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News and Commentary

Transcriptional repression mediated by the p53 tumour suppressor

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The survival and well-being of multicellular organisms is dependent on appropriate cellular responses to a myriad of external and internal signals. Accordingly, critical cellular regulators exist to integrate these signals and coordinate reactions to them. One such 'master' regulator is the p53 tumour suppressor protein. Upon exposure to stress stimuli such as DNA damage, hypoxia, oncogene activation, or nucleotide depletion, p53 becomes activated and promotes cell cycle arrest and apoptosis. The ability of p53 to control cell growth in this manner is considered important for its function as a tumour suppressor. p53 is a transcription factor that binds to DNA in a sequence-specific manner to activate transcription of target genes. The consensus DNA-binding sequence for p53 consists of two repeats of the 10 bp motif 5′-PuPuPuC(A/T)(A/T)GPyPyPy-3′ separated by 0–13 bp.[1] Mutated p53 alleles typically found in tumours encode defective products no longer capable of binding to DNA or activating transcription. There is now compelling evidence that the transcriptional activity of p53 is required for its growth suppressing and tumour suppressing activities.[2–4] For instance, *p21^{WAF1}*, *GADD45*, and *14-3-3σ* represent three well-characterized p53 target genes that are involved in mediating cell cycle arrest by p53.[5–9] The pathway through which p53 promotes apoptosis is less well understood, but is believed to involve transcriptional regulation of a different subset of genes as well as transcription-independent functions of p53, possibly reflecting distinct mechanisms of p53 action in different cell types.[4,10–17] p53 activates transcription of a variety of apoptosis-associated genes including *Bax*,[18] *PUMA*,[19,20] *Pidd*,[21] *Killer/DR5*,[22] *Fas/APO-1*,[23,24] *Noxa*,[25] *p53AIP1*,[26] and *Ei24/PIG8*.[27–29] Most studies have focused on the transactivation function of p53 because of the strong association between transactivation and tumour suppression. However, p53 is also able to repress transcription from various promoters and emerging evidence indicates that transcriptional repression by p53 is important for its ability to promote apoptosis. The ability of p53 to repress transcription at various viral and cellular promoters has been known for some time,[30–34] but the underlying mechanism and functional consequences of transcriptional repression have remained largely unexplored. Until more recently, the simplistic view had been that p53 activates transcription from genes that contain a p53-binding site and that p53 has a general repressive effect on promoters that lack a p53-binding site, possibly by sequestering components of the basal transcriptional machinery.

Involvement of p53 Transrepression Activity in Apoptosis

At least in some cell types, p53-dependent apoptosis can proceed in the presence of transcription and translation inhibitors, indicating that *de novo* expression of p53-activated target genes is not essential for apoptosis.[10,11] Additional evidence indicates that p53-dependent apoptosis can be dissociated from transactivation. For example, ectopic expression of certain p53 mutants, defective in their ability to activate various known p53 target promoters, promotes apoptosis in HeLa cells,[12] Saos-2 cells,[35] and HCT116 colon carcinoma cells.[36] Deletion of the proline-rich domain of p53 blocks its ability to induce apoptosis without impairing its ability to transactivate target genes such as *p21^{WAF1}*, *Mdm2*, and *Bax*.[16,37,38] Importantly, the proline-rich domain of p53 was shown to be required for transcriptional repression.[16] Together, these studies raise the possibility that transactivation-independent functions of p53 such as transcriptional repression and/or interactions with other proteins are required for p53-dependent apoptosis.

Consistent with the view that transcriptional repression by p53 is important for its apoptosis-inducing function, expression of Bcl-2, adenovirus E1B 19 K protein, or WT-1 was found to abrogate p53-dependent apoptosis; interestingly, these proteins interfere with p53-mediated repression, but not with p53-mediated transactivation.[39–41] Furthermore, Koumenis *et al*.[42] reported that p53-mediated apoptosis in response to hypoxia was associated with transcriptional repression, and not with the transactivation of known p53-target genes such as *GADD45*, *p21*, *Mdm2*, and *Bax*. Finally, ectopic expression of various p53-repressed genes including *Bcl-2*,[43,44] *survivin*,[45,46] *MAP4*,[47] *PIK3CA* (the p110α catalytic subunit of PI3 K),[48] and *p202*[49] was shown to inhibit p53-dependent apoptosis. Conversely, inhibition of *PIK3CA* expression by antisense oligonucleotide or by p53 overexpression led to a decrease in cell survival.[48] An intriguing model that arises from these observations is that p53-dependent apoptosis requires not only the activation of proapoptotic genes, but also the repression of antiapoptotic genes. Of note, the ability of p53 to activate and repress transcription is not unique, as various other transcription factors have been shown to possess dual activation and repression properties.[50]

