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# Binding of MAR-DNA Elements by Mutant p53: Possible Implications for Its Oncogenic Functions

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**Abstract** The tumor suppressor p53 is a multifunctional protein whose main duty is to preserve the integrety of the genome. This function of wild-type p53 as "guardian of the genome" is achieved at different levels, as a cell cycle checkpoint protein, halting the cell cycle upon DNA damage, and via a direct involvement in processes of DNA repair. Alternatively, p53 can induce apoptosis. Mutations in the p53 gene occur in about 50% of all human tumors and eliminate the tumor suppressor functions of p53. However, many mutant p53 proteins have not simply lost tumor suppressor functions but have gained oncogenic properties which contribute to the progression of tumor cells to a more malignant phenotype. The molecular basis for this gain of function of mutant p53 is still unknown. However, mutant (mut) p53 specifically binds to nuclear matrix attachment region (MAR) DNA elements. MAR elements constitute important higher order regulatory elements of chromatin structure and function. By binding to these elements, mut p53 could modulate important cellular processes, like gene expression, replication, and recombination, resulting in phenotypic alterations of the tumor cells. Mut p53 thus could be the first representative of a new class of oncogenes, which exert their functions via long-range alterations or perturbation of chromatin structure and function. © 1996 Wiley-Liss, Inc.

**Key words:** chromatin structure, nuclear matrix, transcriptional activation, replication, recombination, differentiation

## WILD-TYPE p53: GUARDIAN OF THE GENOME

p53 is a molecule of some celebrity: mutations in its gene constitute the most frequent alteration in a single gene in human cancer [Soussi et al., 1994], and in 1993 p53 made it to "molecule of the year" [Marx, 1993]! Like most celebrities, p53 has a complex personality and a complex history. Wild-type (wt) p53 now is recognized as a tumor suppressor, whose main function is to preserve the integrity of the genome. As "guardian of the genome" [Lane, 1992], p53 acts as a cell cycle checkpoint protein which becomes activated upon DNA damage and halts the cell cycle by upregulating the expression of genes whose products function as negative regulators of cell-cycle progression. The most famous one is the $p21^{WAF1/CIP1}$ protein, a potent inhibitor of cyclin-dependent kinases (cdk), whose activities are required for cell-cycle progression. $p21^{WAF1/CIP1}$ also is able to block replicative (but not repair) DNA synthesis by interacting with PCNA, the auxiliary subunit of polymerase δ [Cox and Lane, 1995]. Upregulation of p53 target genes critically depends on the function of p53 as a sequence-specific transactivator. Consequently, sequence-specific DNA binding to p53 consensus DNA elements is considered to be one of the most important biochemical functions of p53. This view is strongly supported by the finding that most mutations in the p53 gene target the DNA binding domain of the p53 molecule (Fig. 1), leading to a mutant (mut) p53 protein with impaired DNA binding properties [Cho et al., 1994]. Although sequence-specific DNA binding and transactivation of p53 target genes are important functions of wt p53, stalling of cell-cycle progression is achieved not only by upregulation of p53 target genes, as p53 can also suppress transcription by interacting with transcription factors $TAF_{II}40$ and $TAF_{II}60$ and possibly also with TBP, the TATA box binding protein. Targets for transcriptional repression by p53 are proliferation-associated genes (e.g., *c-fos* and PCNA) [Cox and Lane, 1995]. In addition to mediating DNA damage, growth arrest and possibly also apoptosis [Oren, 1994] by modulating cellular transcription, p53 has a number of other biochemical activities, which directly relate to its function as a superior control element in

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preserving the integrity of the cells' genetic information:

1. p53 binds nonspecifically to both double-stranded and single-stranded DNA and to RNA, an activity performed by an independent RNA/DNA binding domain in the C-terminal region of the p53 molecule (Fig. 1) [Foord et al., 1991; Mosner et al., 1995; Steinmeyer and Deppert, 1988].
2. p53 can also bind to, and thereby mark, bulges of damaged DNA resulting from DNA mismatch; this activity requires both the central core domain and the C-terminus of p53 [Lee et al., 1995].
3. p53 has an intrinsic 3′ → 5′ exonuclease activity which might be required for excising damaged DNA before repair. This activity is also mediated by the p53 core domain [Mummenbrauer et al., submitted].
4. p53 binds to internal stretches of single-stranded DNA via its core domain and to single-stranded DNA at the ends of single-strand/double-strand overhangs, and via its DNA • DNA reannealing activity it is able to mediate reannealing of complementary DNA strands [Bakalkin et al., 1994, 1995], thereby probably preventing unscheduled recombination.

