[Cell Cycle 3:7, 905-911; July 2004]; ©2004 Landes Bioscience

Review: Spotlighht on p53

KeePin' the p53 Family in Good Shape

Fiamma Mantovani[1,2]
Monica Gostissa[1,†]
Licio Collavin[1,2]
Giannino Del Sal[1,2,*]

[1]Laboratorio Nazionale C.I.B.; Area Science Park; Trieste, Italy

[2]Dipartimento di Biochimica; Biofisica e Chimica delle Macromolecole; Università di Trieste; Trieste, Italy

[†]Present address: Children's Hospital; 1 Blackfan Circle; Boston, Massachusetts USA

*Correspondence to: Giannino Del Sal; Laboratorio Nazionale C.I.B.; Area Science Park; Padriciano 99; I-34012 Trieste, Italy; Tel.: 39040398992; Fax: 39040398990; Email: delsal@lncib.it

Received 05/27/04; Accepted 06/02/04

Previously published online as a *Cell Cycle* E-Publication:
http://www.landesbioscience.com/journals/cc/abstract.php?id=999

KEY WORDS

p53, p73, tumor suppressor, Pin1, prolyl isomerization

ACKNOWLEDGEMENTS

We apologize to all colleagues whose work has not been cited owing to space limitations. We wish to thank the scientists of LNCIB for helpful discussion.

The work of G.D.S. is supported by grants from the Associazione Italiana per la Ricerca sul Cancro (AIRC) and Telethon.

ABSTRACT

The tumor suppressor p53 and the prolyl isomerase Pin1 are both highly connected proteins, lying at the crossroads between many signaling pathways that control cell proliferation and transformation. By catalyzing conformational changes in a large number of phosphorylated proteins, Pin1 has been implicated in the regulation of major cellular events, such as cell cycle progression, transcription, proliferation and differentiation. Recently, a role for Pin1 has emerged also in the DNA damage response, through modulation of p53 functions upon genotoxic stress. A further level of control has now been unveiled by showing that also the p53 sibling p73 requires Pin1 for its apoptotic activity.

© 2004 Landes Bioscience. Do Not Distribute

INTRODUCTION

The p53 tumor suppressor has long been recognized as a key factor in safeguarding over the genome's integrity and in protecting it from potentially dangerous mutations that might arise upon exposure to DNA damaging agents.

p53 is a tetrameric transcription factor that becomes active following treatment of a cell with a wide range of stimuli impinging on genomic stability, and that is able to specifically bind to target sequences within the promoters of a continuously expanding set of genes.[1-4] Most of these downstream targets are either involved in mediating cell cycle arrest or in inducing programmed cell death, the final outcome of p53 response being determined by the coordinate expression of specific gene subsets.[2,5,6] Given its potent growth suppressive activity, improper activation of p53 must be carefully avoided in normal growing cells. p53 functions are indeed controlled through multiple mechanisms, involving modulation of protein stability, post-translational modifications and interaction with other cellular partners.[7,8] While, for purpose of research, which needs to be reductive, we generally try to analyze separately the various aspects of p53 regulation, they are instead tightly interrelated. The importance of p53 in preventing cancer onset has made it the subject of intense research efforts, yielding an impressive wealth of knowledge about its biochemical and biological functions. Still, however, this vast amount of data may result somehow confusing and even contradictory, raising the need of organizing the information into a coordinate and comprehensive picture of p53 action within the cell.

MECHANISMS OF REGULATION OF p53 FUNCTIONS

p53 has an intrinsically short half-life, estimated to less than 30 minutes in fibroblasts,[9] that depends on efficient degradation by the ubiquitin-proteasome system. Master regulator of p53 stability is its downstream target Mdm2, which interacts with p53 and mediates its ubiquitination inducing its degradation.[10] Moreover, Mdm2 can also directly inhibit p53 transcriptional activity through binding its N-terminal transactivation domain,[11-13] and possibly affecting its subcellular localization.[14] p53, in fact, possesses both nuclear localization (NLS) and nuclear export (NES) signals,[15] but the NES appears to be masked in the active, tetrameric form of the protein.[16] Mdm2-mediated ubiquitination results in NES exposure and p53 export to the cytoplasm.[16-18] While nuclear export does not seem to be required for p53 degradation,[19,20] cytoplasmic sequestration may well be an alternative mechanism to restrain p53 function.

Following cell exposure to DNA damaging agents, such as UV, ionizing radiation or chemotherapeutic drugs, p53 becomes rapidly stabilized and functionally activated, as a consequence of post-translational modifications affecting both its N-terminal transactivation and C-terminal oligomerization domains.[21,22] In particular, DNA damage triggers the

activation of the ATM/ATR kinases, which directly phosphorylate p53 on Ser15 and mediate activation of the downstream kinases Chk1 and 2 that in turn target the neighboring residue Ser20. These modifications render p53 unable to bind Mdm2, resulting in stabilization of the protein. Cellular stress causes also in the activation of other kinases, such as JNK and MAPK, which are responsible for modifying several residues within p53 N- and C-terminus.[21] Moreover, p53 can be activated by modifications of C-terminal lysine residues, such as acetylation mediated by the acetyl-transferases p300/CPB and PCAF,[22] or sumoylation.[23]

Until some years ago, the model for p53 activation that could be drawn from the available evidences was, if not simple, quite straight. Phosphorylation of p53 N-terminus would be responsible for relieving the interaction with Mdm2. On the other hand, modifications in the C-terminus would contribute to turn the protein from a "latent" to an "active" DNA binder, rendering it more able to transactivate its downstream targets. Nowadays, however, the story appears far more complex, since new players have been added to the picture and more subtle correlations have emerged between different post-translational modifications.

In the last year two novel ubiquitin-ligases for p53 have been identified, which are encoded respectively by the newly discovered Pirh2 gene[24] and by the mammalian homologue of COP1, a gene involved in plant photomorphogenesis.[25] Both Pirh2 and COP1 regulate p53 levels in physiological contexts and, similar to Mdm2, these two genes are downstream p53 targets, establishing a peculiar negative feedback circuitry for regulation of the tumor suppressor. Whether Mdm2, Pirh2 and COP1 share overlapping functions or can be differentially activated and regulated still awaits elucidation. However, the fact that Mdm2 knock-out mice are early embryonic lethal and that this effect can be rescued by contemporary deletion of the p53 gene[26,27] suggests that, at least in mice, Mdm2 functions cannot be completely substituted by other proteins. Moreover, while contemporary ablation of Mdm2 and Pirh2 expression show additive effects, assigning them to parallel yet separated pathways, Mdm2 and COP1 can instead work cooperatively.[25] Further experimental work will be required to elucidate these and other issues.

