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Review

Transcriptional regulation by p53: one protein, many possibilities

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Abstract

The p53 tumor suppressor protein is a DNA sequence-specific transcriptional regulator that, in response to various forms of cellular stress, controls the expression of numerous genes involved in cellular outcomes including among others, cell cycle arrest and cell death. Two key features of the p53 protein are required for its transcriptional activities: its ability to recognize and bind specific DNA sequences and to recruit both general and specialized transcriptional co-regulators. In fact, multiple interactions with co-activators and co-repressors as well as with the components of the general transcriptional machinery allow p53 to either promote or inhibit transcription of different target genes. This review focuses on some of the salient features of the interactions of p53 with DNA and with factors that regulate transcription. We discuss as well the complexities of the functional domains of p53 with respect to these interactions.

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Abbreviations: AQP3, aquaporin 3; ARF, alternate open reading frame; (d)ADP, (deoxy)adenosine diphosphate; (d)ATP, (deoxy)adenosine triphosphate; CARM1, coactivator-associated arginine methyltransferase 1; Cdc2, cell division cycle 2; Chk1, checkpoint kinase 1; CRF, chromatin remodeling factor; CTD, C-terminal basic domain; DBD, DNA-binding core domain; EMSA, electrophoretic mobility shift assay; Ets-1, V-ets erythroblastosis virus E26 oncogene homolog 1 (avian); GADD45, growth arrest and DNA damage inducible gene 45; (d)GTP, (deoxy)guanosine triphosphate; HAT, histone transacetylase; HDAC, histone deacetylase; IGFBP3, insulin-like growth factor binding protein 3; MDM2, mouse double minute 2; MDR1, P-glycoprotein (multidrug resistance 1); NAD^+, nicotinamide adenine dinucleotide; NMR, nuclear magnetic resonance; PIG3, p53-induced gene 3; Pin, peptidyl-prolyl cis/trans isomerase; PRMT1, protein arginine methyltransferase 1; RE, p53 DNA consensus recognition element; RNA Pol I/II/III, DNA-dependent RNA Polymerase I or II or III; rRNA, ribosomal RNA; tRNA, transfer RNA; SAGE, serial analysis of gene expression; SnoN, SKI-like; mSin3a, transcriptional regulator SIN3A; TA, N-terminal transactivation domain; TDP, thiamine diphosphate; TFIIA, transcription factor IIA; TFIID, transcription factor IID; TFIIIB, transcription factor IIIB; TXSA, thromboxane synthase; VP16, Herpes simplex virus transactivator VP16; p21/CDKN1, cyclin-dependent kinase inhibitor 1A; p52, nuclear factor of kappa light polypeptide gene enhancer in B-cells 2, p49/p100; p53, tumor suppressor p53; p300, transcriptional co-activator protein p300

Introduction

P53 sits at the hub of an extremely complex network within the living cell. Multiple signals, perhaps the most well studied being DNA damage, lead to the functional activation of p53 which can upregulate or downregulate numerous target genes, thus, initiating a series of events resulting in cell-cycle arrest, senescence or apoptosis among other outcomes (reviewed in Vogelstein *et al*[1], Prives and Hall[2]).

The complexity of p53 as a protein mirrors the functional complexity of p53-dependent events. Active p53 protein exists in the cell as a tetramer made of four identical subunits.[3] Each monomer, in turn, consists of several well-defined domains including a multipartite N-terminal transactivation (TA) domain (residues 1–73) a proline-rich region (63–97), the centrally located and highly conserved DNA-binding core domain (DBD) (residues 94–312) and within the C-terminus are located its tetramerization domain (residues 324–355) followed by an unstructured basic domain (CTD) (residues 360–393).

An additional layer to p53 complexity is added by the numerous post-translational modifications this protein may undergo, the most important of which seem to be phosphorylation, acetylation and ubiquitination (reviewed in Brooks and Gu[4], Appella and Anderson[5]). Site- and time-specific modifications of certain p53 residues are likely to regulate its activity as well as its half-life although contradictory findings in the literature imply great complexity in this regard.

Though recent studies have demonstrated that p53 can also produce apoptosis through non-transcriptional processes that occur in the cytoplasm (reviewed in Erster and Moll[6]), in this review we will focus on the roles and regulation of p53 as a transcriptional activator and repressor. From that vantage point p53 may be viewed as possessing two critical functions and their related modules: DNA-binding and co-factor recruiting. We would then suggest that the other regions of p53 serve to assist these two primary modules in performing their functions.

