liu", "given" : "Geng", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Diot", "given" : "Alexandra", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Xirodimas", "given" : "Dimitris P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Saville", "given" : "Mark K.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lane", "given" : "David P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Genes and Development", "id" : "ITEM-2", "issue" : "18", "issued" : { "date-parts" : [["2005"]] }, "page" : "2122-2137", "title" : "p53 isoforms can regulate p53 transcriptional activity", "type" : "article-journal", "volume" : "19" }, "uris" : ["http://www.mendeley.com/documents/?uuid=87bfab4c-0377-4811-b35f-c1e089298fe3"] }, { "id" : "ITEM-3", "itemData" : { "DOI" : "10.1177/1947601911408893", "ISBN" : "1947-6027 (Electronic)\\r1947-6019 (Linking)", "ISSN" : "1947-6019", "PMID" : "21779513", "abstract" : "Normal function of the p53 pathway is ubiquitously lost in cancers either through mutation or inactivating interaction with viral or cellular proteins. However, it is difficult in clinical studies to link p53 mutation status to cancer treatment and clinical outcome, suggesting that the p53 pathway is not fully understood. We have recently reported that the human p53 gene expresses not only 1 but 12 different p53 proteins (isoforms) due to alternative splicing, alternative initiation of translation, and alternative promoter usage. p53 isoform proteins thus contain distinct protein domains. They are expressed in normal human tissues but are abnormally expressed in a wide range of cancer types. We have recently reported that p53 isoform expression is associated with breast cancer prognosis, suggesting that they play a role in carcinogenesis. Indeed, the cellular response to damages can be switched from cell cycle arrest to apoptosis by only manipulating p53 isoform expression. This may provide an explanation to the hitherto inconsistent relationship between p53 mutation, treatment response, and outcome in breast cancer. However, the molecular mechanism is still unknown. Recent reports suggest that it involves modulation of gene expression in a p53-dependent and -independent manner. In this review, we summarize our current knowledge about the biological activities of p53 isoforms and propose a molecular mechanism conciliating our current knowledge on p53 and integrating p63 and p73 isoforms in the p53 pathway.", "author" : [{ "dropping-particle" : "", "family" : "Khoury", "given" : "M. P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bourdon", "given" : "J.-C.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Genes & Cancer", "id" : "ITEM-3", "issue" : "4", "issued" : { "date-parts" : [["2011"]] }, "page" : "453-465", "title" : "p53 Isoforms: An Intracellular Microprocessor?", "type" : "article-journal", "volume" : "2" }, "uris" : ["http://www.mendeley.com/documents/?uuid=9d530c4a-b7e0-4241-a1b4-7a5bc16f78ad"] }, { "id" : "ITEM-4", "itemData" : { "DOI" : "10.1038/onc.2009.138", "ISSN" : "0950-9232", "author" : [{ "dropping-particle" : "", "family" : "Grover", "given" : "R", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Candeias", "given" : "M M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "F\u00e5hraeus", "given" : "R", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Das", "given" : "S", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Oncogene", "id" : "ITEM-4", "issue" : "30", "issued" : { "date-parts" : [["2009", "7", "30"]] }, "page" : "2766-2772", "publisher" : "Nature Publishing Group", "title" : "p53 and little brother p53/47: linking IRES activities with protein functions", "type" : "article-journal", "volume" : "28" }, "uris" : ["http://www.mendeley.com/documents/?uuid=a2c00776-613b-3466-92ee-5dcdef86c2fb"] }], "mendeley" : { "formattedCitation" : "(1,34,40,41)", "plainTextFormattedCitation" : "(1,34,40,41)", "previouslyFormattedCitation" : "(1,34,40,41)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**

Δ40p53γ lacks the first 40 amino acids and as a γ isoform (devoid of the canonical tetramerization and α domain) it ends with an additional 15 amino acids - *MLLDLR WCYFLINSS.* Again, this is attributed to the alternative splicing of exon 9γ. It can be translated from a sixth mRNA transcript (xi), in the same token as the other Δ40p53 isoforms, from mRNA transcript (iii) due to the presence of an IRES. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1038/sj.embor.7400623", "ISBN" : "1469-221X (Print)\\r1469-221X (Linking)", "ISSN" : "1469-221X", "PMID" : "16440000", "abstract" : "The p53 tumour suppressor protein has a crucial role in cell\u2010cycle arrest and apoptosis. Previous reports show that the p53 messenger RNA is translated to produce an amino\u2010terminal\u2010deleted isoform (\u0394N\u2010p53) from an internal initiation codon, which acts as a dominant\u2010negative inhibitor of full\u2010length p53. Here, we show that two internal ribosome entry sites (IRESs) mediate the translation of both full\u2010length and \u0394N\u2010p53 isoforms. The IRES directing the translation of full\u2010length p53 is in the 5\u2032\u2010untranslated region of the mRNA, whereas the IRES mediating the translation of \u0394N\u2010p53 extends into the protein\u2010coding region. The two IRESs show distinct cell\u2010cycle phase\u2010dependent activity, with the IRES for full\u2010length p53 being active at the G2\u2013M transition and the IRES for \u0394N\u2010p53 showing highest activity at the G1\u2013S transition. These results indicate a novel translational control of p53 gene expression and activity.", "author" : [{ "dropping-particle" : "", "family" : "Ray", "given" :

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2.3 Δ133p53α, Δ133p53β, Δ133p53γ

Within intron-4 lies an internal promoter; named here as P2. Whilst the p53 and Δ40p53 isoforms are attributable to P1, the Δ133p53 isoforms are named so due to the initiation of translation at the 133rd amino acid – as a result of P2. Notably, in response to stress, FLp53 binds and transactivates the internal promoter, thus regulating the expression of its own isoforms. In addition to p53, at least four p63/p73 isoforms regulate Δ133p53's transcription. (57)

As indicated above the Δ133p53 isoforms are devoid of the first 132 amino acids and thus lack the canonical transactivation domain (TA), the proline domain (PRD) and part of the DNA – binding domain (DBD). **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1101/gad.1339905", "ISBN" : "2514458412", "ISSN" : "08909369", "PMID" : "16131611", "abstract" : "The recently discovered p53-related genes, p73 and p63, express multiple splice variants and N-terminally truncated forms initiated from an alternative promoter in intron 3. To date, no alternative promoter and multiple splice variants have been described for the p53 gene. In this study, we show that p53 has a gene structure similar to the p73 and p63 genes. The human p53 gene contains an alternative promoter and transcribes multiple splice variants. We show that p53 variants are expressed in normal human tissue in a tissue-dependent manner. 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Expanding upon the previous arrangement, Δ133p53α will thus lack the transactivation domain, the proline domain and part of the DNA – binding domain and being an α isoform the rest mirrors FLp53. It is translated from mRNA transcript (vii). {ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1101/gad.1339905", "ISBN" : "2514458412", "ISSN" : "08909369", "PMID" : "16131611", "abstract" : "The recently discovered p53-related genes, p73 and p63, express multiple splice variants and N-terminally truncated forms initiated from an alternative promoter in intron 3. To date, no alternative promoter and multiple splice variants have been described for the p53 gene. In this study, we show that p53 has a gene structure similar to the p73 and p63 genes. The human p53 gene contains an alternative promoter and transcribes multiple splice variants. We show that p53 variants are expressed in normal human tissue in a tissue-dependent manner. 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Δ133p53β due to the presence of exon 9β and being translated from P2, will lack the TA domain, PRD, DBD, the canonical tetramerization domain and the α - domain instead concluding with 10 amino acids – *DQTSFQKENC.* It is translated from the eighth mRNA transcript (viii). **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1101/gad.1339905", "ISBN" : "2514458412", "ISSN" : "08909369", "PMID" : "16131611", "abstract" : "The recently discovered p53-related genes, p73 and p63, express multiple splice variants and N-terminally truncated forms initiated from an alternative promoter in intron 3. To date, no alternative promoter and multiple splice variants have been described for the p53 gene. In this study, we show that p53 has a gene structure similar to the p73 and p63 genes. The human p53 gene contains an alternative promoter and transcribes multiple splice variants. 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P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bourdon", "given" : "J.-C.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Genes & Cancer", "id" : "ITEM-2", "issue" : "4", "issued" : { "date-parts" : [["2011"]] }, "page" : "453-465", "title" : "p53 Isoforms: An Intracellular Microprocessor?", "type" : "article-journal", "volume" : "2" }, "uris" : ["http://www.mendeley.com/documents/?uuid=9d530c4a-b7e0-4241-a1b4-7a5bc16f78ad"] }], "mendeley" : { "formattedCitation" : "(1,34)", "plainTextFormattedCitation" : "(1,34)", "previouslyFormattedCitation" : "(1,34)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**

Unsurprisingly, Δ133p53γ will lack the TA domain, PRD and DBD being Δ133p53 isoform, and being γ isoform is also pared of the canonical tetramerization and the α domain due to exon 9γ. It is translated from the ninth mRNA transcript (ix). **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1101/gad.1339905", "ISBN" : "2514458412", "ISSN" : "08909369", "PMID" : "16131611", "abstract" : "The recently discovered p53-related genes, p73 and p63, express multiple splice variants and N-terminally truncated forms initiated from an alternative promoter in intron 3. To date, no alternative promoter and multiple splice variants have been described for the p53 gene. In this study, we show that p53 has a gene structure similar to the p73 and p63 genes. The human p53 gene contains an alternative promoter and transcribes multiple splice variants. We show that p53 variants are expressed in normal human tissue in a tissue-dependent manner. 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P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bourdon", "given" : "J.-C.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Genes & Cancer", "id" : "ITEM-2", "issue" : "4", "issued" : { "date-parts" : [["2011"]] }, "page" : "453-465", "title" : "p53 Isoforms: An Intracellular Microprocessor?", "type" : "article-journal", "volume" : "2" }, "uris" : ["http://www.mendeley.com/documents/?uuid=9d530c4a-b7e0-4241-a1b4-7a5bc16f78ad"] }], "mendeley" : { "formattedCitation" : "(1,34)", "plainTextFormattedCitation" : "(1,34)", "previouslyFormattedCitation" : "(1,34)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**

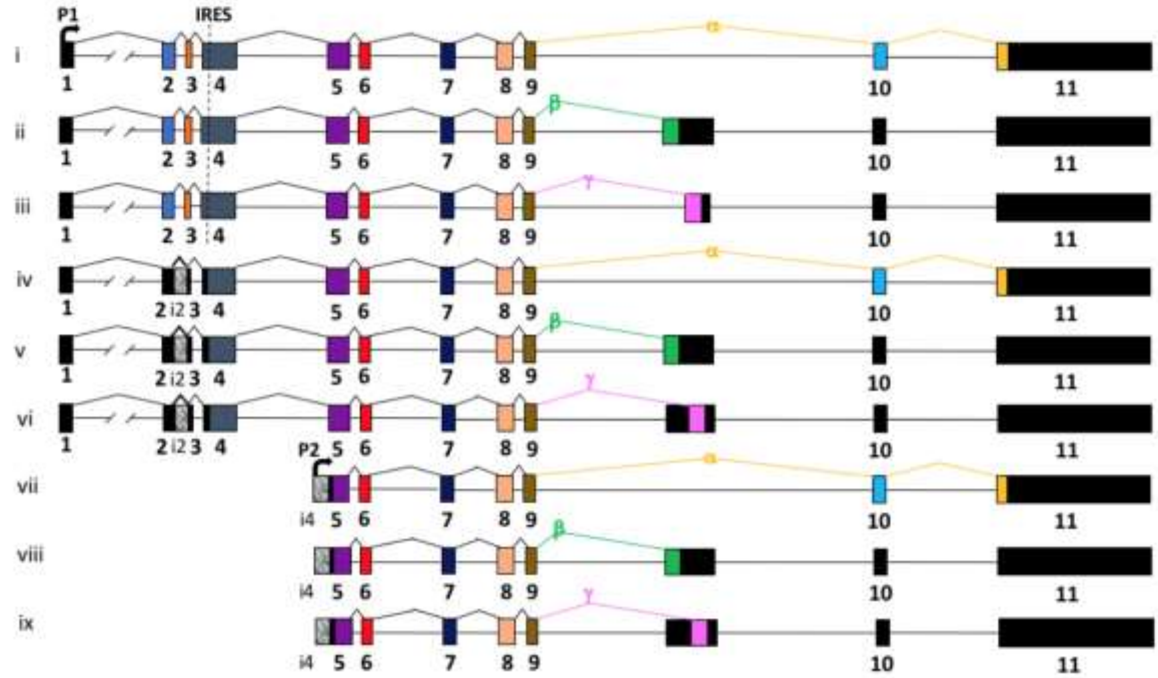
2.4 Δ160p53α, Δ160p53β, Δ160p53γ

The Δ160p53 isoforms are all generated through the alternative initiation of translation at ATG 160 of the Δ133p53 transcripts. These isoforms all lack the first 159 amino acids.

The α, β and γ Δ160p53 isoforms all echo the previous isoforms in terms of their C-terminal structure. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1016/j.febslet.2010.10.005", "ISBN" : "1873-3468 (Electronic)\\r0014-5793 (Linking)", "ISSN" : "00145793", "PMID" : "20937277", "abstract" : "p53 gene expresses several protein isoforms modulating p53-mediated responses through regulation of gene expression. Here, we identify a novel p53 isoform, \u0394160p53, lacking the first 159 residues. By knockdown experiments and site-directed mutagenesis, we show that \u0394160p53 is encoded by \u0394133p53 transcript using ATG160 as translational initiation site. This hypothesis is supported by endogenous expression of \u0394160p53 in U2OS, T47D and K562 cells, the latter ones carrying a premature stop codon that impairs p53 and \u0394133p53 protein expression but not the one of \u0394160p53. Overall, these results show that the \u0394133p53 transcript generates two different p53 isoforms, \u0394133p53 and \u0394160p53. \u00a9 2010 Federation of European Biochemical Societies.", "author" : [{ "dropping-particle" : "", "family" : "Marcel", "given" : "Virginie", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Perrier", "given" : "St\u00e9phane", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Aoubala", "given" : "Mustapha", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Ageorges", "given" : "Sylvain", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Groves", "given" : "Michael J.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Diot", "given" : "Alexandra", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Fernandes", "given" : "Kenneth", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Tauro", "given" : "Sudhir", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bourdon", "given" : "Jean Christophe", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "FEBS Letters", "id" : "ITEM-1", "issue" : "21", "issued" : { "date-parts" : [["2010"]] }, "page" : "4463-4468", "title" : "\u0394160p53 is a novel N-terminal p53 isoform encoded by

\u0394133p53 transcript", "type" : "article-journal", "volume" : "584" }, "uris" : ["http://www.mendeley.com/documents/?uuid=25cb923a-cb50-419c-b1af-dbe54c5e2949"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.1177/1947601911408893", "ISBN" : "1947-6027 (Electronic)\\r1947-6019 (Linking)", "ISSN" : "1947-6019", "PMID" : "21779513", "abstract" : "Normal function of the p53 pathway is ubiquitously lost in cancers either through mutation or inactivating interaction with viral or cellular proteins. However, it is difficult in clinical studies to link p53 mutation status to cancer treatment and clinical outcome, suggesting that the p53 pathway is not fully understood. We have recently reported that the human p53 gene expresses not only 1 but 12 different p53 proteins (isoforms) due to alternative splicing, alternative initiation of translation, and alternative promoter usage. p53 isoform proteins thus contain distinct protein domains. They are expressed in normal human tissues but are abnormally expressed in a wide range of cancer types. We have recently reported that p53 isoform expression is associated with breast cancer prognosis, suggesting that they play a role in carcinogenesis. Indeed, the cellular response to damages can be switched from cell cycle arrest to apoptosis by only manipulating p53 isoform expression. This may provide an explanation to the hitherto inconsistent relationship between p53 mutation, treatment response, and outcome in breast cancer. However, the molecular mechanism is still unknown. Recent reports suggest that it involves modulation of gene expression in a p53-dependent and -independent manner. In this review, we summarize our current knowledge about the biological activities of p53 isoforms and propose a molecular mechanism conciliating our current knowledge on p53 and integrating p63 and p73 isoforms in the p53 pathway.", "author" : [{ "dropping-particle" : "", "family" : "Khoury", "given" : "M. P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bourdon", "given" : "J.-C.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Genes & Cancer", "id" : "ITEM-2", "issue" : "4", "issued" : { "date-parts" : [["2011"]] }, "page" : "453-465", "title" : "p53 Isoforms: An Intracellular Microprocessor?", "type" : "article-journal", "volume" : "2" }, "uris" : ["http://www.mendeley.com/documents/?uuid=9d530c4a-b7e0-4241-a1b4-7a5bc16f78ad"] }], "mendeley" : { "formattedCitation" : "(1,35)", "plainTextFormattedCitation" : "(1,35)", "previouslyFormattedCitation" : "(1,35)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**

3A.