Recently, also the model of "latent" p53 has been challenged. Several evidences suggested that p53 DNA binding activity is influenced by structural features of the target DNA within a defined chromatin context[28-30] rather than by C-terminal modifications. In particular, the role of acetylation is somehow controversial,[28,31] and p300/CBP and PCAF seem to contribute to activation of p53-responsive genes in at least two ways, by directly modifying p53 and by promoting histone acetylation and chromatin access at p53-bound promoters.[29,31,32] Moreover, an unpredicted role for p300 has emerged following the demonstration that, while Mdm2 preferentially catalyzes the addition of a single ubiquitin moiety on several C-terminal lysine residues in p53,[33] the contemporary action of Mdm2 and p300 results in the formation of the polyubiquitin tree necessary for degradation.[34] Other reports, however, demonstrated that Mdm2 itself, when present in large amounts, is able to effectively polyubiquitinate p53.[35] It is conceivable that the relative levels of Mdm2 and p300, as well as the pattern of p53 post-translational modifications, are crucial in determining p53 fate. Accordingly, N-terminal phosphorylation is not only required for relieving p53 interaction with Mdm2 but can favor subsequent C-terminal acetylation,[36] and deacetylation of C-terminal lysines is a prerequisite for p53 ubiquitination and degradation.[37,38]

In addition to its roles in DNA damage response, a functional cooperation between p53 and TGF-β has been recently revealed, which relies on association between p53 and the SMAD complexes to activate TGF-β target genes both in Xenopus laevis and in mammalian cells.[39] These findings imply a role for p53 in mediating the cytostatic effects of TGF-β signaling, and suggest potential functions of p53 in development, which remind of the other family members activities. The molecular changes required to activate these functions of p53 are presently unknown. Dynamic phosphorylation and acetylation of p53 are likely to play important roles during DNA damage response as well as upon other signaling events, and post-translational modifications at specific sites may then affect the overall conformation of the protein, thereby altering its ability to interact with other factors and influencing modifications to other, even distant, sites.

THE PROLYL ISOMERASE Pin1

Phosphorylation-directed prolyl-isomerization has recently emerged as a potent and widespread post-translational signaling mechanism. In a few years frame, a growing number of reports have unveiled the elusive mechanisms capable of transducing specific phosphorylation events into conformational changes of important cellular proteins such as cdc25c, β-catenin and Myc, thereby regulating their functions. Triggering these reactions is an enzyme called Pin1,[40] which belongs to a family of prolyl isomerases (PPIases). These are chaperone enzymes able to switch the peptide bond between an amino acid and the adjacent proline from the *cis* to the *trans* conformation and vice versa.[41,42] Among PPIases, Pin1 has a unique two-domain structure: an N-terminal WW domain specifically recognizes Serine-Proline and Threonine-Proline motifs in which the first amino acid is phosphorylated (pSer/pThr-Pro),[43-45] and a C-terminal catalytic domain then isomerizes the peptidyil-prolyl bond.[46] Pin1 therefore specifically induces conformational changes following Ser/Thr-Pro directed phosphorylation of its substrates, thus affecting their phosphorylation status, turnover, catalytic activity, protein-protein interactions and subcellular localization, ultimately regulating their functions in the cell. Pin1 recognition sites are generated by Proline-directed kinases, pivotal players in signaling pathways regulating cell proliferation.[47] Among them are cyclin-dependent kinases (CDKs), which govern cell cycle transitions, and many mitogen-activated protein kinases (MAPKs), as well as GSK-3β that functions in cell signaling.[48] The importance of isomerizing Ser/Thr-Pro bonds depends on the ability of kinases such as MAPK and CDK2, as well as phosphatases such as PP2A, to recognize these sites only in the *trans* conformation.[49,50] Acting in concert with specific kinases and phosphatases, Pin1 behaves as a central transducer of different signals and modulates the function of several substrates involved in regulating diverse cellular processes, including transcription and splicing (PolII,[51-53] c-Jun,[54] c-Myc[55]), proliferation (cdc25C, Myt1, Wee1[56-58]), signaling (β-catenin,[59] NF-κB,[60] cyclin D1[61]), DNA damage responses (p53,[62-64] p73[65] (for recent reviews on Pin1, see ref. 66). Pin1 also targets tau, a protein forming part of the neuronal cytoskeleton, which is hyper-phosphorylated in patients suffering from Alzheimer's disease (AD) and could therefore be involved in the pathogenesis of AD.[67-69]

p53 ACTIVATION UPON GENOTOXIC STRESS REQUIRES Pin1

Both p53 and Pin1 are highly connected proteins, participating to many signaling pathways that control cell proliferation and

© 2004 Landes Bioscience. Do Not Distribute

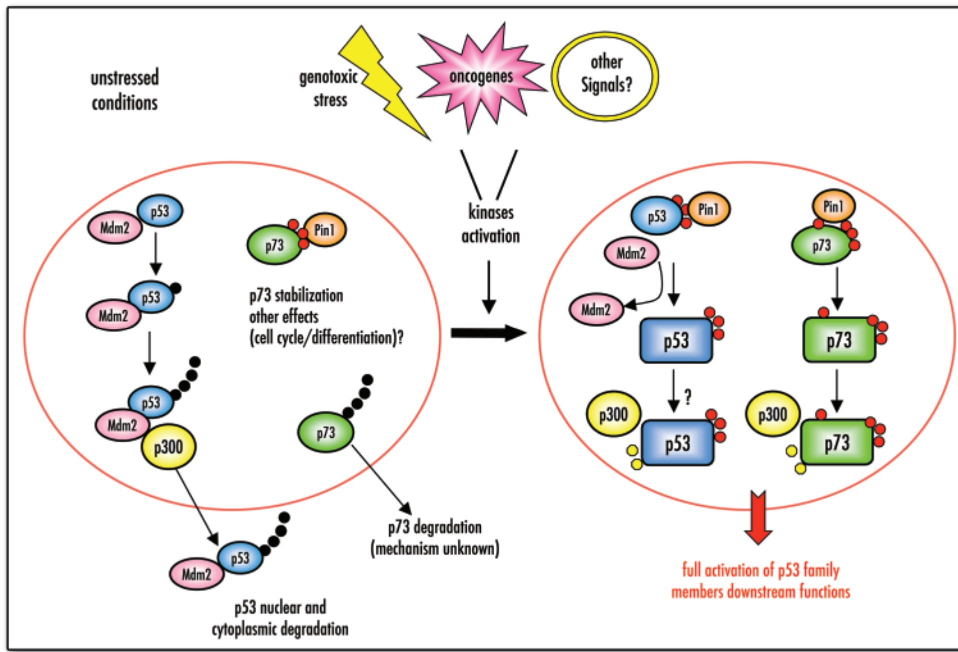

Figure 1. Phosphorylation-dependent prolyl isomerization catalyzed by Pin1 regulates the activities of wild-type p53 and p73. Under normal conditions p53 does not bind to Pin1 and it is targeted by Mdm2 and p300, that induce its ubiquitin-mediated degradation; in contrast, p73 is bound and stabilized by Pin1, which might also regulate its cell cycle-dependent functions. Following genotoxic stress, and possibly also upon other signals, activation of cellular kinases enhance the association of both p53 and p73 with Pin1. As a result, p53 and p73 become stabilized and fully activated as a result of detachment from Mdm2 and increased binding to p300, respectively.

transformation. It was therefore conceivable for the prolyl isomerase to be also involved in DNA damage response, possibly by regulation of the p53 tumor suppressor. Indeed, it has been demonstrated that DNA damage-induced phosphorylation of p53 promotes its binding to Pin1. The interaction between p53 and Pin1, mediated by the N-terminal WW domain of the isomerase, is exquisitely dependent on p53 phosphorylation. While almost undetectable in normal growing conditions, it can be promoted by several stimuli activating p53, such as gamma and UV irradiation, treatment with chemotherapeutic drugs and overexpression of activated oncogenes (Fig. 1). Different DNA-damaging agents result in phosphorylation of different Ser/Thr-Pro motifs in p53, rendering them sites for Pin1 binding. For example UV irradiation or treatment of cells with doxorubicin recruits Pin1 to Ser33, Thr81 and Ser315 of p53, while γ-irradiation stimulates also Pin1 interaction with Ser46.[62-64] At present, the questions as to which phosphorylation events are important in different conditions, and how Pin1 activity at different Ser/Thr-Pro sites impinges on the overall p53 conformation, are still difficult to answer. However, it is clear that the catalytic activity of Pin1 can modify p53 conformation and this mediates efficient detachment of Mdm2 from p53, resulting in full stabilization of the protein.[64] Accordingly, p53 accumulation following UV irradiation is reduced in the absence of Pin1 and its half-life is shortened. However, an effect of Pin1 on DNA binding and transactivation capability of p53 has also been observed, which does not simply depend on stabilization. In agreement with these findings, p53 downstream responses, such as transcriptional activation of endogenous target genes as well as induction of apoptosis and growth arrest, are impaired in cells lacking Pin1.[62-64]