Since the discovery of the first transcription targets of p53 in the early 1990s (*p21, GADD45, cyclin G, bax* and others,

reviewed in Ko and Prives[7]) the list of genes whose expression depends on p53 has grown dramatically and continues to expand. Such p53 targets have been identified either as single genes or using different screening techniques such as DNA microarrays or SAGE technology. In the current review we will focus mainly on a number of aspects of the p53 protein's function as a transcription factor and its ability to modulate the transcription of downstream genes in a positive and negative manner. We will also discuss some cis- and trans-elements participating in these processes. P53 is one of the most extensively scrutinized mammalian regulatory genes to have been examined in recent decades. Given the confines of the format of this review, it has been therefore impossible to cite all of the excellent studies that have focused on its roles as a transcription factor. We sincerely apologize in advance to those whose work we have unintentionally omitted in this article.

p53 Binding to DNA

The p53 DNA consensus recognition element (RE)

To initiate the chain of events resulting in either inhibition of cell-cycle progression or programmed cell death, p53 must recognize and bind to its recognition elements (REs) that are located in the vicinities of its target genes. In most cases, p53 REs are found within a few thousand base pairs of transcriptional start site and frequently p53 target genes have at least two widely spaced p53 REs. The consensus p53 DNA RE consists of two pairs (half-sites) of head-to-head arranged pentamers, 5′-PuPuPuCA/TA/TGPyPyPy-3′ (Pu is purine, Py is pyrimidine) separated by 0–13 nucleotides.[8] The sequence within the pentamers as well as the pentamers mutual orientation is the important determinant that may influence both, p53 binding ability and activity.[9,10] Strong p53 REs have been shown to possess certain general features. The most important of them are (i) the presence of highly conserved and obligate C and G residues (ii) either 0 or 1 bp spacing between the two half-sites, and (iii) no more than 3 non-consensus bases within RE.[11,12] Interestingly, the presence of AT residues in the middle of each half-site results in the strongest positive activation, whereas non-consensus bases are associated with low functionality noticeably affecting p53-dependent transactivation.[12]

p53 may also recognize REs whose structure is somewhat different from the consensus RE. For instance, one that is weakly induced by p53 is AQP3, in which, the RE is made up of three pairs of pentamers.[13] Another example is the p53 RE located within the promoter of the MDR1 gene (see below).[14] A third is the microsatellite region within the PIG3 gene that was shown to function even more effectively as a p53 RE than a more canonical binding site within the same promoter.[15] Finally, Walter *et al*.[16] have recently demonstrated the ability of p53 to recognize and bind to CTG·CAG trinucleotide repeats with the subsequent induction of topological alterations in DNA.

It is noteworthy that among p53-regulated genes their respective levels of activation or inhibition of transcription vary broadly. This is due, at least in part, to the variation within the individual p53 REs. When tested in a yeast model system such variations resulted in up to 1000-fold difference in transactivation.[10,17]

Yeast-based assays also have been used by recent studies to identify new potential p53 REs and to evaluate the impact of genetic variation within the REs on p53-dependent transactivation.[11] In addition to the discovery of a number of new p53 potential targets, they established a link between particular p53 RE alleles and their influences on p53 transactivation.

It should be noted, however, that such differences observed in yeast systems may not be replicated in mammalian cells.

P53 has two autonomous DNA–binding domains

The p53 core domain

The large central core DBD demonstrates high affinity toward the consensus RE (see above), whereas the small, C-terminally located highly basic domain (CTD) has been shown to bind to DNA without sequence specificity (reviewed in Jayaraman and Prives[18], Kim and Deppet[19], Liu and Kulesz-Martin[20]). On the basis of crystallographic data a model has been suggested in which each pentamer of the RE interacts with the DBDs comprising a p53 tetramer.[21] The crystal structure of the p53 core DBD revealed that its complex β-sheet sandwich and loop-sheet-helix motif are the sequence-specific DNA-binding determinants of the core. This model has been validated in a number of NMR-based and biochemical studies.[22–24]

Among more than 18 000 currently known mutations in p53 that result in either partial or complete loss of its wild-type (wt) functions, amino acids within the p53 DBD are by far the most frequent mutational targets.[25] The mutations situated in the DBD can disrupt p53-specific DNA binding by several possible ways. Mutations at some positions (e.g. R273) decrease the binding ability of p53 by simply eliminating direct contacts between the protein and DNA,[21,26] while some other mutations (e.g. R175, G245, R249, R282) diminish binding by destabilizing the tertiary structure of p53 DBD.[27,28] Mutation at position 248 (R248), in addition to breaking DNA-protein contacts, also introduces extensive structural changes into the DBD.[27] Among these mutations are also those that lead to the loss or significant decrease in Zn^{2+} ions, normally chelated by C176 and H179 of the L2 loop and by C238 and C242 of the L3 loop.[21] In fact, Zn^{2+} release from the wild-type DBD of p53 leads to a conformational change of L2 and L3 loops and facilitates conversion of an active soluble protein into one that is insoluble and inactive.[29] Importantly, the loss of Zn^{2+} ions is facilitated by elevating temperature, a finding which may provide an explanation of the unusual loss-of-function phenomenon demonstrated by p53 at 37°C[30] although the N-terminus has also been shown to be involved in stabilization of temperature-sensitive DNA binding by wild-type[31] and mutant[32] forms of p53.

