Transcriptional Activities of Mutant p53: When Mutations Are More Than a Loss

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Abstract   The dominant oncogenic properties of mutant p53 have been recognized as a phenomenon associated with tumor progression a long time ago, even before it was realized that the major function of wild type p53 is that of a tumor suppressor. Recent advances in this fascinating area in tumor cell biology reveal that the community of mutant p53 proteins is comprised of proteins that are extremely diverse both structurally and functionally, and elicit a multitude of cellular responses that not only are entirely distinct from those mediated by wild type p53, but also vary among different mutant p53 proteins. Aberrant regulation of transcription is one of the mechanisms underlying the ability of some mutant p53 proteins to act as oncogenic factors. Systematic analyses of the transcriptional activities of mutant p53 suggest that not the loss of transcriptional activity as such, but alterations of target DNA selectivity may be the driving force of mutant p53 specific transcription underlying the growth-promoting effects of mutant p53. This article focuses on mechanistic aspects of mutp53 ''gain-of-function'' with the emphasis on possible mechanisms underlying transcriptional activation by mutp53. J. Cell. Biochem. 93: 878–886, 2004.   © 2004 Wiley-Liss, Inc.

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The tumor suppressor p53 mediates various physiological responses that enable cells to avoid the accumulation of genomic alterations induced by genotoxic insults and thereby sustain the intactness of the genome. Mutational inactivation of p53 is common in human cancers and renders cells non-responsive to signals that challenge genomic integrity, thereby promoting the acquisition of novel phenotypes that are characteristic for cancer cells such as resistance to apoptosis, neoangiogenesis, an increased proliferative and invasive potential, and formation of metastasis. A characteristic feature of the *p53* mutational spectrum is the frequency of missense point mutations within the region encoding the central DNA binding domain of the protein, with six codons (hot-spots) being most frequently targeted in the *p53* gene. The unusually high representation of missense *p53* point mutations in human cancers suggests that the presence of the resulting mutant p53 (mutp53) proteins, rather than the sheer lack of wtp53 activities may confer a selective advantage during tumor cell evolution [Greenblatt et al., 1994; Hussain et al., 2000]. Indeed, it has been demonstrated that mutp53 can be a causative factor for tumor progression, as expression of some mutp53 proteins in tumor cells with a p53-null background leads to an increase of their tumorigenic potential in vitro and in vivo (reviewed in [Sigal and Rotter, 2000]). The realization that some mutp53 proteins may play important roles as oncogenic factors in cancer progression led to the formulation of the "mutp53 gain-of-function" paradigm according to which mutp53 proteins, while having lost activities that prevent uncontrolled growth and protect cells from genomic alterations, may acquire novel activities that actually promote cell growth and survival. While several recent reviews have described the key findings that have been crucial for the establishment of the mutp53 "gain-of-function" concept [Deppert et al., 2000; Sigal and Rotter, 2000] this article focuses on the mechanistic aspects of mutp53

"gain-of-function" with the emphasis on possible mechanisms underlying transcriptional activities of mutp53.

mutp53 proteins are often referred to as being transcriptionally inactive due to the fact that most mutp53 proteins can not activate transcription from promoters that are positively controlled by wtp53. However, the fact that some mutp53 proteins that are unable to activate transcription from wtp53-inducible promoters can potently activate transcription of genes associated with growth- or survival-promoting activities (reviewed in [Sigal and Rotter, 2000] and Table I) indicates that the transcriptional deficiency of such mutp53 proteins only applies to a specific set of genes. This further implies that it is not the transcriptional potential as such, but the target gene specificity that is altered in mutp53, and that target gene specificity is a major feature distinguishing transcriptional activation by mutp53 from that of wtp53. Indeed, the spectrum of genes activated by mutp53 is quite distinct from that of wtp53 and includes genes whose activities contribute to the establishment of tumor phenotypes, which constitute the hallmarks of the progressing cancer, such as resistance to apoptosis, increased invasive and metastatic potential, and neo-angiogenesis (Table I). How the specificity of mutp53-mediated transactivation is achieved is poorly defined with the central question—is DNA binding involved?—having remained open. However, unveiling such mechanisms is of paramount importance considering that transcriptional activation by mutp53 has been implicated as a major activity determining the oncogenic properties of some mutp53 proteins.