Mechanisms of p53 Transrepression

With the recognition that p53 transrepression plays a role in apoptosis, a number of studies have investigated the mechanism of p53-mediated repression. Transcriptional repressors are generally thought to function through one of the following mechanisms (see Figure 1):

1. Interference with the functions of DNA-binding transcriptional activators.
2. Interference with the basal transcriptional machinery.
3. Alteration of chromatin structure at the promoters of target genes by recruiting proteins such as histone deacetylases.

p53-Mediated transcriptional repression has been associated with each of these mechanisms. Selected examples are discussed below.

Repression by interference with the functions of activators

In this model, transcriptional repression by p53 falls into two categories. In the first category, repression is mediated by p53 binding to consensus DNA elements. In the second category, repression occurs in the apparent absence of DNA binding by p53 at consensus sites. p53 represses the alpha-fetoprotein (*AFP*) gene by inhibiting the promoter binding of hepatic nuclear factor 3 (HNF-3), a transcription factor that activates *AFP* transcription.[51] The overlapping of p53 and HNF-3 binding sites in the *AFP* promoter results in competitive binding and displacement of HNF-3 from the *AFP* promoter.[51] Crowe *et al.*[52] demonstrated that HNF-3 could activate *AFP* transcription by promoting a more open and accessible chromatin structure at the *AFP* promoter. In contrast, the binding of p53 to the *AFP* promoter was associated with a decrease in promoter accessibility.[53] Interestingly, using cells that lack HNF-3, Lee and co-workers[51] found that p53 actually stimulated *AFP* transcription in transient transfection experiments. This suggests that p53, a weak transactivator of *AFP*, may repress *AFP* transcription by displacing a more potent transactivator. A similar situation is observed at the hepatitis B virus (HBV) promoter, where p53 represses transcription in the presence of the EP-enhancer element, while in its absence, p53 conferred transcriptional activation to the promoter.[54] Such 'net' repression because of weaker transactivation is an intriguing notion that casts a new perspective on our understanding of the actions of transcriptional repressors. Another example of competitive displacement resulting from the binding of p53 to a consensus site on DNA is provided by the repression of the human DNA polymerase δ catalytic subunit gene (*POLD1*), where p53 binding overlaps and competes with Sp1 proteins at the promoter.[55] Hoffman *et al.*[46] reported that a p53-binding site at the *survivin* promoter was required for p53-mediated transcriptional repression, and that p53 might interfere with the function of E2F at an overlapping E2F binding site. In contrast, Mirza *et al.*[45] found that the p53-binding site in the *survivin* promoter was dispensable for p53-mediated transcriptional repression.

Transcriptional repression by p53 that is dependent on noncompetitive DNA binding has also been reported. The human *IEX-1* promoter contains two distinct negative and positive *cis*-acting elements corresponding with the p53 and Sp1 response elements, respectively. At this promoter, however, these proteins do not interfere with each other's binding to DNA and they are believed to control *IEX-1* expression independently.[56] Similarly, p53 and the transcription factor Brn-3a have been shown to bind to adjacent but nonoverlapping sites in the *Bcl-2* P2 promoter and to interact with one another, both *in vitro* and *in vivo*.[57] Here, p53 may interfere with the functions of Brn-3a not necessarily by