The reannealing activity of wild-type p53 at least in vitro is even more efficient in reannealing complementary strands of RNA [Oberosler et al., 1993]. This provides p53 with the possibility to regulate gene expression at the translational level by attenuating translation of mRNAs with an extended secondary structure in their 5′-untranslated region (5′-UTR). An important target of this translational repression is the p53 mRNA itself. Repression of p53 mRNA translation is rapidly relieved when the cells encounter DNA damage, as p53 then becomes translocated into the cell nucleus and activated for its functions as a guardian of the genome [Mosner et al., 1995]. The multifunctionality of the p53 molecule as outlined here is further underscored by the finding that p53 binds to and interacts with a plethora of poteins which are involved in transcription and DNA replication or repair [Deppert, 1994b], as summarized in Figure 2.

## MUTANT P53: A DOMINANT ONCOGENE

Given this multifunctional nature of the p53 molecule, it is astounding that single missense point mutations in the p53 molecule should totally eliminate p53 function, as has been previously advocated [see, e.g., Vogelstein and Kinzler, 1994]. In fact, already the selection of missense point mutations (which account for about 90% of all mutations in the p53 gene) over truncations and deletions or over inactivation of p53 gene expression [Soussi et al., 1994] is an indicator for mut p53 still exerting important functions. This view fits very well into the history of the p53 molecule, which is marked by a radical change from being dubbed an oncogene in the early days of p53 research to its current listing as a tumor suppressor [Deppert, 1993, 1994a,b]. The classification of p53 as an oncogene resulted from the observation that the p53 cDNAs then available were able to immortalize primary rodent cells and to cooperate with an activated *ras* gene in phenotypic transformation, putting the p53 gene into the same class of oncogenes as the *myc* gene. It was not until one found out that all the oncogenic properties of the p53 cDNAs used at that time were due to these DNAs containing point mutations and that a true wt p53 encoding cDNA actually suppressed cellular transformation rather than furthering it [Deppert, 1993, 1994a] that research on p53 focussed on the properties of wt p53 as a tumor suppressor.

However, in addition to the transforming properties of mut p53 as outlined above, further observations provided strong evidence that at least some mut p53 molecules are truly oncogenic in the sense that they contribute to the progression of tumor cells to a more aggressive phenotype; transfection of a mut p53 gene into growth-arrested mouse Swiss 3T3 cells abrogated the requirement of these cells for platelet derived growth factor (PDGF) for the induction of cellular DNA synthesis [Kaczmarek et al., 1986]; and, when overexpressed in normal rat 1 fibroblasts, mut p53 conferred a tumorigenic phenotype to these cells without inducing a transformed phenotype [Eliyahu et al., 1985]. Whereas the oncogenic properties of mut p53 in the transfection experiments described above still could be explained by a dominant-negative effect of the (overexpressed) exogenous mut p53 over the endogenously expressed wt p53 [Hinds et al., 1989; Milner and Medcalf, 1991], there is also ample evidence for endogenous dominant-oncogenic functions of mut p53 in p53-deficient cells. Mut p53 enhanced the tumorigenic phenotype of the p53-deficient, weakly tumorigenic Abelson murine leukemia virus transformed

