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Modulation of immune responses by the tumor suppressor p53

Julie Lowe, Maria Shatz, Michael A. Resnick*, Daniel Menendez*

Chromosome Stability Section, Laboratory of Molecular Genetics, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC 27709, United States of America

Abstract

The commonly held view of the tumor suppressor p53 as a regulator of cell proliferation, apoptosis and senescence has expanded greatly in recent years to cover many biological processes as well as external and internal stress responses. Since the discovery over 30 years ago of p53 as a cellular protein that co-precipitates with the large T antigen of Simian Virus SV40, there has been an intertwining of p53 activities with immune-related processes, especially as relates to cancer. A variety of interactions between the p53 and the immune stress systems are currently being addressed that suggest opportunities to utilize p53 in modulating immunological activities. Here, we discuss those interactions along with implications for human disease.

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***Corresponding Authors:** Michael A. Resnick, email: resnick@niehs.nih.gov; Daniel Menendez, email: menendez@niehs.nih.gov

List of abbreviations: ChIP, chromatin immunoprecipitation; CPEB, cytoplasmic polyadenylation element binding protein; HSC, hematopoietic stem cell; ISRE, interferon-sensitive response element; miRNAs, microRNAs; NOS, nitrogen species; p53RE, p53 response element; ROS, reactive oxygen species; TLR, Toll-like receptor; TNFα, tumor necrosis factor alpha; wild type, WT

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p53 in the immune response: the ace up the sleeve

The tumor suppressor p53 is a sequence-specific transcription factor that is activated in response to various cellular stresses such as DNA damage, oncogene over-expression and associated uncontrolled cell proliferation. p53 functions mainly as a transcription factor and is a key component in preventing cancer development through regulation of apoptosis, cell cycle and senescence genes thereby helping to maintain genome stability within an organism. Alterations of p53 function through mutation or misregulation in the p53 network are common features in human cancers with over 80-90% of tumors having an altered p53 pathway [1, 2]. However, in recent years this "guardian of the genome" has been established as central to many additional biological processes including autophagy, fertility, "stemness," nutritional responses, development of cell motility/migration and cell-cell communication [3-5]. Recent studies have emphasized the role of p53 in modulating the human immune system, one of the most important defenses against external as well as internal threats including tumorigenesis.

In this review we explore the interactions between p53 and the immune system. The focus is mainly on the role that wild type (WT) p53 plays in immune-related processes such as inflammation, innate and adaptive responses as well as functional interactions of p53 with NF-kB, which is considered a key regulator in immune responses. Emphasis is placed on p53 as a transcription factor in modulating expression of target genes involved

in immunity pathways (see Figure 1).

The immune system is a collection of biological processes whose tasks in preventing disease include identification and destruction of pathogens and tumor cells. Given the broad diversity in p53 controls and functions, it is not surprising that p53 touches multiple aspects of immunity. For example, DNA damage can trigger p53 responses that help orchestrate clearance of damaged cells via the innate immune system [6, 7], which can influence tumor suppression. In addition p53 is up-regulated at sites of inflammation [8, 9], likely due to the appearance of reactive oxygen species (ROS) that might damage DNA and proteins. The seminal work of Xue and colleagues [10] demonstrated the functional relationship between p53 and the immune system in a mouse liver carcinoma model containing a "switchable" p53. In this study they showed that p53 and the immune system can cooperate to promote tumor clearance. They found that p53-dependent tumor regression was related to induction of a tumor cell-senescence program, associated differentiation, up-regulation of pro-inflammatory cytokines and activation of innate immune response.

p53 also appears to be involved during the generation of immune cells. In agreement with its role as a modulator in stem cell appearance, p53 can limit expansion of hematopoietic stem cells (HSC) [11, 12]. The HSC are multipotent, self-renewing progenitor cells for all differentiated blood cells in the lymphoid and myeloid lineages. Some responses during the interplay of p53 with the inflammatory and innate immune response appear also to be evolutionarily conserved across species. Recently, Fuhrman and collaborators [13] found that in the worm *Caenorhabditis elegans* the nucleolar proteins and p53 transcriptional activity play a role in defense responses against bacterial infections. They observed that activation of innate immunity through inhibition of nucleolar proteins requires potential immune effectors whose expression in worms in response to stress is regulated by the p53 homologue CEP-1 .

Inflammation and p53: maintaining homeostasis

Inflammation, a common immune response, is a protective first-responder attempt to remove injurious stimuli and to initiate healing. It is a complex signal-mediated reaction by vascular tissues to cellular insults such as pathogens and infectious agents, toxins, physical stress or damaged cells. Acute inflammation is an important mode of immune response, while chronic inflammation can cause tissue destruction or even autoimmunity.

p53 has several roles in inflammation including modifying cell growth and cellular behavior in response to DNA and inflammatory stressors. p53 is activated by DNA damage that is induced by both ROS and reactive nitrogen species (NOS) that are produced during inflammation [5, 14]. Also, the regulation of cellular ROS levels has been suggested to involve interaction of WT p53 with its Δ40-p53 and Δ133-p53 isoforms [14]. Mice that constitutively express an analogue of human Δ133-p53 (Δ122-p53) develop an autoimmune phenotype characterized by increased production of autoantibodies and pro-inflammatory cytokines [15]. p53 is also responsive to other inflammatory stressors such as TNFα [16].

As a transcription factor, p53 can modulate expression

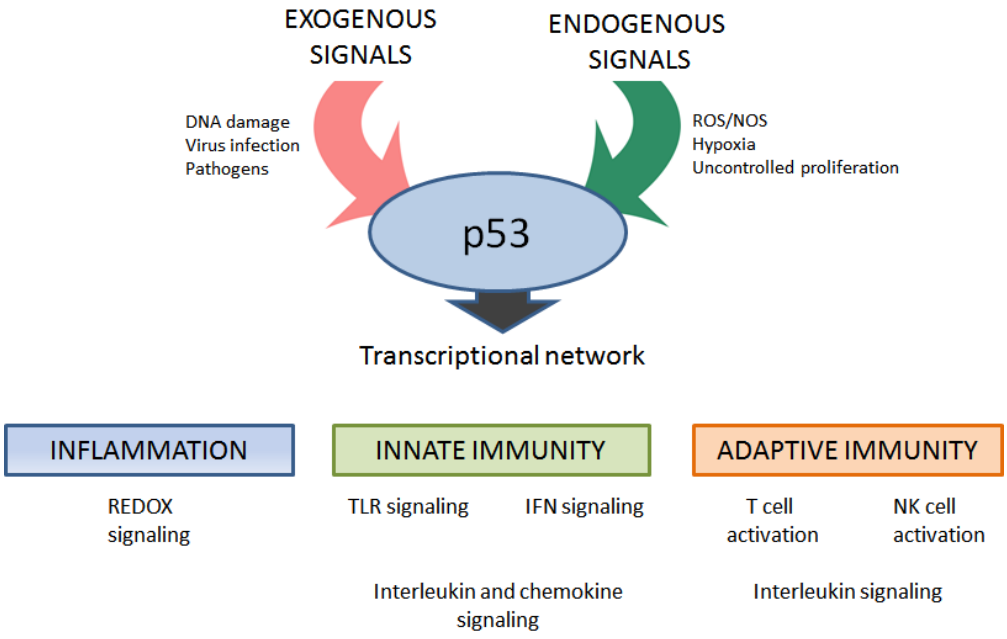

Figure 1. Interactions of p53 with the immune system.

of several genes encoding enzymes involved in both production or elimination of reactive species contributing to inflammation including, for example, up-regulation of the antioxidant glutathione peroxidase (*GPX1*) [17], aldehyde dehydrogenase 4 (*ALDH1*) [18] and cyclooxygenase 2 (*COX2*) [19]. p53 also transactivates genes encoding pro-oxidant or redox active proteins, including the ROS generating enzyme proline oxidase (*POX*) [20] and *NCF2/p67hox* [21]. NCF2 is the cytosolic subunit of the NADPH oxidase enzyme complex involved in production of $NADP^+$ and superoxide from molecular oxygen. Also, p53 can mediate repression of genes affecting ROS repression including the inducible nitric oxide synthase *NOS2* genes and the mitochondrial superoxide dismutase *SOD2* [22].