"HOT-SPOT" mutp53-SPECIFIC DNA BINDING AND ITS RELATION TO mutp53 TRANSCRIPTIONAL ACTIVITIES

The question of whether mutp53 transactivation may require the direct binding of mutp53 proteins to DNA has been discussed controversially, mainly due to the fact that it is unclear whether mutp53 proteins can bind DNA specifically. A major challenge in delineating the parameters of mutp53 DNA binding is the lack of knowledge about the nature of a common denominator, such as a mutp53-specific sequence motif that would be specifically recognized by different mutp53 proteins. One of the major pitfalls in defining the specificity of mutp53: DNA interactions so far is that specificity of mutp53 DNA binding had been judged mainly from the ability of mutp53 proteins to bind sequences specifically recognized by wtp53, whereby the lack of an appreciable binding activity was interpreted as inability of mutp53 to bind DNA specifically. However, most promoters activated by mutp53 do not contain sequences resembling the p53 consensus, suggesting that mutp53 may regulate transcription via response elements that are distinct from wtp53-REs [Dittmer et al., 1993; Gualberto et al., 1995; Tsutsumi-Ishii et al., 1995; Frazier et al., 1998; Yang et al., 1999]. Indeed, the dissociation of mutp53 DNA binding from sequence-specific DNA binding (SSDB) of wtp53 becomes apparent, when DNA binding is examined with mutp53-regulated promoters, and not with wtp53-REs [Bargonetti et al., 1997; Chicas et al., 2000; Lee et al., 2000; Zalcenstein et al., 2003]. Analyses of mutp53 DNA binding by chromatin immunoprecipitation (ChIP)

TABLE I. Functional Spectrum of Some Genes Activated by Mutant p53 Proteins Deficient for wtp53-Specific Transactivation

Activated gene	Associated cancerous phenotype	Reference
MDR-1	Chemoresistance of cancer cells	[Lin et al., 1995]
IGF-I-R	Inhibition of apoptosis	[Werner et al., 1996]
IGF-II P3/P4	Inhibition of apoptosis	[Zhang et al., 1996; Lee et al., 2000]
hMMP-13	Invasion/metastasis	[Sun et al., 2000]
BAG-1	Inhibition of apoptosis	[Yang et al., 1999]
HSP70	Antiapoptotic protein chaperone	[Tsutsumi-Ishii et al., 1995]
c-fos	Increased proliferation	[Preuss et al., 2000]
c-myc	Increased proliferation	[Frazier et al., 1998]
PCNA	Increased proliferation	[Deb et al., 1992; Shivakumar et al., 1995]
DUTPase	Resistance to fluoropyrimidine drugs	[Pugacheva et al., 2002]
EGF-R	Angiogenesis	[Ludes-Meyers et al., 1996]
Asparagine synthetase	Growth promotion/resistance to apoptosis	[Scian et al., 2004]
Human TERT	De-regulated synthesis of telomeric DNA	[Scian et al., 2004]
L37, RPP-1, and S2	Increased synthesis of ribosomal proteins	[Loging and Reisman, 1999]

revealed that mutp53 proteins do physically associate with their responsive promoters in vivo, indicating that mutp53 proteins are targeted to DNA in a specific manner, yet independently from the presence of canonical p53 binding sites [Zalcenstein et al., 2003]. Intriguingly, different promoters activated by mutp53 show no sequence homology, suggesting that sequence-specific recognition is unlikely to be a parameter determining specificity of mutp53 DNA binding. This may explain why attempts to identify putative mutp53-specific response elements in genes regulated by mutp53 proteins have been unsuccessful thus far and did not yield any specific sequence motifs that qualified as mutp53-specific binding sites when tested in vitro using conventional DNA binding assays.

Our laboratory since many years has fostered the idea that the interaction of mutp53 with DNA is determined in large by the recognition of DNA structure, and by not specific sequence motifs. The idea derived from the finding that various mutp53 proteins, but not wtp53, bound with high affinity to MAR elements, which are regulatory DNA sequences important for higher-order chromatin organization, long-range enhancer function, and propagation of chromatin modifications. Due to the known structural flexibility of MAR elements, in vitro binding of mutp53 to MAR elements is independent of the presence of any consensus motif, but is greatly dependent on the length of DNA [Weissker et al., 1992]. The mechanism underlying the interaction of mutp53 with MAR elements remained obscure for a long time until very recently, when the picture of the specific interaction of wtp53 with DNA changed significantly. It now appears that specificity of mutp53 DNA binding might have derived from some crucial features of the interactions of wtp53 with DNA, which turned out to be more complex than it was thought earlier. wtp53 can interact with DNA in various modes that can be formally divided into SSDB or non-sequence-specific interactions (non-SSDB). Non-sequence-specific interactions include high affinity binding to double-stranded and single-stranded DNA, secondary DNA structures, and binding to aberrant sites in DNA such as mismatched bases and DNA bulges (reviewed in [Kim and Deppert, 2003]). Whereas sequence-specific recognition of linear (duplex) DNA is mediated solely by the p53 core DNA binding