Additionally, Butler and Loh[33] have described the ability of some DBD mutants (G245S, R249S, R282Q) to facilitate the loss of p53 function by causing DBD to cycle unusually rapidly between folded and unfolded states. During such cycling a fraction of DBD caught in a functionally inactive state continually increases.

Recognition and making contact with the different bases within a consensus RE requires a significant level of flexibility of the p53 DBD within a tetramer. The same flexibility, though, seems to be responsible for the ability of some p53 mutants to bind and inactivate the other two p53 relatives, p63 and p73,[34–37] as well as to force wild-type p53 molecules (translated from the remaining wild-type p53 allele) into a mutant conformation.

Surprisingly, while the existence of even one mutated p53 allele in the cell results in a gain-of-function phenotype,[38,39] Chan *et al*.[40] found that at least three DNA-binding defective molecules of p53 are needed in order to effectively inactivate the tetramer. They reported that in their experiments the presence of one or two mutated DBD molecules within a tetramer does not significantly reduce p53 transcriptional activation. Speculatively, the existence of partially active tetramers in the cell may lead to a new phenotype via appearance of an unusual binding surface on a p53 molecule, which may change the pattern of coactivators/corepressors interacting with p53 or even promote new contacts. Alternatively, mutations in the DBD may either result in the ability of p53 to bind selectively to target genes or (more speculatively) to some novel DNA sequences thus altering the normal global transcriptional response to p53.

The p53 C-terminal DNA-binding domain

The small CTD of p53 initially attracted attention because of its ability to bind to nonspecific sequences in DNA, and also its potential ability to directly regulate binding by the p53 sequence-specific DBD. Unstructured and rich in both serine and lysine residues, the CTD can be subjected to several types of modification the most well studied being phosphorylation and acetylation.[5,41,42]. In addition, it has been suggested that C-terminal lysines of p53 may be involved in the regulation of stability of p53, as they are subjected to MDM2-mediated ubiquitination. In fact, the same lysine residues are acetylated by histone acetyl transferases (HATs) which result in p53 stabilization and activation.[43–45] Finally, there are data that neddylation,[44] methylation,[46] and sumoylation (reviewed in Muller *et al*.[47]) of the CTD can regulate p53 functions.

What is the meaning of such C-terminal modifications? It was originally observed that, using the electrophoretic mobility shift assay (EMSA), either binding by the C-terminal antibody PAb 421 or phosphorylation of the penultimate residue, S392 leads to increased ability of p53 to bind to DNA. It was hypothesized that after DNA damage, the CTD of p53 becomes modified by phosphorylation leading to increased binding to its transcriptional target genes (Reviewed in Ahn and Prives[48]). This suggestion was extended to a proposal that upon such modification p53 normally in a latent state in cells undergoes a modification-induced allosteric conformational shift that somehow positively affects the ability of the core domain to bind to DNA. In fact, *in vitro* and *in vivo* obtained data suggested that not only phosphorylation but CTD acetylation also enhances the sequence-specific DNA binding of p53.[49–51] This concept was also supported by the observation that deletion of the C-terminus increases its ability to bind to DNA using similar experimental conditions. The allosteric model was subsequently challenged by Anderson *et al*. who showed that the interactions of p53 with PAb 421 or long DNA molecules had respectively stimulatory or inhibitory effects on its ability to bind to a short RE-containing oligonucleotide.[52] They proposed that the C-terminus binding to long DNA interferes with the ability of the core to bind to DNA and that modification of the C-terminus prevents such interference by blocking its ability to bind to nonspecific DNA. Their hypothesis was supported by NMR analysis that showed that both full length and C-terminally deleted versions of p53 have essentially similar structures[53] and by experiments from the group of Fersht showing that when fully acetylated the C-terminus completely loses DNA binding capacity.[54] Relevantly, Espinosa and Emerson reported that although acetylation appears to increase the p53-binding affinity toward short double-stranded DNA fragments it does not affect ability of p53 to bind to its specific RE in the context of chromatin or longer DNA molecules.[55] It has become clear that evaluating the p53 DNA binding using short double-strand oligonucleotides does not provide a complete picture. Importantly as well, quantitative chromatin immunoprecipitation analysis has failed to demonstrate allosteric regulation of DNA binding of p53: neither of the two groups of p53 target genes – with relatively high promoter occupancy *in vivo* or with much weaker DNA binding exhibit significant enrichment in p53 binding after genotoxic stress.[56] Finally, it was recently shown that substitution of all p53 CTD lysines for arginines does not significantly affect the activities or stability of p53 in a mouse model.[57,58]