Thus, p53 can play a significant role in modulating intracellular ROS/NOS levels to aid in appropriate balance of the inflammatory responses. In addition, since p53 is subject to modifications in the presence of reactive compounds, it can be considered a cellular sensor of redox changes [23]. Modulations of the p53 redox state can affect cell signaling as well as influence cell and tissue integrity [24].

The relationship between p53 and pathogenesis of inflammation-associated cancer and other immune related diseases extends beyond induction/restriction of inflammatory responses, all of which can be affected by p53 expression, mutation or alterations in its regulatory pathway. For example, there is greater invasion of inflammatory and fibroblast cells into IR damaged tissues in p53-null compared to WT mice [25]. Several autoimmune disorders characterized by increased or deregulated inflammation including rheumatoid arthritis, ulcerative colitis and lupus (systemic lupus erythematosus-SLE) exhibit elevated p53 protein or defective p53 functions [26-31], tying p53 dysfunction to autoimmunity. Furthermore, increased p53 protein expression within inflamed tissues has been associated with the appearance of somatic dominant-negative p53 mutations [29, 32, 33].

Innate and adaptive immune responses in p53 null mice can be skewed toward pro-inflammation, suggesting p53 may act as a negative regulator of inflammation (34-40). Additionally, p53 null mice are susceptible to autoimmune diseases including collagen-induced arthritis [31] and experimentally induced autoimmune encephalitis [34]. Also, p53 can directly repress *IL-4* [35], *IL-6* [36] and *IL-12* [37] promoter activities in murine cells, consistent with the view that p53 may inhibit autoimmune inflammation by suppressing the expression of inflammatory cytokine encoding genes. Moreover, as discussed below, p53 may inhibit inflammation through suppressing the mostly pro-inflammatory NF-kappa B transcription factor [38, 39].

p53, viral infections and immune responses

Up-regulation of p53 in response to viral infections is a part of host cell defenses. For example, increased p53-dependent apoptosis can reduce viral replication [40]. Furthermore, "super p53 mice" that carry an extra p53 gene have slightly increased immune response over that in mice with 2 copies, and they are more resistant to viral infections than p53 null mice, which is due in part to the absence of a p53 apoptotic response in null mice [41].

Since the discovery over 30 years ago of p53 as a binding partner of SV40 LTag [42], its interaction with viral proteins provided early insights into p53 function [43-47]. Over the years, infections by several viruses, including Epstein-Barr, adenovirus, influenza A and HIV-1, were shown to activate the p53 pathway. The induction of p53 can lead to cell cycle arrest and apoptosis of the infected cells, which can result in control or elimination of the infection in human cells [48-50]. (Also, see recent reviews by Lazo and Santos [51] and Sato [52] for extensive descriptions of p53-virus interactions as well as mechanisms of inactivation.)

The ability of viruses to alter p53 functions and pathways is an important step in their establishment and pathogenesis in animal hosts. Described in Table 1 are examples of viral proteins that interact with p53. Viruses can disrupt p53 functions either directly or through cellular factors involved in downstream activities so as to override cell-cycle checkpoints or protect cells from p53-dependent apoptosis. p53 can be sequestered and/or inactivated by posttranslational modifications (phosphorylation, ubiquitination) induced by viral proteins or by modulation of host enzymes such as Mdm2 that promote proteasome degradation of p53 (see review by Lazo and Santos [51]). Soria and colleagues [53] recently reported that in addition to degradation of p53, which can be induced by adenovirus E1B-55k protein, another adenoviral protein E4-ORF3 promotes *de novo* H3K9me3 heterochromatin silencing at p53 target promoters, blocking p53–DNA binding. p53 can also positively regulate viral replication as found for HIV-1 viral infectivity factor (VIF) that interacts with p53 and promotes cell cycle arrest to facilitate HIV-1 replication [54].

In response to viral infections, one of the most efficient and rapid responses triggered by the immune system is induction of type I interferon mediated signaling. This response involves activation of the STAT (signal transducer and activator of transcription) signaling pathway and subsequent expression of antiviral genes. Several years ago, the seminal discovery of Takaoka *et al.* [40] revealed the existence of crosstalk between p53 and the IFN pathway when an interferon-sensitive response

Table 1. Examples of viral proteins that interact with p53.

Virus	Viral protein	Reference
DNA viruses		
Simian Virus 40	T large antigen	[137]
Adenovirus	E1B55K, E4-ORF3	[53, 138]
Epstein -Barr virus	EBNA-3C, BZLF1	[139, 140]
Human Papillovirus	E6	[141]
Kaposi's Sarcoma -Associated Herpes Virus	LANA	[142]
Hepatitis B	HBV-X	[143]
RNA viruses		
Hepatitis C virus	NS5A, NS3	[144, 145]
Human immunodeficiency virus 1	Tat	[146]
Influenza A	NS1	[147]
Human T-lymphotropic virus Type I	Tax	[148]
Parainfluenza virus 5	V protein	[149]

element (ISRE) was found in the promoter of the *p53* gene. *p53* was identified as one of the transcriptional targets of a type I IFN response following stimulation of cells with interferon-alpha/beta. Later, other studies revealed that p53 can also be activated indirectly by other IFN-inducible proteins such as STAT-1 or promyelocytic leukemia protein [55, 56]. In addition, IFN-β can activate p53 in a dose-dependent manner in human peripheral blood mononuclear cells. This activation leads to altered expression of several genes involved in the p53 signal pathway, including p53 itself, which regulate cell proliferation and cell death following stimulation with IFN-β [57].

Alternatively, p53 can influence both IFN production and signaling, enhancing the antiviral response through direct transcriptional up-regulation of several IFN-inducible genes. Included are transcriptional activators such as interferon regulatory factor 9 (*IRF9*) [58] and *IRF5* [59], the toll-like receptor 3 (*TLR3*) whose gene product is involved in recognition of virus infection through sensing of double-stranded RNA [60] and activated protein kinase R (*PKR*) [61]. Interestingly, PKR is able to phosphorylate p53 *in vitro* [61-62], suggesting a possible functional loop. p53 also induces expression of IFN-stimulated gene 15 (*ISG15*) that encodes a ubiquitin homologue capable of modifying several antiviral proteins, protecting them from degradation [63, 64]. The ubiquitin E3 ligase TRIM22 is another IFN inducible protein that is also a p53 target gene [65]. It co-localizes with the centrosome in primary human mononuclear cells where it appears that both viral replication and protein degradation may occur [66].

Overall, these findings have established important roles for p53 transcriptional activities in host defense against viral infection and support the relevance of p53 in antiviral innate immunity.

p53 general influence on immune response pathways

While there is substantial evidence that p53 protects against inflammation (mostly under chronic conditions), recent studies in mouse and human cells reveal that p53 may promote acute inflammation and immune responses ([67]; Lowe, Menendez and Resnick, unpublished), suggesting a delicate balance in the influence of p53 on immunity pathways. Nearly 25% of p53 null mice die before tumor development due to unresolved infections [68], suggesting a defective innate immune system. p53 knockout mice are also more severely affected by influenza A virus due in part to reduction in cytokine and interferon production [69]. Below, we provide an overview of p53 modulation and enhancement of innate and adaptive immune responses.

p53 can influence several innate and adaptive immune pathways through regulation of genes involved in signaling (chemokines, interleukins), pathogen recognition (TLRs) and activation of specific subsets of immune cells such as T and B lymphocytes, NK cells and macrophages. Interleukins and chemokines are signaling molecules that affect a variety of cellular functions and are stimulated when tissue homeostasis is altered. Both are mediators of inflammation and play critical roles in host defense

by attracting and activating specific subsets of effector leukocytes, cells from the monocyte/macrophage lineage as well as natural killer (NK) cells.