domain, non-SSDB is more complex, involving either solely the C-terminal DNA binding domain, or the p53 core domain and the p53 C-terminus [Yakovleva et al., 2002]. It has been proposed that the various modes of DNA binding are associated with different activities of wtp53, with SSDB mediating p53 transcriptional control and non-SSDB modes being implicated in p53 functions in DNA repair and recombination. However, recent developments in the field revealed that the various types of DNA binding are not specific for certain activities of wtp53, but also contribute to its major activity—SSDB and transcriptional activation. It turns out that SSDB of wtp53 is not only sequence-specific, but also DNA structure-dependent, and is regulated by the non-SSDB activity of the p53 C-terminus (reviewed in [Kim and Deppert, 2003]). The dual control of DNA binding by sequence-specific and DNA structure-dependent recognition might confer specificity to wtp53-SSDB, as the presence of a specific sequence alone is not sufficient to support high affinity binding of wtp53, if the stereo-specific conformation of the DNA is not favorable [Gohler et al., 2002; McKinney and Prives, 2002]. The changing picture of wtp53-SSDB also puts the issue of mutp53-specific DNA binding in a new perspective and urges to consider the impact of DNA topology on the DNA binding and transcriptional activities of mutp53. The realization that DNA structure-dependent recognition is an important component in determining the specificity of wtp53-SSDB uncovers an earlier unknown aspect, which may be relevant for mutp53 DNA interaction, namely that specificity of mutp53 DNA binding may be determined mainly by the recognition of DNA structure. The idea is also supported by the finding that mutp53 DNA binding requires the same p53 domains as wtp53-SSDB to non-linear DNA, namely the core domain and the C-terminus [Muller et al., 1996; Will et al., 1998a]. The finding that transactivation of some promoters by mutp53 281G requires both CTD and the core domain [Frazier et al., 1998; Lanyi et al., 1998] lends further credit to this assumption. DNA structure-dependent recognition by mutp53 proteins would explain the lack of sequence similarity between different mutp53-responsive promoters, and the lack of success in attempts to delineate a common sequence denominator such as a mutp53-specific consensus binding

site. The idea that mutp53 proteins bind in a DNA structure-specific mode is strongly supported by the finding that mutp53 proteins bind preferentially to DNA sequences with a high propensity to undergo structural transitions [Will et al., 1998b; Koga and Deppert, 2000]. Direct demonstration that mutp53 proteins bind in a DNA structure-selective mode recently was provided by our studies with rationally designed DNA substrates that recapitulate different types of secondary DNA structures, such as stem-loop and four-way junction DNA structures. We found that most mutp53 proteins bind to non-linear DNA structures in a highly structure-selective manner, while being unable to bind the same sequences when presented in linear DNA (Goehler et al., submitted). The DNA structure-selective mode of DNA binding explains the high affinity binding ($K_D \sim 10^{-11}$ M) of mutp53 to MAR elements [Weissker et al., 1992] in vitro, and the prevalance of repetitive sequences among genomic sequences bound by mutp53 in vivo [Koga and Deppert, 2000; Brazdova et al., in preparation]. In contrast to wtp53-SSDB, which is controlled by both, sequence-specific and DNA topology-dependent recognition, the specificity of mutp53 DNA binding is determined exclusively by DNA topology, due to the impairment of sequence-specific recognition affected by mutations in the core domain. The apparent preference of mutp53 for non-linear DNA implies that the stereo-specific conformation of the DNA rather than the presence of specific sequence motifs will define whether a given promoter will be responsive or non-responsive to mutp53 (Fig. 1). An important implication emanating from the finding that mutp53 proteins bind preferentially to non-linear DNA is that identification of specific structural elements in the DNA rather than common sequence motifs may be a more meaningful strategy in the search for mutp53-specific response elements.

Fig. 1. Loss of sequence-specific DNA binding (SSDB) accompanied by the acquisition of mutp53-specific (non-linear?) DNA binding as a mechanism for mutant p53 gain-of-function.