Clearly, the exact molecular mechanisms underlying Pin1-mediated regulation of p53 functions still need to be analyzed in detail. In particular, it will be interesting to determine whether, similar to Mdm2, Pin1-induced conformational shift affects the binding of p53 with some of its numerous partners, thus modulating its functions. In fact, the problem of how specificity is achieved in the p53 response remains

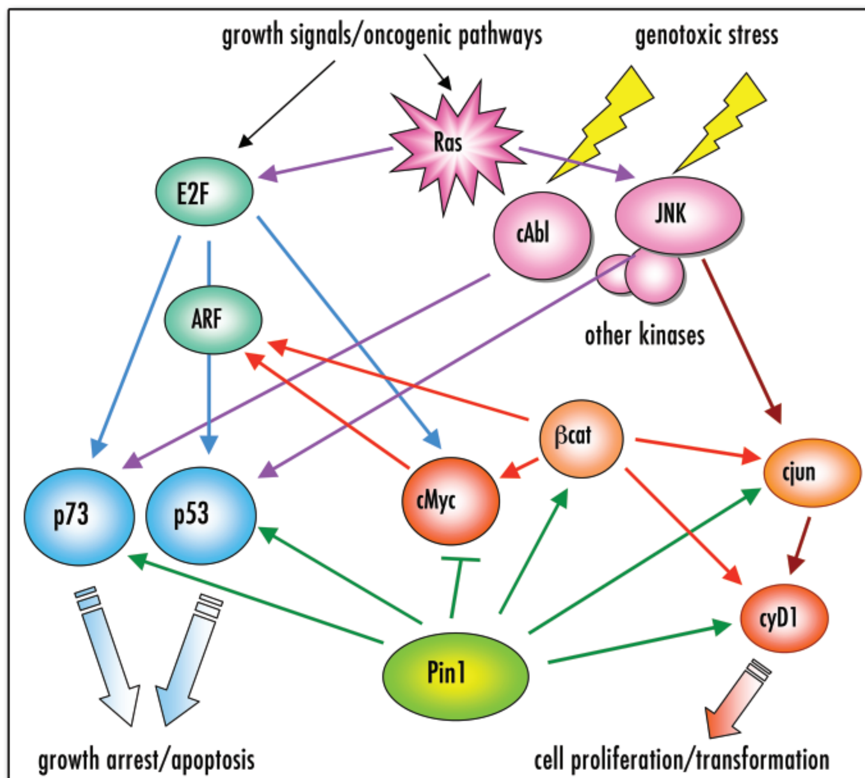

Figure 2. Crosstalk between tumor promoting and tumor suppressive substrates of Pin1. Pin1 triggers prolyl isomerization of many cellular proteins upon their signal-dependent phosphorylation, thereby regulating their localization, stability and catalytic activity. Some of these substrates, such as c-Jun, β-catenin and their transcriptional target cyclin D1 have positive roles in proliferation. Others, such as p53 and p73 have growth suppressive effects, while c-Myc can induce either proliferation or apoptosis depending on the cellular context. However, tumor promoting and tumor suppressive pathways catalyzed by Pin1 are tightly interrelated.

open. It is believed that the choice between p53-induced cell cycle arrest and apoptosis depends on the type and intensity of the DNA damage, as well as on the particular cell type. Several evidences indicate that p53 can be directed toward pro-apoptotic targets by interaction with cofactors, such as ASPP[70] or its homologues p73 and p63.[71] Pin1 might play a role in this context, and indeed we have observed, at least under some conditions, that Pin1 may preferentially increase transactivation of p53-responsive genes involved in apoptosis.[64] In addition, Pin1 might possibly affect transcriptional-independent apoptotic activities of p53. On the other hand, recent data have suggested that the role of p53 as a caretaker in maintaining genomic stability is separable from its apoptotic activity,[72] supporting a multistep tumor suppression mechanism adopted by p53. The contribution of Pin1 in controlling genomic stability, both p53-dependent and independent, is surely worth investigating.

When considering the functional aspects of the p53/Pin1 interaction, it is important to keep in mind that Pin1 is an enzyme with a large number of possible substrates. The overall outcomes of its action depend on which subset of substrates is expressed and phosphorylated in a particular cell type and in a given moment. This may help explaining subtle differences that have been reported for Pin1-mediated effects in different cell types as well as upon different stimuli. For instance, p53 stabilization as induced by doxorubicin does not seem to be significantly reduced in the absence of Pin1, nevertheless p53 responses, in particular growth arrest, are impaired under these conditions.[63]

Therefore, Pin1 can be envisioned as a catalyst for integrating signals deriving from different kinase pathways, a fine-tuner of p53 activity and, probably, of the global cellular environment.

Pin1 UNVEILS THE MECHANISM OF p73 ACTIVATION

After having long been neglected as minor siblings of p53 in inducing cell death, p73 and p63 have recently been found to be required for the ability of p53 to promote apoptosis in mouse fibroblasts.[71] On the other hand, p73 is capable of inducing apoptosis in response to both E2F overexpression and chemotherapeutic compounds also in the absence of p53.[73-75] This represents an important anti-tumorigenic safeguard mechanism and a determinant of cellular sensitivity to oncotoxic drugs in tumors lacking functional p53.[74-76] The high degree of structural and functional similarity[77] among p53 family members would argue for common regulatory pathways integrating their activities, and some similarities have indeed appeared. ASPP1 and ASPP2 have been recently indentified as common regulators of the apoptotic functions of p53, p63 and p 73.[78] E2F-1 and c-Abl induce both p53 and p73, albeit through different mechanisms.[79] Finally, the p300 acetyltransferase stimulates p53-dependent transcriptional activity,[80-82] and it has been also shown to acetylate p73, thereby inducing its recruitment to proapoptotic promoters[83] (for an updated review, see Blandino and Dobbelstein, pp. 886–894).