Expression of chemokines and cytokines are subject to p53, depending on stimulus and cell type. p53 can increase transcription of several cytokines involved in innate immunity including colony-stimulating factor 1 (*CSF1*) and monocyte chemotactic protein (*MCP1*), chemokine CXC motif ligand (*CXCL1*) and interleukin 15 (*IL-15*) that attract macrophages, neutrophils, and natural killer cells, contributing to immune elimination of senescent cells [10, 70]. Activation of p53 also results in expression of *fractalkine*, a CX3C chemotactic factor for monocytes, NK cells, and T lymphocytes [71]. p53 is also able to repress directly or indirectly the expression of chemokines since loss of p53 has been found to result in overexpression of proinflammatory chemokines such as *CXCL2, -3, -5* and *-8*, *CCL20*, *CCL28* and *CXR4* in breast, ovarian and lung human cancer cells [72-75].

Chemokines also can influence p53 activities. For example, the macrophage migration inhibitory factor (MIF), a product of activated macrophages, sustains macrophage survival and pro-inflammatory function by inhibiting p53 [76], while MCP-1 can induce endothelial cell apoptosis *in vitro* through a p53-dependent mitochondrial pathway [77]. In addition, ROS production and subsequent premature senescence in response to CXCR2 activation is partially dependent on p53 [78]. Expression of the RANTES chemokine receptor CCR5 increases p53 transcriptional activity in breast cancer cells through activated protein kinase–dependent mechanisms by pertussis toxin, JAK2, and p38 mitogen. Importantly, this signaling circuit between p53 and CCR5 is involved in regulating proliferation of breast tumor cells *in vivo* [79].

The expression of several surface markers on cells involved in immune responses is subject to p53 regulation. Genotoxic activation of p53 leads to up-regulation of intracellular-adhesion molecule-1 (*ICAM-1*) mRNA and protein [80]. ICAM-1 (also known as CD54) is a member of the immunoglobulin gene superfamily and binds to several surface molecules that participate in cell-cell interactions. It can contribute to initiation of immune responses and is a co-stimulatory molecule for T-cell activation. The p53/ICAM-1 relationship may be important for immune surveillance since activation of ICAM-1 by p53 has been implicated in leukocyte infiltration during tumor-targeted inflammation, suggesting intercellular as well as intracellular guardian roles for p53 [81]. Other genes encoding surface cell markers targeted by p53 include *CD200* that is regulated during apoptosis and provides immune tolerance in murine dendritic cells (DCs) [82] and *CD59* (or *MIRL*, membrane inhibitor of reactive lysis) involved in complement signaling regulation [83]. Another surface marker CD43/leukosialin is repressed by p53. CD43 is an important contributor to immune homeostasis and is expressed on most hematopoietic cells. It regulates immune cell adhesion and proliferation [84]. Also, overexpression of CD43 activates the ARF-p53 tumor-suppressor pathway, which can lead to cell death [85].

Boosting innate and adaptive immune responses with p53

Recently, employing a genome-wide *in silico* search we found that most members of the human Toll Like Receptor (TLR) gene family contain potential p53 targets [86]. The *TLR* genes (10 in humans) mediate innate immunity, providing front-line protection against pathogens through recognition of common features referred to as PAMPs (pathogen-associated molecular patterns). Many of the targets did not match the consensus sequence that contains two decamers of RRRCWWGYYY (where R = G,A; Y= C,T; W = A,T). Instead the p53 targets contained only a ½-site (single decamer) or a ¾-site, which we discovered earlier could support p53-mediated transactivation directly or in cooperation with other transcription factors such as estrogen receptor [87-90].

Using primary lymphocytes and alveolar macrophages from healthy subjects [86] as well as various cancer cell lines [91], we established that chromosomal damage can affect the innate immune system by altering expression of most *TLRs*. Furthermore, common anti-tumor agents led to p53-dependent regulation of expression of most *TLR* genes, resulting in modulation of downstream responses to cognate ligands. These results suggest new chemotherapeutic strategies based on agonists or antagonists targeting the TLR pathway [92]. Using an established tumor-bearing human p53 knock-in (Hupki) mouse model, Ishizaki *et al.* [93] demonstrated that treatment with the TLR ligands polyinsosinic:polycytidylic acid (TLR3) and CpG-oligodeoxynucleotide (TLR9) in combination with heterologous p53 immunization enhances tumor regression.

p53 also has transcriptional targets in antigen cell-signaling pathways of T and B lymphocytes. The TAP1 protein (transporter associated with antigen processing) is required for the major histocompatibility complex (MHC) class I antigen presentation pathway that plays a key role in host tumor surveillance. In response to DNA damage, *TAP1* expression is induced by p53 in cooperation with its family member protein p73. This up-regulation enhances transport of MHC class I peptides, expression of surface MHC-peptide complexes and activation of the MHC class I pathway [94]. On the other hand, it has been reported that p53 reduces expression of *RGS13* [95], which inhibits G protein-coupled receptor signaling in B cells and mast

cells (MCs).

Regulation of the NK cells activities provides another example of p53 influence on the host immune system. These cells are specialized immune cells that eliminate foreign, stressed, transformed and senescent cells through specialized surface receptors, such as NKG2D [96, 97]. p53 can activate an antitumor immune response via direct transcriptional regulation of NK ligands *ULBP1* and *ULBP2* in cancer cells, which enhances NK cell activation [97, 98].

Innate and adaptive immunity are also connected to p53 through transcriptional regulation of microRNAs (miRNAs), which are small non-coding endogenous RNAs that bind complementary sequences of target mRNAs and regulate translation of specific genes. miRNAs affect inflammation and cancer [99] and are required for differentiation of immune cells [100]. Many miRNAs have been validated as p53 targets in immune cells including miR15a, miR16-1, miR34 a,b,c, let-7 miRNA and several members of the miR-17–92 cluster. Included in the miRNA targets are genes involved in immune related activities such as *Myb*, *BCL2* and *ULBP2* [96, 101]. Furthermore, dysregulation of these miRNAs is generally associated with poor clinical outcomes in several lymphoid malignancies. (See [102] for a description of the functional and clinical importance of microRNAs regulated by p53 in human lymphocytes.)

p53 as a direct target in cancer immunotherapy

Since the immune system must distinguish between self and non-self antigens, p53 has been considered a target for immunotherapy. First identified in the sera of cancer patients more than 30 years ago [103, 104], the appearance of circulating antibodies against p53 has led to an alternative p53 antigen approach to cancer therapy. In addition to alteration of the p53 regulatory network in most human cancers, the overexpression of mutated p53 protein in several human tumors [105] suggests it could be a potential antigen in cancer immunotherapy since mutated p53 has features of non-self antigen [106]. One strategy is based on the observation that most p53 mutants are due to single amino acid changes that extend protein half-life, leading to accumulation in tumor cells [105, 107, 108]. Degradation of overexpressed mutant p53 in tumor cells might result in generation of peptide fragments specific for tumor cells. However, the large number of hotspot mutations in the DNA binding domain could limit development of vaccines against mutant p53 for use in "personalized medicine" [109]. In addition, the p53-specific T-cell repertoire may be restricted due to the ubiquitous expression of WT p53 in normal somatic tissues [110]. A variety of p53-based vaccines have proved effective in animal models and have led to several clinical trials using immunization with p53 derived peptides [111-115]. Overall, immune responses to both WT and mutant p53 have provided opportunities in treating cancer patients including diagnosis, prognosis and immunotherapy [116, 117].

p53 and NF-kB cross-talk in immune responses

As described above, roles for p53 in immunity are continually emerging. However, these must be considered in light of the other well-established modulators of immunity and inflammation especially NF-κB, a master regulator of immune responses .

Most discussions of p53 and NF-κB interactions have focused on their roles in cancer. While p53 and NF-κB are generally considered to be opposing factors where p53 promotes apoptosis while NF-κB enhances survival (reviewed in [118, 119]). They are capable of directly inhibiting each other resulting in opposing functional consequences. However, there are also positive interactions between these two transcription factors in a manner that is often context dependent (see below).

The complicated relationship between p53 and NF-κB is also seen in the context of immune responses. p53 can play an inhibitory role in NF-κB signaling and consequently the inflammatory response. For example, p53 inhibits IKK β and NF-κB mediated transactivation in IgE-mediated degranulation of mast cells and anaphylaxis [120]. Additionally, glucocorticoid inhibition of NF-κB activation and inflammation is dependent on p53 since p53 loss enhances NF-κB activation and impairs glucocorticoid rescue of death in an LPS shock mouse model [121]. Recently, Madenspacher and colleagues [122] showed up-regulation of several pro-inflammatory genes in the lungs of naïve p53 deficient mice compared to the WT counterparts, which appeared to be through enhanced NF-κB activation since the promoter region of nearly all of these genes contained a NF-κB DNA binding motif sequence.