P1
IRES
P2
i
ii
iii
iv
v
vi
vii
viii
ix
1 2 3 4 5 6 7 8 9 10 11
2 i2 3 4
i4 5 6 7 8 9 10 11
α
β
γ

3B.

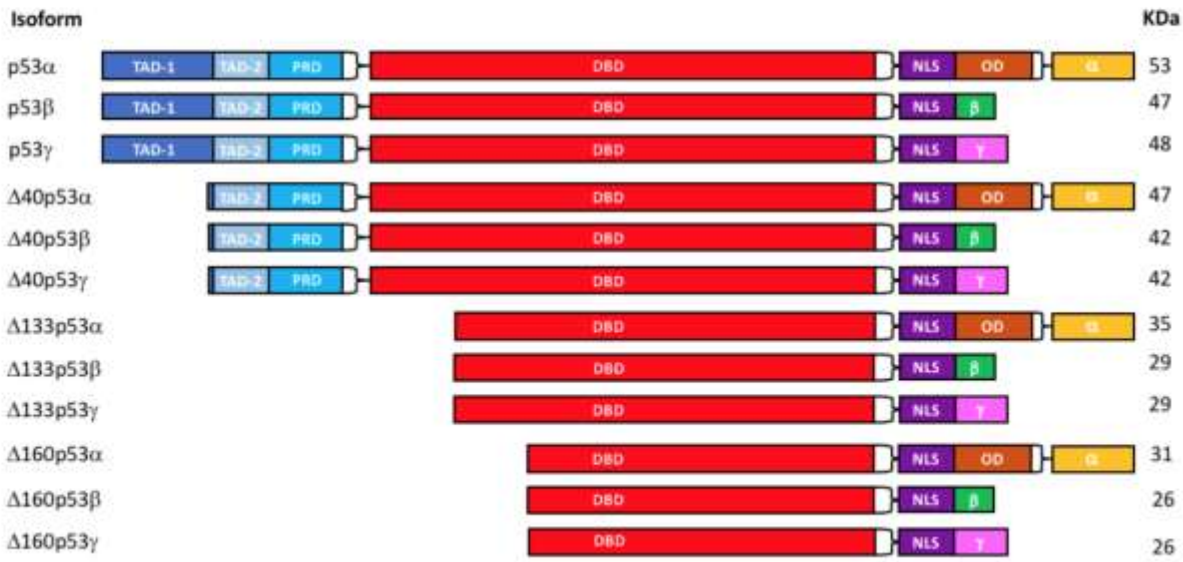

Isoform
KDa
p53α 53
p53β 47
p53γ 48
Δ40p53α 47
Δ40p53β 42
Δ40p53γ 42
Δ133p53α 35
Δ133p53β 29
Δ133p53γ 29
Δ160p53α 31
Δ160p53β 26
Δ160p53γ 26
TAD-1
TAD-2
PRD
DBD
NLS
OD
α
β
γ

Figure 3. *(A) A schematic of the 9 p53 mRNA transcripts produced in humans, i-ix. Exons are to scale with a condensed intron 1. Non-coding exons are blacked out. Features of the mRNA transcripts are included; splicing, promoter usage, the presence of an IRES and intron retention. (B) A schematic of the 12 p53 protein isoforms produced by the 9 mRNA transcripts; p53α, p53β, p53γ, Δ40p53α, Δ40p53β, Δ40p53γ, Δ133p53α, Δ133p53β, Δ133p53γ, Δ160p53α, Δ160p53β and Δ160p53γ. Theoretical molecular weight is noted on the right. Promoter 1 is responsible for initiation of translation for transcripts i-vi. mRNA i-iii encode for the full-length protein isoforms. The retention of intron 2 (i2) in mRNA iv-vi and consequentially several stop codons, leads to initiation of translation from codon 40 and thus the production of the Δ40p53 isoforms. The Δ40p53 isoforms can also be produced by mRNA i-iii via the indicated IRES. The usage of an alternative promoter in intron 4 (promoter 2) is used for initiation of translation of mRNA vii-ix, which is utilised for translation of the Δ133p53 and Δ160p53 isoforms. Alternative splicing of intron 9 (colour coded) produces alternative C terminal regions, designated α, β and γ.*

3- Biological Activities of the p53 Isoform

3.1 Normal Tissue Specific Expression of the Isoforms

The p53 mRNA variants are differentially expressed in a tissue dependent manner. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1101/gad.1339905", "ISBN" : "2514458412", "ISSN" : "08909369", "PMID" : "16131611", "abstract" : "The recently discovered p53-related genes, p73 and p63, express multiple splice variants and N-terminally truncated forms initiated from an alternative promoter in intron 3. To date, no alternative promoter and multiple splice variants have been described for the p53 gene. In this study, we show that p53 has a gene structure similar to the p73 and p63 genes. The human p53 gene contains an alternative promoter and transcribes multiple splice variants. We show that p53 variants are expressed in normal human tissue in a tissue-dependent manner. We determine that the alternative promoter is conserved through evolution from Drosophila to man, suggesting that the p53 family gene structure plays an essential role in the multiple activities of the p53 family members. Consistent with this hypothesis, p53 variants are differentially expressed in human breast tumors compared with normal breast tissue. We establish that p53beta can bind differentially to promoters and can enhance p53 target gene expression in a promoter-dependent manner, while Delta133p53 is dominant-negative toward full-length p53, inhibiting p53-mediated apoptosis. The differential expression of the p53 isoforms in human tumors may explain the difficulties in linking p53 status to the biological properties and drug sensitivity of human cancer.", "author" : [{ "dropping-particle" : "", "family" : "Bourdon", "given" : "Jean Christophe", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Fernandes", "given" : "Kenneth", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Murray-Zmijewski", "given" : "Fiona", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Liu", "given" : "Geng", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Diot", "given" : "Alexandra", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Xirodimas", "given" : "Dimitris P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Saville", "given" : "Mark K.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lane", "given" : "David P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Genes and Development", "id" : "ITEM-1", "issue" : "18", "issued" : { "date-parts" : [["2005"]] }, "page" : "2122-2137", "title" : "p53 isoforms can regulate p53 transcriptional activity", "type" : "article-journal", "volume" : "19" }, "uris" : ["http://www.mendeley.com/documents/?uuid=87bfab4c-0377-4811-b35f-c1e089298fe3"] }], "mendeley" : { "formattedCitation" : "(34)", "plainTextFormattedCitation" : "(34)", "previouslyFormattedCitation" : "(34)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**
p53β/Δ40p53β mRNA variants for example, are expressed in most normal tissue but could be detected in brain, lung, prostate, muscle, foetal brain, spinal cord and foetal liver. Likewise, p53γ/Δ40p53γ does not manifest within lung, spleen, testis, foetal brain, spinal cord and foetal liver (but is otherwise found in all other tissue).

Δ133/Δ160p53α mRNA variants are expressed in most normal tissue with the exception of prostate, uterus, skeletal muscle and breast.
Δ133/Δ160p53β mRNA on the other hand, are only detectable within the colon, bone marrow, testis, foetal brain and intestine.
Δ133/Δ160p53γ are similarly expressed in most normal tissue, with the exception of brain, heart, lung, foetal liver, salivary gland, breast and intestine.

3.2 Subcellular Localisation of the protein Isoforms (ectopic expression)

P53 is never expressed as a single protein. Several p53 isoforms are always co-expressed in cells. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1101/gad.1339905", "ISBN" : "2514458412", "ISSN" : "08909369", "PMID" : "16131611", "abstract" : "The recently discovered p53-related genes, p73 and p63, express multiple splice variants and N-terminally truncated forms initiated from an alternative promoter in intron 3. To date, no alternative promoter and multiple splice variants have been described for the p53 gene. In this study, we show that p53 has a gene structure similar to the p73 and p63 genes. The human p53 gene contains an alternative promoter and transcribes multiple splice variants. We show that p53 variants are expressed in normal human tissue in a tissue-dependent manner. We determine that the alternative promoter is conserved through evolution from Drosophila to man, suggesting that the p53 family gene structure plays an essential role in the multiple activities of the p53 family members. Consistent with this hypothesis, p53 variants are differentially expressed in human breast tumors compared with normal breast tissue. We establish that p53beta can bind differentially to promoters and can enhance p53 target gene expression in a promoter-dependent manner, while Delta133p53 is dominant-negative toward full-length p53, inhibiting p53-mediated apoptosis. The differential expression of the p53 isoforms in human tumors may explain the difficulties in linking p53 status to the biological properties and drug sensitivity of human cancer.", "author" : [{ "dropping-particle" : "", "family" : "Bourdon", "given" : "Jean Christophe", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Fernandes", "given" : "Kenneth", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Murray-Zmijewski", "given" : "Fiona", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Liu", "given" : "Geng", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Diot", "given" : "Alexandra", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Xirodimas", "given" : "Dimitris P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Saville", "given" : "Mark K.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lane", "given" : "David P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Genes and Development", "id" : "ITEM-1", "issue" : "18", "issued" : { "date-parts" : [["2005"]] }, "page" : "2122-2137", "title" : "p53 isoforms can regulate p53 transcriptional activity", "type" : "article-journal", "volume" : "19" }, "uris" : ["http://www.mendeley.com/documents/?uuid=87bfab4c-0377-4811-b35f-c1e089298fe3"] }], "mendeley" : { "formattedCitation" : "(34)", "plainTextFormattedCitation" : "(34)", "previouslyFormattedCitation" : "(34)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}** However, the lack of isoform specific

antibodies prevents to study the endogenous subcellular localisation of each p53 isoforms. Therefore, the subcellular locations of some p53 protein isoform was first investigated after transfection of single p53 isoform cDNA in cells devoid of endogenous p53 expression. Here below are the summary of the findings.
Ectopically expressed Full length p53 (p53α) is localised within the nucleus. Ectopic p53β appears to localise predominantly within the nucleus, but low amounts were also present within the cytoplasm. However, p53γ was pinpointed within both the nucleus and the cytoplasm (a result dependent on the cell type that was tested), suggesting that p53γ would also shuttle between the nucleus and the cytoplasm.
Δ133p53α is localised both in the nucleus and cytoplasm. Δ133p53β is likewise confined within both the nucleus and cytoplasm with some speckles staining in some cells. Δ133p53γ is interesting in that it centralises only within the cytoplasm of a cell; as mentioned previously Δ133p53β and Δ133p53γ differ through the last amino acids (ending with 10 and 15 respectively), strongly suggesting that the sequence of amino acids located within the C terminus of the isoforms can alter their subcellular localisation. (48)

Δ40p53α is noteworthy in that it can alter subcellular localisation of other isoforms. Residing within the cytoplasm (whilst p53α is mostly nuclear), the presence of Δ40p53α alters the localisation of p53α from the nucleus to the cytoplasm where Δ40p53α dwells. This observation occurs particularly in times of cellular stress. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1128/MCB.24.18.7987-7997.2004", "ISBN" : "0270-7306", "ISSN" : "0270-7306", "PMID" : "15340061", "abstract" : "The development of cancer is a multistep process involving mutations in proto-oncogenes, tumor suppressor genes, and other genes which control cell proliferation, telomere stability, angiogenesis, and other complex traits. Despite this complexity, the cellular pathways controlled by the p53 tumor suppressor protein are compromised in most, if not all, cancers. In normal cells, p53 controls cell proliferation, senescence, and/or mediates apoptosis in response to stress, cell damage, or ectopic oncogene expression, properties which make p53 the prototype tumor suppressor gene. Defining the mechanisms of regulation of p53 activity in normal and tumor cells has therefore been a major priority in cell biology and cancer research. The present study reveals a novel and potent mechanism of p53 regulation originating through alternative splicing of the human p53 gene resulting in the expression of a novel p53 mRNA. This novel p53 mRNA encodes an N-terminally deleted isoform of p53 termed p47. As demonstrated within, p47 was able to effectively suppress p53-mediated transcriptional activity and impair p53-mediated growth suppression. It was possible to select for p53-null cells expressing p47 alone or coexpressing p53 in the presence of p47 but not cells expressing p53 alone. This showed that p47 itself does not suppress cell viability but could control p53-mediated growth suppression. Interestingly, p47 was monoubiquitinated in an Mdm2-independent manner, and this was associated with its export out of the nucleus. In the presence of p47, there was a reduction in Mdm2-mediated polyubiquitination and degradation of p53, and this was also associated with increased monoubiquitination and nuclear export of p53. The expression of p47 through alternative splicing of the p53 gene thus has a major influence over p53 activity at least in part through controlling p53 ubiquitination and cell localization.", "author" : [{ "dropping-particle" : "", "family" : "Ghosh", "given" : "Anirban", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Stewart", "given" : "Deborah", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-