Recently, phosphorylation-induced prolyl isomerization mediated by Pin1 has emerged as an important common mechanism activating both p53 and p73 upon certain types of stress[62-65] (Fig. 1). Differently to p53 however, a consistent fraction of p73 in unstressed cells is found associated with Pin1,[65] and this binding is restricted to the long isoforms alpha and beta. Whether this association plays a role in regulating cell cycle-dependent activities of p73 remains to be determined. Genotoxic stimuli, mediated by the stress-activated c-Abl kinase, further increase the association of p73 with the prolyl isomerase. Although this Tyrosine-kinase cannot directly phosphorylate Pin1-binding sites, it nonetheless promotes Threonine phosphorylation of p73 by p38 MAP kinase,[84] which in turn stimulates p73 binding to Pin1.[65] Probably other, as yet unidentified, Pro-directed kinases become also involved in promoting the p73-Pin1 connection in response to specific stimuli. Stress-dependent activation of c-Abl/MAPK induces p73 accumulation[84,85] and, indeed, this requires Pin1. Similar to p53, Pin1 affects also p73 transcriptional activity, and it appears to be required for efficient recruitment of p73 to the proapoptotic promoter p53AIP1 upon doxorubicin treatment.[65] Notably, this activity has been shown to rely on c-Abl dependent phosphorylation of p73[86] and subsequent acetylation by p300.[83] Biochemical dissection of this mechanism revealed that the conformational shift induced by Pin1 on p73 stimulates binding to p300, thus enhancing p73 acetylation and activation of proapoptotic targets. Accordingly, also p73 apoptotic activity is dependent on the action of the prolyl isomerase.[65]

Intriguingly, p300 appears to play a role also in Pin1-induced stabilization of p73.[65] However, our knowledge of the regulation of p73 turnover is still vague: in contrast to p53, Mdm2 fails to target p73 for nuclear export or degradation, rather it has been reported to increase its stability.[87,88] The complex interplay between p53 family members, p300, Mdm2 and Pin1 surely awaits elucidation. Despite no experimental data are presently available to support this hypothesis, it is possible that Pin1 influences also the interaction between p300 and p53. The action of Pin1, promoting p53 binding to p300 while at the same time displacing Mdm2, might therefore favor the acetyltransferase versus the ubiquitin-ligase activity of p300, further contributing to full p53 activation.

p53, p73 AND Pin1: DUAL ROLES IN ONCOGENESIS

A growing number of reports point towards a role for Pin1 as a transducer of many different signals inside the cell, coordinating various metabolic pathways. Its ability to influence the activity of a number of different substrates with opposing functions (Fig. 2) indicates that this enzyme is likely to exert multiple effects, which may be dependent on the cellular context. In this respect, despite Pin1 being an indispensable positive regulator of the apoptotic response induced by p53 and p73 upon genotoxic stress, Pin1-null mice do not spontaneously develop tumors, although sensitivity to mutagenic treatments has not been challenged. On the other hand, Pin1 deficiency is associated with proliferative defects, and results in low levels of the cell cycle regulator cyclin D1.[40,61,89] In addition Pin1 stabilizes β-catenin, and its overexpression in both breast[54] and HCC cancers[90] has been shown to correlate with increased β-catenin levels.[59,90] Upregulation of Pin1 has been detected also in some cases of other tumors such as prostate,[91] cervix, brain, lung and colon.[92]

Further studies are needed in order to better understand the physiological functions of Pin1 in normal cells and to distinguish them from the effects of its deregulated expression in pathological conditions. In fact, sustained Pin1 overexpression does not cause growth alterations in cell culture (Mantovani F, Del Sal G, unpublished observations). However, it can be easily envisaged how elevated levels of Pin1, possibly due to deregulation of the Rb/E2F pathway[93] upon early transforming events,[94] could catalyze tumorigenic processes. This might occur when activation of oncogenic pathways lead to phosphorylation of either a growth promoting substrate of Pin1, for instance β-catenin or cyclin D1, or an antiapoptotic target such as NF-κB.[60] Pin1 has indeed been reported to facilitate

© 2004 Landes Bioscience. Do Not Distribute

transformation by oncogenic Neu or Ras in mammary epithelial cells.[93] However, enforced expression of Pin1 in a wild-type (wt) p53 background would be expected to stimulate p53 indirectly, through the concomitant activation of either β-catenin or NF-κB pathways.[95-97] Rather, Pin1 overexpression is likely to represent a cancer risk factor when p53 is not functional, due to mutation or inactivation. Consistent with its different effects on multiple substrates, variations in Pin1 levels could be critical at different stages of tumor progression. While its silencing could represent a selective advantage at early stages, leading to inhibition of wild-type p53 and p73 activities as well as stabilization of c-Myc,[55] its overexpression could synergize with later events occurring upon p53 mutation. At present however, although p53 mutations represent the most frequent genetic alteration found in human cancer, occurring in about 50% of all cases, the status of p53 in tumors overexpressing Pin1 has not been assessed. The majority of p53 mutations are missense, giving rise to full-length proteins that are unable of sequence-specific DNA binding and of activating p53 target genes, leading to loss of wild-type activities. A critical question is whether mutant p53 (mutp53) forms are capable of interacting with Pin1. This appears to be indeed the case for mutp53 proteins derived from tumor cell lines. Intriguingly, in most cases an interaction can occur even in the absence of DNA damage, suggesting that mutp53 proteins are constitutively phosphorylated on critical Ser/Thr-Pro sites upon activation of oncogenic pathways (Gostissa M, Del Sal G, unpublished observations). Mutations disrupting established Pin1 binding sites on p53 have been observed in human cancers,[98] however these are relatively rare events,[99] and in fact no single amino acid substitution has been found sufficient for abolishing the Pin1-p53 interaction, which involves the contribution of different Ser/Thr-Pro sites. Another intriguing possibility is that mutations create new Pin1 binding sites in p53, as might result from the frequent Arg-Ser substitution at position 249 identified in hepatocellular carcinomas, and caused by dietary exposure to aflatoxin B_1.[100,101]

The effects of this interaction could however differ from those exerted on the wild-type protein. Most mutp53 forms are indeed defective for transactivation, and, failing to activate the Mdm2 negative loop, result intrinsically stable.[102,103] One important feature of the oncogenic activity of p53 mutants is their ability to interfere with the functions of wtp53 and of the other family members by a dominant negative mechanism[104-106] that involves heteromerization.[107] In addition, mutp53 could interact with other proteins, and the structural changes triggered by Pin1 on wild-type, and possibly also on mutp53, might affect these interactions.

Besides competitive effects, some mutant p53 proteins have been proposed to gain additional biochemical and biological properties, through which they might actively contribute to cancer progression.[108-110] Indeed, conformational-defective p53 mutants have been reported to increase resistance of tumor cells to anticancer treatment,[111,112] and some mutp53-expressing tumors are more aggressive and have a worse prognosis than p53-null cancers.[113,114] The ability of tumor-derived p53 mutants to associate with p73 and p63, inhibiting their transcriptional and growth suppressive activities, has been proposed as one of the possible molecular events underlying the chemoresistant phenotype.[75] Since it has been suggested that the conformation of mutant p53 can influence the interaction with p73[74,115] and given that Pin1 also interacts with p73, elucidation of the interplay between these proteins could better clarify this issue.