Positive p53/NF-κB relationships in the immune response have also been described. p53 stabilization by treatment of cells with Nutlin-3 was able to enhance retrovirus-induced apoptosis of host cells in part through augmented activation of NF-κB [123]. p53 is also important in *Helicobacter pylori* infection; however, truncated p53 isoforms rather than WT p53 are implicated. Although *H. pylori* infection results in p53 degradation [124], the Δ133p53 and Δ160p53 isoforms are transcriptionally up-regulated through enhanced alternative P2 promoter activity within the p53 gene in a manner dependent on the *H. pylori* type IV secretion system (the syringe-like pilus structure whereby bacterial components are transferred

to host cells). The isoforms then enhance NF-κB transcriptional activity, but inhibit WT p53- and p73- pro-apoptotic and cell cycle arrest effects, which may provide a mechanism of adaptation of *H. pylori* in host gastric cells [125]. In another example of a p53/ NF-κB positive relationship in the immune response, p53 containing the P72 codon 72 polymorphism, but not the R72 variant, was able to bind to the p65 NF-κB subunit in the mouse thymus and cooperatively induced caspase 4/11 as well as some inflammatory-related genes including *Gdf-15* in response to DNA damage [67]. Thus, although signaling interactions between p53 and NF-κB in the immune response are generally negative, there are clear examples of positive interactions.

p53 and NF-kB in senescence

In recent years, both p53 and NF-κB have been shown to play a role in senescence (irreversible cell cycle arrest) based on a strong link with inflammation [126]. After a limited number of divisions in somatic cells, senescence can be triggered by excessive DNA damage and by oncogenic stress to prevent transformation to a cancerous phenotype. The senescence process involves cell cycle arrest, which requires p53. On the other hand the senescence-associated secretory phenotype (SASP), and the production and secretion of cytokines and chemokines, require NF-κB [126-128]. All these factors appear to be linked through IL-6 signaling [128, 129]. In murine fibroblasts, activation of NF-κB by ATM in the DDR pathway directly induces the expression of the senescence regulator *IL-6*, which then causes further p53 and CPEB (cytoplasmic polyadenylation element binding protein) dependent signal transduction, ultimately leading to senescence (Figure 2) [128, 129]. In addition to the SASP requirement for senescence, an opposing SASP function can trigger immune system responses including recruitment of immune cells that destroy senescent cells. Interestingly, reactivation of p53 in tumor cells led to tumor regression in a mouse model through triggering senescence, expression of inflammatory genes and infiltration of immune cells that destroyed the senescent tumor cells [10]. While there is no evidence yet that p53 and NF-κB directly regulate each other during senescence, both factors have independent but positive roles in regulating senescence and the associated inflammatory phenotype, as summarized in Figure 2.

The connection between p53 and immunity: concluding remarks

p53 has an important role in innate and adaptive immune responses where activation of p53 can be both beneficial and detrimental. In addition to cancer, there are many infectious disease implications, as we had proposed for a loop between pathogen detection by TLRs, inflammation and p53 induction [4, 86, 92]. Typical of p53 functions, the overall picture of interactions between the tumor suppressor p53 and immune system is complex and subject to specific scenarios including activating stimuli, cell type and even species.

The p53/immune interaction is especially relevant to cancer as indicated in a recent review of "hallmarks of cancer" by Hanahan and Weinberg [130], revisiting a

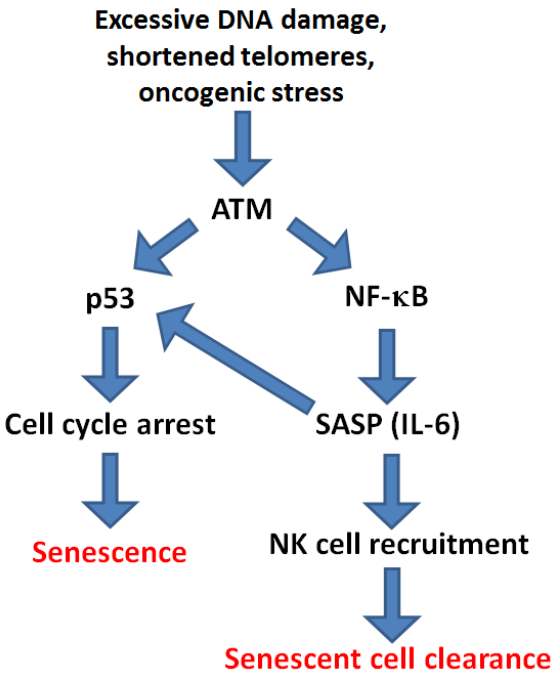

Figure 2. p53 and NF-κB signaling in senescence and SASP.

concept they developed a decade earlier [131]. Included in the hallmarks were avoidance of the immune response and tumor inflammation, highlighting the importance of the immune system. p53 is intimately related with these as well as other hallmarks [132]. Alteration of p53 expression can affect growth and death of cells that are directly responsible for tumors, modify immune surveillance and enhance inflammation. Thus, new opportunities in cancer/disease diagnosis and in chemotherapeutic strategies are expected to develop with further understanding of the interactions between p53 and the immune system.

Although there are nearly 30 immune-related genes (including miRNAs) targeted by p53, many new targets are expected to be identified in the near future through genome-wide methods. The combination of chromatin immunoprecipitation (ChIP) with high throughput sequencing (ChIP-seq) and expression analysis has already been used to map sites of p53 binding among the hundreds of thousands of potential target sequences in the human genome and to identify candidate p53 target genes [133-135]. The next-gen sequencing approaches when applied to primary cells of the immune system (Menendez and Resnick, unpublished), along with "rules" for recognizing p53 bindings sites [88, 136] will provide powerful tools in determining direct roles for p53 regulation in immunity.