particle" : "", "family" : "Matlashewski", "given" : "Greg", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Molecular and cellular biology", "id" : "ITEM-1", "issue" : "18", "issued" : { "date-parts" : [["2004"]] }, "page" : "7987-97", "title" : "Regulation of human p53 activity and cell localization by alternative splicing.", "type" : "article-journal", "volume" : "24" }, "uris" : ["http://www.mendeley.com/documents/?uuid=71e0792b-5ecc-4c98-9de8-f3fab0418d45"] }], "mendeley" : { "formattedCitation" : "(42)", "plainTextFormattedCitation" : "(42)", "previouslyFormattedCitation" : "(42)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }}
Δ40p53α was first discovered as the "little brother" of p53, with its consequences on p53 being of particular interest. {ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1038/sj.onc.1205874", "ISBN" : "0950-9232 (Print)\\n0950-9232 (Linking)", "ISSN" : "0950-9232", "PMID" : "12360399", "abstract" : "The tumor suppressor protein p53 is ubiquitously expressed as a major isoform of 53 kD, but several forms of lower molecular weight have been observed. Here, we describe a new isoform, DeltaN-p53, produced by internal initiation of translation at codon 40 and lacking the N-terminal first transactivation domain. This isoform has impaired transcriptional activation capacity, and does not complex with the p53 regulatory protein Mdm2. Furthermore, DeltaN-p53 oligomerizes with full-length p53 (FL-p53) and negatively regulates its transcriptional and growth-suppressive activities. Consistent with the lack of Mdm2 binding, DeltaN-p53 does not accumulate in response to DNA-damage, suggesting that this isoform is not involved in the response to genotoxic stress. However, in serum-starved cells expressing wild-type p53, DeltaN-p53 becomes the predominant p53 form during the synchronous progression into S phase after serum stimulation. These results suggest that DeltaN-p53 may play a role as a transient, negative regulator of p53 during cell cycle progression.", "author" : [{ "dropping-particle" : "", "family" : "Courtois", "given" : "St\u00e9phanie", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Verhaegh", "given" : "Gerald", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "North", "given" : "Sophie", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Luciani", "given" : "Maria-Gloria", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lassus", "given" : "Patrice", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Hibner", "given" : "Ula", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Oren", "given" : "Moshe", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Hainaut", "given" : "Pierre", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Oncogene", "id" : "ITEM-1", "issue" : "44", "issued" : { "date-parts" : [["2002"]] }, "page" : "6722-8", "title" : "DeltaN-p53, a natural isoform of p53 lacking the first transactivation domain, counteracts growth suppression by wild-type p53.", "type" : "article-journal", "volume" : "21" }, "uris" : ["http://www.mendeley.com/documents/?uuid=1e218c4f-6825-422c-a440-21b1d83a4b3a"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.1038/ncb801", "ISBN" : "1465-7392 (Print)\\r1465-7392 (Linking)", "ISSN" : "1465-7392", "PMID" : "12032546", "abstract" : "Activation of the p53 tumour suppressor protein can lead to cell-cycle arrest or apoptosis. p53 function is controlled by the mdm2 oncogene product, which targets p53 for proteasomal degradation. In this report we demonstrate that Mdm2 induces translation of the p53 mRNA from two alternative initiation sites, giving full-length p53 and another

protein with a relative molecular mass (M(r)) of approximately 47K; we designate this protein as p53/47. This translation induction requires Mdm2 to interact directly with the nascent p53 polypeptide. The alternatively translated p53/47 does not contain the Mdm2-binding site and it lacks the most amino-terminal transcriptional-activation domain of p53. Increased expression of p53/47 stabilizes p53 in the presence of Mdm2, and alters the expression levels of p53-induced gene products. These results show how the interaction of Mdm2 with p53 leads to a change in the ratio of full-length p53 to p53/47 by inducing translation of both p53 proteins and the subsequent selective degradation of full-length p53. Thus, Mdm2 controls the expression levels of p53 through a dual mechanism that involves induction of synthesis and targeting for degradation.", "author" : [{ "dropping-particle" : "", "family" : "Yin", "given" : "Yili", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Stephen", "given" : "C W", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Luciani", "given" : "M Gloria", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "F\u00e5hraeus", "given" : "Robin", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Nature cell biology", "id" : "ITEM-2", "issue" : "6", "issued" : { "date-parts" : [["2002"]] }, "page" : "462-7", "title" : "p53 Stability and activity is regulated by Mdm2-mediated induction of alternative p53 translation products.", "type" : "article-journal", "volume" : "4" }, "uris" : ["http://www.mendeley.com/documents/?uuid=f4bb2be0-2921-4b66-9fae-06eb7ecbdafa"] }], "mendeley" : { "formattedCitation" : "(43,44)", "plainTextFormattedCitation" : "(43,44)", "previouslyFormattedCitation" : "(43,44)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }} Of all the isoforms, Δ40p53α has been the most intensively studied, unveiling many functions relevant to our understanding of the isoforms. For example, despite loss of TAD1, the presence of the second transactivation domain allows Δ40p53α to induce expression of genes . {ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1074/jbc.M005676200", "ISBN" : "0021-9258", "ISSN" : "00219258", "PMID" : "10982799", "abstract" : "The p53 protein contains several functional domains necessary for inducing cell cycle arrest and apoptosis. The C-terminal basic domain within residues 364-393 and the proline-rich domain within residues 64-91 are required for apoptotic activity. In addition, activation domain 2 within residues 43-63 is necessary for apoptotic activity when the N-terminal activation domain 1 within residues 1-42 is deleted (DeltaAD1) or mutated (AD1(-)). Here we have discovered that an activation domain 2 mutation at residues 53-54 (AD2(-)) abrogates the apoptotic activity but has no significant effect on cell cycle arrest. We have also found that p53-(DeltaAD2), which lacks activation domain 2, is inert in inducing apoptosis. p53-(AD2(-)DeltaBD), which is defective in activation domain 2 and lacks the C-terminal basic domain, p53-(DeltaAD2DeltaBD), which lacks both activation domain 2 and the C-terminal basic domain, and p53-(DeltaPRDDeltaBD), which lacks both the proline-rich domain and the C-terminal basic domain, are also inert in inducing apoptosis. All four mutants are still capable of inducing cell cycle arrest, albeit to a lesser extent than wild-type p53. Interestingly, we have found that deletion of the N-terminal activation domain 1 alleviates the requirement of the C-terminal basic domain for apoptotic activity. Thus, we have generated a small but potent p53-(DeltaAD1DeltaBD) molecule. Furthermore, we have determined that at least two of the three domains (activation domain 1, activation domain 2, and the proline-rich domain), are required for inducing cell cycle arrest. Taken together, our results suggest that activation domain 2 and the proline-rich domain form an activation

domain for inducing pro-apoptotic genes or inhibiting anti-apoptotic genes. The C-terminal basic domain is required for maintaining this activation domain competent for transactivation or transrepression.", "author" : [{ "dropping-particle" : "", "family" : "Zhu", "given" : "Jianhui", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Zhang", "given" : "Shunzhen", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Jiang", "given" : "Jieyuan", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Chen", "given" : "Xinbin", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Journal of Biological Chemistry", "id" : "ITEM-1", "issue" : "51", "issued" : { "date-parts" : [["2000"]] }, "page" : "39927-39934", "title" : "Definition of the p53 functional domains necessary for inducing apoptosis", "type" : "article-journal", "volume" : "275" }, "uris" : ["http://www.mendeley.com/documents/?uuid=02990603-fc1b-4d6b-b4e5-98ce02e502e5"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.1074/jbc.273.21.13030", "ISBN" : "0021-9258 (Print)\\r0021-9258 (Linking)", "ISSN" : "00219258", "PMID" : "9582339", "abstract" : "The ability of p53 to induce apoptosis requires its sequence-specific DNA binding activity; however, the transactivation-deficient p53(Gln22-Ser23) can still induce apoptosis. Previously, we have shown that the region between residues 23 and 97 in p53 is necessary for such activity. In an effort to more precisely map a domain necessary for apoptosis within the N terminus, we found that deletion of the N-terminal 23 amino acids compromises, but does not abolish, p53 induction of apoptosis. Surprisingly, p53(Delta1-42), which lacks the N-terminal 42 amino acids and the previously defined activation domain, retains the ability to induce apoptosis to an even higher level than wild-type p53. A more extensive deletion, which eliminates the N-terminal 63 amino acids, renders p53 completely inert in mediating apoptosis. In addition, we found that both p53(Delta1-42) and p53(Gln22-Ser23) can activate a subset of cellular p53 targets. Furthermore, we showed that residues 53 and 54 are critical for the apoptotic and transcriptional activities of both p53(Delta1-42) and p53(Gln22-Ser23). Taken together, these data suggest that within residues 43-63 lie an apoptotic domain as well as another transcriptional activation domain. We therefore postulate that the apoptotic activity in p53(Gln22-Ser23) and p53(Delta1-42) is still transcription-dependent.", "author" : [{ "dropping-particle" : "", "family" : "Zhu", "given" : "Jianhui", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Zhou", "given" : "Wenjing", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Jiang", "given" : "Jieyuan", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Chen", "given" : "Xinbin", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Journal of Biological Chemistry", "id" : "ITEM-2", "issue" : "21", "issued" : { "date-parts" : [["1998"]] }, "page" : "13030-13036", "title" : "Identification of a novel p53 functional domain that is necessary for mediating apoptosis", "type" : "article-journal", "volume" : "273" }, "uris" : ["http://www.mendeley.com/documents/?uuid=dfd2f8f2-e561-4b4f-a0bb-101b5ef7bb78"] }], "mendeley" : { "formattedCitation" : "(5,6)", "plainTextFormattedCitation" : "(5,6)", "previouslyFormattedCitation" : "(5,6)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**
Δ40p53α has also been shown to modulate full length p53's ability to transcribe genes, by binding and forming a Δ40p53α/p53α hetero-complex via tetramerization; a concept also explaining the location shift p53 shows (from nucleus to cytoplasm) in the presence of

Δ40p53α. The formation of the Δ40p53α/p53α complex requires a functional oligomerization domain. Other notable functions of Δ40p53α are modulation of FLp53 breakdown by MDM2 and the obstruction of p53 – induced apoptosis; therefore explaining why it was "oversimplified" as being dominant negative towards canonical p53. **{**ADDIN
CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1128/MCB.24.18.7987-7997.2004", "ISBN" : "0270-7306", "ISSN" : "0270-7306", "PMID" : "15340061", "abstract" : "The development of cancer is a multistep process involving mutations in proto-oncogenes, tumor suppressor genes, and other genes which control cell proliferation, telomere stability, angiogenesis, and other complex traits. Despite this complexity, the cellular pathways controlled by the p53 tumor suppressor protein are compromised in most, if not all, cancers. In normal cells, p53 controls cell proliferation, senescence, and/or mediates apoptosis in response to stress, cell damage, or ectopic oncogene expression, properties which make p53 the prototype tumor suppressor gene. Defining the mechanisms of regulation of p53 activity in normal and tumor cells has therefore been a major priority in cell biology and cancer research. The present study reveals a novel and potent mechanism of p53 regulation originating through alternative splicing of the human p53 gene resulting in the expression of a novel p53 mRNA. This novel p53 mRNA encodes an N-terminally deleted isoform of p53 termed p47. As demonstrated within, p47 was able to effectively suppress p53-mediated transcriptional activity and impair p53-mediated growth suppression. It was possible to select for p53-null cells expressing p47 alone or coexpressing p53 in the presence of p47 but not cells expressing p53 alone. This showed that p47 itself does not suppress cell viability but could control p53-mediated growth suppression. Interestingly, p47 was monoubiquitinated in an Mdm2-independent manner, and this was associated with its export out of the nucleus. In the presence of p47, there was a reduction in Mdm2-mediated polyubiquitination and degradation of p53, and this was also associated with increased monoubiquitination and nuclear export of p53. The expression of p47 through alternative splicing of the p53 gene thus has a major influence over p53 activity at least in part through controlling p53 ubiquitination and cell localization.", "author" : [{ "dropping-particle" : "", "family" : "Ghosh", "given" : "Anirban", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Stewart", "given" : "Deborah", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Matlashewski", "given" : "Greg", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Molecular and cellular biology", "id" : "ITEM-1", "issue" : "18", "issued" : { "date-parts" : [["2004"]] }, "page" : "7987-97", "title" : "Regulation of human p53 activity and cell localization by alternative splicing.", "type" : "article-journal", "volume" : "24" }, "uris" : ["http://www.mendeley.com/documents/?uuid=71e0792b-5ecc-4c98-9de8-f3fab0418d45"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.1038/sj.onc.1205874", "ISBN" : "0950-9232 (Print)\\n0950-9232 (Linking)", "ISSN" : "0950-9232", "PMID" : "12360399", "abstract" : "The tumor suppressor protein p53 is ubiquitously expressed as a major isoform of 53 kD, but several forms of lower molecular weight have been observed. Here, we describe a new isoform, DeltaN-p53, produced by internal initiation of translation at codon 40 and lacking the N-terminal first transactivation domain. This isoform has impaired transcriptional activation capacity, and does not complex with the p53 regulatory protein Mdm2. Furthermore, DeltaN-p53 oligomerizes with full-length p53 (FL-p53) and negatively regulates its transcriptional and growth-suppressive activities. Consistent with the lack of Mdm2 binding, DeltaN-p53 does not accumulate in response to DNA-damage, suggesting

that this isoform is not involved in the response to genotoxic stress. However, in serum-starved cells expressing wild-type p53, DeltaN-p53 becomes the predominant p53 form during the synchronous progression into S phase after serum stimulation. These results suggest that DeltaN-p53 may play a role as a transient, negative regulator of p53 during cell cycle progression.", "author" : [{ "dropping-particle" : "", "family" : "Courtois", "given" : "St\u00e9phanie", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Verhaegh", "given" : "Gerald", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "North", "given" : "Sophie", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Luciani", "given" : "Maria-Gloria", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lassus", "given" : "Patrice", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Hibner", "given" : "Ula", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Oren", "given" : "Moshe", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Hainaut", "given" : "Pierre", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Oncogene", "id" : "ITEM-2", "issue" : "44", "issued" : { "date-parts" : [["2002"]] }, "page" : "6722-6728", "title" : "\u0394N-p53, a natural isoform of p53 lacking the first transactivation domain, counteracts growth suppression by wild-type p53", "type" : "article-journal", "volume" : "21" }, "uris" : ["http://www.mendeley.com/documents/?uuid=c9cf92e6-91bc-4ae8-9662-6d1c61a82804"] }], "mendeley" : { "formattedCitation" : "(37,42)", "plainTextFormattedCitation" : "(37,42)", "previouslyFormattedCitation" : "(37,42)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**