Adding a further level of complexity, the TP73 gene, besides the transcriptionally active TAp73, encodes a set of amino-terminally truncated dominant negative ΔNp73 proteins. These lack the transactivation domain and display antiapoptotic features,[116] and some forms have been found expressed in cancer cells.[116-118] However, only one study has identified expression of a ΔNp73 form as a strong adverse prognostic marker in neuroblastoma.[119] Although the Ser/Thr-Pro sites involved in recognition of TAp73 by Pin1 are conserved in ΔNp73, that can indeed interact with Pin1 when overexpressed (Mantovani F, Del Sal G, unpublished results), the phosphorylation state of the endogenous proteins in normal and neoplastic cells has not been investigated. Assuming that Pin1 can stabilize both TA and ΔN forms of p73, the final outcome of the interaction will be dictated by the cellular context, that is, by the TA:ΔN ratio. Interestingly, both TA and ΔNp73 proteins play roles in neuronal development.[120-123] Since neuronal-specific activities of Pin1 have also been reported,[67-69] future studies could unveil an effect of Pin1 either in normal neuronal development or in the genesis of tumors such as neuroblastoma, where the transcriptional ratio TA:ΔN has been shown to by strongly modulated in favor of ΔNp73 through selective promoter methylation.[119]

Recently, attention has been paid also to p53 variants, although their roles and regulation have not been investigated in detail, and the results still remain controversial.[124] It appears that the expression of several isoforms is a common trait of the p53 family,[77,124] and growing evidences indicate that the stress-induced, growth suppressive activities of the full-length forms can be modulated, either positively or negatively, by truncated isoforms. These are likely to perform distinct functions on their own, by controlling physiological processes such as differentiation. In this respect, it is tempting to predict that the activities of all p53 family members, including p53, p73 and p63 protein variants, can be modulated through phosphorylation-dependent prolyl-isomerization.

CONCLUDING REMARKS

Although interaction with Pin1 invariably leads to a conformational change in its substrates, the consequences can be different depending on the cellular context, which is a paradigm in the case of p53. Prolyl isomerization by Pin1 regulates the timing of p53 activation rendering it suitable for subsequent modifications, including conformation-selective dephosphorylation at specific sites and interaction with DNA and cofactors. However, the final outcome varies according to tissue- and signal-dependent expression of the protein partners involved.

Pin1 is an enzyme whose activity depends on phosphorylation of its substrates, and has pleiotropic effects that appear contradictory. While its absence is associated with defects in proliferation, on the other hand Pin1 is required for physiological destabilization of c-Myc.[55] Tumor-associated myc alleles bear mutations at the site of Pin1-mediated dephosphorylation,[125] however Pin1 is overexpressed in several tumors. Consistent with its reported role in inducing stabilization and nuclear localization of the p65 subunit of NF-κB, a subgroup of breast cancers overexpressing Pin1 shows constitutive nuclear expression of p65, nonetheless the NF-κB pathway appears to be normal in Pin1 KO mice.[60] Despite Pin1 might represent a good prognostic marker in some human cancers, genetic evidence of a role for this enzyme in oncogenesis is lacking. A possible involvement of Pin1 in modulating tumor growth could be unmasked upon deregulation of oncogenic or tumor suppressor pathways, and more data are needed to shed light on the specific roles that Pin1 might play depending on the particular genetic background. Given its

© 2004 Landes Bioscience. Do Not Distribute

capacity to enhance oncogenic pathways, Pin1 has been suggested as a potential target for anticancer therapy. This appears counterintuitive, since Pin1 is also required for p53 and p73-dependent sensitivity to genotoxic stress, and its inhibition is associated with resistance to apoptosis as induced by irradiation and chemotherapy.[62-65] The feasibility of finding therapeutical opportunities to block tumor progression depends on our knowledge of the complex interplay between tumor promoting and tumor suppressive substrates of Pin1 at critical stages of specific cancer types.

In conclusion, not only Pin1 has an apparent dual role in cell transformation, but also some of its target proteins, such as p53, p73 and Myc, display both positive and negative functions on cell growth and survival. The future direction is to develop an integrated view of these networks, since keeping in good shape the *p53* family, as well as other targets of Pin1, can be important to prevent cancer and other diseases.