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References

1. Petitjean A, Mathe E, Kato S, Ishioka C, Tavtigian SV, Hainaut P et al. Impact of mutant p53 functional properties on TP53 mutation patterns and tumor phenotype: lessons from recent developments in the IARC TP53 database. *Hum Mutat* 2007; 28: 622-629.
2. Soussi T. The history of p53. A perfect example of the drawbacks of scientific paradigms. *EMBO Rep* 2010; **11**: 822-826.
3. Lane D, Levine A. p53 Research: the past thirty years and the next thirty years. Cold Spring *Harb Perspect Biol* 2010; **2**: a000893.
4. Menendez D, Inga A, Resnick MA. Potentiating the p53 network. *Discov Med* 2010; **10**: 94-100.
5. Vousden KH, Prives C. Blinded by the Light: The Growing Complexity of p53. *Cell* 2009; **137**: 413-431.
6. Martins CP, Brown-Swigart L, Evan GI. Modeling the therapeutic efficacy of p53 restoration in tumors. *Cell* 2006; **127**: 1323-1334.
7. Ventura A, Kirsch DG, McLaughlin ME, Tuveson DA, Grimm J, Lintault L et al. Restoration of p53 function leads to tumour regression in vivo. *Nature* 2007; **445**: 661-665.
8. Hofseth LJ, Saito S, Hussain SP, Espey MG, Miranda KM, Araki Y et al. Nitric oxide-induced cellular stress and p53 activation in chronic inflammation. *Proc Natl Acad Sci U S A* 2003; **100**: 143-148.
9. Moon C, Kim S, Wie M, Kim H, Cheong J, Park J et al. Increased expression of p53 and Bax in the spinal cords of rats with experimental autoimmune encephalomyelitis. *Neurosci Lett* 2000; **289**: 41-44.
10. Xue W, Zender L, Miething C, Dickins RA, Hernando E, Krizhanovsky V et al. Senescence and tumour clearance is triggered by p53 restoration in murine liver carcinomas. *Nature* 2007; **445**: 656-660.
11. Akala OO, Park IK, Qian D, Pihalja M, Becker MW, Clarke MF. Long-term haematopoietic reconstitution by Trp53-/-p16Ink4a-/-p19Arf-/- multipotent progenitors. *Nature* 2008; **453**: 228-232.
12. TeKippe M, Harrison DE, Chen J. Expansion of hematopoietic stem cell phenotype and activity in Trp53-null mice. *Exp Hematol* 2003; **31**: 521-527.
13. Fuhrman LE, Goel AK, Smith J, Shianna KV, Aballay A. Nucleolar Proteins Suppress Caenorhabditis elegans Innate Immunity by Inhibiting p53/CEP-1. *Plos Genetics* 2009; **5:** e1000657.
14. Hafsi H, Hainaut P. Redox control and interplay between p53 isoforms: roles in the regulation of basal p53 levels, cell fate and senescence. *Antioxid Redox Signal* 201; **15**:1655-1667.
15. Campbell HG, Slatter TL, Jeffs A, Mehta R, Rubio C, Baird M et al. Does Delta133p53 isoform trigger inflammation and autoimmunity? *Cell Cycle* 2012; **11**: 446-450.
16. Donato NJ, Perez M. Tumor necrosis factor-induced apoptosis stimulates p53 accumulation and p21WAF1 proteolysis in ME-180 cells. *J Biol Chem* 1998; **273**: 5067-5072.
17. Tan M, Li S, Swaroop M, Guan K, Oberley LW, Sun Y. Transcriptional activation of the human glutathione peroxidase promoter by p53. *J Biol Chem* 1999; **274**: 12061-12066.
18. Yoon KA, Nakamura Y, Arakawa H. Identification of ALDH4 as a p53-inducible gene and its protective role in cellular stresses. *J Hum Genet* 2004; **49**: 134-140.
19. de Moraes E, Dar NA, de Moura Gallo CV, Hainaut P. Cross-talks between cyclooxygenase-2 and tumor suppressor protein p53: Balancing life and death during inflammatory stress and carcinogenesis. *Int J Cancer* 2007; **121**: 929-937.
20. Rivera A, Maxwell SA. The p53-induced gene-6 (proline oxidase) mediates apoptosis through a calcineurin-dependent pathway. *J Biol Chem* 2005; **280**: 29346-29354.
21. Italiano D, Lena AM, Melino G, Candi E. Identification of NCF2/p67phox as a novel p53 target gene. *Cell Cycle* 2012; **11**: 4589-4596.
22. Forrester K, Ambs S, Lupold SE, Kapust RB, Spillare EA, Weinberg WC et al. Nitric oxide-induced p53 accumulation and regulation of inducible nitric oxide synthase expression by wild-type p53. *Proc Natl Acad Sci U S A* 1996; **93**: 2442-2447.
23. Velu CS, Niture SK, Doneanu CE, Pattabiraman N, Srivenugopal KS. Human p53 is inhibited by glutathionylation of cysteines present in the proximal DNA-binding domain during oxidative stress. *Biochemistry* 2007; **46**: 7765-7780.
24. Maillet A, Pervaiz S. Redox regulation of p53, redox effectors regulated by p53: a subtle balance. *Antioxid Redox Signal* 2012; **16**: 1285-1294.
25. Komarova EA, Kondratov RV, Wang K, Christov K, Golovkina TV, Goldblum JR et al. Dual effect of p53 on radiation sensitivity in vivo: p53 promotes hematopoietic injury, but protects from gastro-intestinal syndrome in mice. *Oncogene* 2004; **23**: 3265-3271.
26. Herkel J, Mimran A, Erez N, Kam N, Lohse AW, Marker-Hermann E et al. Autoimmunity to the p53 protein is a feature of systemic lupus erythematosus (SLE) related to anti-DNA antibodies. *J*