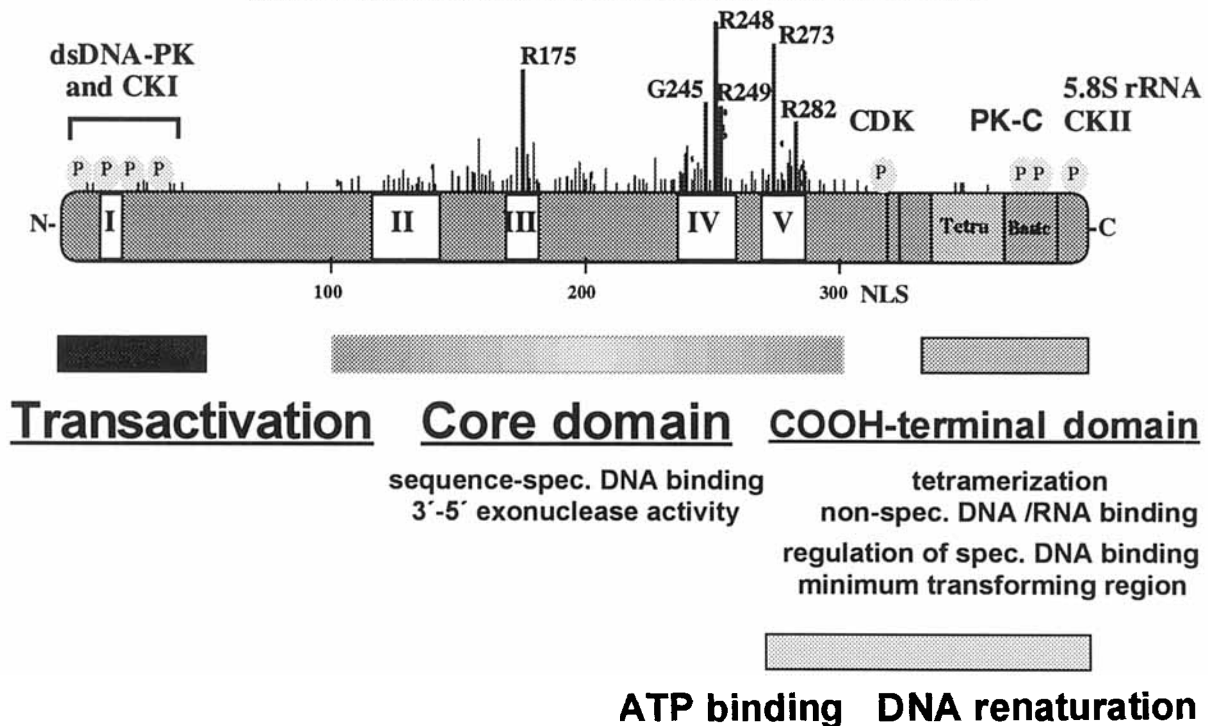


**Fig. 1.** Structural domains of p53. Roman numerals represent the five regions of p53 that are conserved from all vertebrates. The main nuclear localization signal (NLS) and the oligomerisation domain (tetra) are shown; known phosphorylation sites, phosphorylated by the respective kinases, are indicated above. The squares in the center indicate residues mutated in human tumors (mutational hot spots are identified by amino acid number). Shown below is the current information concerning the biological activities of various domains of p53.

mouse L12 cells [Shaulsky et al., 1991]. Mut p53 also increased the metastatic capacity of cells of a p53-deficient murine bladder carcinoma cell line [Pohl et al., 1988]. Furthermore, transfection of a variety of tumor *mut p53* genes into p53-negative human SAOS-2 and BALB/c mouse (10)3 cells enhanced the proliferation rate and the tumorigenicity of these cells [Dittmer et al., 1993]. All these data strongly support the concept that mut p53 not only is characterized by the loss of p53 tumor suppressor functions but also by a gain of function, conferring an active oncogenic potential to this molecule. Thus, a single point mutation could score as two hits in one, as it converts a tumor suppressor into a dominant oncogene [Deppert, 1994a].

## ACTIVITIES OF MUTANT p53 RELATING TO ITS ONCOGENIC FUNCTIONS

The molecular basis for this gain of function of mut p53 is still elusive. Mut p53 has retained some of the biochemical activities of the wt protein, like non-sequence-specific DNA binding and nonspecific binding to RNA as well as specific binding to RNA with extensive secondary structures [Mosner et al., 1995; Steinmeyer and Deppert, 1988]. Combined with the retention of mut p53's ability to bind to various cellular proteins and the loss of certain wt functions, these activities could contribute to mut p53's oncogenic potential simply via a deregulated interaction of mut p53 with nucleic acids and

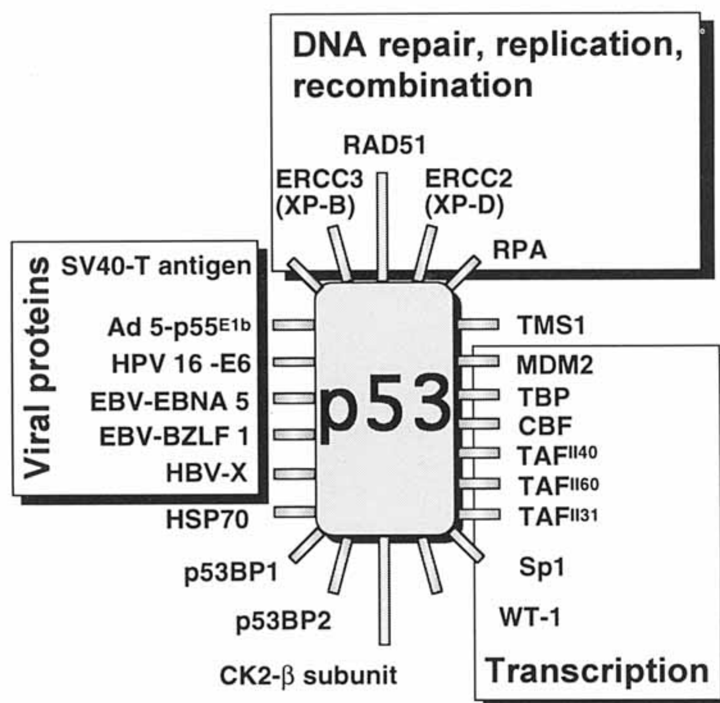


**Fig. 2.** p53 protein interactions. p53 binds to an ever-increasing number of cellular and viral proteins involved in DNA repair, replication, recombination, and transcription.