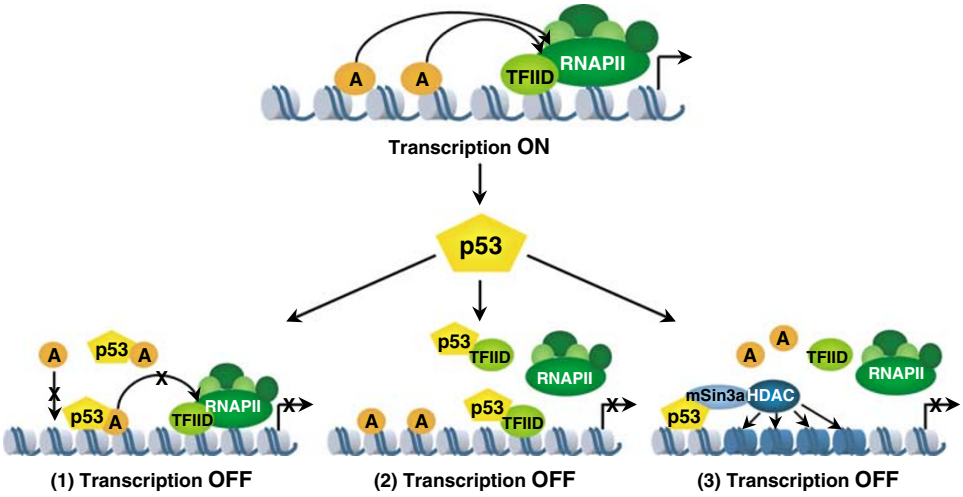

Figure 1 Models of p53-dependent transcriptional repression. Transcriptional repression by p53 is mediated through several mechanisms. In model (1), p53 interferes with the functions of DNA-binding transcriptional activators (A). p53 may interact with activators at the promoter of the target gene and/or in solution, thus interfering with the functions of the activator. It may also prevent the binding of activators to the promoter, possibly through overlapping DNA binding sites. The second mechanism (2) involves interference with the basal transcriptional machinery by p53. Here, p53 may interact with components of the basal transcriptional machinery at the gene promoter and/or in solution. This may disrupt transcriptional processes such as preinitiation complex assembly. Finally, in model (3), p53 recruits chromatin-modifying factors such as histone deacetylases (HDAC). Alterations in chromatin structure may reduce promoter accessibility to the transcriptional machinery and/or activator proteins

preventing its DNA-binding activity, but perhaps by disrupting its interactions with other components of the transcriptional machinery.[57] An independent study carried out using haematopoietic cells, however, reported that p53-dependent repression of *Bcl-2* was maintained despite progressive deletions of the *Bcl-2* promoter to the minimal region. This study concluded that the TATA sequence in the *Bcl-2* P2 minimal promoter was the target for repression by p53, and that the interaction between p53 and TBP was most likely responsible for the repression.[58] The contradictory and conflicting reports could be attributed to different cell types. It is possible that differences in the levels of p53 and transcriptional activators determine which mechanism of repression takes precedence.

Under category 2, p53-dependent transcriptional repression can occur in the apparent absence of p53 binding to a classical consensus DNA element. In this model, repression may be achieved through the physical interaction of p53 with transcriptional activators. Consistent with this notion, p53 has been shown to bind Sp1, rendering the protein inactive for Sp1-mediated transcription.[59] In addition, p53 has been shown to interact with the glucocorticoid receptor,[60] oestrogen receptor,[61] thyroid hormone receptor,[62] and hepatocyte nuclear factor 4α1 (HNF4α1).[63] It is also possible that p53 may bind DNA through degenerate or novel elements instead of through the classical consensus site. For instance, transcriptional repression of the *MDR1* gene has been reported to be mediated through the direct binding of p53 to a novel DNA element at the promoter.[64]

It is interesting to note that p53 represses various promoters by interfering with the functions of prevalent activator proteins that are involved in the regulation of many genes. For instance, p53-dependent repression at the gene promoters of *telomerase reverse transcriptase*,[65] *insulin receptor*,[66] *insulin-like growth factor-I receptor*,[67] *VEGF*,[68] and *POLD1*[55] is believed to involve interference with Sp1 activity. Other general transcriptional regulators including AP-1 and C/EBP have been shown to be the targets of p53-mediated transrepression at genes such as *collagenase-1*[69] and *albumin*.[70] By interacting with these transcriptional regulators in solution or at the target gene promoters, p53 may coordinately modulate the expression of a large number of genes, a property that may be necessary for the tumour suppressor function of p53.

The repression of certain genes is complex and may even occur indirectly. For example, p53 appears to repress the *cdc2* (*cdk1*) promoter through a CCAAT element bound by the NF-Y transcription factor.[71,72] In addition, p53-dependent transactivation of *p21^{WAF1}* results in the inhibition of cyclin-dependent kinase activity and maintenance of the p130:E2F4 repressor complex that targets the *cdc2* promoter.[73] p53-mediated repression of *CHK1* is also likely to be mediated by p21 since the expression of p21 alone facilitated, and its deficiency abrogated, the repression of the *CHK1* gene.[74]