Autoimmun 2001; **17**: 63-69.
27. Kuhn HM, Kromminga A, Flammann HT, Frey M, Layer P, Arndt R. p53 autoantibodies in patients with autoimmune diseases: a quantitative approach. *Autoimmunity* 1999; **31**: 229-235.
28. Sun Y, Cheung HS. p53, proto-oncogene and rheumatoid arthritis. *Semin Arthritis Rheum* 2002; **31**: 299-310.
29. Tak PP, Zvaifler NJ, Green DR, Firestein GS. Rheumatoid arthritis and p53: how oxidative stress might alter the course of inflammatory diseases. *Immunol Today* 2000; **21**: 78-82.
30. Vousden KH, Lane DP. p53 in health and disease. *Nat Rev Mol Cell Biol* 2007; **8**: 275-283.
31. Yamanishi Y, Boyle DL, Rosengren S, Green DR, Zvaifler NJ, Firestein GS. Regional analysis of p53 mutations in rheumatoid arthritis synovium. *Proc Natl Acad Sci U S A* 2002; **99**: 10025-10030.
32. Hussain SP, Amstad P, Raja K, Ambs S, Nagashima M, Bennett WP et al. Increased p53 mutation load in noncancerous colon tissue from ulcerative colitis: a cancer-prone chronic inflammatory disease. *Cancer Res* 2000; **60**: 3333-3337.
33. Tapinos NI, Polihronis M, Moutsopoulos HM. Lymphoma development in Sjogren's syndrome: novel p53 mutations. *Arthritis Rheum* 1999; **42**: 1466-1472.
34. Okuda Y, Okuda M, Bernard CC. Regulatory role of p53 in experimental autoimmune encephalomyelitis. *J Neuroimmunol* 2003; **135**: 29-37.
35. Pesch J, Brehm U, Staib C, Grummt F. Repression of interleukin-2 and interleukin-4 promoters by tumor suppressor protein p53. *J Interferon Cytokine Res* 1996; **16**: 595-600.
36. Santhanam U, Ray A, Sehgal PB. Repression of the interleukin 6 gene promoter by p53 and the retinoblastoma susceptibility gene product. *Proc Natl Acad Sci U S A* 1991; **88**: 7605-7609.
37. Zheng SJ, Lamhamedi-Cherradi SE, Wang P, Xu L, Chen YH. Tumor suppressor p53 inhibits autoimmune inflammation and macrophage function. *Diabetes* 2005; **54**: 1423-1428.
38. Komarova EA, Krivokrysenko V, Wang KH, Neznanov N, Chernov MV, Komarov PG et al. p53 is a suppressor of inflammatory response in mice. *Faseb Journal* 2005; **19**: 1030-1032.
39. Liu G, Park YJ, Tsuruta Y, Lorne E, Abraham E. p53 Attenuates lipopolysaccharide-induced NF-kappaB activation and acute lung injury. *J Immunol* 2009; **182**: 5063-5071.
40. Takaoka A, Hayakawa S, Yanai H, Stoiber D, Negishi H, Kikuchi H et al. Integration of interferon-alpha/beta signalling to p53 responses in tumour suppression and antiviral defence. *Nature* 2003; **424**: 516-523.
41. Munoz-Fontela C, Garcia MA, Garcia-Cao I, Collado M, Arroyo J, Esteban M et al. Resistance to viral infection of super p53 mice. *Oncogene* 2005; **24**: 3059-3062.
42. Lane DP, Crawford LV. T antigen is bound to a host protein in SV40-transformed cells. *Nature* 1979; **278**: 261-263.
43. DeLeo AB, Jay G, Appella E, Dubois GC, Law LW, Old LJ. Detection of a transformation-related antigen in chemically induced sarcomas and other transformed cells of the mouse. *Proc Natl Acad Sci U S A* 1979; **76**: 2420-2424.
44. Linzer DI, Levine AJ. Characterization of a 54K dalton cellular SV40 tumor antigen present in SV40-transformed cells and uninfected embryonal carcinoma cells. *Cell* 1979; **17**: 43-52.
45. Melero JA, Stitt DT, Mangel WF, Carroll RB. Identification of new polypeptide species (48-55K) immunoprecipitable by antiserum to purified large T antigen and present in SV40-infected and -transformed cells. *Virology* 1979; **93**: 466-480.
46. Rotter V, Witte ON, Coffman R, Baltimore D. Abelson murine leukemia virus-induced tumors elicit antibodies against a host cell protein, P50. *J Virol* 1980; **36**: 547-555.
47. Soussi T. p53 Antibodies in the sera of patients with various types of cancer: a review. *Cancer Res* 2000; **60**: 1777-1788.
48. Genini D, Sheeter D, Rought S, Zaunders JJ, Susin SA, Kroemer G et al. HIV induces lymphocyte apoptosis by a p53-initiated, mitochondrial-mediated mechanism. *FASEB J* 2001; **15**: 5-6.
49. Sato Y, Shirata N, Murata T, Nakasu S, Kudoh A, Iwahori S et al. Transient increases in p53-responsible gene expression at early stages of Epstein-Barr virus productive replication. *Cell Cycle* 2010; **9**: 807-814.
50. Turpin E, Luke K, Jones J, Tumpey T, Konan K, Schultz-Cherry S. Influenza virus infection increases p53 activity: role of p53 in cell death and viral replication. *J Virol* 2005; **79**: 8802-8811.
51. Lazo PA, Santos CR. Interference with p53 functions in human viral infections, a target for novel antiviral strategies? *Rev Med Virol* 2011; **21**: 285-300.
52. Sato Y, Tsurumi T. Genome guardian p53 and viral infections. *Rev Med Virol* 2012; DOI: 10.1002/rmv.1738.
53. Soria C, Estermann FE, Espantman KC, O'Shea CC. Heterochromatin silencing of p53 target genes by a small viral protein. *Nature* 2010; **466**: 1076-1081.
54. Izumi T, Io K, Matsui M, Shirakawa K, Shinohara M, Nagai Y et al. HIV-1 viral infectivity factor interacts with TP53 to induce G2 cell cycle arrest and positively regulate viral replication. *Proc Natl Acad Sci U S A* 2010; **107**: 20798-20803.
55. Pampin M, Simonin Y, Blondel B, Percherancier Y, Chelbi-Alix MK. Cross talk between PML and p53 during poliovirus infection: implications for antiviral defense. *J Virol* 2006; **80**: 8582-8592.
56. Townsend PA, Scarabelli TM, Davidson SM, Knight RA, Latchman DS, Stephanou A. STAT-1 interacts with p53 to enhance DNA damage-induced apoptosis. *J Biol Chem* 2004; **279**: 5811-5820.
57. Zhang F, Sriram S. Identification and characterization of the interferon-beta-mediated p53 signal pathway in human peripheral blood mononuclear cells. *Immunology* 2009; **128**: e905-918.
58. Munoz-Fontela C, Macip S, Martinez-Sobrido L, Brown L, Ashour J, Garcia-Sastre A et al. Transcriptional role of p53 in interferon-mediated antiviral immunity. *J Exp Med* 2008; **205**: 1929-1938.
59. Mori T, Anazawa Y, Iiizumi M, Fukuda S, Nakamura Y, Arakawa H. Identification of the interferon regulatory factor 5 gene (IRF-5) as a direct target for p53. *Oncogene* 2002; **21**: 2914-2918.
60. Taura M, Eguma A, Suico MA, Shuto T, Koga T, Komatsu K et al. p53 regulates Toll-like receptor 3 expression and function in human epithelial cell lines. *Mol Cell Biol* 2008; **28**: 6557-6567.
61. Yoon CH, Lee ES, Lim DS, Bae YS. PKR, a p53 target gene, plays a crucial role in the tumor-suppressor function of p53. *Proc Natl Acad Sci U S A* 2009; **106**: 7852-7857.
62. Cuddihy AR, Li S, Tam NW, Wong AH, Taya Y, Abraham N et al. Double-stranded-RNA-activated protein kinase PKR enhances transcriptional activation by tumor suppressor p53. *Mol Cell Biol* 1999; **19**: 2475-2484.
63. Hummer BT, Li XL, Hassel BA. Role for p53 in gene induction by double-stranded RNA. *J Virol* 2001; **75**: 7774-7777.
64. Pitha-Rowe IF, Pitha PM. Viral defense, carcinogenesis and ISG15: novel roles for an old ISG. *Cytokine Growth Factor Rev* 2007; **18**: 409-417.
65. Obad S, Brunnstrom H, Vallon-Christersson J, Borg A, Drott K, Gullberg U. Staf50 is a novel p53 target gene conferring reduced clonogenic growth of leukemic U-937 cells. *Oncogene* 2004; **23**: 4050-4059.
66. Petersson J, Lonnbro P, Herr AM, Morgelin M, Gullberg U, Drott K. The human IFN-inducible p53 target gene TRIM22 colocalizes with the centrosome independently of cell cycle phase. *Exp Cell Res* 2010; **316**: 568-579.
67. Frank AK, Leu JI, Zhou Y, Devarajan K, Nedelko T, Klein-Szanto A et al. The codon 72 polymorphism of p53 regulates interaction with NF-kB and transactivation of genes involved in immunity and inflammation. *Mol Cell Biol* 2011; **31**:1201-1213.