3.3 Apoptosis and Cell Cycle Arrest

Although p53 isoforms are co-expressed at physiological level, the biochemical and biological activities were investigated as single agents by ectopic expression in p53-null cells. The activity of p53β and Δ133p53α in inducing apoptosis was investigated by transfection. Δ133p53α, when transfected in cells devoid of any p53 gene, was found to be inert in promoting apoptosis. In animal models, zebrafish Δ113p53 is homologous to human Δ133p53. Depletion of Δ113p53 by morpholino injection in zebrafish embryos still expressing the other p53 isoforms, promotes embryos death in response to sublethal ionising radiation, suggesting that Δ113p53 modulates p53 pro-apoptotic activities and favours p53 pro-survival activities. Interestingly, sublethal ionising radiation triggered a p53-induced Δ113p53 isoforms expression, suggesting a positive feedback loop in response to ionising radiation. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1101/gad.1761609", "ISBN" : "1549-5477", "ISSN" : "08909369", "PMID" : "19204115", "abstract" : "p53 is a well-known tumor suppressor and is also involved in processes of organismal aging and developmental control. A recent exciting development in the p53 field is the discovery of various p53 isoforms. One p53 isoform is human Delta133p53 and its zebrafish counterpart Delta113p53. These N-terminal-truncated p53 isoforms are initiated from an alternative p53 promoter, but their expression regulation and physiological significance at the organismal level are not well understood. We show here that zebrafish Delta113p53 is directly transactivated by full-length p53 in response to developmental and DNA-damaging signals. More importantly, we show that Delta113p53

functions to antagonize p53-induced apoptosis via activating bcl2L (closest to human Bcl-x(L)), and knockdown of Delta113p53 enhances p53-mediated apoptosis under stress conditions. Thus, we demonstrate that the p53 genetic locus contains a new p53 response gene and that Delta113p53 does not act in a dominant-negative manner toward p53 but differentially modulates p53 target gene expression to antagonize p53 apoptotic activity at the physiological level in zebrafish. Our results establish a novel feedback pathway that modulates the p53 response and suggest that modulation of the p53 pathway by p53 isoforms might have an impact on p53 tumor suppressor activity.", "author" : [{ "dropping-particle" : "", "family" : "Chen", "given" : "Jun", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Ng", "given" : "Sok Meng", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Chang", "given" : "Qing", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Zhang", "given" : "Zhenhai", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bourdon", "given" : "Jean Christophe", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lane", "given" : "David P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Peng", "given" : "Jinrong", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Genes and Development", "id" : "ITEM-1", "issue" : "3", "issued" : { "date-parts" : [["2009"]] }, "page" : "278-290", "title" : "P53 isoform ??113p53 is a p53 target gene that antagonizes p53 apoptotic activity via BclxL activation in zebrafish", "type" : "article-journal", "volume" : "23" }, "uris" : ["http://www.mendeley.com/documents/?uuid=525af791-d3ad-4ddf-894d-fbadc0fe9366"] }], "mendeley" : { "formattedCitation" : "(45)", "plainTextFormattedCitation" : "(45)", "previouslyFormattedCitation" : "(45)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**
In human osteosarcoma U2OS cells expressing WT TP53 gene and treated with doxorubicin, Δ133p53α expression is induced compared to other p53 isoforms in a p53-dependent manner. In response to low-dose of doxorubicin, U2OS cells trigger a p53-mediated cell cycle arrest in G2. However, after depletion of Δ133p53, U2OS cells promotes cell death and G1 cell cycle arrest in response to doxorubicin. Re-introduction of Δ133p53α restored G2 cell cycle arrest in response to doxorubicin, while inhibiting p53-mediated apoptosis and G1 cell cycle arrest. (61) The G2 cell cycle arrest may enable Δ133p53α-mediated DNA repair by homologous recombination as recently reported. (62)

The data suggest that Δ133p53α contribute to the p53-mediated cell fate decision in response to ionising radiation or doxorubicin treatment. This observation, in the words of Aoubala et al, "indicates that Δ133p53α does not exclusively inactivate FLp53." **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1038/cdd.2010.91", "ISBN" : "1382496400", "ISSN" : "1476-5403", "PMID" : "20689555", "abstract" : "We have previously reported that the human p53 gene encodes at least nine different p53 isoforms, including \u0394133p53\u03b1, which can modulate p53 transcriptional activity and apoptosis. In this study, we aimed to investigate the regulation of \u0394133p53\u03b1 isoform expression and its physiological role in modulating cell cycle arrest and apoptosis. We report here that in response to a low dose of doxorubicin (which induces cell cycle arrest without promoting apoptosis), p53 directly transactivates the human p53 internal promoter, inducing \u0394133p53\u03b1 protein expression. The induced \u0394133p53\u03b1 then inhibits p53-dependent apoptosis and G1 arrest without inhibiting p53-dependent G2 arrest. Therefore, endogenous \u0394133p53\u03b1 does not exclusively function in a dominant-negative manner toward p53, but differentially regulates cell cycle arrest and apoptosis.", "author" : [{ "dropping-particle" : "", "family" : "Aoubala", "given" : "M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Murray-Zmijewski", "given" : "F", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Khoury", "given" : "M P", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Fernandes", "given" : "K", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Perrier", "given" : "S", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bernard", "given" : "H", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Prats", "given" : "A-C", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lane", "given" : "D P", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bourdon", "given" : "J-C", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Cell death and differentiation", "id" : "ITEM-1", "issue" : "2", "issued" : { "date-parts" : [["2011"]] }, "page" : "248-58", "title" : "p53 directly transactivates \u0394133p53\u03b1, regulating cell fate outcome in response to DNA damage.", "type" : "article-journal", "volume" : "18" }, "uris" : ["http://www.mendeley.com/documents/?uuid=72caef41-561b-46ed-a12b-928cb5767416"] }], "mendeley" : { "formattedCitation" : "(46)", "plainTextFormattedCitation" : "(46)", "previouslyFormattedCitation" : "(46)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**.

<u>3.4 Cellular Senescence</u>

Following in a similar vein, the isoforms (p53β and Δ133p53α) were investigated for their function in cellular senescence. It was noted that when cells underwent senescence, the levels of p53β was elevated to the point of being detectable, whilst the protein level of Δ133p53α was distinctly lower. It was also proven that amplified levels of Δ133p53α thwarted cellular senescence and promoted proliferative activity by repressing p21 and miR34 expression. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1038/ncb1928", "ISBN" : "1465-7392", "ISSN" : "1476-4679", "PMID" : "19701195", "abstract" : "The finite proliferative potential of normal human cells leads to replicative cellular senescence, which is a critical barrier to tumour progression in vivo. We show that the human p53 isoforms Delta133p53 and p53beta function in an endogenous regulatory mechanism for p53-mediated replicative senescence. Induced p53beta and diminished Delta133p53 were associated with replicative senescence, but not oncogene-induced senescence, in normal human fibroblasts. The replicatively senescent fibroblasts also expressed increased levels of miR-34a, a p53-induced microRNA, the antisense inhibition of which delayed the onset of replicative senescence. The siRNA (short interfering RNA)-mediated knockdown of endogenous Delta133p53 induced cellular senescence, which was attributed to the regulation of p21(WAF1) and other p53 transcriptional target genes. In overexpression experiments, whereas p53beta cooperated with full-length p53 to accelerate cellular senescence, Delta133p53 repressed miR-34a expression and extended the cellular replicative lifespan, providing a functional connection of this microRNA to the p53 isoform-mediated regulation of senescence. The senescence-associated signature of p53 isoform expression (that is, elevated p53beta and reduced Delta133p53) was observed in vivo in colon adenomas with senescent phenotypes. The increased Delta133p53 and decreased p53beta isoform expression found in colon carcinoma may signal an escape from the senescence barrier during the progression from adenoma to carcinoma.", "author" : [{ "dropping-particle" : "", "family" : "Fujita", "given" : "Kaori", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Mondal", "given" : "Abdul M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Horikawa", "given" : "Izumi", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Nguyen", "given" : "Giang H", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kumamoto", "given" : "Kensuke", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Sohn", "given" : "Jane J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bowman", "given" : "Elise D", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Mathe", "given" : "Ewy A", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Schetter", "given" : "Aaron J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Pine", "given" : "Sharon R", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Ji", "given" : "Helen", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Vojtesek", "given" : "Borivoj", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bourdon", "given" : "Jean-Christophe", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lane", "given" : "David P", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Harris", "given" : "Curtis C", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Nature cell biology", "id" : "ITEM-1", "issue" : "9", "issued" : { "date-parts" : [["2009"]] }, "page" : "1135-42", "title" : "p53 isoforms Delta133p53 and p53beta are endogenous regulators of replicative cellular senescence.", "type" : "article-journal", "volume" : "11" }, "uris" : ["http://www.mendeley.com/documents/?uuid=5d4c66ac-e9a1-43c0-bf52-f17f72757143"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.1177/1947601911408893", "ISBN" : "1947601911", "ISSN" : "1947-6027", "PMID" : "21779513", "abstract" : "Normal function of the p53 pathway is ubiquitously lost in cancers either through mutation or inactivating interaction with viral or cellular proteins. However, it is difficult in clinical studies to link p53 mutation status to cancer treatment and clinical outcome, suggesting that the p53 pathway is not fully understood. We have recently reported that the human p53 gene expresses not only 1 but 12 different p53 proteins (isoforms) due to alternative splicing, alternative initiation of translation, and alternative promoter usage. p53 isoform proteins thus contain distinct protein domains. They are expressed in normal human tissues but are abnormally expressed in a wide range of cancer types. We have recently reported that p53 isoform expression is associated with breast cancer prognosis, suggesting that they play a role in carcinogenesis. Indeed, the cellular response to damages can be switched from cell cycle arrest to apoptosis by only manipulating p53 isoform expression. This may provide an explanation to the hitherto inconsistent relationship between p53 mutation, treatment response, and outcome in breast cancer. However, the molecular mechanism is still unknown. Recent reports suggest that it involves modulation of gene expression in a p53-dependent and -independent manner. In this review, we summarize our current knowledge about the biological activities of p53 isoforms and propose a molecular mechanism conciliating our current knowledge on p53 and integrating p63 and p73 isoforms in the p53 pathway.", "author" : [{ "dropping-particle" : "", "family" : "Khoury", "given" : "Marie P", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bourdon", "given" : "Jean-Christophe", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Genes & cancer", "id" : "ITEM-2", "issue" : "4", "issued" : { "date-parts" : [["2011"]] }, "page" : "453-65", "title" : "p53 Isoforms: An Intracellular Microprocessor?", "type" : "article-journal", "volume" : "2" }, "uris" : ["http://www.mendeley.com/documents/?uuid=b46dbe63-aad3-455b-a645-16cb306ba816"] }], "mendeley" : { "formattedCitation" : "(47,48)", "plainTextFormattedCitation" : "(47,48)", "previouslyFormattedCitation" : "(47,48)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**

3.5 Role of p53 Isoforms in Regeneration

Because regeneration and tumorigenesis share common molecular pathways, p53 pathway plays a major role in controlling regeneration. It is known that fluctuations in expression ratio of different p53 isoforms are involved in tissue and organ regeneration. For example, in mouse, the genetic investigation of one of the p53 isoforms - MΔ41p53α (also named p44), which is the mouse counterpart of the human Δ40p53α, has revealed that MΔ41p53α increased expression compared to the other p53 isoforms promote premature ageing phenotype, neurodegeneration, atherosclerosis, osteoporosis and impaired β-cell proliferation. However, mice did not develop cancer (4,65).

3.6 Additional Notable Biological Functions

The expression of isoforms under certain cellular conditions is still under research – however it is known that under standard cellular conditions, p53β and Δ133p53β can be co-expressed. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1101/gad.1339905", "ISBN" : "2514458412", "ISSN" : "08909369", "PMID" : "16131611", "abstract" : "The recently discovered p53-related genes, p73 and p63, express multiple splice variants and N-terminally truncated forms initiated from an alternative promoter in intron 3. To date, no alternative promoter and multiple splice variants have been described for the p53 gene. In this study, we show that p53 has a gene structure similar to the p73 and p63 genes. The human p53 gene contains an alternative promoter and transcribes multiple splice variants. We show that p53 variants are expressed in normal human tissue in a tissue-dependent manner. We determine that the alternative promoter is conserved through evolution from Drosophila to man, suggesting that the p53 family gene structure plays an essential role in the multiple activities of the p53 family members. Consistent with this hypothesis, p53 variants are differentially expressed in human breast tumors compared with normal breast tissue. We establish that p53beta can bind differentially to promoters and can enhance p53 target gene expression in a promoter-dependent manner, while Delta133p53 is dominant-negative toward full-length p53, inhibiting p53-mediated apoptosis. The differential expression of the p53 isoforms in human tumors may explain the difficulties in linking p53 status to the biological properties and drug sensitivity of human cancer.", "author" : [{ "dropping-particle" : "", "family" : "Bourdon", "given" : "Jean Christophe", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Fernandes", "given" : "Kenneth", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Murray-Zmijewski", "given" : "Fiona", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Liu", "given" : "Geng", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Diot", "given" : "Alexandra", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Xirodimas", "given" : "Dimitris P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Saville", "given" : "Mark K.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lane", "given" : "David P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Genes and Development", "id" : "ITEM-1", "issue" : "18", "issued" : { "date-parts" : [["2005"]] }, "page" : "2122-2137", "title" : "p53 isoforms can regulate p53 transcriptional activity", "type" : "article-journal", "volume" : "19" }, "uris" : ["http://www.mendeley.com/documents/?uuid=87bfab4c-0377-4811-b35f-c1e089298fe3"] }], "mendeley" : { "formattedCitation" : "(34)", "plainTextFormattedCitation" : "(34)", "previouslyFormattedCitation" : "(34)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}** More recently, it was discovered that levels of both p53α and Δ40p53α increase under conditions of glucose deprivation; achieved through the IRES – mediated translation of mRNA (i). IRES translation for p53 in general appears to occur under situations of cellular stress. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1038/cdd.2014.220", "ISBN" : "1476-5403 (Electronic)\\r1350-9047 (Linking)", "ISSN" : "1476-5403", "PMID" : "25721046", "abstract" : "Tumor suppressor protein p53 is a master transcription regulator, indispensable for controlling several cellular pathways. Earlier work in our laboratory led to the identification of dual internal ribosome entry site (IRES) structure of p53 mRNA that regulates translation of full-length p53 and \u039440p53. IRES-mediated translation of both isoforms is enhanced under different stress conditions that induce DNA damage, ionizing radiation and endoplasmic reticulum stress, oncogene-induced senescence and cancer. In this study, we addressed nutrient-mediated translational regulation of p53 mRNA using glucose depletion. In cell lines, this nutrient-depletion stress relatively induced p53 IRES activities from bicistronic reporter constructs with concomitant increase in levels of p53 isoforms. Surprisingly, we found scaffold/matrix attachment region-binding protein 1 (SMAR1), a predominantly nuclear protein is abundant in the cytoplasm under glucose deprivation. Importantly under these conditions polypyrimidine-tract-binding protein, an established p53 ITAF did not show nuclear-cytoplasmic relocalization highlighting the novelty of SMAR1-mediated control in stress. In vivo studies in mice revealed starvation-induced increase in SMAR1, p53 and \u039440p53 levels that was reversible on dietary replenishment. SMAR1 associated with p53 IRES sequences ex vivo, with an increase in interaction on glucose starvation. RNAi-mediated-transient SMAR1 knockdown decreased p53 IRES activities in normal conditions and under glucose deprivation, this being reflected in changes in mRNAs in the p53 and \u039440p53 target genes involved in cell-cycle arrest, metabolism and apoptosis such as p21, TIGAR and Bax. This study provides a new physiological insight into the regulation of this critical tumor suppressor in nutrient starvation, also suggesting important functions of the p53 isoforms in these conditions as evident from the downstream transcriptional target activation.Cell Death and Differentiation advance online publication, 27 February 2015; doi:10.1038/cdd.2014.220.", "author" : [{ "dropping-particle" : "", "family" : "Khan", "given" : "D", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Katoch", "given" : "a", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Das", "given" : "a", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Sharathchandra", "given" : "a", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lal", "given" : "R", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Roy", "given" : "P", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Das", "given" : "S", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Chattopadhyay", "given" : "S", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Cell death and differentiation", "id" : "ITEM-1", "issue" : "7", "issued" : { "date-parts" : [["2015"]] }, "page" : "1-16", "title" : "Reversible induction of translational isoforms of p53 in glucose deprivation.", "type" : "article-journal", "volume" : "22" }, "uris" : ["http://www.mendeley.com/documents/?uuid=b2bf4047-fc0c-435e-b588-cee59565f874"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.1080/23723556.2015.1039689", "ISSN" : "2372-3556", "PMID" : "27308557", "abstract" : "p53 and its isoforms are integral in modulating transcriptional gene expression programs and maintaining cellular homeostasis. We recently reported that glucose deprivation/caloric restriction induced translational control of p53 mRNA by scaffold/matrix attachment region binding-protein 1 (SMAR1), adding a cytoplasmic role of SMAR1 to its traditional nuclear role as a transcription factor.", "author" : [{ "dropping-particle" : "", "family" : "Khan", "given" : "Debjit", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Chattopadhyay", "given" : "Samit", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Das", "given" : "Saumitra", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Molecular & Cellular Oncology", "id" : "ITEM-2", "issue" : "1", "issued" : { "date-parts" : [["2016", "1", "2"]] }, "page" : "e1039689", "title" : "Influence of metabolic stress on translation of p53 isoforms", "type" : "article-journal", "volume" : "3" }, "uris" : ["http://www.mendeley.com/documents/?uuid=f77735da-94a3-37b4-bcef-465c522c81a3"] }], "mendeley" : { "formattedCitation" : "(49,50)", "plainTextFormattedCitation" : "(49,50)", "previouslyFormattedCitation" : "(49,50)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**