Repression by direct interference with the basal transcriptional machinery

In contrast to the genes described above, some promoters are repressed by p53 without an apparent need to act through gene-specific activators or their binding sites. For instance, *cyclin B* is downregulated in a p53-dependent manner.[75] p53-dependent repression, however, was not affected by progressive deletions of the *cyclin B2* promoter, or by mutations in the binding sites of known regulators such as Sp1 and NF-Y.[75] Although deletions and mutations led to an overall decrease in promoter activity, the p53-dependent repression pattern was maintained. Hence, p53 appears to act through the basal promoter to modulate *cyclin B2* transcription. In fact, the proposal that p53 targets the basal transcriptional machinery directly is not new. Earlier studies by Mack *et al*.[34] suggested that p53 represses TATA-dependent, rather than initiator-mediated, transcription. These authors proposed a model in which p53 acts on specific components of the general transcriptional machinery to interfere with processes such as preinitiation complex assembly or transcriptional initiation. Consistent with this proposal, p53 was found to interact with TATA-binding protein (TBP) and certain TAFs.[33,76–79] Potentially, these interactions could interfere with the binding of general transcription factors/coactivators to certain promoters. This has been substantiated by the finding that wild-type, but not mutant, p53 abrogates the binding of TBP to a TATA-containing DNA fragment *in vitro*, even though both the wild-type and mutant p53 proteins are able to bind TBP.[80] In another study, p53 was shown to compete with TBP for binding to a promoter fragment derived from the cyclooxygenase-2 (*Cox-2*) gene, providing a possible mechanism to explain p53-dependent repression of the *Cox-2* promoter.[81] Caution must be exercised in interpreting studies that rely on p53 overexpression because of the associated nonspecific squelching effects that are irrelevant within the native setting. Nevertheless, these studies provide an indication that p53 is capable of acting directly on components of the basal transcriptional machinery, and, hence, could modulate the expression of target genes through this mechanism.

Repression through recruitment of histone deacetylases and chromatin remodelling

A number of transcriptional regulators have been shown to alter chromatin structure at their target genes via the recruitment of histone acetyltransferases, histone deacetylases, and chromatin remodelling complexes. An indication that p53 may repress target promoters through alteration of chromatin structure was obtained from studies using trichostatin A (TSA), an inhibitor of histone deacetylases (HDAC). TSA was shown to abolish p53-mediated repression at the promoters of *Map4*,[82] α-*tubulin*,[42] and *survivin*.[45] In addition, the presence of wild-type p53 at the p53-repressed *survivin* promoter was associated with a decrease in acetylated histone H3 at the promoter.[45,46] The effects of TSA are consistent with the ability of p53 to associate with HDAC via the corepressor mSin3a. The association between p53 and mSin3a, which can be increased by DNA damage, was detected at the *Map4* promoter using chromatin immunoprecipitation assays.[82] In another study, hypoxia, which appears to activate preferentially the repression rather than the transactivation function of p53, was shown to promote the interaction between p53 and mSin3a.[42] These observations

raise the possibility that p53 may repress transcription, at least for a subset of genes, by the recruitment of chromatin-modifying factors to target promoters. The recent demonstration that p53 can interact with the SWI/SNF chromatin remodelling complex *in vitro* and *in vivo*[83] suggests that this interaction may also be important in regulating the ability of p53 to transactivate or repress gene transcription. Although the recruitment of SWI/SNF to promoters has been associated with transcriptional activation, there is evidence showing that chromatin-remodelling complexes are also involved in transcriptional repression.[84–87] Hence, the association and/or recruitment of SWI/SNF by p53 may lead to alterations in chromatin structure resulting in transcriptional repression of a subset of target genes.

Determinants of p53 Transrepression Potential

A number of studies have investigated the domains of p53 that are required for its transrepression activity. The N-terminus of p53 appears to be important[88,89] and this was confirmed recently with the demonstration that the ser25/arg26 p53 mutant is defective in its ability to repress the transcription of the *Map4* gene.[47] In addition, deletion of the C-terminal region of p53 abrogated transrepression, while fusion of the C-terminal region to GAL4 facilitated repression at heterologous reporter constructs.[78,88,89] Phosphorylation of p53 at serine 386 appears necessary for transrepression.[90] When this residue, which is believed to be a target of casein kinase II,[91] was mutated to alanine to abolish phosphorylation, the repression of the c-fos and SV40 early promoters was diminished, while p53-mediated transactivation was unaffected.[90] A p53 mutant containing aspartic acid instead of serine at this position retained partial repressor activity at the SV40 promoter. The negative charge contributed by the aspartic acid substitution often mimics certain aspects of phosphorylation. Finally, as described previously, the proline-rich domain of p53 was found to be important for the transrepression activity of p53.[16] Importantly, this region is required for the interaction between p53 and mSin3a, an association that is believed to form the basis of repression for certain p53 target genes.[82,92] Hence, it appears that the N-terminus, the proline-rich domain, and the C-terminus each contribute to the transrepressor activity of p53. If p53 mediates transcriptional repression through various different mechanisms (involving consensus and nonconsensus DNA-binding, protein–protein interactions, etc.), it is likely that different regions of p53 will be required to repress different promoters.