68. Donehower LA, Harvey M, Slagle BL, McArthur MJ, Montgomery CA, Jr., Butel JS et al. Mice deficient for p53 are developmentally normal but susceptible to spontaneous tumours. *Nature* 1992; **356**: 215-221.
69. Munoz-Fontela C, Pazos M, Delgado I, Murk W, Mungamuri SK, Lee SW et al. p53 Serves as a Host Antiviral Factor That Enhances Innate and Adaptive Immune Responses to Influenza A Virus. *Journal of Immunology* 2011; **187**: 6428-6436.
70. Tang X, Asano M, O'Reilly A, Farquhar A, Yang Y, Amar S. p53 is an important regulator of CCL2 gene expression. *Curr Mol Med* 2012; **12**: 929-943.
71. Shiraishi K, Fukuda S, Mori T, Matsuda K, Yamaguchi T, Tanikawa C et al. Identification of fractalkine, a CX3C-type chemokine, as a direct target of p53. *Cancer Research* 2000; **60**: 3722-3726.
72. Mehta SA, Christopherson KW, Bhat-Nakshatri P, Goulet RJ, Jr., Broxmeyer HE, Kopelovich L et al. Negative regulation of chemokine receptor CXCR4 by tumor suppressor p53 in breast cancer cells: implications of p53 mutation or isoform expression on breast cancer cell invasion. *Oncogene* 2007; **26**: 3329-3337.
73. Son DS, Kabir SM, Dong YL, Lee E, Adunyah SE. Inhibitory effect of tumor suppressor p53 on proinflammatory chemokine expression in ovarian cancer cells by reducing proteasomal degradation of IkappaB. *PLoS One* 2012; **7**: e51116.
74. Son DS, Parl AK, Rice VM, Khabele D. Keratinocyte chemoattractant (KC)/human growth-regulated oncogene (GRO) chemokines and pro-inflammatory chemokine networks in mouse and human ovarian epithelial cancer cells. *Cancer Biol Ther* 2007; **6**: 1302-1312.
75. Yeudall WA, Vaughan CA, Miyazaki H, Ramamoorthy M, Choi MY, Chapman CG et al. Gain-of-function mutant p53 upregulates CXC chemokines and enhances cell migration. *Carcinogenesis* 2012; **33**: 442-451.
76. Mitchell RA, Liao H, Chesney J, Fingerle-Rowson G, Baugh J, David J et al. Macrophage migration inhibitory factor (MIF) sustains macrophage proinflammatory function by inhibiting p53: Regulatory role in the innate immune response. *Proc Natl Acad Sci U S A* 2002; **99**: 345-350.
77. Zhang X, Liu X, Shang H, Xu Y, Qian M. Monocyte chemoattractant protein-1 induces endothelial cell apoptosis in vitro through a p53-dependent mitochondrial pathway. *Acta Biochim Biophys Sin (Shanghai)* 2011; **43**: 787-795.
78. Acosta JC, O'Loghlen A, Banito A, Raguz S, Gil J. Control of senescence by CXCR2 and its ligands. *Cell Cycle* 2008; **7**: 2956-2959.
79. Manes S, Mira E, Colomer R, Montero S, Real LM, Gomez-Mouton C et al. CCR5 expression influences the progression of human breast cancer in a p53-dependent manner. *J Exp Med* 2003; **198**: 1381-1389.
80. Gorgoulis VG, Zacharatos P, Kotsinas A, Kletsas D, Mariatos G, Zoumpourlis V et al. p53 activates ICAM-1 (CD54) expression in an NF-kappa B-independent manner. *EMBO Journal* 2003; **22**: 1567-1578.
81. Yakes FM, Wamil BD, Sun F, Yan HP, Carter CE, Hellerqvist CG. CM101 treatment overrides tumor-induced immunoprivilege leading to apoptosis. *Cancer Res* 2000; **60**: 5740-5746.
82. Rosenblum MD, Olasz E, Woodliff JE, Johnson BD, Konkol MC, Gerber KA et al. CD200 is a novel p53-target gene involved in apoptosis-associated immune tolerance. *Blood* 2004; **103**: 2691-2698.
83. Donev RM, Cole DS, Sivasankar B, Hughes TR, Morgan BP. p53 regulates cellular resistance to complement lysis through enhanced expression of CD59. *Cancer Res* 2006; **66**: 2451-2458.
84. Kadaja-Saarepuu L, Looke M, Balikova A, Maimets T. Tumor suppressor p53 down-regulates expression of human leukocyte marker CD43 in non-hematopoietic tumor cells. *Int J Oncol* 2012; **40**: 567-576.
85. Kadaja L, Laos S, Maimets T. Overexpression of leukocyte marker CD43 causes activation of the tumor suppressor proteins p53 and ARF. *Oncogene* 2004; **23**: 2523-2530.
86. Menendez D, Shatz M, Azzam K, Garantziotis S, Fessler MB, Resnick MA. The Toll-Like Receptor Gene Family Is Integrated into Human DNA Damage and p53 Networks. *PLoS Genet* 2011; **7**: e1001360.
87. Jordan JJ, Menendez D, Inga A, Nourredine M, Bell D, Resnick MA. Noncanonical DNA motifs as transactivation targets by wild type and mutant p53. *PLoS Genet* 2008; **4**: e1000104.
88. Menendez D, Inga A, Resnick MA. The expanding universe of p53 targets. *Nat Rev Cancer* 2009; **9**: 724-737.
89. Menendez D, Inga A, Snipe J, Krysiak O, Schonfelder G, Resnick MA. A single-nucleotide polymorphism in a half-binding site creates p53 and estrogen receptor control of vascular endothelial growth factor receptor 1. *Mol Cell Biol* 2007; **27**: 2590-2600.
90. Menendez D, Krysiak O, Inga A, Krysiak B, Resnick MA, Schonfelder G. A SNP in the flt-1 promoter integrates the VEGF system into the p53 transcriptional network. *Proc Natl Acad Sci USA* 2006; **103**: 1406-1411.
91. Shatz M, Menendez D, Resnick MA. The human TLR innate immune gene family is differentially influenced by DNA stress and p53 status in cancer cells. *Cancer Res* 2012; **72**: 3948-3957.
92. Menendez D, Shatz M, Resnick MA. Interactions between the tumor suppressor p53 and immune responses. *Current Opinion in Oncology* 2013; **25**: 85-92.
93. Ishizaki H, Song GY, Srivastava T, Carroll KD, Shahabi V, Manuel ER et al. Heterologous prime/boost immunization with p53-based vaccines combined with toll-like receptor stimulation enhances tumor regression. *J Immunother* 2010; **33**: 609-617.
94. Zhu K, Wang J, Zhu J, Jiang J, Shou J, Chen X. p53 induces TAP1 and enhances the transport of MHC class I peptides. *Oncogen*e 1999; **18**: 7740-7747.
95. Iwaki S, Lu Y, Xie Z, Druey KM. p53 negatively regulates RGS13 protein expression in immune cells. *J Biol Chem* 2011; **286**: 22219-22226.
96. Heinemann A, Zhao F, Pechlivanis S, Eberle J, Steinle A, Diederichs S et al. Tumor suppressive microRNAs miR-34a/c control cancer cell expression of ULBP2, a stress-induced ligand of the natural killer cell receptor NKG2D. *Cancer Res* 2012; **72**: 460-471.
97. Textor S, Fiegler N, Arnold A, Porgador A, Hofmann TG, Cerwenka A. Human NK cells are alerted to induction of p53 in cancer cells by upregulation of the NKG2D ligands ULBP1 and ULBP2. *Cancer Res* 2011; **71**: 5998-6009.
98. Li H, Lakshmikanth T, Garofalo C, Enge M, Spinnler C, Anichini A et al. Pharmacological activation of p53 triggers anticancer innate immune response through induction of ULBP2. *Cell Cycle* 2011; **10**: 3346-3358.
99. Schetter AJ, Heegaard NH, Harris CC. Inflammation and cancer: interweaving microRNA, free radical, cytokine and p53 pathways. *Carcinogenesis* 2010; **31**: 37-49.
100. Lu LF, Liston A. MicroRNA in the immune system, microRNA as an immune system. *Immunology* 2009; **127**: 291-298.
101. Fabbri M, Bottoni A, Shimizu M, Spizzo R, Nicoloso MS, Rossi S et al. Association of a microRNA/TP53 feedback circuitry with pathogenesis and outcome of B-cell chronic lymphocytic leukemia. *JAMA* 2011; **305**: 59-67.
102. Xu-Monette ZY, Medeiros LJ, Li Y, Orlowski RZ, Andreeff M, Bueso-Ramos CE et al. Dysfunction of the TP53 tumor suppressor gene in lymphoid malignancies. *Blood* 2012; **119**: 3668-3683.
103. Caron de Fromentel C, May-Levin F, Mouriesse H, Lemerle J, Chandrasekaran K, May P. Presence of circulating antibodies against cellular protein p53 in a notable proportion of children with B-cell lymphoma. *Int J Cancer* 1987; **39**: 185-189.