Bourdon *et al* (2005) also researched the activity of p53β in the presence of p53α, divulging notable results. p53α preferentially binds to the promoter of MDM2, but not to the pro – apoptotic BAX; a contrast to p53β which appears to bind avidly to BAX / p21 promoters rather than MDM2 – a result suggesting that the p53β isoform plays a significant role in enhancing p53 transcription upon the BAX promoter. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1101/gad.1339905", "ISBN" : "2514458412", "ISSN" : "08909369", "PMID" : "16131611", "abstract" : "The recently discovered p53-related genes, p73 and p63, express multiple splice variants and N-terminally truncated forms initiated from an alternative promoter in intron 3. To date, no alternative promoter and multiple splice variants have been described for the p53 gene. In this study, we show that p53 has a gene structure similar to the p73 and p63 genes. The human p53 gene contains an alternative promoter and transcribes multiple splice variants. We show that p53 variants are expressed in normal human tissue in a tissue-dependent manner. We determine that the alternative promoter is conserved through evolution from Drosophila to man, suggesting that the p53 family gene structure plays an essential role in the multiple activities of the p53 family members. Consistent with this hypothesis, p53 variants are differentially expressed in human breast tumors compared with normal breast tissue. We establish that p53beta can bind differentially to promoters and can enhance p53 target gene expression in a promoter-dependent manner, while Delta133p53 is dominant-negative toward full-length p53, inhibiting p53-mediated apoptosis. The differential expression of the p53 isoforms in human tumors may explain the difficulties in linking p53 status to the biological properties and drug sensitivity of human cancer.", "author" : [{ "dropping-particle" : "", "family" : "Bourdon", "given" : "Jean Christophe", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Fernandes", "given" : "Kenneth", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Murray-Zmijewski", "given" : "Fiona", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Liu", "given" : "Geng", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Diot", "given" : "Alexandra", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Xirodimas", "given" : "Dimitris P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Saville", "given" : "Mark K.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lane", "given" : "David P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Genes and Development", "id" : "ITEM-1", "issue" : "18", "issued" : { "date-parts" : [["2005"]] }, "page" : "2122-2137", "title" : "p53 isoforms can regulate p53 transcriptional activity", "type" : "article-journal", "volume" : "19" }, "uris" : ["http://www.mendeley.com/documents/?uuid=87bfab4c-0377-4811-b35f-c1e089298fe3"] }], "mendeley" : { "formattedCitation" : "(34)", "plainTextFormattedCitation" : "(34)", "previouslyFormattedCitation" : "(34)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**

More recently, the link between induced pluripotent stem cells (iPS) and $\Delta133p53\alpha$ was studied. iPS cells are cells that have been reprogrammed back into a pluripotent state, opening up the specialisation of any cell type and thus expanding the potential in regenerative medicine. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1016/j.cell.2007.11.019", "ISBN" : "0092-8674 (Print) 0092-8674 (Linking)", "ISSN" : "0092-8674", "PMID" : "18035408", "abstract" : "Takahashi, K., Tanabe, K., Ohnuki, M., Narita, M., Ichisaka, T., Tomoda, K., & Yamanaka, S. (2007). Induction of pluripotent stem cells from adult human fibroblasts by defined factors. cell, 131(5), 861-872.", "author" : [{ "dropping-particle" : "", "family" : "Takahashi", "given" : "K.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Tanabe", "given" : "K.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Ohnuki", "given" : "M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Narita", "given" : "M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Ichisaka", "given" : "T.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Tomoda", "given" : "K.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Yamanaka", "given" : "S", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Cell", "id" : "ITEM-1", "issue" : "5", "issued" : { "date-parts" : [["2007"]] }, "page" : "861-872", "title" : "Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors", "type" : "article-journal", "volume" : "107" }, "uris" : ["http://www.mendeley.com/documents/?uuid=2f7c55fd-5991-445f-8cfe-55be8fc2f2ea"] }], "mendeley" : { "formattedCitation" : "(51)", "plainTextFormattedCitation" : "(51)", "previouslyFormattedCitation" : "(51)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }} During cell reprogramming, the quantity of Δ133p53α increased, suggesting that the isoform contributes to such a function – and concurring with other research, elevated levels of Δ133p53α appear to arrest apoptosis during the reprogramming of iPS cells and increasing genome intergrity. Other effects of Δ133p53α ascertained include assisting DNA double strand break repair (by stimulating the expression of RAD51, LIG4 and RAD52) and its presence correlating to a lower rate of chromosomal abnormalities within iPS cells. {ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1038/srep37281", "ISSN" : "2045-2322", "PMID" : "27874035", "abstract" : "Human induced pluripotent stem (iPS) cells have great potential in regenerative medicine, but this depends on the integrity of their genomes. iPS cells have been found to contain a large number of de novo genetic alterations due to DNA damage response during reprogramming. Thus, to maintain the genetic stability of iPS cells is an important goal in iPS cell technology. DNA damage response can trigger tumor suppressor p53 activation, which ensures genome integrity of reprogramming cells by inducing apoptosis and senescence. p53 isoform \u0394133p53 is a p53 target gene and functions to not only antagonize p53 mediated apoptosis, but also promote DNA double-strand break (DSB) repair. Here we report that \u0394133p53 is induced in reprogramming. Knockdown of \u0394133p53 results 2-fold decrease in reprogramming efficiency, 4-fold increase in chromosomal aberrations, whereas overexpression of \u0394133p53 with 4 Yamanaka factors showes 4-fold increase in reprogamming efficiency and 2-fold decrease in chromosomal aberrations, compared to those in iPS cells induced only with 4 Yamanaka factors. Overexpression of \u0394133p53 can inhibit cell apoptosis and promote DNA DSB repair foci formation during reprogramming. Our finding demonstrates that the overexpression of \u0394133p53 not only enhances reprogramming efficiency, but also results better genetic quality in iPS cells.", "author" : [{ "dropping-particle" : "", "family" : "Gong", "given" : "Lu", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Pan", "given" : "Xiao", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Chen", "given" : "Haide", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Rao", "given" : "Lingjun", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Zeng", "given" : "Yelin", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Hang", "given" : "Honghui", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Peng", "given" : "Jinrong", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Xiao", "given" : "Lei", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Chen", "given" : "Jun", "non-dropping-particle" : "", "parse-names" :

false, "suffix" : "" }], "container-title" : "Scientific Reports", "id" : "ITEM-1", "issue" : "July", "issued" : { "date-parts" : [["2016"]] }, "page" : "37281", "title" : "P53 Isoform \u0394133P53 Promotes Efficiency of Induced Pluripotent Stem Cells and Ensures Genomic Integrity During Reprogramming", "type" : "article-journal", "volume" : "6" }, "uris" : ["http://www.mendeley.com/documents/?uuid=acd2d9d8-2985-49be-819c-9e611c888281"] }], "mendeley" : { "formattedCitation" : "(52)", "plainTextFormattedCitation" : "(52)", "previouslyFormattedCitation" : "(52)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**.

4- Link Between p53 pathway and Cancer

It is established that *TP53* is the most frequently mutated gene in human cancers and that when *TP53* is not mutated, WT *TP53* activities are compromised in almost all tumours. (70-73). Moreover, mutant p53α has an oncogenic potential because it would act as a dominant-negative inhibitor toward wild-type p53. (70)

The role of *TP53* in the development of many forms of malignancy has recently been highlighted by the International Cancer Genome Consortium (IGCC). As of the 3rd August 2017, the IGCC have released data from more than 17500 cancer donors demonstrating that *TP53* is by far the most commonly mutated gene in cancer. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "URL" : "https://dcc.icgc.org/", "accessed" : { "date-parts" : [["2017", "8", "3"]] }, "id" : "ITEM-1", "issued" : { "date-parts" : [["0"]] }, "title" : "Welcome | ICGC Data Portal", "type" : "webpage" }, "uris" : ["http://www.mendeley.com/documents/?uuid=7f5c6211-8d18-35ca-82bc-4110acf3c0ef"] }], "mendeley" : { "formattedCitation" : "(68)", "plainTextFormattedCitation" : "(68)", "previouslyFormattedCitation" : "(68)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**

4.1 Human Papilloma Virus and p53α

As mentioned, nearly all cervical cancer cases are linked to persistent infection with HPV - three genes out of eight within HPV16 are significant in this progression. They are E2, E6 and E7. E6 is a viral oncogene that mediates the degradation of p53α whilst E7, also a viral oncogene, binds to and inactivates pRB (another tumour suppression protein). Significant evidence exists to suggest that a key role in the development of cervical cancer is the loss of the viral E2 gene. The E2 gene is a viral tumour suppressor, stifling the activities of E6 and E7 – an observation confirmed by its absence in cervical tumours. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1158/0008-5472.CAN-07-2754", "ISBN" : "1538-7445 (Electronic) 0008-5472 (Linking)", "ISSN" : "00085472", "PMID" : "18172324", "abstract" : "Chromosomal integration of high-risk human papillomavirus (HR-HPV) genomes is believed to represent a significant event in the pathogenesis of cervical cancer associated with progression from preneoplastic lesions to invasive carcinomas. This hypothesis is based on experimental data suggesting that integration-dependent disruption of HR-HPV E2 gene functions is important to achieve neoplastic transformation and on clinical data gathered by analyzing lesions induced by human papillomavirus (HPV) 16 and

18 that revealed integrated viral genome copies in the vast majority of cervical cancer cells. However, a substantial fraction of cervical cancers is associated with other HR-HPV types for which virtually no data concerning their integration status have been reported so far. Here, we compared integration frequencies of the five most common oncogenic HPV types (HPV16, 18, 31, 33, and 45) in a series of 835 cervical samples using a specific mRNA-based PCR assay (Amplification of Papillomavirus Oncogene Transcripts). Most precancerous lesions displayed exclusively episomal viral genomes, whereas 62% of the carcinomas had integrated viral genomes. However, the frequency of integrated HR-HPV genomes showed marked differences for individual HR-HPV types. HPV16, 18, and 45 were found substantially more often in the integrated state compared with HPV types 31 and 33. The analysis of the median age of patients with high-grade precancerous lesions and invasive cancers suggests that precancers induced by HPV types 18, 16, and 45 progress to invasive cervical cancer in substantially less time compared with precancers induced by HPV types 31 and 33. These findings suggest that integration of oncogenic HPV genomes in cervical lesions is a consequence rather than the cause of chromosomal instability induced by deregulated HR-HPV E6-E7 oncogene expression. Distinct HR-HPV types apparently provoke chromosomal instability in their host cells to a different extent than is reflected by their integration frequencies in advanced lesions and the time required for CIN 3 lesions to progress to invasive cancer.", "author" : [{ "dropping-particle" : "", "family" : "Vinokurova", "given" : "Svetlana", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Wentzensen", "given" : "Nicolas", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kraus", "given" : "Irene", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Klaes", "given" : "Ruediger", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Driesch", "given" : "Corina", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Melsheimer", "given" : "Peter", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kisseljov", "given" : "Fjodor", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "D\u00fcrst", "given" : "Mattias", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Schneider", "given" : "Achim", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Doeberitz", "given" : "Magnus Von Knebel", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Cancer Research", "id" : "ITEM-1", "issue" : "1", "issued" : { "date-parts" : [["2008"]] }, "page" : "307-313", "title" : "Type-dependent integration frequency of human papillomavirus genomes in cervical lesions", "type" : "article-journal", "volume" : "68" }, "uris" : ["http://www.mendeley.com/documents/?uuid=ed0471c2-e91b-44e1-8cec-b3096c1129cf"] }], "mendeley" : { "formattedCitation" : "(70)", "plainTextFormattedCitation" : "(70)", "previouslyFormattedCitation" : "(70)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}** When it ceases to function, the uncontrollable transcription of genes E6 and E7 occur, resulting in decreased expression of pRB and p53α **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.4143/crt.2005.37.6.319", "ISBN" : "2005-9256 (Electronic)\\n1598-2998 (Linking)", "ISSN" : "2005-9256", "PMID" : "19956366", "abstract" : "Cervical cancer is one of the leading world causes of cancer morbidity and mortality in woman, with more than 98% related to a human papillomavirus (HPV) infection origin.

Infection with specific subtypes of HPV has been strongly implicated in cervical carcinogenesis. The identification and functional verification of host proteins associated with HPV E6 and E7 oncoproteins may provide useful information in understanding cervical carcinogenesis and the development of cervical cancer-specific markers. The advent of functional genomics and proteomics has provided hope of discovering novel biological markers for use in the screening, early diagnosis, prognostication and prediction of response to therapy. Herein, we review the studies where the profiles of host proteins associated with HPV E6 and E7 oncoproteins in cervical cancer were generated.", "author" : [{ "dropping-particle" : "", "family" : "Yim", "given" : "Eun-Kyoung", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Park", "given" : "Jong-Sup", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Cancer research and treatment : official journal of Korean Cancer Association", "id" : "ITEM-1", "issue" : "6", "issued" : { "date-parts" : [["2005"]] }, "page" : "319-24", "title" : "The role of HPV E6 and E7 oncoproteins in HPV-associated cervical carcinogenesis.", "type" : "article-journal", "volume" : "37" }, "uris" : ["http://www.mendeley.com/documents/?uuid=53618b76-e87b-42b8-b946-4566f538eb27"] }, { "id" : "ITEM-2", "itemData" : { "ISBN" : "2156-6976 (Electronic)", "PMID" : "21968515", "abstract" : "The papillomavirus (PV) E2 proteins have been shown to exert many functions in the viral cycle including pivotal roles in transcriptional regulation and in viral DNA replication. Besides these historical roles, which rely on their aptitude to bind to specific DNA sequences, E2 has also been shown to modulate the host cells through direct protein interactions mainly through its amino terminal transactivation domain. We will describe here some of these new functions of E2 and their potential implication in the HPV-induced carcinogenesis. More particularly we will focus on E2-mediated modulation of the host cell cycle and consequences to cell transformation. In all, the HPV E2 proteins exhibit complex functions independent of transcription that can modulate the host cells in concert with the viral vegetative cycle and which could be involved in early carcinogenesis.", "author" : [{ "dropping-particle" : "", "family" : "Bellanger", "given" : "S", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Tan", "given" : "C L", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Xue", "given" : "Y Z", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Teissier", "given" : "S", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Thierry", "given" : "F", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Am J Cancer Res", "id" : "ITEM-2", "issued" : { "date-parts" : [["2011"]] }, "page" : "373-389", "title" : "Tumor suppressor or oncogene? A critical role of the human papillomavirus (HPV) E2 protein in cervical cancer progression", "type" : "article-journal", "volume" : "1" }, "uris" : ["http://www.mendeley.com/documents/?uuid=b29f495a-0aa3-4cbb-83b4-af8bc15cd302"] }], "mendeley" : { "formattedCitation" : "(61,71)", "plainTextFormattedCitation" : "(61,71)", "previouslyFormattedCitation" : "(61,71)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**.