Though controversial, the importance of the CTD in p53 functioning has been continuing to reveal itself in a number of more recent publications. McKinney and Prives,[59] Fojta *et al*.,[60] and Palecek *et al*.[61] have shown that the CTD is important for binding to various non-linear DNAs. In another study, McKinney *et al*.[62] have demonstrated the involvement of CTD in the ability of p53 to diffuse linearly on DNA. Both, McKinney *et al*.[62] and Liu *et al*.[63] showed as well that the CTD is required for efficient promoter activation *in vivo* by p53. Moreover, Harms and Chen[64] have recently reported that the CTD inhibits p53-dependent induction of IGFBP3 gene. In this case it is HAT-related inhibitory activity, but not p53 DNA binding ability, that is bound to CTD.

The ability of p53 to interact with DNA sequences can be modulated by the presence of small molecules. First, as has been demonstrated, elevating concentrations of transition metals such as Zn^{2+}, Ni^{2+}, and Co^{2+} inhibit p53 binding to the DNA RE.[65] Of these three, Zn^{2+} ions have had the most devastating effect when added in the concentration 5–20 μM. Second, the presence of ADP or dADP has been found to stabilize p53-DNA complexes, while addition of ATP dATP, GTP or dGTP apparently can facilitate the release of p53 from such complexes.[66]

Two other molecules, thiamine diphosphate (TDP) and nicotinamide adenine dinucleotide (NAD^+) have been recently shown to bind to p53, induce conformational changes, and inhibit DNA binding.[67] The authors propose that the level and rate of NAD^+ synthesis may directly modify p53 DNA specificity. In addition to small molecules, other factors, like the supercoiled nature of the DNA or local DNA bending, may facilitate p53-DNA interactions.[59,61] Importantly, it has been

demonstrated earlier that there is a direct correlation between the stability of p53-DNA complexes and the ability of the DNA to be bent by the p53 DBD upon binding.[68] A summary of the above regulatory effectors is shown in Figure 1. For the purpose of simplicity and clarity we have omitted from Figure 1 the numerous post-translational modifications and protein factors previously reported to regulate p53 DNA binding. Furthermore, as discussed above some of these modifications (e.g. acetylation) and proteins have been shown to either stimulate or inhibit p53 DNA binding depending on the experimental context.

The Complexity of the p53 Transactivation Domain

The first suggestion that p53 functions as a transcriptional regulator came from that observation that its N-terminus (TA) when fused to a heterologous DNA-binding domain can serve as an activation domain in yeast. Owing to the relatively high number of paired aspartate and glutamate residues located within it, this domain belongs to the class of 'acidic' activation domains that are known to interact with a number of proteins that populate the general transcription machinery (reviewed in Ko and Prives[7]). Although the conclusions based on these observations that p53 is a transcriptional activator turned out to be correct, formal proof that p53 is a sequence-specific transcriptional activator was only obtained when full-length p53 was studied in that context.

The TA domain is one of the several unstructured regions within p53.[69] Though the entire N-terminal region of p53 is natively unfolded, and that seems to be its functional state,[70] NMR-based studies have found several small 'islands' of secondary structure within the TA: the helix formed by residues Thr18–Leu26, and the two turns are shaped by residues Met40–Met44 and Asp48–Trp53, respectively.[71] It has been suggested that these regions may represent recognition scaffolds for p53-interacting proteins. Interestingly, as is the case with other activation domains, single-point mutations within the TA domain do not demonstrate such a devastating effect as in the case of DBD.[72] Thus, the overall shape of the TA polypeptide chain may not be affected by single amino-acid changes and would seem to be more important for recognition and protein interaction rather than any specific residues. Nevertheless, simultaneous mutation of two hydrophobic residues Leu22 and Trp23 markedly impairs (but does not abolish) transactivation by p53.[72] Interestingly, mutation of residues Trp53 and Phe54 appears to affect specifically the ability of p53 to regulate some of its pro-apoptotic target genes in some settings.[73]