RESIDUAL SSDB AS THE MECHANISM FOR GENE-SELECTIVE TRANSCRIPTIONAL ACTIVATION BY NON-"HOT-SPOT" mutp53 PROTEINS

The potential to induce genes with counteracting activities is a fundamental and the most intriguing feature of the transcriptional r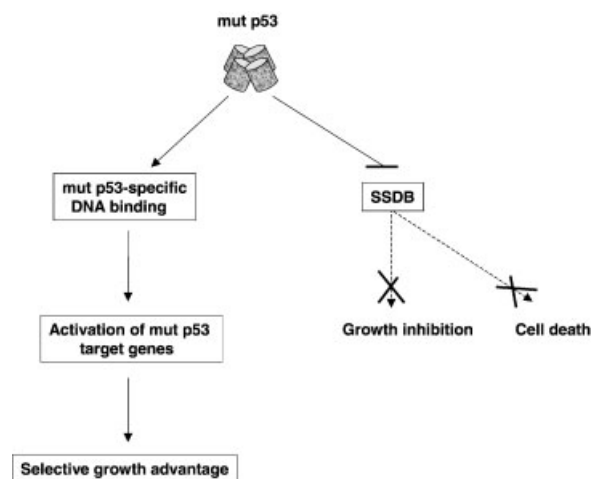esponse mediated by wtp53. Indeed, genes activated by wtp53 are functionally diverse and constitute downstream effectors of signaling pathways that elicit diverse responses such as cell survival, senescence or programmed cell death [Nakamura, 2004]. Reflecting the functional diversity of p53 target genes, a broad range of physiological responses can result from transcriptional activation mediated by wtp53, out of which transient arrest of the cell cycle or apoptosis are the most distinct ones (Fig. 2A). Whereas hot-spot mutations completely eliminate wtp53-SSDB as outlined above, partial inactivation of SSDB by non-"hot-spot" mutations appears to be another mechanism by which mutp53 proteins may shift the balance between distinct transcriptional responses in favor for those promoting growth and survival and thereby promote tumor progression. Analyses of a large number of mutp53 proteins revealed that different mutations within the DNA binding domain of p53 unequivocally affect the potential to activate transcription via wtp53 response elements (wtp53-REs). The effects of *p53* mutations on the transactivating potential of mutp53 proteins have been analyzed most intensively with wtp53-responsive promoters of genes that are involved in the regulation of cell cycle or in apoptosis. It appears that the loss of transactivation observed with individual mutp53 proteins is selective with respect to individual wtp53-REs; as some tumor-derived non-"hot-spot" mutp53 proteins to a varying degree often retain the potential to utilize some, but not all wtp53-REs as specific response
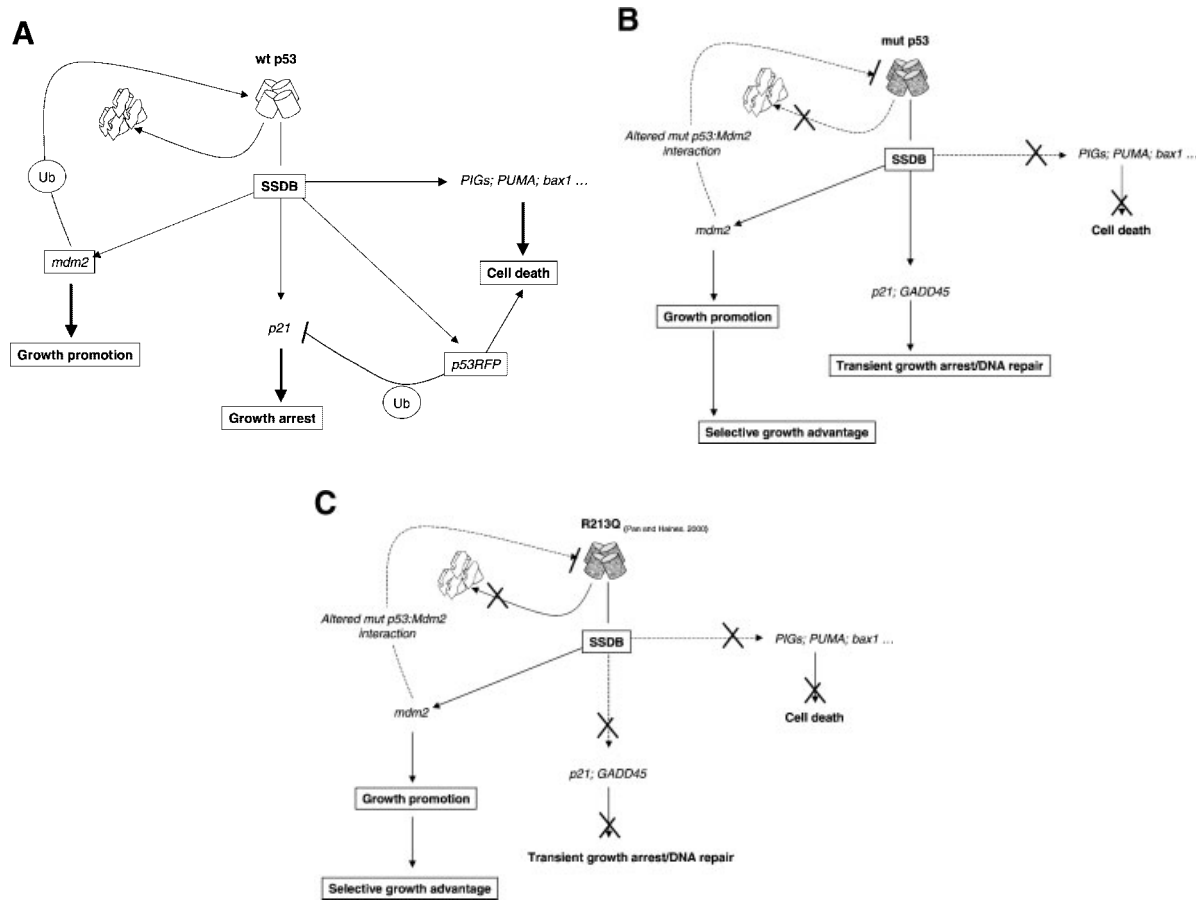
Fig. 2. **A**: Functional diversity and inter-dependent regulation of transcriptional responses elicited by wtp53. **B**: Selective aboliton of SSDB as a mechanism for mutp53-dependent alterations of cellular phenotypes. **C**: Promoter-selective transactivation as a mechanism for mutp53-dependent alterations of cellular phenotypes.