E6 degrades p53α through a pathway entitled the ubiquitin – proteasome pathway. E6 proteins do not directly affiliate with p53α, but instead reassign E6AP (E6 associated protein – an enzyme that targets other proteins for breakdown) to p53α. This marks p53α for ubiquitination and proteasome degradation by 26S, explaining the uncharacteristically low levels of p53α in cervical cancer and thus promoting carcinogenesis by inhibiting the apoptosis of malignant cells; in other words, inhibiting the role that p53α plays within cells. {ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.4143/crt.2005.37.6.319", "ISBN" : "2005-9256 (Electronic)\\n1598-2998 (Linking)", "ISSN" : "2005-9256", "PMID" : "19956366", "abstract" : "Cervical cancer is one of the leading world causes of cancer morbidity and mortality in woman, with more than 98% related to a human papillomavirus (HPV) infection origin. Infection with specific subtypes of HPV has been strongly implicated in cervical carcinogenesis. The identification and functional verification of host proteins associated with HPV E6 and E7 oncoproteins may provide useful information in understanding cervical carcinogenesis and the development of cervical cancer-specific markers. The advent of functional genomics and proteomics has provided hope of discovering novel biological markers for use in the screening, early diagnosis, prognostication and prediction of response to therapy. Herein, we review the studies where the profiles of host proteins associated with HPV E6 and E7 oncoproteins in cervical cancer were generated.", "author" : [{ "dropping-particle" : "", "family" : "Yim", "given" : "Eun-Kyoung", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Park", "given" : "Jong-Sup", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Cancer research and treatment : official journal of Korean Cancer Association", "id" : "ITEM-1", "issue" : "6", "issued" : { "date-parts" : [["2005"]] }, "page" : "319-24", "title" : "The role of HPV E6 and E7 oncoproteins in HPV-associated cervical carcinogenesis.", "type" : "article-journal", "volume" : "37" }, "uris" : ["http://www.mendeley.com/documents/?uuid=53618b76-e87b-42b8-b946-4566f538eb27"] }], "mendeley" : { "formattedCitation" : "(61)", "plainTextFormattedCitation" : "(61)", "previouslyFormattedCitation" : "(61)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }}

4.2 Hepatitis B and p53

Hepatitis B can repress p53 mediated apoptosis. The oncoprotein HBx (produced by hepatitis B), forms a protein complex with p53α by interacting through a sequence of residues in its C – terminus. This appears to occur in the cytoplasm, resulting in the arresting of apoptosis and thus contributing to the development of hepatocellular carcinoma. {ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1073/pnas.94.26.14707", "ISBN" : "0027-8424", "ISSN" : "0027-8424", "PMID" : "9405677", "abstract" : "We have reported previously that the hepa-titis B virus oncoprotein, HBx, can bind to the C terminus of p53 and inhibit several critical p53-mediated cellular pro-cesses, including DNA sequence-specific binding, transcrip-tional transactivation, and apoptosis. Recognizing the impor-tance of p53-mediated apoptosis for maintaining homeostasis and preventing neoplastic transformation, here we further examine the physical interaction between HBx and p53 as well as the functional consequences of this association. In vitro binding studies indicate that the ayw and adr viral subtypes of HBx bind similar amounts of glutathione S-transferase-p53 with the distal C terminus of HBx (from residues 111 to 154) being critical for this interaction. Using a microinjection technique, we show that this same C-terminal region of HBx is necessary for sequestering p53 in the cytoplasm and abro-gating p53-mediated apoptosis. The transcriptional transac-tivation domain of HBx also maps to its C terminus; however, a comparison of the ability of full-length and truncated HBx protein to abrogate p53-induced apoptosis versus transacti-vate simian virus 40-or human nitric oxide synthase-2 promoter-driven reporter constructs indicates that these two functional properties are distinct and thus may contribute to hepatocarcinogenesis differently. Collectively, our data indi-cate that the distal C-terminal domain of HBx, independent of its transactivation activity, complexes with p53 in the cyto-plasm, partially preventing its nuclear entry and ability to induce apoptosis. These pathobiological effects of HBx may contribute to the early stages of hepatocellular carcinogenesis.", "author" : [{ "dropping-particle" : "", "family" : "Elmore", "given" : "Lynne W", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Hancock", "given" : "Amy R", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Chang", "given" : "Shau-Feng", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Wang", "given" : "Xin W", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Chang", "given" : "Seung", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Callahan", "given" : "Christiana P", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Geller", "given" : "David A", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Will", "given" : "Hans", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Harris", "given" : "Curtis C", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Proc. Natl. Acad. Sci. USA", "id" : "ITEM-1", "issue" : "December", "issued" : { "date-parts" : [["1997"]] }, "page" : "14707-14712", "title" : "Hepatitis B virus X protein and p53 tumor suppressor interactions in the modulation of apoptosis", "type" : "article-journal", "volume" : "94" }, "uris" : ["http://www.mendeley.com/documents/?uuid=dde19e1f-e96a-471d-bfeb-708c59d9310f"] }], "mendeley" : { "formattedCitation" : "(72)", "plainTextFormattedCitation" : "(72)", "previouslyFormattedCitation" : "(72)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**

4.3 Mutant p53 and an Associated Specific Mutation

Certain mutant p53 proteins can bind to wt p53α, compromising its activities and thus promoting abnormal cell proliferation. It is interesting to note that complexes between mutant p53α and wt p53α tend to involve the oligomerization domain –**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1128/MCB.11.1.12", "ISBN" : "0270-7306 (Print)\\r0270-7306 (Linking)", "ISSN" : "0270-7306", "PMID" : "1986215", "abstract" : "It has been suggested that the dominant effect of mutant p53 on tumor progression may reflect the mutant protein binding to wild-type p53, with inactivation of suppressor function. To date, evidence for wild-type/mutant p53 complexes involves p53 from different species. To investigate wild-type/mutant p53 complexes in relation to natural tumor progression, we sought to identify intraspecific complexes, using murine p53. The mutant phenotype p53-246(0) was used because this phenotype is immunologically distinct from wild-type p53-246+ and thus permits immunological analysis for wild-type/mutant p53 complexes. The p53 proteins were derived from genetically defined p53 cDNAs expressed in vitro and also from phenotypic variants of p53 expressed in vivo. We found that the mutant p53 phenotype was able to form a complex with the wild type when the two p53 variants were cotranslated. When mixed in their native states (after translation), the wild-type and mutant p53 proteins did not exhibit any binding affinity for each other in vitro. Under identical conditions, complexes of wild-type human and murine p53 proteins were formed. For murine p53, both the wild-type and mutant p53 proteins formed high-molecular-weight complexes when translated in vitro. This oligomerization appeared to involve the carboxyl terminus, since truncated p53 (amino acids 1 to 343) did not form complexes. We suggest that the ability of the mutant p53 phenotype to complex with wild type during cotranslation may contribute to the transforming function of activated mutants of p53 in vivo.", "author" : [{ "dropping-particle" : "", "family" : "Milner", "given" : "J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Medcalf", "given" : "E A", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Cook", "given" : "A C", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Molecular and cellular biology", "id" : "ITEM-1", "issue" : "1", "issued" : { "date-parts" : [["1991"]] }, "page" : "12-19", "title" : "Tumor suppressor p53: analysis of wild-type and mutant p53 complexes", "type" : "article-journal", "volume" : "11" }, "uris" : ["http://www.mendeley.com/documents/?uuid=66e666f5-1cb2-460a-b201-34831c1b8dbf"] }], "mendeley" : { "formattedCitation" : "(73)", "plainTextFormattedCitation" : "(73)", "previouslyFormattedCitation" : "(73)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**

One of the more common alterations that occur upon *TP53* is the R175H mutation, as labelled within the COSMIC database. It is a single base substitution at codon 524, exchanging guanine → adenine, and has a high functional impact with this mutation particularly occurring in colorectal cancers. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "URL" : "http://cancer.sanger.ac.uk/cosmic/mutation/overview?id=10648", "accessed" : { "date-parts" : [["2017", "8", "3"]] }, "id" : "ITEM-1", "issued" : { "date-parts" : [["0"]] }, "title" : "COSMIC: Mutation overview page TP53 - p.R175H (Substitution - Missense)", "type" : "webpage" }, "uris" : ["http://www.mendeley.com/documents/?uuid=85e5ce7b-91ac-3651-9003-0e4731ba9d54"] }], "mendeley" : { "formattedCitation" : "(75)", "plainTextFormattedCitation" : "(75)", "previouslyFormattedCitation" : "(75)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}** p53 R175H impairs recruitment of ATM (mediated by MRN in response to DNA double strand break damage), thus encouraging the proliferation of anomalies within cells. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1038/onc.2009.376.A", "ISBN" : "1476-5594 (Electronic)\\r0950-9232 (Linking)", "ISSN" : "0950-9232", "PMID" : "19881536", "abstract" : "The critical tumor suppressor p53 is mutated in over half of all human cancers. The majority of p53 cancer mutations are missense mutations, which can be classified into contact mutations that directly disrupt the DNA-binding of p53 but have modest impact on p53 conformation and structural mutations that greatly disrupt p53 conformation. Many p53 cancer mutants, including the hot spot mutations (R175H, R248W and R273H), not only lose p53-dependent tumor-suppressor activities, but also acquire new oncogenic activities to promote cancer. Therefore, it is critical to elucidate the gain of oncogenic function of p53 cancer mutants. Using humanized p53-mutant knock-in mouse models, we have identified a gain of oncogenic function shared by the most common p53 contact mutants (R273H and

R248W) and structural mutant (R175H). This gain of function inactivates Mre11/ATM-dependent DNA damage responses, leading to chromosomal translocation and defective G(2)/M checkpoint. Considering the critical roles of ATM in maintaining genetic stability and therapeutic responses to many cancer treatments, the identification of this common gain of function of p53 cancer mutants will have important implication on the drug resistance of a significant portion of human cancers that express either the contact or structural p53 cancer mutants.", "author" : [{ "dropping-particle" : "", "family" : "Liu", "given" : "D P", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Song", "given" : "H", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Xu", "given" : "Y", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Oncogene", "id" : "ITEM-1", "issue" : "7", "issued" : { "date-parts" : [["2010"]] }, "page" : "949-956", "title" : "A common gain of function of p53 cancer mutants in inducing genetic instability.", "type" : "article-journal", "volume" : "29" }, "uris" : ["http://www.mendeley.com/documents/?uuid=cd064754-933f-4281-b0aa-1036aaaf5a3c"] }], "mendeley" : { "formattedCitation" : "(76)", "plainTextFormattedCitation" : "(76)", "previouslyFormattedCitation" : "(76)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}** It is relevant to mention that R175H occurs within the DNA Binding Domain of p53 proteins – it is within the DBD that the majority of mutations occur.

4.4 Other Interactions of Mutant p53

As mentioned, mutant p53α can bind to wtp53α, altering its transcriptional activity. An example of this relates to p63, a family member of TP53 gene. Briefly, mutant p53α can inhibit the activity of p63 protein isoforms which then results in the unregulated expression of genes such as *DICER1*, *SHARP1* and *CCNG2*. The abnormal expression of these genes enhances the release of growth receptors and integrins, leading to increased and uncontrolled cell division. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1038/ncb2641", "ISBN" : "1476-4679", "ISSN" : "1465-7392", "PMID" : "23263379", "abstract" : "In the past fifteen years, it has become apparent that tumour-associated\\np53 mutations can provoke activities that are different to those\\nresulting from simply loss of wild-type tumour-suppressing p53 function.\\nMany of these mutant p53 proteins acquire oncogenic properties that\\nenable them to promote invasion, metastasis, proliferation and cell\\nsurvival. Here we highlight some of the emerging molecular mechanisms\\nthrough which mutant p53 proteins can exert these oncogenic functions.", "author" : [{ "dropping-particle" : "", "family" : "Muller", "given" : "Patricia A J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Vousden", "given" : "Karen H", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Nature Cell Biology", "id" : "ITEM-1", "issue" : "1", "issued" : { "date-parts" : [["2013"]] }, "page" : "2-8", "title" : "p53 mutations in cancer", "type" : "article-journal", "volume" : "15" }, "uris" : ["http://www.mendeley.com/documents/?uuid=8dc72922-5fe5-4edd-8a7a-45b5e95565fc"] }], "mendeley" : { "formattedCitation" : "(78)", "plainTextFormattedCitation" : "(78)", "previouslyFormattedCitation" : "(78)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**

Whilst mutant p53α interacts with many proteins (all of which cannot be mentioned), one that is important to reference is its interaction with the SWI / SNF complex. Established as a nucleosome remodelling complex, it is a collection of proteins that interact with the packaging process of DNA, altering DNA interaction with histones and thus gene transcription. Mutant p53α relies upon the SWI / SNF complex to displace nucleosomes that regulates thus DNA accessibility for transcription factors, explaining how mutant p53 can promote the plasticity of cancers, being able to trans-differentiate or de -differentiate with ease and thus escape treatment. {ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1101/gad.263202.115", "ISSN" : "1549-5477", "PMID" : "26080815", "abstract" : "Mutant p53 impacts the expression of numerous genes at the level of transcription to mediate oncogenesis. We identified vascular endothelial growth factor receptor 2 (VEGFR2), the primary functional VEGF receptor that mediates endothelial cell vascularization, as a mutant p53 transcriptional target in multiple breast cancer cell lines. Up-regulation of VEGFR2 mediates the role of mutant p53 in increasing cellular growth in two-dimensional (2D) and three-dimensional (3D) culture conditions. Mutant p53 binds near the VEGFR2 promoter transcriptional start site and plays a role in maintaining an open conformation at that location. Relatedly, mutant p53 interacts with the SWI/SNF complex, which is required for remodeling the VEGFR2 promoter. By both querying individual genes regulated by mutant p53 and performing RNA sequencing, the results indicate that >40% of all mutant p53-regulated gene expression is mediated by SWI/SNF. We surmise that mutant p53 impacts transcription of VEGFR2 as well as myriad other genes by promoter remodeling through interaction with and likely regulation of the SWI/SNF chromatin remodeling complex. Therefore, not only might mutant p53-expressing tumors be susceptible to anti VEGF therapies, impacting SWI/SNF tumor suppressor function in mutant p53 tumors may also have therapeutic potential.", "author" : [{ "dropping-particle" : "", "family" : "Pfister", "given" : "Neil T", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Fomin", "given" : "Vitalay", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Regunath", "given" : "Kausik", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Zhou", "given" : "Jeffrey Y", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Zhou", "given" : "Wen", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Silwal-Pandit", "given" : "Laxmi", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Freed-Pastor", "given" : "William A", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Laptenko", "given" : "Oleg", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Neo", "given" : "Suat Peng", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bargonetti", "given" : "Jill", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Hoque", "given" : "Mainul", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Tian", "given" : "Bin", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Gunaratne", "given" : "Jayantha", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Engebraaten", "given" : "Olav", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Manley", "given" : "James L", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" :