Though the results obtained by mutational analysis of p53 TA have demonstrated the presence of two highly important subdomains within it and set its boundaries between the residues 1–42 and 43–73,[74] several other regions of TA (as well as amino acids located within them) have been shown to participate in the process of transcriptional regulation. For example, some co-activators have been shown to interact with p53 within residues 63–97.[75] Residues 63–97 span a proline-rich region shown to be important for the Pin-induced modification of the TA structure,[76,77] and to interact directly with p300.[78] One more functionally divergent region within the N-terminal part of p53 is a recently identified repression domain.[79] As defined by mutation analysis, it is located between proline-rich domain and DNA-core domain (residues 100–116). Importantly, this domain can function as an independent heterologous repressor, and has been shown to decrease VP16-driven activation up to 20 times in human embryonal carcinoma cells, when being fused to VP16 transactivator.[79] As wild-type p53 is found to be over-expressed in some type of tumors, it has been proposed that the newly identified domain may play an important role in repression of the basal activity of p53. Factors that are or can be specifically recruited by this domain, and that might be essential for the repression phenomenon found, are not known at present. Thus, these and other experiments further highlight the likelihood that transcriptional regulation by p53 involves several different regions within its N-terminus.

In addition to the multipartite nature of the activation domain of p53, there are three other reasons why this is an exceeding complex region. First, it is the region to which its negative regulator Mdm2 binds and targets p53 for both repression of its transcriptional regulation functions and also for proteasome-mediated degradation (reviewed in Bond *et al.*[80]). Second, it was reported to possess a previously unknown nuclear export signal spanning the residues 11–27.[81] Finally,

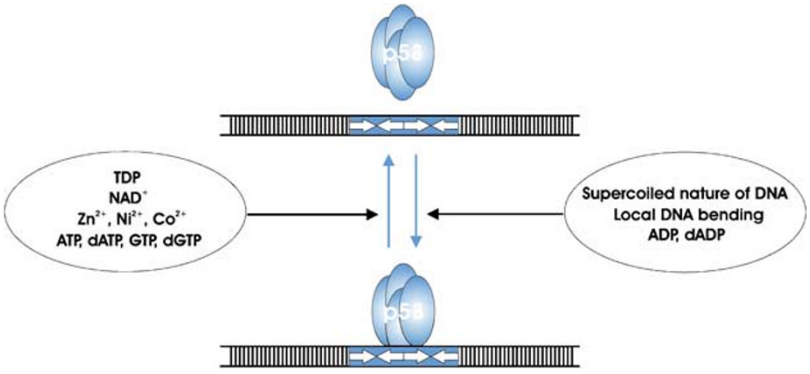

Figure 1 Factors known to have an effect on p53-DNA interaction. p53 tetramer is schematically shown as four blue ovals. DNA is shown as linear fragment with four white arrows within representing p53 RE made of four head-to-head arranged pentamers

the N-terminus of p53 is extensively modified. Site-specific phosphorylation of the TA domain is important for both, p53 stability[82,83] and activity[50,84–87] and has been shown to be interdependent.[88] There are also qualitative differences in phosphorylation in response to different genotoxic agents. For example, phosphorylation of Thr18 has been shown to be stronger when cells are exposed to ionizing radiation and adriamycin rather than to UV light while phosphorylation at Ser33, Ser37, and Ser46 has been more pronounced in case of UV treatment.[88]

As in the case with p53 CTD modifications, the role of site-specific phosphorylation of the key serines within TA domain has been challenged by earlier[89] and some more recent data. Thompson *et al*.[90] using Nutlin-3, a recently developed small molecule MDM2 antagonist, have not detected any induction in the phosphorylation of p53 and yet both its DNA sequence-specific binding and ability to transactivate its target genes were unaltered when compared to p53 that is induced after forms of DNA damage that lead to extensive N-terminal modifications.

Transcription Regulation by p53

Several views exist on the mechanism by which p53 may promote transcription. The first one is built on the assumption that the promoter region of the gene to be activated by p53 is usually not accessible to the general transcription factors and RNA polymerase. In this scenario binding of p53 to its REs within a promoter would facilitate promoter opening via recruiting either chromatin remodeling factors (CRF)[91,92] (though see reference Hill *et al*.[93]) or histone transacetylases (HAT)[94–97] and/or methyltransferases[98] (Figure 2). This view has been validated recently in a significant number of studies. Physical and functional interactions between p53 and p300 HAT have been well documented.[49,55,94–97] The involvement of PRMT1 and CARM1 methyltransferases in p53 function has been also demonstrated in the *in vitro* study utilizing a chromatin template with GADD45 p53 RE.[98] Thus, histone modifications and the subsequent alterations in chromatin structure and function seem to be one of the major outcomes of p53 binding to the RE.