elements [Pan and Haines, 2000; Kato et al., 2003; Resnick and Inga, 2003]. Studies in yeast have been instrumental in unveiling the striking relationship between the extent of impairment of the transactivating potential, and the impact of individual mutations on the overall structure of a mutp53 protein. Importantly, such studies provided valuable insights into the understanding, how different missense mutations may lead to the establishment of diverse phenotypes by shifting the fine-tuned balance between different p53 transcriptional responses [Kato et al., 2003; Resnick and Inga, 2003]. Considering the extreme functional diversity of the genes activated by wtp53, alterations in promoter selectivity due to partial and non-ubiquitous loss of SSDB would ultimately lead to distinct palettes of diverse functional outcomes characteristic for individual non-"hotspot" mutants as proposed by [Resnick and

Inga, 2003] in the "master gene hypothesis" (Fig. 2B). One likely explanation for promoter-selective transactivation by mutp53 is that it may reflect the different binding affinities to various wtp53-REs. Indeed, the varying potential of mutp53 proteins to activate transcription from various wtp53-REs often parallels that of wtp53, generally with a stronger preference towards wtp53-REs from so-called "immediate early p53 response genes" that are involved in cell cycle arrest or DNA repair. In vitro binding studies indicate that the specific architecture of the DNA may be the parameter determining the different binding affinities of wtp53 to various wtp53-REs [Nagaich et al., 1997], which can be conditionally classified as "strong" and "weak" p53 binding sites. It ought to be expected that the effects of mutations targeting SSDB of wtp53 would be much more profound on the interaction of mutp53 with "weak" wtp53-REs

than with "strong" ones. In such a scenario, promoter selective activation by mutp53 would emerge as a consequence of the complete loss of SSDB with "weak" wtp53-REs and retention of residual binding to "strong" wtp53-REs.