References

1. El-Deiry WS. The role of p53 in chemosensitivity and radiosensitivity. Oncogene 2003; 22:7486-95.
2. Oren M. Decision making by p53: Life, death and cancer. Cell Death Differ 2003; 10:431-42.
3. Mirza A, Wu Q, Wang L, McClanahan T, Bishop WR, Gheyas F, et al. Global transcriptional program of *p53* target genes during the process of apoptosis and cell cycle progression. Oncogene 2003; 22:3645-54.
4. Kho PS, Wang Z, Zhuang L, Li Y, Chew JL, Ng HH, et al. p53-regulated transcriptional program associated with genotoxic stress-induced apoptosis. J Biol Chem 2004; I279:21183-92.
5. Vousden KH, Lu X. Live or let die: The cell's response to p53. Nat Rev Cancer 2002; 2:594-604.
6. Fridman JS, Lowe SW. Control of apoptosis by p53. Oncogene 2003; 22:9030-40.
7. Ryan KM, Phillips AC, Vousden KH. Regulation and function of the p53 tumor suppressor protein. Curr. Opin. Cell Biol 2001; 13:332-7.
8. Gostissa M, Hofmann TG, Will H, Del Sal G. Regulation of p53 functions: Let's meet at the nuclear bodies. Curr Opin Cell Biol 2003; 15:351-7.
9. Maltzman W, Czyzyk L. UV irradiation stimulates levels of p53 cellular tumor antigen in nontransformed mouse cells. Mol Cell Biol 1984; 4:1689-94.
10. Yang Y, Li CC, Weissman AM. Regulating the p53 system through ubiquitination. Oncogene 2004; 23:2096-106.
11. Chen J, Lin J, Levine AJ. Regulation of transcription functions of the p53 tumor suppressor by the mdm-2 oncogene. Mol Med 1995; 1:142-52.
12. Thut CJ, Goodrich JA, Tjian R. Repression of p53-mediated transcription by MDM2: A dual mechanism. Genes Dev 1997; 11:1974-86.
13. Mirnezami AH, Campbell SJ, Dary M, Primrose JN, Johnson PW, Blaydes JP. Hdm2 recruits a hypoxia-sensitive corepressor to negatively regulate p53-dependent transcription. Curr Biol 2003; 13:1234-9.
14. Roth J, Dobbelstein M, Freedman DA, Shenk T, Levine AJ. Nucleo-cytoplasmic shutling of the mdm2 oncoprotein regulates the levels of the p53 protein via a pathway used by the human immunodeficiency virus rev protein. EMBO J 1998; 17:554-64.
15 Middeler G, Zerf K, Jenovai S, Thulig A, Tschodrich-Rotter M, Kubitscheck U, et al. The tumor suppressor p53 is subject to both nuclear import and export, and both are fast, energy-dependent and lectin-inhibited. Oncogene 1997; 14:1407-17.
16 Stommel JM, Marchenko ND, Jimenez GS, Moll UM, Hope TJ, Wahl GM. A leucine-rich nuclear export signal in the p53 tetramerization domain: Regulation of subcellular localization and p53 activity by NES masking. EMBO J 1999; 18:1660-72.
17. Lohrum MA, Woods DB, Ludwig RL, Balint E, Vousden KH. C-terminal ubiquitination of p53 contributes to nuclear export. Mol Cell Biol 2001; 21:8521-32.
18. Geyer RK, Yu ZK, Maki CG. The MDM2 RING-finger domain is required to promote p53 nuclear export. Nat Cell Biol 2000; 2:569-73.
19. Xirodimas DP, Stephen CW, Lane DP. Cocompartmentalization of p53 and Mdm2 is a major determinant for Mdm2-mediated degradation of p53. Exp Cell Res 2001; 270:66-77.
20. Joseph TW, Zaika A, Moll UM. Nuclear and cytoplasmic degradation of endogenous p53 and HDM2 occurs during down-regulation of the p53 response after multiple types of DNA damage. Faseb J 2003; 17:1622-30.
21. Xu Y. Regulation of p53 responses by post-translational modifications. Cell Death Differ 2003; 10:400-3.
22. Brooks CL, Gu W. Ubiquitination, phosphorylation and acetylation: The molecular basis for p53 regulation. Curr Opin Cell Biol 2003; 15:164-71.
23. Melchior F, Hengst L. SUMO-1 and p53. Cell Cycle 2002; 1:245-9.
24. Leng RP, Lin Y, Ma W, Wu H, Lemmers B, Chung S, et al. Pirh2, a p53-induced ubiquitin-protein ligase, promotes p53 degradation. Cell 2003; 112:79-1.
25. Dornan D, Wertz I, Shimizu H, Arnott D, Frantz GD, Dowd P, et al. The ubiquitin ligase COP1 is a critical negative regulator of p53. Nature 2004; 429:86-92.
26. Jones SN, Roe AE, Donehower LA, Bradley A. Rescue of embryonic lethality in Mdm2-deficient mice by absence of p53. Nature. 1995; 378:206-8.
27. Montes de Oca Luna R, Wagner O, Lozano G. Rescue of early embryonic lethality in mdm2-deficient mice by deletion of p53. Nature 1995; 378:203-6.
28. Espinosa JM, Emerson BM. Transcriptional regulation by p53 through intrinsic DNA/chromatin binding and site-directed cofactor recruitment. Mol Cell 2001; 8:57-69.
29. Kaeser MD, Iggo RD. Chromatin immunoprecipitation analysis fails to support the latency model for regulation of p53 DNA binding activity in vivo. Proc Natl Acad Sci USA 2002; 99:95-100.
30. McKinney K, Prives C. Efficient specific DNA binding by p53 requires both its central and C-terminal domains as revealed by studies with high-mobility group 1 protein. Mol Cell Biol 2002; 22:6797-808.
31. Luo J, Nikolaev AY, Imai S, Chen D, Su F, Shiloh A, et al. Negative control of p53 by Sir2alpha promotes cell survival under stress. Cell 2001; 107:137-48.
32. Liu G, Xia T, Chen X. The activation domains, the proline-rich domain, and the C-terminal basic domain in p53 are necessary for acetylation of histones on the proximal p21 promoter and interaction with p300/CREB-binding protein. J Biol Chem 2003; 278:17557-65.
33. Lai Z, Ferry KV, Diamond MA, Wee KE, Kim YB, Ma J, et al. Human mdm2 mediates multiple mono-ubiquitination of p53 by a mechanism requiring enzyme isomerization. J Biol Chem 2001; 276:31357-67.
34. Grossman SR, Deato ME, Brignone C, Chan HM, Kung AL, Tagami H, et al. Polyubiquitination of p53 by a ubiquitin ligase activity of p300. Science 2003; 300:342-4.
35. Li M, Brooks CL, Wu-Baer F, Chen D, Baer R, Gu W. Mono- versus polyubiquitination: Differential control of p53 fate by Mdm2. Science 2003; 302:1972-5.
36. Lambert PF, Kashanchi F, Radonovich MF, Shiekhattar R, Brady JN. Phosphorylation of p53 serine 15 increases interaction with CBP. J Biol Chem 1998; 273:33048-53.
37. Ito A, Kawaguchi Y, Lai CH, Kovacs JJ, Higashimoto Y, Appella E, et al. MDM2-HDAC1-mediated deacetylation of p53 is required for its degradation. EMBO J 2002; 21:6236-45.
38. Li M, Luo J, Brooks CL, Gu W. Acetylation of p53 inhibits its ubiquitination by Mdm2. J Biol Chem 2002; 277:50607-11.
39. Cordenonsi M, Dupont S, Maretto S, Insinga A, Imbriano C, Piccolo S. Links between tumor suppressors: P53 is required for *TGF*-β gene responses by cooperating with Smads. Cell 2003; 113:301-14.
40. Lu KP, Hanes SD, Hunter T. A human peptidyl-prolyl isomerase essential for regulation of mitosis. Nature 1996; 380:544-7.
41. Schmid FX. Protein folding. Prolyl isomerases join the fold. Curr Biol 1995; 5:993-4.
42. Hunter T. Prolyl isomerases and nuclear function. Cell 1998; 92:141-3.
43. Lu PJ, Zhou XZ, Shen M, Lu KP. Function of WW domains as phosphoserine- or phosphothreonine-binding modules. Science 1999; 283:1325-8.
44. Verdecia MA, Bowman ME, Lu KP, Hunter T, Noel JP. Structural basis for phosphoserine-proline recognition by group IV WW domains. Nat Struct Biol 2000; 7:639-43.
45. Wintjens R, Wieruszeki JM, Drobecq H, Rousselot-Pailley P, Buee L, Lippens G, et al. {super1}H NMR study on the binding of Pin1 WW domain with phosphothreonine peptides. J Biol Chem 2001; 19:19.
46. Ranganathan R, Lu KP, Hunter T, Noel JP. Structural and functional analysis of the mitotic rotamase Pin1 suggests substrate recognition is phosphorylation dependent. Cell 1997; 89:875-86.
47. Yaffe MB, Schutkowski M, Shen M, Zhou XZ, Stukenberg PT, Rahfeld JU, et al. Sequence-specific and phosphorylation-dependent proline isomerization: A potential mitotic regulatory mechanism. Science 1997; 278:1957-60.
48. Lu KP, Liou YC, Zhou XZ. Pinning down proline-directed phosphorylation signaling. Trends Cell Biol 2002; 12:164-72.
49. Brown NR, Noble ME, Endicott JA, Johnson LN. The structural basis for specificity of substrate and recruitment peptides for cyclin-dependent kinases. Nat Cell Biol 1999; 1:438-43.
50. Weiwad M, Kullertz G, Schutkowski M, Fischer G. Evidence that the substrate backbone conformation is critical to phosphorylation by p42 MAP kinase. FEBS Lett 2000; 478:39-42.
51. Xu YX, Hirose Y, Zhou XZ, Lu KP, Manley JL. Pin1 modulates the structure and function of human RNA polymerase II. Genes Dev 2003; 17:2765-76.
52. Kops O, Zhou XZ, Lu KP. Pin1 modulates the dephosphorylation of the RNA polymerase II C-terminal domain by yeast Fcp1. FEBS Lett 2002; 513:305-11.
53. Wu X, Wilcox CB, Devasahayam G, Hackett RL, Arevalo-Rodriguez M, Cardenas ME, et al. The Ess1 prolyl isomerase is linked to chromatin remodeling complexes and the general transcription machinery. Embo J 2000; 19:3727-38.
54. Wulf GM, Ryo A, Wulf GG, Lee SW, Niu T, Petkova V, et al. Pin1 is overexpressed in breast cancer and cooperates with Ras signaling in increasing the transcriptional activity of c-Jun towards cyclin D1. Embo J 2001; 20:3459-72.
55. Yeh E, Cunningham M, Arnold H, Chasse D, Monteith T, Ivaldi G, et al. A signalling pathway controlling c-Myc degradation that impacts oncogenic transformation of human cells. Nat Cell Biol 2004; 6:308-18.
56. Shen M, Stukenberg PT, Kirschner MW, Lu KP. The essential mitotic peptidyl-prolyl isomerase Pin1 binds and regulates mitosis-specific phosphoproteins. Genes Dev 1998; 12:706-20.
57. Zhou XZ, Kops O, Werner A, Lu PJ, Shen M, Stoller G, et al. Pin1-dependent prolyl isomerization regulates dephosphorylation of Cdc25C and tau proteins. Mol Cell 2000; 6:873-83.
58. Stukenberg PT, Kirschner MW. Pin1 acts catalytically to promote a conformational change in Cdc25. Mol Cell 2001; 7:1071-83.
59. Ryo A, Nakamura M, Wulf G, Liu Y-C, Lu KP. Pin1 regulates turnover and subcelllular localization of β-catenin by inhibiting its interaction with APC. Nat Cell Biol 2001; 3:793-801.