104. Crawford LV, Pim DC, Bulbrook RD. Detection of antibodies against the cellular protein p53 in sera from patients with breast cancer. *Int J Cancer* 1982; **30**: 403-408.
105. Hollstein M, Sidransky D, Vogelstein B, Harris CC. p53 mutations in human cancers. *Science* 1991; **253**: 49-53.
106. Ito D, Visus C, Hoffmann TK, Balz V, Bier H, Appella E et al. Immunological characterization of missense mutations occurring within cytotoxic T cell-defined p53 epitopes in HLA-A*0201+ squamous cell carcinomas of the head and neck. *Int J Cancer* 2007; **120**: 2618-2624.
107. Dowell SP, Wilson PO, Derias NW, Lane DP, Hall PA. Clinical utility of the immunocytochemical detection of p53 protein in cytological specimens. *Cancer Res* 1994; **54**: 2914-2918.
108. Zambetti GP, Levine AJ. A comparison of the biological activities of wild-type and mutant p53. *FASEB J* 1993; **7**: 855-865.
109. Carbone DP, Ishida T, Chada S, Stipanov M, Gabrilovich DI. Dendritic cells transduced with wild type p53 gene elicit potent antitumor immune responses. *Journal of Leukocyte Biology* 1998: 11-11.
110. Lauwen MM, Zwaveling S, de Quartel L, Ferreira Mota SC, Grashorn JA, Melief CJ et al. Self-tolerance does not restrict the CD4+ T-helper response against the p53 tumor antigen. *Cancer Res* 2008; **68**: 893-900.
111. Cheok CF, Verma CS, Baselga J, Lane DP. Translating p53 into the clinic. *Nat Rev Clin Oncol* 2011; **8**: 25-37.
112. Chiappori AA, Soliman H, Janssen WE, Antonia SJ, Gabrilovich DI. INGN-225: a dendritic cell-based p53 vaccine (Ad.p53-DC) in small cell lung cancer: observed association between immune response and enhanced chemotherapy effect. *Expert Opin Biol Ther* 2010; **10**: 983-991.
113. Met O, Balslev E, Flyger H, Svane IM. High immunogenic potential of p53 mRNA-transfected dendritic cells in patients with primary breast cancer. *Breast Cancer Res Treat* 2011; **125**: 395-406.
114. Nijman HW, Lambeck A, van der Burg SH, van der Zee AG, Daemen T. Immunologic aspect of ovarian cancer and p53 as tumor antigen. *J Transl Med* 2005; **3**: 34.
115. Speetjens FM, Kuppen PJ, Welters MJ, Essahsah F, Voet van den Brink AM, Lantrua MG et al. Induction of p53-specific immunity by a p53 synthetic long peptide vaccine in patients treated for metastatic colorectal cancer. *Clin Cancer Res* 2009; **15**: 1086-1095.
116. Lane DP, Cheok CF, Lain S. p53-based cancer therapy. *Cold Spring Harb Perspect Biol* 2010; **2**: a001222.
117. Vermeij R, Leffers N, van der Burg SH, Melief CJ, Daemen T, Nijman HW. Immunological and clinical effects of vaccines targeting p53-overexpressing malignancies. *J Biomed Biotechnol* 2011; **2011**: 702146.
118. Ak P, Levine AJ. p53 and NF-kappaB: different strategies for responding to stress lead to a functional antagonism. *FASEB J* 2010; **24**: 3643-3652.
119. Gudkov AV, Gurova KV, Komarova EA. Inflammation and p53: A Tale of Two Stresses. *Genes Cancer* 2011; **2**: 503-516.
120. Suzuki K, Murphy SH, Xia Y, Yokota M, Nakagomi D, Liu F et al. Tumor suppressor p53 functions as a negative regulator in IgE-mediated mast cell activation. *PLoS One* 2011; **6**: e25412.
121. Murphy SH, Suzuki K, Downes M, Welch GL, De Jesus P, Miraglia LJ et al. Tumor suppressor protein (p)53, is a regulator of NF-kappaB repression by the glucocorticoid receptor. *Proc Natl Acad Sci U S A* 2011; **108**: 17117-17122.
122. Madenspacher JH, Azzam KM, Gowdy KM, Malcolm CK, Nick JA, Dixon D et al. p53 integrates host defense and cell fate during bacterial pneumonia. *J Experimental Medicine* 2013; **210**: 891-904.
123. Pan D, Pan LZ, Hill R, Marcato P, Shmulevitz M, Vassilev LT et al. Stabilisation of p53 enhances reovirus-induced apoptosis and virus spread through p53-dependent NF-kappaB activation. *Br J Cancer* 2011; **105**: 1012-1022.
124. Wei J, Nagy TA, Vilgelm A, Zaika E, Ogden SR, Romero-Gallo J et al. Regulation of p53 tumor suppressor by Helicobacter pylori in gastric epithelial cells. *Gastroenterology* 2010; **139**: 1333-1343.
125. Wei J, Noto J, Zaika E, Romero-Gallo J, Correa P, El-Rifai W et al. Pathogenic bacterium Helicobacter pylori alters the expression profile of p53 protein isoforms and p53 response to cellular stresses. *Proc Natl Acad Sci U S A* 2012; **109**: E2543-2550.
126. Salminen A, Kauppinen A, Kaarniranta K. Emerging role of NF-kappaB signaling in the induction of senescence-associated secretory phenotype (SASP). *Cell Signal* 2012; **24**: 835-845.
127. Kuilman T, Michaloglou C, Mooi WJ, Peeper DS. The essence of senescence. *Genes Dev* 2010; **24**: 2463-2479.
128. Groppo R, Richter JD. CPEB Control of NF{kappa}B Nuclear Localization and IL-6 Production Mediates Cellular Senescence. *Mol Cell Biol* 2011; **31**: 2707-2714
129. Kuilman T, Michaloglou C, Vredeveld LC, Douma S, van Doorn R, Desmet CJ et al. Oncogene-induced senescence relayed by an interleukin-dependent inflammatory network. *Cell* 2008; **133**: 1019-1031.
130. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011; **144**: 646-674.
131. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell* 2000; **100**: 57-70.
132. Hainaut P. Chapter 1: *TP53 Coordinator of the Processes that Underlie the Hallmarks of Cancer.* Hainaut P, Olivier M, Wiman KG (eds), p53 in the Clinics 2013; DOI 10.1007/978-1-4614-3676-8_1, Springer Science, New York, NY, USA: 1-23.
133. Nikulenkov F, Spinnler C, Li H, Tonelli C, Shi Y, Turunen M et al. Insights into p53 transcriptional function via genome-wide chromatin occupancy and gene expression analysis. *Cell Death Differ* 2012; **19**: 1992-2002.
134. Smeenk L, van Heeringen SJ, Koeppel M, Gilbert B, Janssen-Megens E, Stunnenberg HG et al. Role of p53 serine 46 in p53 target gene regulation. *PLoS One* 2011; **6**: e17574.
135. Wei CL, Wu Q, Vega VB, Chiu KP, Ng P, Zhang T et al. A global map of p53 transcription-factor binding sites in the human genome. *Cell* 2006; **124**: 207-219.
136. Jegga AG, Inga A, Menendez D, Aronow BJ, Resnick MA. Functional evolution of the p53 regulatory network through its target response elements. *Proc Natl Acad Sci U S A* 2008; **105**: 944-949.
137. Lilyestrom W, Klein MG, Zhang R, Joachimiak A, Chen XS. Crystal structure of SV40 large T-antigen bound to p53: interplay between a viral oncoprotein and a cellular tumor suppressor. *Genes Dev* 2006; **20**: 2373-2382.
138. Steegenga WT, Riteco N, Jochemsen AG, Fallaux FJ, Bos JL. The large E1B protein together with the E4orf6 protein target p53 for active degradation in adenovirus infected cells. *Oncogene* 1998; **16**: 349-357.
139. Yi F, Saha A, Murakami M, Kumar P, Knight JS, Cai Q et al. Epstein-Barr virus nuclear antigen 3C targets p53 and modulates its transcriptional and apoptotic activities. *Virology* 2009; **388**: 236-247.
140. Zhang Q, Gutsch D, Kenney S. Functional and physical interaction between p53 and BZLF1: implications for Epstein-Barr virus latency. *Mol Cell Biol* 1994; **14**: 1929-1938.
141. Scheffner M, Huibregtse JM, Vierstra RD, Howley PM. The HPV-16 E6 and E6-AP complex functions as a ubiquitin-protein ligase in the ubiquitination of p53. *Cell* 1993; **75**: 495-505.
142. Friborg J, Jr., Kong W, Hottiger MO, Nabel GJ. p53 inhibition by the LANA protein of KSHV protects against cell death. *Nature* 1999; **402**: 889-894.
143. Takada S, Kaneniwa N, Tsuchida N, Koike K. Cytoplasmic

retention of the p53 tumor suppressor gene product is observed in the hepatitis B virus X gene-transfected cells. *Oncogene* 1997; **15**: 1895-1901.
144. McGivern DR, Lemon SM. Tumor suppressors, chromosomal instability, and hepatitis C virus-associated liver cancer. *Annu Rev Pathol* 2009; **4**: 399-415.
145. Deng L, Nagano-Fujii M, Tanaka M, Nomura-Takigawa Y, Ikeda M, Kato N et al. NS3 protein of Hepatitis C virus associates with the tumour suppressor p53 and inhibits its function in an NS3 sequence-dependent manner. *J Gen Virol* 2006; **87**: 1703-1713.
146. Ariumi Y, Kaida A, Hatanaka M, Shimotohno K. Functional cross-talk of HIV-1 Tat with p53 through its C-terminal domain. *Biochem Biophys Res Commun* 2001; **287**: 556-561.
147. Wang X, Shen Y, Qiu Y, Shi Z, Shao D, Chen P et al. The non-structural (NS1) protein of influenza A virus associates with p53 and inhibits p53-mediated transcriptional activity and apoptosis. *Biochem Biophys Res Commun* 2010; **395**: 141-145.
148. Pise-Masison CA, Choi KS, Radonovich M, Dittmer J, Kim SJ, Brady JN. Inhibition of p53 transactivation function by the human T-cell lymphotropic virus type 1 Tax protein. *J Virol* 1998; **72**: 1165-1170.
149. Sun M, Fuentes SM, Timani K, Sun D, Murphy C, Lin Y et al. Akt plays a critical role in replication of nonsegmented negative-stranded RNA viruses. *J Virol* 2008; **82**: 105-114.