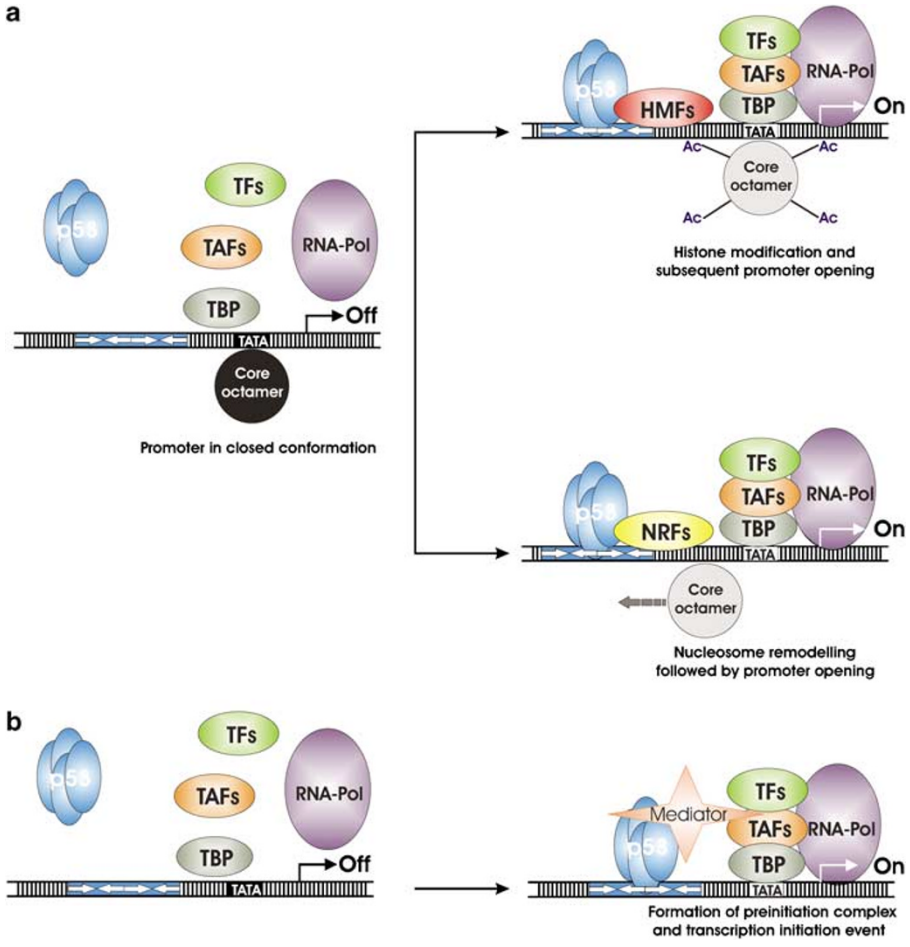

Figure 2 Different modes of p53-dependent transcriptional activation. Abbreviations : Ac, acetate; TATA, TATA box; TBP, TATA-binding protein; TAFs, transcription-associated factors; TFs, other transcription factors; RNA-Pol, RNA Polymerase; HMFs, histone modifying factors; NRFs, nucleosome remodelling factors. p53 consensus RE is shown by four white arrows; 'Off' and 'On' stand for transcription switched off or on, respectively. For simplicity, DNA is shown as linear fragment. (**a**) Transcriptional activation via recruiting HMFs (for example, HAT p300) (upper panel) or NRFs (for example, SWI/SNF complex) (lower panel). (**b**) Transcriptional activation via interaction with the components of mediator complex and subsequent formation of preinitiation complex

In addition, p53 has been shown to facilitate formation of preinitiation complex via direct interactions with the components of Mediator complex.[99,100] p53 can also stimulate transcription by enhancing the recruitment of the basal transcription factors, such as TFIIA and TFIID through the direct interactions with them, and by inducing conformational change(s) in these complexes.[7,101]

Another view of p53-depending transcriptional activation is based on the observation that the regions of chromatin within the vicinity of several p53 responsive promotes (including GADD45 and MDM2) exist in open conformations regardless of the conditions (normal *versus* genotoxic).[102–104] Constitutive hypersensitivity of these promoters to DNase I led to the suggestion that they might be nucleosome-free, and do not require significant chromatin alterations to become activated. By analogy with some genes, which are regulated by promoter proximal pausing and factors facilitating reinitiation of stalled RNA Polymerase, p53 has been suggested to induce reinitiation of transcription.[104] For further evaluation this model clearly requires more data.