Some tumor-derived non-"hot-spot" mutants exhibit apparently distinct preferences towards various wtp53-REs and show patterns of trans-activation that do not correspond to those of wtp53 [Pan and Haines, 2000; Resnick and Inga, 2003]. Non-"hot-spot" mutation thus can change the DNA binding preferences and result in promoter-selective transactivation of mutp53 via wtp53-REs. For example, mutp53 R213Q, while severely compromised in activating tran-scription of the *p21* and *PIG 3* and *PIG 11* genes, is potent in inducing *mdm2* transcription [Pan and Haines, 2000]. Considering the p53-inde-pendent growth-promoting effects of Mdm2, (reviewed in [Daujat et al., 2001]), the selective transactivation of *mdm2* may lead to a growth advantage (Fig. 2C).

PROMOTER-SPECIFIC TARGETING BY OTHER TRANSCRIPTION FACTORS

As an alternative for explaining how pro-moter-specific activation can be mediated by mutp53 proteins that have lost the ability to bind DNA in a sequence-specific manner, the possibility that mutp53 targets promoters re-gulated by other sequence-specific binding proteins has been explored intensively. In-deed, mutp53 proteins interact with several sequence-specific transcription factors, which are direct activators of genes that are also responsive to mutp53. One such factor is Sp-1, which regulates transcription by binding to Sp-1 response elements (Sp-1-REs) and interacts with wtp53 as well as with mutp53 proteins [Gualberto and Baldwin, 1995; Chicas et al., 2000]. Whether mutp53 DNA binding is in-volved in the co-operative transactivation by mutp53 and Sp-1 is unclear. While it has been proposed that mutp53 may be tethered to spe-cific promoters by interacting with Sp1 (or with other transcription factors) rather that by binding to DNA directly [Subler et al., 1994; Scian et al., 2004], experimental evidence sup-ports the view that DNA binding may be essen-tial for the co-operative effects of mutp53 on Sp1-dependent transcription [Gualberto et al., 1995; Bargonetti et al., 1997; Chicas et al., 2000]. It is important to note that in some

studies the DNA binding potential of mutp53 was assessed with a wtp53-consensus sequence, and not with DNA from the regulated promoters [Scian et al., 2004]. Such analyses may not be indicative for the DNA binding activity of mutp53 due to the reasons discussed earlier. Interestingly, the p53:Sp1-1 interaction can lead to opposite transcriptional outcomes de-pending on the status of the p53 protein: While wtp53 inhibits Sp1-dependant activation, pre-sumably by interfering with DNA binding of Sp-1 [Bargonetti et al., 1997], mutp53 proteins elicit co-operative effects and amplify the act-ivating effects of Sp-1 on transcription. Simi-larly, the physical association between wtp53 and the proto-oncoprotein Ets-1 is inhibitory to Ets-1 activity [Pastorcic and Das, 2000; Kim et al., 2003], whereas the mutp53:ets-1 interac-tion potentiates ets-1 transcription [Sampath et al., 2001]. The findings may indicate that stereo-specific multiprotein complexes contain-ing either wtp53 or mutp53 are functionally distinct. On the other hand, transcriptional regulation of the *MDR1*-promoter by wtp53 or by mutp53 is mediated by different promoter regions [Sampath et al., 2001], suggesting that the assembly of functionally distinct complexes may also be determined by different mechan-isms. Although DNA binding of wtp53 does not seem to be essential for Ets-1 inhibition [Pastorcic and Das, 2000; Kim et al., 2003], the possibility that mutp53 may enhance Ets-1 transcription by binding to DNA can not be excluded. Such a mechanism has been propos-ed to explain how Sp-1 transcription can be stimulated by mutp53, which binds to Sp1-sites and enhances DNA binding of Sp-1 [Chicas et al., 2000; Lee et al., 2000].

CHROMATIN MODIFICATIONS AND TRANSCRIPTIONAL ACTIVITIES OF mutp53

Recent studies revealed that p53 transcrip-tion is tightly associated with chromatin mod-ifying activities, which play a crucial role in the regulation of the p53 transcriptional response [Espinosa and Emerson, 2001; An et al., 2004]. Intriguingly, in a pioneering work the group of J. Milner recently has provided direct evidence that p53 itself is a chromatin accessibility factor by demonstrating that wtp53 can mediate global relaxation of the chromatin in response to UV-irradiation [Rubbi and Milner, 2003]. Furthermore, the same group has shown that