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5- Relevance of p53 Isoforms to Cancer

5.1 Breast Tumours

In 2005, whilst researching the isoforms, Bourdon *et al* also identified the abnormal expression of isoforms within breast tumours. Within normal breast tissue, the co-expression of p53α, p53β and p53γ mRNA was detected but none of the Δ133p53 isoforms mRNAs. However, an interesting observation was noted within the breast tumours (of which 30 were investigated) - p53γ, Δ133p53β and Δ133p53γ were absent from the breast cancer tissue; p53β was detected in only 10 out of 30. Interestingly however, Δ133p53α was co-expressed in 24 out of the 30 tumours – an indication that this isoform may play a role in the development of certain malignancies. Out of all 30 breast tumours, only 5 expressed mutant TP53, suggesting that the isoforms may play a greater role in tumorigenesis than TP53 mutation. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1101/gad.1339905", "ISBN" : "2514458412", "ISSN" : "08909369", "PMID" : "16131611", "abstract" : "The recently discovered p53-related genes, p73 and p63, express multiple splice variants and N-terminally truncated forms initiated from an alternative promoter in intron 3. To date, no alternative promoter and multiple splice variants have been described for the p53 gene. In this study, we show that p53 has a gene structure similar to the p73 and p63 genes. The human p53 gene contains an alternative promoter and transcribes multiple splice variants. We show that p53 variants are expressed in normal human tissue in a tissue-dependent manner. We determine that the alternative promoter is conserved through evolution from Drosophila to man, suggesting that the p53 family gene structure plays an essential role in the multiple activities of the p53 family members. Consistent with this hypothesis, p53 variants are differentially expressed in human breast tumors compared with normal breast tissue. We establish that p53beta can bind differentially to promoters and can enhance p53 target gene expression in a promoter-dependent manner, while Delta133p53 is dominant-negative toward full-length p53, inhibiting p53-mediated apoptosis. The differential expression of the p53 isoforms in human tumors may explain the difficulties in linking p53 status to the biological properties and drug sensitivity of human cancer.", "author" : [{ "dropping-particle" : "", "family" : "Bourdon", "given" : "Jean Christophe", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Fernandes", "given" : "Kenneth", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Murray-Zmijewski", "given" : "Fiona", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Liu", "given" : "Geng", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Diot", "given" : "Alexandra", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Xirodimas", "given" : "Dimitris P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Saville", "given" : "Mark K.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lane", "given" : "David P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Genes and Development", "id" : "ITEM-1", "issue" : "18", "issued" : { "date-parts" : [["2005"]] }, "page" : "2122-2137", "title" : "p53 isoforms can regulate p53 transcriptional activity", "type" : "article-journal", "volume" : "19" }, "uris" : ["http://www.mendeley.com/documents/?uuid=87bfab4c-0377-4811-b35f-c1e089298fe3"] }], "mendeley" : { "formattedCitation" : "(34)", "plainTextFormattedCitation" : "(34)", "previouslyFormattedCitation" : "(34)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**

Consistently, a more recent study of 127 breast tumours revealed that only 36% of breast tumours recorded p53β expression, 37% of breast tumours expressed p53γ and 19% of tumours co-expressed both p53β and p53γ. (85)

It was also found that the expression of both isoforms was not random – indeed, their expression was linked. The mutant *TP53* breast cancer patients co-expressing p53γ also had better prognosis than mutant *TP53* patients not expressing p53γ. Patients that did not produce p53γ were, in fact, reported to have a particularly poor prognosis. (85)

5.2 *Δ133p53 Isoforms*

When co-expressed with other p53 isoforms, Δ133p53β has been shown to play a role in the regulation of apoptosis (a major function of p53) in colorectal cancer cells through its connection with the anti – apoptotic protein, RhoB. When bound to RhoB, it inhibits the activity of RhoB and so, in the case of colorectal cancer cells, shields it from apoptosis (since RhoB is considered a tumour suppressor gene). **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1371/journal.pone.0172125", "ISSN" : "1932-6203", "PMID" : "28212429", "abstract" : "The TP53 gene plays essential roles in cancer. Conventionally, wild type (WT) p53 is thought to prevent cancer development and metastasis formation, while mutant p53 has transforming abilities. However, clinical studies failed to establish p53 mutation status as an unequivocal predictive or prognostic factor of cancer progression. The recent discovery of p53 isoforms that can differentially regulate cell cycle arrest and apoptosis suggests that their expression, rather than p53 mutations, could be a more clinically relevant biomarker in patients with cancer. In this study, we show that the p53 isoform delta133p53\u00df is involved in regulating the apoptotic response in colorectal cancer cell lines. We first demonstrate delta133p53\u00df association with the small GTPase RhoB, a well-described anti-apoptotic protein. We then show that, by inhibiting RhoB activity, delta133p53\u00df protects cells from camptothecin-induced apoptosis. Moreover, we found that high delta133p53 mRNA expression levels are correlated with higher risk of recurrence in a series of patients with locally advanced rectal cancer (n = 36). Our findings describe how a WT TP53 isoform can act as an oncogene and add a new layer to the already complex p53 signaling network.", "author" : [{ "dropping-particle" : "", "family" : "Arsic", "given" : "Nikola", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Ho-Pun-Cheung", "given" : "Alexandre", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Evelyne", "given" : "Crapez", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Assenat", "given" : "Eric", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Jarlier", "given" : "Marta", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Anguille", "given" : "Christelle", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Colard", "given" : "Manon", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Pezet", "given" : "Mika\u00ebl", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Roux", "given" : "Pierre", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Gadea", "given" : "Gilles", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "PloS one", "id" : "ITEM-1", "issue" : "2", "issued" : { "date-parts" : [["2017"]] }, "page" : "e0172125", "publisher" : "Public Library of Science", "title" : "The p53 isoform delta133p53\u00df regulates cancer cell apoptosis in a RhoB-dependent manner.", "type" : "article-journal", "volume" : "12" }, "uris" : ["http://www.mendeley.com/documents/?uuid=d9aa21b5-5b66-366e-bc43-ccb27fd03644"] }], "mendeley" : { "formattedCitation" : "(82)", "plainTextFormattedCitation" : "(82)", "previouslyFormattedCitation" : "(82)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}** This results in the inevitable conclusion of it being a stimulant of tumourigenesis.

Linking in with breast tumours, it was discovered that Δ133p53β co-expression with p53 isoforms was also interrelated to the stage of breast cancer and thus a worse prognosis – whilst the Δ133p53α and Δ133p53γ isoforms displayed no such association. It was also identified that in breast tumours where Δ133p53β and/or Δ133p53γ was detected, Δ133p53α was always present. Perhaps the most interesting discovery, however, was the observation that expression of Δ133p53 isoforms seemingly drives invasion in breast cancer cells. MDA-MB-231 D3H2LN cells, when paralleled with the parental form MDA-MB-231, showed a higher metastatic potential; the D3H2LN cells express at the endogenous level a higher amount of Δ133p53β protein than the parental MDA-MD-231 cells. This was confirmed when re-introduction of mutant Δ133p53β-R280K isoforms in D3H2LN cells previously depleted in Δ133p53β isoform; began to invade. A reduction in levels of the Δ133 or β isoform variants stalled invasion drastically **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.7554/eLife.14734", "ISSN" : "2050084X", "PMID" : "27630122", "abstract" : "TP53 is conventionally thought to prevent cancer formation and progression to metastasis, while mutant TP53 has transforming activities. However, in the clinic, TP53 mutation status does not accurately predict cancer progression. Here we report, based on clinical analysis corroborated with experimental data, that the p53 isoform \u0394133p53\u03b2 promotes cancer cell invasion, regardless of TP53 mutation status. \u0394133p53\u03b2 increases risk of cancer recurrence and death in breast cancer patients. Furthermore \u0394133p53\u03b2 is critical to define invasiveness in a panel of breast and colon cell lines, expressing WT or mutant TP53. Endogenous mutant \u0394133p53\u03b2 depletion prevents invasiveness without affecting mutant full-length p53 protein expression. Mechanistically WT and mutant \u0394133p53\u03b2 induces EMT. Our findings provide explanations to 2 long-lasting and important clinical conundrums: how WT TP53 can promote cancer cell invasion and reciprocally why mutant TP53 gene does not systematically induce cancer progression.", "author" : [{ "dropping-particle" : "", "family" : "Gadea", "given" : "Gilles", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Arsic", "given" : "Nikola", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Fernandes", "given" : "Kenneth", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Diot", "given" : "Alexandra", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Joruiz", "given" : "S\u00e9bastien M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Abdallah", "given" : "Samer", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Meuray", "given" : "Valerie", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Vinot", "given" : "St\u00e9phanie", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Anguille", "given" : "Christelle", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Remenyi", "given" : "Judit", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Khoury", "given" : "Marie P.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Quinlan", "given" : "Philip R.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Purdie", "given" : "Colin A.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Jordan", "given" : "Lee B.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "V.", "family" : "Fuller-Pace", "given" : "Frances", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Toledo", "given" : "Marion", "non-dropping-particle" : "De", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Cren", "given" : "Ma\u00eflys", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Thompson", "given" : "Alastair M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bourdon", "given" : "Jean Christophe", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Roux", "given" : "Pierre", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "eLife", "id" : "ITEM-1", "issue" : "September2016", "issued" : { "date-parts" : [["2016"]] }, "title" : "TP53 drives invasion through expression of its \u0394133p53\u03b2 variant", "type" : "article-journal", "volume" : "5" }, "uris" : ["http://www.mendeley.com/documents/?uuid=c20a0653-7292-47de-9dc1-c9c7b28fb6ee"] }], "mendeley" : { "formattedCitation" : "(83)", "plainTextFormattedCitation" : "(83)", "previouslyFormattedCitation" : "(83)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**.

Δ133p53 isoforms is not always a "marker of poor prognosis". In serous ovarian tumours expressing mutant *TP53*, the elevated expression of Δ133p53α is associated to lower relapse rate (43% risk reduction for recurrence) and a better survival prognostic rate (64% risk reduction for death). {ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1038/bjc.2011.433", "ISSN" : "1532-1827", "PMID" : "22009029", "abstract" : "BACKGROUND: We aimed to evaluate the clinical relevance of p53 and p73 isoforms that modulate the function of p53.\\n\\nMETHODS: This prospective multicentre study included 154 patients with stage III and IV serous ovarian cancer. A functional yeast-based assay and subsequent sequencing were performed to analyse the p53 mutational status. Expression of p53 and p73 isoforms was determined using RT-qPCR.\\n\\nRESULTS: \u0394133p53 expression constituted an independent prognostic marker for recurrence-free (hazard ratio=0.571, P=0.016, 95% CI: 0.362-0.899) and overall survival (hazard ratio=0.365, P=0.004, 95% CI: 0.182-0.731) in patients with p53 mutant ovarian cancer (n=121). High \u039440p53 expression was associated with favourable tumour grading (P=0.037) and improved recurrence-free survival (33.4 vs 19.6 months, P=0.029), but not overall survival (43.1 vs 33.6 months, P=0.139), in patients with p53 wild-type cancer (n=33). Neither the p53 mutational status nor p73 isoform expression possessed prognostic significance in the examined ovarian cancer cases.\\n\\nCONCLUSION: \u0394133p53 expression was associated with prognosis in the vast majority of ovarian cancer cases, that is, patients with p53 mutant advanced serous carcinomas. Thus, our findings underline the importance of considering the complex p53 regulatory network.", "author" : [{ "dropping-particle" : "", "family" : "Hofstetter", "given" : "G", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Berger", "given" : "a", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Schuster", "given" : "E", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Wolf", "given" : "a", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Hager", "given" : "G", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Vergote", "given" : "I", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Cadron", "given" : "I", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Sehouli", "given" : "J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Braicu", "given" : "E I", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Mahner", "given" : "S", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Speiser", "given" : "P", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Marth", "given" : "C", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Zeimet", "given" : "a G", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Ulmer", "given" : "H", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Zeillinger", "given" : "R", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Concin", "given" : "N", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "British journal of cancer", "id" : "ITEM-1", "issue" : "10", "issued" : { "date-parts" : [["2011"]] }, "page" : "1593-9", "title" : "\u0394133P53 Is an Independent Prognostic Marker in P53 Mutant Advanced Serous Ovarian Cancer.", "type" : "article-journal", "volume" : "105" }, "uris" : ["http://www.mendeley.com/documents/?uuid=7e71cf85-f5da-4359-990c-c5ee2ebd61e7"] }], "mendeley" : { "formattedCitation" : "(84)", "plainTextFormattedCitation" : "(84)", "previouslyFormattedCitation" : "(84)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }}

5.3 Δ40p53α

Δ40p53α can directly transactivate gene and therefore does not systematically act in a dominant-negative manner. Overexpression of Δ40p53α (through the use of a lentivirus) in cells co-expressing p53 isoforms led to the death of WT *TP53* A375 melanoma cell. This is interesting as melanomas, relative to other forms of cancer, have fewer *TP53* mutations. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1038/jid.2013.391", "ISSN" : "1523-1747", "PMID" : "24037342", "abstract" : "The TP53 gene encodes 12 distinct isoforms, some of which can alter p53 activity in the absence of genomic alteration. Endogenous p53 isoforms have been identified in cancers; however, the function of these isoforms remains unclear. In melanoma, the frequency of TP53 mutations is relatively low compared with other cancers, suggesting that these isoforms may have a larger role in regulating TP53 activity. We hypothesized that p53 function and therefore cell fate might be altered by the presence of \u039440p53, an embryonic isoform missing the first 40 N-terminal amino acids of the full-length protein including the transactivation and Mdm2-binding domains. To test this hypothesis, we transduced tumor and normal cells with a lentivirus encoding \u039440p53. We found that exogenous \u039440p53 caused apoptosis and increased the levels of endogenous, activated p53 in both cancerous and non-cancerous cells, which led to significant levels of cell death, particularly in cancer cells. Activated p53 molecules formed nuclear heterotetramers with \u039440p53 and altered downstream p53 transcription target levels including p53-induced protein with death domain and cyclin-dependent kinase inhibitor, p21. \u039440p53 altered the promoter occupancy of these downstream p53 target genes in such a way that it shifted cell fate toward apoptosis and away from cell cycle arrest. We show that tumor suppression by p53 can occur via an alternate route that relies on its interaction with \u039440p53.", "author" : [{ "dropping-particle" : "", "family" : "Takahashi R, Markovic SN, and Scrable HJ", "given" : "", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "J Invest Dermatol.", "id" : "ITEM-1", "issue" : "3", "issued" : { "date-parts" : [["2014"]] }, "page" : "791-800", "title" : "Dominant effects of \u039440p53 on p53 function and melanoma cell fate.", "type" : "article-journal", "volume" : "134" }, "uris" : ["http://www.mendeley.com/documents/?uuid=98a8f6f5-ab81-4b14-8b06-9777836bce26"] }], "mendeley" : { "formattedCitation" : "(85)", "plainTextFormattedCitation" : "(85)", "previouslyFormattedCitation" : "(85)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**