The subject of p53-dependent transcription activation, including an up-to-date list of positively regulated genes, has been more than adequately covered in a series of recent reviews.[105,106]

Negative regulation of transcription by p53

Although well established as a transcriptional activator, p53 has also been shown to suppress the transcription of certain genes. Indeed, in addition to identification of multiple targets that are activated by p53, expression arrays have indicated that significant numbers of genes are downregulated after induction of p53 in many cases.[107–110] The molecular background of negative regulation of gene expression by p53 seems to be more diverse. Interestingly, earlier reports have suggested that transcriptional repression by p53 is the key activity that is required for its ability to induce cell death.[7]

p53 can efficiently inhibit transcription driven by all three mammalian RNA polymerases (Pol I, Pol II and Pol III). With respect to Pol II inhibition, several mechanisms have been documented (Figure 3). These include repression of transcription activators by physical interaction with and preventing them from activating the promoter[111–116] or by displacing them from the adjusting or overlapping binding sites within the promoter,[117–120] interference with the assembly of transcription machinery,[7,121] repression through the recruitment of histone deacetylase (HDAC) and, possibly, other chromatin modifying factors,[122–124] and finally through novel REs with the unique architecture that dictates the outcome of p53 binding.[14,125] Combination of two of the above mechanisms has been also documented.[126] It should be noted, that the p53-dependent transcriptional repression that depends on HDAC recruitment, has perhaps the most complicated scenario, and in many cases it is mediated by the presence of additional protein(s). The known mediators include mSin3a,[122,127] SnoN[128] and p52.[129]

In certain cases p53-induced repression seems to depend on the activation of p53-dependent targets. p53 mediated repression of Chk1,[130] or Cdc2, Cyclin A2, survivin and some other genes may occur indirectly through the transcriptional activation of p21.[131] In such cases p21 alone is sufficient to inhibit the transcription to the same extent as p53.

Whatever the nature of p53-dependent repression, it is clear that it requires functionally active p53 protein. Surprisingly, mutations in almost all domains of p53 – TA, DBD, proline-rich and CTD – may abrogate its inhibitory ability, suggesting the specific role for each of the domains during inhibition. For example, p53 TA-deficient mutants lose the ability to repress the transcription of the Map4 gene,[132] whereas a p53 mutant lacking the proline-rich domain cannot repress a series of promoters as efficiently as wild-type p53.[133] This domain is also important for p53-Sin3a-mediated transcription inhibition.[75,122] The C-terminal domain of p53 is required for the interaction between p53 and Ets-1 protein, which is necessary for TXSA repression.[112]

It is intriguing that the presence of a functionally active DBD is required for the inhibition to occur even if binding of p53 to the RE is not necessary. In this context it should be noted that promoters of some downregulated genes have one or more potential p53 REs, not participating in p53-mediated regulation.[112,134,135] The human small nuclear RNA U1 gene has been shown to contain a high-affinity RE within its promoter which nevertheless seems to be dispensable for p53-mediated repression of U1.[135] Whether recognition of such 'latent' REs depends on the intracellular conditions and/or external stimuli, remains to be found.

Recently, transcriptional repression that results from the binding of p53 to a novel type of 'repression site' RE has been described in the MDR1 promoter.[14,125] Interestingly, it is orientation of pentamers – 'head-to-tail', instead of 'head-to-head' – within the RE that dictates the type of p53 activity on this promoter. The change of the orientation back to 'normal' results in the significant activation of MDR1. The same authors propose that the inhibition of several other genes, namely, cyclin A, cyclin B1, and ARF, may be driven by the same mechanism, as identical head-to-tail REs have been identified within their promoters.[14] For cyclin B1, this might be an alternative mechanism, as its repression has been shown to depend on p21/CDKN1.[131] Surprisingly, two p53 homologues, p63 and p73, do not recognize the Mdr1 repression site RE and are unable to inhibit transcription at MDR1 promoter, suggesting some unique properties for DBD domain of each type.[125]

Taking into account that activity of p53-repressed genes usually correlates with cell proliferation or malignant progression, it is not surprising that p53 may also suppress such activities in a more general way by targeting the components of protein biosynthesis machinery. p53 does it by inhibiting the expression of RNA Pol I[136,137] and RNA Pol III[135,138,139] transcribed genes. Pol I-driven transcription is repressed by p53 interference with the assembly of a productive initiation complex on the rRNA promoter,[136,137] whereas transcription of tRNAs seems to be downregulated directly, through the interaction with the components of Pol III transcription machinery,[138,139] and indirectly, by p53-dependent degradation of TFIIIB.[140] Both, rRNA and tRNA synthesis is significantly elevated in fibroblasts from p53-knockout mice.[137,141]