site-specific modifications of histone H3, accompanying chromatin relaxation coupled to transcription, are dependent on p53 [Allison and Milner, 2003]. It has been proposed that DNA binding may be an essential component enabling site-specific targeting of p53 transcriptional co-activators such as acetyltransferases p300/CBP [Gu et al., 1997] or arginine methyltransferases PRMT1 and CARM1 [An et al., 2004]. The unifying model emerging from these findings is that p53 is directly involved in the alterations of chromatin structure and thereby may influence transcription at specific loci in the chromatin. Whereas the dynamics and the impact of chromatin modifying activities in transcriptional control by wtp53 are beginning to be unveiled, the roles of chromatin structure in transcriptional control by mutp53 have not yet been addressed. Considering that mutp53 proteins can bind DNA with a specificity distinct from that of wtp53, the intriguing possibility arises that mutp53 is directly involved in re-organization of global chromatin structure. Due to the altered DNA binding specificity mutp53 proteins would target chromatin-modifying activities to chromatin loci distinct from those targeted by wtp53. The constitutive association of high amounts of mutp53 with chromatin would provide conditions for the stable maintenance of altered structural profiles in the chromatin, which may lead to the establishment of novel patterns of gene expression. Such alterations in chromatin structure might be especially furthered by the demonstrated binding of mutp53 proteins to MAR elements. Such a function of mutp53 would not be without any predecessors: The nuclear matrix protein SATB1 orchestrates the temporal and spatial expression of multiple genes during T-cell development [Alvarez et al., 2000], and the closely related SATB2 protein modulates immunoglobulin mu gene expression [Dobreva et al., 2003]. A function of mutp53 proteins in chromatin remodeling is also consistent with the constitutive association of mutp53 proteins with enzymes that are involved in the modulation of chromatin topology, like e.g., topoisomerases I and II [Gobert et al., 1999]. Further analyses of genomic sequences bound by mutp53 in vivo, their relation to genes regulated by mutp53, and of protein partners associating with mutp53 in vivo will shed light on the mechanism of mutp53 gene expression induced by chromatin remodeling.

CONCLUDING REMARKS

If one considers transcriptional activation by wtp53 to be complex, then transcriptional activation by mutp53 proteins is even more complex. The higher complexity arises from the fact that several rather distinct mechanisms lead to altered gene expression in cell expressing mutp53 compared to cells expressing a wtp53 or no p53 at all. Most easy to grasp is the altered interaction of mutp53 proteins with wtp53-REs, leading to transcriptional responses which in the end favor growth promotion and challenge the genetic stability due to accumulation of further mutations, i.e., loss of wtp53 repair activities and an inability to induce apoptosis. However, this mode of mutp53 specific gene expression seems to be reserved to a rather small spectrum of non-"hot spot" mutp53 proteins. That an altered interaction of mutp53 proteins with other transcription factors will lead to changes in gene expression also is understandable, although the mechanisms how mutp53 proteins change the inhibitory effect of wtp53 into a stimulatory one are not at all understood. Finally, the purely DNA structure-selective binding of mutp53 proteins emerges as a novel means how mutp53 proteins could modulate transcription. The importance of structure-selective DNA binding for mutp53 "gain-of-function" is underscored by the fact that structure-selective DNA binding is a property closely associated with "hot-spot" mutp53 proteins. Structure-selective DNA binding of mutp53 most likely is the base for the long reported, but so far hardly understood interaction of mutp53 proteins with MAR DNA elements. Binding of mutp53 proteins to MAR elements, together with the ability of mutp53 proteins to interact with proteins involved in chromatin remodeling, provides a novel means for modulating gene expression. Binding of mutp53 to MARs will solely depend on the availability of structural features in the MAR-DNA favorable for mutp53 binding and therefore will be statistical, i.e., non-selective for certain genes or gene families. Chromatin remodeling induced by mutp53 may promote the acquisition of stereo-specific features favoring mutp53 interaction with structurally flexible DNA such as MAR regions, thereby defining them as specific targets for mutp53. One thus could envision that mutp53 could induce an increased epigenetic instability of tumor cells,

which facilitates and accelerates the evolution of the tumor, i.e., tumor progression. The hypothesis could explain the cell-specific changes in gene expression associated with mutp53, and the apparent difficulties in deciphering the mechanisms underlying the dominant-oncogenic functions of mutp53 due to transcriptional activation of tumor-associated genes. Clearly, the hypothesis is speculative for the moment and needs further experimental substantiation. However, further analyses of the impact of mutp53 specific DNA interaction in transcriptional activities mediated by mutp53, and the interrelation of chromatin structure to gene expression will further our understanding of mutp53 "gain-of-function," which is a prerequisite for targeting mutp53 in tumor therapy.

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