©2004 Landes Bioscience. Do Not Distribute.

60. Ryo A, Suizu F, Yoshida Y, Perrem K, Liou YC, Wulf G, et al. Regulation of NF-κB signaling by Pin1-dependent prolyl isomerization and ubiquitin-mediated proteolysis of p65/RelA. Mol Cell 2003; 12:1413-26.
61. Liou YC, Ryo A, Huang HK, Lu PJ, Bronson R, Fujimori F, et al. Loss of Pin1 function in the mouse causes phenotypes resembling cyclin D1-null phenotypes. Proc Natl Acad Sci USA 2002; 99:1335-40.
62. Wulf GM, Liou YC, Ryo A, Lee SW, Lu KP. Role of Pin1 in the regulation of p53 stability and p21 transactivation, and cell cycle checkpoints in response to DNA damage. J Biol Chem 2002; 277:47976-9.
63. Zheng H, You H, Zhou XZ, Murray SA, Uchida T, Wulf G, et al. The prolyl isomerase Pin1 is a regulator of p53 in genotoxic response. Nature 2002; 419:849-53.
64. Zacchi P, Gostissa M, Uchida T, Salvagno C, Avolio F, Volinia S, et al. The prolyl isomerase Pin1 reveals a mechanism to control p53 functions after genotoxic insults. Nature 2002; 419:853-7.
65. Mantovani F, Piazza S, Gostissa M, Strano S, Zacchi P, Mantovani R, et al. Pin1 links the activities of c-Abl and p300 in regulating p73 function. Molecular Cell 2004; 14:625-36.
66. Ryo A, Liou YC, Lu KP, Wulf G. Prolyl isomerase Pin1: A catalyst for oncogenesis and a potential therapeutic target in cancer. J Cell Sci 2003; 116:773-83.
67. Liou YC, Sun A, Ryo A, Zhou XZ, Yu ZX, Huang HK, et al. Role of the prolyl isomerase Pin1 in protecting against age-dependent neurodegeneration. Nature 2003; 424:556-61.
68. Lu PJ, Wulf G, Zhou XZ, Davies P, Lu KP. The prolyl isomerase Pin1 restores the function of Alzheimer-associated phosphorylated tau protein. Nature 1999; 399:784-8.
69. Holzer M, Gartner U, Stobe A, Hartig W, Gruschka H, Bruckner MK, et al. Inverse association of Pin1 and tau accumulation in Alzheimer's disease hippocampus. Acta Neuropathol (Berl) 2002; 104:471-81.
70. Samuels-Lev Y, O'Connor DJ, Bergamaschi D, Trigiante G, Hsieh JK, Zhong S, et al. ASPP proteins specifically stimulate the apoptotic function of p53. Mol Cell 2001; 8:781-94.
71. Flores ER, Tsai KY, Crowley D, Sengupta S, Yang A, McKeon F, et al. p63 and p73 are required for p53-dependent apoptosis in response to DNA damage. Nature 2002; 416:560-4.
72. Liu G, Parant JM, Lang G, Chau P, Chavez-Reyes A, El-Naggar AK, et al. Chromosome stability, in the absence of apoptosis, is critical for suppression of tumorigenesis in Trp53 mutant mice. Nat Genet 2004; 36:63-8.
73. Irwin M, Marin MC, Phillips AC, Seelan RS, Smith DI, Liu W, et al. Role for the p53 homologue p73 in E2F-1-induced apoptosis. Nature 2000; 407:645-8.
74. Bergamaschi D, Gasco M, Hiller L, Sullivan A, Syed N, Trigiante G, et al. p53 polymorphism influences response in cancer chemotherapy via modulation of p73-dependent apoptosis. Cancer Cell 2003; 3:387-402.
75. Irwin MS, Kondo K, Marin MC, Cheng LS, Hahn WC, Kaelin WG. Chemosensitivity linked to p73 function. Cancer Cell 2003; 3:403-10.
76. Stiewe T, Putzer BM. Role of the p53-homologue p73 in E2F1-induced apoptosis. Nat Genet 2000; 26:464-9.
77. Levrero M, De Laurenzi V, Costanzo A, Gong J, Wang JY, Melino G. The p53/p63/p73 family of transcription factors: Overlapping and distinct functions. J Cell Sci 2000; 113:1661-70.
78. Bergamaschi D, Samuels Y, Jin B, Duraisingham S, Crook T, Lu X. ASPP1 and ASPP2: Common activators of p53 family members. Mol Cell Biol 2004; 24:1341-50.
79. Lohrum MA, Vousden KH. Regulation and activation of p53 and its family members. Cell Death Differ 1999; 6:1162-8.
80. Avantaggiati ML, Ogryzko V, Gardner K, Giordano A, Levine AS, Kelly K. Recruitment of p300/CBP in p53-dependent signal pathways. Cell 1997; 89:1175-84.
81. Gu W, Roeder RG. Activation of p53 sequence-specific DNA binding by acetylation of the p53 C-terminal domain. Cell 1997; 90:595-606.
82. Lill NL, Grossman SR, Ginsberg D, DeCaprio J, Livingston DM. Binding and modulation of p53 by p300/CBP coactivators. Nature 1997; 387:823-7.
83. Costanzo A, Merlo P, Pediconi N, Fulco M, Sartorelli V, Cole PA, et al. DNA damage-dependent acetylation of p73 dictates the selective activation of apoptotic target genes. Mol Cell 2002; 9:175-86.
84. Sanchez-Prieto R, Sanchez-Arevalo VJ, Servitja JM, Gutkind JS. Regulation of p73 by c-Abl through the p38 MAP kinase pathway. Oncogene 2002; 21:974-9.
85. Gong JG, Costanzo A, Yang HQ, Melino G, Kaelin Jr WG, Levrero M, et al. The tyrosine kinase c-Abl regulates p73 in apoptotic response to cisplatin-induced DNA damage. Nature 1999; 399:806-9.
86. Yuan ZM, Shioya H, Ishiko T, Sun X, Gu J, Huang YY, et al. p73 is regulated by tyrosine kinase c-Abl in the apoptotic response to DNA damage. Nature 1999; 399:814-7.
87. Ongkeko WM, Wang XQ, Siu WY, Lau AW, Yamashita K, Harris AL, et al. MDM2 and MDMX bind and stabilize the p53-related protein p73. Curr Biol 1999; 9:829-32.
88. Zeng X, Chen L, Jost CA, Maya R, Keller D, Wang X, et al. MDM2 suppresses p73 function without promoting p73 degradation. Mol Cell Biol 1999; 19:3257-66.
89. Fujimori F, Takahashi K, Uchida C, Uchida T. Mice lacking Pin1 develop normally, but are defective in entering cell cycle from G_0 arrest. Biochem Biophys Res Commun 1999; 265:658-63.
90. Pang R, Yuen J, Yuen MF, Lai CL, Lee TK, Man K, et al. PIN1 overexpression and *β-catenin* gene mutations are distinct oncogenic events in human hepatocellular carcinoma. Oncogene 2004; 23:4182-6.
91. Ayala G, Wang D, Wulf G, Frolov A, Li R, Sowadski J, et al. The prolyl isomerase Pin1 is a novel prognostic marker in human prostate cancer. Cancer Res 2003; 63:6244-51.
92. Bao L, Kimzey A, Sauter G, Sowadski JM, Lu KP, Wang DG. Prevalent overexpression of prolyl isomerase pin1 in human cancers. Am J Pathol 2004; 164:1727-37.