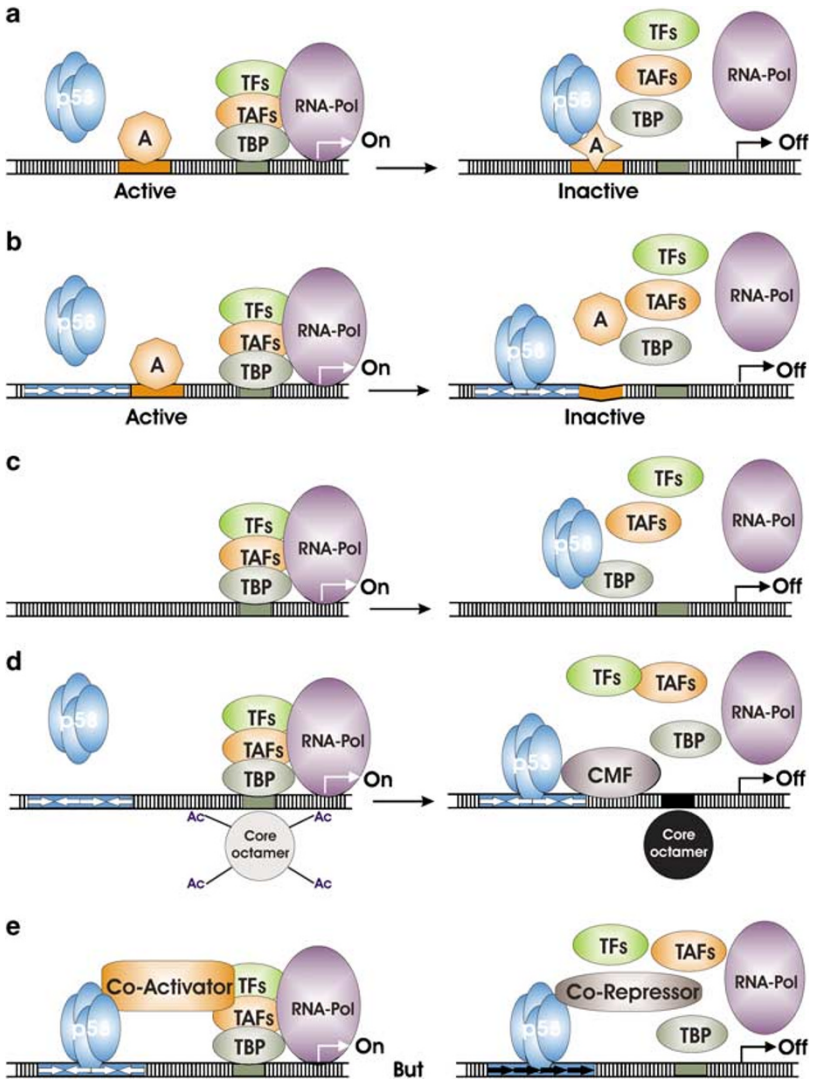

Figure 3 Different modes of p53-dependent transcriptional repression. Abbreviations: A, site-specific transcriptional activator; CMF, chromatin-modifying factor; the other abbreviations are as in Figure 2. (**a**) p53 inhibits transcription by physical interaction and inactivation of the specific activator or (**b**) by displacing it from the adjusting or overlapping binding sites within the promoter. (**c**) Transcriptional repression by affecting the assembly of transcription machinery though the direct interaction with basal transcription factor(s). (**d**) Transcriptional repression via recruiting CMF(s) (for example, HDAC) followed by subsequent modification of core histones and promoter closing. (**e**) Transcriptional repression through novel REs (represented by four black arrows) with the unique architecture that dictates the outcome of p53 binding

Concluding Remarks

The ability of p53 to regulate transcription of a number of genes in response to different genotoxic signals lies at the center of its function as a major tumor suppressor. The ongoing process of identification of numerous p53-regulated genes has been slowly revealing the multifaceted and somewhat knotted mechanism by which p53 exerts its functions in cells. p53 clearly demonstrates the interdependence of the many 'discrete' steps in the process of transcription regulation, and their importance for the final outcome. Yet, despite the myriad of studies delving into the mechanisms by which p53 regulates its targets there is still much more to learn about this fascinating protein. Looking ahead into the future we envisage many new avenues to be explored, some of which will require novel or more refined technologies. The contacts made by p53 with components of the transcriptional machinery need to be determined at the atomic level. We would also hope to gain a dynamic or kinetic view of p53 as it regulates transcriptional target genes. How will p53 be affected by the other p53 isoforms recently identified[142,143] or by the presence of isoforms encoded by its sibling genes, p63 and p73 (reviewed in Harms and Chen[144])? Finally, the 'Holy Grail' of p53 research still lies ahead: capitalizing upon past and future basic research discoveries to improve diagnosis and treatment of cancer patients.

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