Within hepatocellular cancer cells, it was noted that Δ40p53α is correlated with increased expression of FLp53, and that it promoted a senescent response in hepatocellular cancer cells (p21 was found to be up-regulated to a greater extent). **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1242/jcs.190736", "ISSN" : "14779137", "abstract" : "Splice variants of certain genes impact on genetic biodiversity in mammals. The tumor suppressor TP53 gene (encoding p53) plays an important role in the regulation of tumorigenesis in hepatocellular carcinoma (HCC). \u039440p53\u03b1 is a naturally occurring p53 isoform that lacks the N-terminal transactivation domain, yet little is known about the role of \u039440p53\u03b1 in the development of HCC. Here, we first report on the role of \u039440p53\u03b1 in HCC cell lines. In the TP53+/\u039440 cell clones, clonogenic activity and cell survival dramatically decreased, whereas the percentage of senescence-associated \u03b2-galactosidase (SA-\u03b2-gal)-positive cells and p21 (also known as WAF1, CIP1 and CDKN1A) expression significantly increased. These observations were clearly attenuated in the TP53+/\u039440 cell clones after \u039440p53\u03b1 knockdown. In addition, exogenous \u039440p53 expression significantly suppressed cell growth in HCC cells with wild-type TP53, and in those that were mutant or null for TP53. Notably, \u039440p53\u03b1-induced tumor suppressor activity was markedly attenuated in cells expressing the hot-spot mutant \u039440p53\u03b1-R175H, which lacks the transcription factor activity of p53. Moreover, \u039440p53\u03b1 expression was associated with increased full-length p53 protein expression. These findings enhance the understanding of the molecular pathogenesis of HCC and show that \u039440p53\u03b1 acts as an important tumor suppressor in HCC cells.", "author" : [{ "dropping-particle" : "", "family" : "Ota", "given" : "Akinobu", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Nakao", "given" : "Haruhisa", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Sawada", "given" : "Yumi", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Karnan", "given" : "Sivasundaram", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Wahiduzzaman", "given" : "Md", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Inoue", "given" : "Tadahisa", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kobayashi", "given" : "Yuji", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Yamamoto", "given" : "Takaya", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Ishii", "given" : "Norimitsu", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Ohashi", "given" : "Tomohiko", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Nakade", "given" : "Yukiomi", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Sato", "given" : "Ken", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Itoh", "given" : "Kiyoaki", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Konishi", "given" : "Hiroyuki", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Hosokawa", "given" : "Yoshitaka", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Yoneda", "given" : "Masashi", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Journal of Cell Science", "id" : "ITEM-1", "issue" : "3", "issued" : { "date-parts" : [["2017"]] }, "title" : "\u039440p53\u03b1 suppresses tumor cell proliferation and induces cellular senescence in hepatocellular carcinoma cells", "type" : "article-journal", "volume" : "130" }, "uris" : ["http://www.mendeley.com/documents/?uuid=bb3fbde7-f170-4f51-bd6e-c21fe22c00ea"] }], "mendeley" : { "formattedCitation" : "(86)", "plainTextFormattedCitation" : "(86)", "previouslyFormattedCitation" : "(86)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**

5.4 Additional Relevant Findings

Within colon carcinoma, Fujita *et al* noted that the expression levels of p53β or Δ133p53α isoform may also contribute to the progression of a tumour from a benign state to malignancy. Colon adenomas were associated with higher levels of p53β and reduced levels of Δ133p53α. In colon carcinoma tissues, however, the inverse was witnessed, suggesting that varying transcription rates may play a role in the progression of cancers from a benign state to being malignant. {ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1038/ncb1928", "ISBN" : "1465-7392", "ISSN" : "1476-4679", "PMID" : "19701195", "abstract" : "The finite proliferative potential of normal human cells leads to replicative cellular senescence, which is a critical barrier to tumour progression in vivo. We show that the human p53 isoforms Delta133p53 and p53beta function in an endogenous regulatory mechanism for p53-mediated replicative senescence. Induced p53beta and diminished Delta133p53 were associated with replicative senescence, but not oncogene-induced senescence, in normal human fibroblasts. The replicatively senescent fibroblasts also expressed increased levels of miR-34a, a p53-induced microRNA, the antisense inhibition of which delayed the onset of replicative senescence. The siRNA (short interfering RNA)-mediated knockdown of endogenous Delta133p53 induced cellular senescence, which was attributed to the regulation of p21(WAF1) and other p53 transcriptional target genes. In overexpression experiments, whereas p53beta cooperated with full-length p53 to accelerate cellular senescence, Delta133p53 repressed miR-34a expression and extended the cellular replicative lifespan, providing a functional connection of this microRNA to the p53 isoform-mediated regulation of senescence. The senescence-associated signature of p53 isoform expression (that is, elevated p53beta and reduced Delta133p53) was observed in vivo in colon adenomas with senescent phenotypes. The increased Delta133p53 and decreased p53beta isoform expression found in colon carcinoma may signal an escape from the senescence barrier during the progression from adenoma to carcinoma.", "author" : [{ "dropping-particle" : "", "family" : "Fujita", "given" : "Kaori", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Mondal", "given" : "Abdul M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Horikawa", "given" : "Izumi", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Nguyen", "given" : "Giang H", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kumamoto", "given" : "Kensuke", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Sohn", "given" : "Jane J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bowman", "given" : "Elise D", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Mathe", "given" : "Ewy A", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Schetter", "given" : "Aaron J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Pine", "given" : "Sharon R", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Ji", "given" : "Helen", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Vojtesek", "given" : "Borivoj", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bourdon", "given" : "Jean-Christophe", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lane", "given" : "David P", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Harris", "given" : "Curtis C", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Nature cell biology", "id" : "ITEM-1", "issue" : "9", "issued" : { "date-parts" : [["2009"]] }, "page" : "1135-42", "title" : "p53 isoforms Delta133p53 and p53beta are endogenous regulators of replicative cellular senescence.", "type" : "article-journal", "volume" : "11" }, "uris" : ["http://www.mendeley.com/documents/?uuid=5d4c66ac-e9a1-43c0-bf52-f17f72757143"] }], "mendeley" : { "formattedCitation" : "(48)", "plainTextFormattedCitation" : "(48)", "previouslyFormattedCitation" : "(48)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**

Ectopic expression of the isoforms within squamous cell carcinomas of the head of the neck also occurs – it was established through investigation of 21 tumour samples that the quantity of p53β, p53γ, Δ133p53β and Δ133p53γ isoforms were elevated. 18/20 tumour samples recorded elevated expression of p53β; p53γ was augmented in 5 tumour samples; Δ133p53β in 3 and Δ133p53γ in 4. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1016/j.ejca.2006.10.019", "ISSN" : "0959-8049", "PMID" : "17215121", "abstract" : "Recent data indicate that, similar to p63 and p73, several different p53 isoforms can be produced in humans through alternative initiation of translation, usage of an internal promoter and alternative splicing. These isoforms are reported to have varying functions and expressions. In squamous cell carcinoma of the head and neck (SCCHN), disruption of the p53 pathway is one of the most common genetic alterations. However, to our knowledge, no studies regarding the expression of different p53 isoforms in SCCHN have so far been performed. We screened for the expression of different p53 isoforms in SCCHN and clinically normal oral epithelia using nested RT-PCR. p53 mRNA was expressed in all tumours, all matched clinically normal tissue adjacent to the tumour and in buccal mucosa from healthy volunteers. Of the novel isoforms, p53beta was detected in the majority of samples analysed, and all of the recently described isoforms were also detected in at least some tumour and normal epithelium samples, with the exception of Deltap53 isoforms. We conclude that p53 variant mRNAs are expressed in both normal oral stratified epithelium and SCCHN. Improvements in methodologies and reagents to detect and quantify p53 isoform expression in clinical material will be required to correlate p53 status with clinical outcomes.", "author" : [{ "dropping-particle" : "", "family" : "Boldrup", "given" : "Linda", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bourdon", "given" : "Jean-Christophe", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Coates", "given" : "Philip J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Sj\u00f6str\u00f6m", "given" : "Bj\u00f6rn", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Nylander", "given" : "Karin", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "European journal of cancer (Oxford, England : 1990)", "id" : "ITEM-1", "issue" : "3", "issued" : { "date-parts" : [["2007"]] }, "page" : "617-23", "title" : "Expression of p53 isoforms in squamous cell carcinoma of the head and neck.", "type" : "article-journal", "volume" : "43" }, "uris" : ["http://www.mendeley.com/documents/?uuid=3508c8fd-87f7-4464-bc50-52d3883d5bad"] }], "mendeley" : { "formattedCitation" : "(87)", "plainTextFormattedCitation" : "(87)", "previouslyFormattedCitation" : "(87)" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**

6- Clinical Applications of the p53 Isoforms – A Potential Predictive Biomarker?

The utility of p53 family members in cancer diagnosis and predicting therapy response has been considered in recent studies. (85, 92-94).

A recurring theme identified within this review is the specific abnormal expression ratio of p53 isoforms in certain cancers. The mechanisms with which these contribute to the development is still under research, but it provides a solid platform for the discussion of potential treatments. The differing, relative elevated expression of certain isoforms in diverse cancers could be used as a marker for severity. To use an example, in colon adenoma's, a potential observation that levels of p53β rising and reducing levels of Δ133p53α could be a clinical indicator that the tumour is progressing to malignancy and so treatment could be tailored accordingly to prepare for malignancy. However, the use of isoforms may not just be relegated to treating the outcome of abnormal expression; but rather, the abnormalities in the isoforms. The rectification of p53 isoform expression could perhaps hold the key to treating and perhaps even reversing the genesis of tumours – a potential example is reintroducing or promoting the transcription of p53γ in breast cancer. As mentioned above, p53γ improves prognosis in breast cancer patients and so research into how p53γ expression can be promoted and the effects it could have in vivo may be worthwhile and part of future studies.

Having demonstrated our ability to modulate, in an inducing or inhibiting manner, the expression of p53 isoforms and thus the nature of p53-mediated cellular effects, the next step is to translate this into the clinic. The p53 isoforms present a fresh weapon in the arsenal of personalised medicine. Advances in methods of biopsy would allow extraction of a tumour sample. The collected sample would be processed via established assays involving techniques such as qPCR and immunostaining, allowing for characterisation of the patient's 'p53 isoform status'. This information would be inputted into a modelling system to determine the best treatment plan in the context of the patient's p53 isoform status, TP53 mutation status, additional genetic background (PIK3CA, PTEN, Ras, EGFR, myc….) and stage of disease, among others. Treatment may include modulation of p53 isoforms for a direct effect via siRNA treatment (an area of intense interest) or bolstering the efficacy of treatments such as the conformation restoring drug APR-246.

One of the major questions asked in recent times is whether the isoforms should be analysed one at a time, or in combination with one another. This review encapsulates that the p53 isoforms are not individual entities – they all combine to orchestrate the adapted cell response to the multiple cell signals. It is the balance of isoform expression that determines the fate of a cell, and so it may seem obvious that all the isoforms should be determined together.

7- ***Expert Commentary:***

TP53 mutation status does not allow to predict patient clinical outcome and to make treatment decision. The recent findings that p53 isoforms are associated to patient clinical outcome in WT and mutant TP53 patients indicate that the p53 isoforms may be the missing link to associate p53 status to clinical outcome. The p53 isoform expressions may be an indicator of the state of pluripotency and ability to resist or be sensitive to different treatments. The determination of p53 isoform expression in the cancer cells and tumour stroma may enable to define most efficient treatment (precision medicine). In this aim, it is essential to determine the cell signals integrated by the different p53 isoforms and how p53 isoforms convey the cell signals to the different gene expression machineries (transcriptional machinery, microRNA processing machinery, splicing machinery (spliceosomes), translation machinery (ribosome), protein degradation machinery (proteasomes), protein/RNA trafficking (subcellular localisation and transport within cells), metabolism, paracrine signalling) to induce a cellular response precisely adapted to the cell context and organ function. It is a daunting task that require scientific rigor, the development of novel scientific tools (antibodies and cellular and animal models) and to work hand-in hand with clinicians to better design clinical studies. The p53 isoform specific antibodies currently in development and characterisation will facilitate rapid progress. Recently published and on-going studies making use of new p53 isoform specific antibodies or qPCR or RNAscope reveal the strong potential of the p53 isoforms to improve cancer treatment. (87, 105)

8- *Five Year View – The Next Step*

Numerous genetic factors predisposing their carriers to common disease (e.g. cancer, diabetes type 2, cardiovascular disease) have been reported in the specialised literature. A significant proportion of these factors are, in fact, polymorphic variants of genes coding for key proteins of DNA repair and maintenance of genomic integrity, including *TP53*. (95-99) Panels of markers for carriership of factors associated with the capacity to detect and repair DNA damage and for self-renewal of cell populations are currently being developed and tested in order to assess their applicability to assessment of risk for various diseases and conditions. (100-102) Different p53 isoforms combination promote different p53-mediated cell responses (proliferation, repair, senescence, motility, differentiation, de-differentiation, trans-differentiation, cell death,…) (103). Recently, it has been proposed that alterations in the activity of splicing factors and in the production of key splice variants of several pivotal genes, including TP53, may have direct effects on cellular senescence and, respectively, the aging of organisms. (104) It is likely that further evidence of abnormal expression in isoforms should be uncovered within the next five years and discussion over how the p53 isoforms could be used in tandem with the clinic will begin to emerge; not only for cancer, but with other potential clinical applications such as regenerative medicine.

Key Issues

- Altogether there are 12 p53 isoforms translated from 9 mRNA transcripts as a result of alternate promotor usage, alternative splicing and alternative initiation of translation. **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" :

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- p53α protein consists of 7 functional domains – transactivation domains 1 and 2 (interact with the RNA-Polymerase II transcription machinery), proline domain, DNA binding domain (where 90% of mutations occur), NLS, tetramerisation domain and DNA damage recognition domain.
- The p53 isoforms mRNA are co-expressed in normal tissue in a tissue-dependent manner and eloquently explain the vast array of physiological roles that p53 pathway is associated with.
- The functions of the p53 isoform result from co-expression ratios (combination of p53 isoforms), rather than individual influence.

- p53 isoforms mRNA are abnormally expressed in a wide range of cancer and can be a useful tool as a predictive biomarker to foretell the nature of a malignancy and to predict response to treatment. Examples include elevated levels of Δ133p53β in many breast cancers.
- The isoforms could thus hold potential in clinical environments, whereby association of certain isoforms expression/absence to certain cancers could allow for a degree of predictably and thus tailor treatment accordingly.

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