93. Ryo A, Liou YC, Wulf G, Nakamura M, Lee SW, Lu KP. PIN1 is an *E2F* target gene essential for Neu/Ras-induced transformation of mammary epithelial cells. Mol Cell Biol 2002; 22:5281-95.
94. Nevins JR. The Rb/E2F pathway and cancer. Hum Mol Genet 2001; 10:699-703.
95. Damalas A, Ben-Ze'ev A, Simcha I, Shtutman M, Leal JF, Zhurinsky J, et al. Excess β-catenin promotes accumulation of transcriptionally active p53. EMBO J 1999; 18:3054-63.
96. Fujioka S, Schmidt C, Sclabas GM, Li Z, Pelicano H, Peng B, et al. Stabilization of p53: A novel mechanism for proapoptotic function of NF-κB. J Biol Chem 2004; 279:27549-59.
97. Saegusa M, Hashimura M, Kuwata T, Hamano M, Okayasu I. β-catenin simultaneously induces activation of the p53-p21^{WAF1} pathway and overexpression of cyclin D1 during squamous differentiation of endometrial carcinoma cells. Am J Pathol 2004; 164:1739-49.
98. Sun XF, Johannsson O, Hakansson S, Sellberg G, Nordenskjold B, Olsson H, et al. A novel p53 germline alteration identified in a late onset breast cancer kindred. Oncogene 1996; 13:407-11.
99. Hernandez-Boussard T, Rodriguez-Tome P, Montesano R, Hainaut P. IARC p53 mutation database: A relational database to compile and analyze p53 mutations in human tumors and cell lines. International Agency for Research on Cancer. Hum Mutat 1999; 14:1-8.
100. Li D, Cao Y, He L, Wang NJ, Gu JR. Aberrations of *p53* gene in human hepatocellular carcinoma from China. Carcinogenesis 1993; 14:169-73.
101. Staib F, Hussain SP, Hofseth LJ, Wang XW, Harris CC. TP53 and liver carcinogenesis. Hum Mutat 2003; 21:201-16.
102. Buschmann T, Minamoto T, Wagle N, Fuchs SY, Adler V, Mai M, et al. Analysis of JNK, Mdm2 and p14^{ARF} contribution to the regulation of mutant p53 stability. J Mol Biol 2000; 295:1009-21.
103. Midgley CA, Lane DP. p53 protein stability in tumour cells is not determined by mutation but is dependent on Mdm2 binding. Oncogene 1997; 15:1779-89.
104. Kern SE, Pietenpol JA, Thiagalingam S, Seymour A, Kinzler KW, Vogelstein B. Oncogenic forms of p53 inhibit *p53*-regulated gene expression. Science 1992; 256:827-30.
105. Strano S, Munarriz E, Rossi M, Cristofanelli B, Shaul Y, Castagnoli L, et al. Physical and functional interaction between p53 mutants and different isoforms of p73. J Biol Chem 2000; 275:29503-12.
106. Strano S, Fontemaggi G, Costanzo A, Rizzo MG, Monti O, Baccarini A, et al. Physical interaction with human tumor-derived p53 mutants inhibits p63 activities. J Biol Chem 2002; 277:18817-26.
107. Unger T, Mietz JA, Scheffner M, Yee CL, Howley PM. Functional domains of wild-type and mutant p53 proteins involved in transcriptional regulation, transdominant inhibition, and transformation suppression. Mol Cell Biol 1993; 13:5186-94.
108. Prives C, Hall PA. The p53 pathway. J Pathol 1999; 187:112-26.
109. Sigal A, Rotter V. Oncogenic mutations of the p53 tumor suppressor: The demons of the guardian of the genome. Cancer Res 2000; 60:6788-93.
110. Blagosklonny MV. p53 from complexity to simplicity: Mutant p53 stabilization, gain-of-function, and dominant-negative effect. Faseb J 2000; 14:1901-7.
111. Aas T, Borresen AL, Geisler S, Smith-Sorensen B, Johnsen H, Varhaug JE, et al. Specific P53 mutations are associated with de novo resistance to doxorubicin in breast cancer patients. Nat Med 1996; 2:811-4.
112. Blandino G, Levine AJ, Oren M. Mutant p53 gain of function: Differential effects of different p53 mutants on resistance of cultured cells to chemotherapy. Oncogene 1999; 18:477-85.
113. Murphy KL, Dennis AP, Rosen JM. A gain of function p53 mutant promotes both genomic instability and cell survival in a novel p53-null mammary epithelial cell model. Faseb J 2000; 14:2291-302.
114. Dittmer D, Pati S, Zambetti G, Chu S, Teresky AK, Moore M, et al. Gain of function mutations in p53. Nat Genet 1993; 4:42-46.
115. Marin MC, Jost CA, Brooks LA, Irwin MS, O'Nions J, Tidy JA, et al. A common polymorphism acts as an intragenic modifier of mutant p53 behaviour. Nat Genet 2000; 25:47-54.
116. Stiewe T, Putzer BM. Role of p73 in malignancy: Tumor suppressor or oncogene? Cell Death Differ. 2002; 9:237-45.
117. Putzer BM, Tuve S, Tannapfel A, Stiewe T. Increased ΔN-p73 expression in tumors by upregulation of the E2F1-regulated, TA-promoter-derived ΔN'-p73 transcript. Cell Death Differ 2003; 10:612-4.
118. Stiewe T, Tuve S, Peter M, Tannapfel A, Elmaagacli AH, Putzer BM. Quantitative TP73 transcript analysis in hepatocellular carcinomas. Clin Cancer Res 2004; 10:626-33.
119. Casciano I, Mazzocco K, Boni L, Pagnan G, Banelli B, Allemanni G, et al. Expression of ΔNp73 is a molecular marker for adverse outcome in neuroblastoma patients. Cell Death Differ 2002; 9:246-51.
120. Meyer G, Perez-Garcia CG, Abraham H, Caput D. Expression of p73 and Reelin in the developing human cortex. J Neurosci 2002; 22:4973-86.
121 Abraham H, Perez-Garcia CG, Meyer G. p73 and reelin in cajal-retzius cells of the developing human hippocampal formation. Cereb Cortex 2004; 14:484-95.
122. Miller FD, Pozniak CD, Walsh GS. Neuronal life and death: An essential role for the p53 family. Cell Death Differ 2000; 7:880-8.
123. De Laurenzi V, Raschella G, Barcaroli D, AnnicchiaricoPetruzzelli M, Ranalli M, Catani MV, et al. Induction of neuronal differentiation by p73 in a neuroblastoma cell line. J Biol Chem 2000; 275:15226-31.
124. Courtois S, de Fromentel CC, Hainaut P. p53 protein variants: Structural and functional similarities with p63 and p73 isoforms. Oncogene 2004; 23:631-8.
125. Pulverer BJ, Fisher C, Vousden K, Littlewood T, Evan G, Woodgett JR. Site-specific modulation of c-Myc cotransformation by residues phosphorylated in vivo. Oncogene 1994; 9:59-70.

©2004 Landes Bioscience. Do Not Distribute