p53, like other transcriptional factors, possesses dual activation and repressor activities. It is important, therefore, to understand how these two activities are regulated, and to identify the *cis*-acting determinants that govern whether a gene will be activated or repressed by p53. The selectivity of the response is likely to be context-dependent. For instance, the location of the p53-binding site at the target gene and its proximity or overlap with the binding sites of other activator or repressor proteins could determine whether transactivation or transrepression occurs. In this regard, Ori *et al*.[54] examined p53-dependent transcriptional repression of the HBV promoter and noted that transcription was repressed in the presence of the native p53-binding site at the HBV enhancer. Repression was also seen when the native p53 site was replaced with the p53-binding site from the *Mdm2* promoter. Upon deletion of an adjacent EP element at the HBV enhancer, p53 activated rather than repressed transcription. Importantly, the insertion of the HBV-derived EP element into the *Mdm2* promoter led to the repression of *Mdm2* in a p53-dependent manner.

It is also possible that subtle differences within the p53-binding site itself may have pivotal effects on the action of p53. Differences in the sequence or spacing of the p53-binding sites at different genes could result in changes in the DNA secondary structure or in the topology of the chromatin. The conformation of the p53 protein that is bound at these sites may be altered affecting the ability of p53 to recruit coactivators or corepressors. Two recent reports support this view. First, deletion of the 3-nucleotide spacer between the two half sites of the p53 response element at the *survivin* promoter altered the response from repression to activation.[46] Second, p53-mediated repression of the *MDR1* gene was reported to be mediated by a novel and atypical p53-binding site within the *MDR1* promoter.[64] This sequence element bound to p53 and conferred p53-dependent repression to a heterologous reporter construct. Moreover, replacement of the repressor element within the *MDR1* promoter with a p53 consensus binding site resulted in p53-dependent transactivation.[64] Thus, the intrinsic nature of the p53-binding site is an important determinant of the transcriptional activity of p53.

Conclusions and perspectives

In this review, only a subset of p53-repressed genes has been described. Numerous others, including *BRCA1*,[93,94] *basic FGF*,[95,96] *presenilin-1*,[97] *FKBP25*,[98] *mIRS-3*,[99] and *fibronectin*,[100] have also been shown to be downregulated by p53. Moreover, genomewide expression analyses using DNA microarrays have been used to estimate that 80% of the p53-responsive genes are repressed rather than activated.[101] Indeed, p53 may potentially suppress the expression of a large number of genes. For many of the candidate genes that are repressed by p53, however, the mechanism of repression is not known and uncertainty exists as to whether these genes represent direct targets of p53 or whether their repression is a consequence of the cellular changes (cell cycle arrest, apoptosis) that are induced by p53. In addition, the physiological significance of p53-mediated repression remains unclear. These are all important questions that must be addressed if we wish to have a clear understanding of how p53 acts as a tumour suppressor.

With the advent of genomewide expression profiling and bioinformatic approaches, the list of p53-activated and repressed genes is rapidly expanding. This may lead to the portrayal of p53 as a haphazard and nonspecific transcriptional regulator. Emerging evidence, however, suggests that p53 may regulate cellular process through a coordinated programme that includes both the activation and the repression of cellular genes. For example, the mediation of G2 arrest by p53 is likely conferred by its ability to activate genes such

as *GADD45* and *14-3-3σ*, as well as to repress genes such as *cyclin B*, *cdc25c*, and *cdc2*.[71–73,75,102,103] In addition, mitogenic signalling by insulin-like growth factor (IGF-1) is inhibited by p53 via its ability to activate *IGF-BP3*,[104] and to repress *IGF-IR*[67,105] and *IRS-3* (insulin receptor substrate-3).[99] In both of these examples, p53-mediated transactivation and transrepression appear to be important. The precise contribution of transactivation and transrepression to the tumour suppressing activity of p53 is difficult to determine and is complicated by the heterogeneity of the p53 response to different stimuli and in different tissues.

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