cellular proteins. However, although the oncogenic effects of mut p53 are pleiotropic, they nevertheless result in specific effects in the particular cells studied. Thus, the interactions of mut p53 with nucleic acids (and with cellular proteins) require additional parameters, which provide these interactions with some kind of specificity. This becomes apparent in analyzing the only activity reproducibly found with mut p53, which is its ability to modulate gene expression in certain cell types. Mut p53 has been shown to upregulate the expression of certain genes that are involved in cell proliferation and tumorigenesis: *mdr-1* gene expression was upregulated by mut p53 in mouse NIH3T3 cells, and, in embryonic kidney cells, mut p53 activated the vascular endothelial growth factor (VEGF), which plays an important role in tumor neoangiogenesis. Furthermore, a whole variety of different mut p53 proteins were shown to stimulate expression of PCNA in HeLa cells. Although the list of tumor-promoting genes reported to be upregulated by mut p53 is constantly growing, one has to be aware that there are many conflicting reports, as upregulation of a particular gene by a transfected mut p53 may be observed in one type of cell but may be totally absent in another one [Deppert, 1994b]. This already indicates that stimulation of gene expression by mut p53 must be due to a different mechanism than the wt p53 specific transactivator function, especially as most mut p53 proteins have lost this property [Deppert, 1994a]. Nevertheless, transactivation of these genes is *directly mediated by the mut p53*, as mutations in the N-terminal transactivator domain of p53 abolish this transactivator function [Lin et al., 1995]. How, then, can one explain the specific upregulation of expression of certain tumor-promoting genes by mut p53 and the fact that this effect seems to be cell-type specific?

## MUTANT p53 SPECIFICALLY BINDS MAR-DNA ELEMENTS

To resolve this problem of specificity, our laboratory has analyzed in detail the DNA binding properties of murine wt and mut p53 with the hope of finding a specific interaction of mut p53

with DNA which is different from that of wt p53. Two possibilities might be considered: 1) mut p53 might show specificity for different DNA consensus sequence elements or 2) display a novel interaction with DNA. Although not known at the time when our studies were initiated, the first possibility now appears unlikely by theoretical considerations. Cocristallization of the p53 core domain with a p53 consensus DNA element revealed that the DNA binding domain of p53 is characterized by the compaction of several individual DNA binding elements which together form the sequence-specific DNA binding domain of wt p53 [Cho et al., 1994]. Mut p53 characteristically displays a conformational "opening" of this domain [Milner, 1995]. This opening can be demonstrated by the accessibility on the native mut p53 molecule of an epitope located in this region of the p53 molecule (the PAb240 epitope). This epitope is not available on native wt p53 but becomes exposed after denaturation. Thus, in mut p53, the individual DNA binding elements most likely are too far apart for forming a sequence-specific DNA binding domain.

Using λ DNA as a model substrate for a DNA which due to its length and complexity contains abundant sequence elements for sequence specific interaction as well as structural elements for more complex interactions of protein with DNA, we were able to demonstrate that highly purified mut p53 from mouse MethA tumor cells was able to specifically bind the 1,215 bp *AluI* fragment of λ DNA. This fragment had both sequence and structure similarities to nuclear matrix attachment region (MAR) DNA elements. Binding of mut p53 to this λ DNA fragment was complex, obviously involving both structure and sequence elements, as it could not be narrowed down to any small consensus oligonucleotide binding; minimally the 818 bp *AseI*/*AluI* fragment contained within the 1,215 bp *AluI* fragment of λ DNA was required for binding by mut p53. Binding also was of high affinity ($K_D \approx 10^{-10}$ M), as demonstrated by Scatchard analysis [Weißker et al., 1992]. Further studies then proved that this type of complex DNA binding indeed reflected binding of MethA p53 to MAR-DNA elements, as it could be extended to several bona fide MAR-DNA elements. These studies also revealed that this binding was specific for mut p53 insofar as the affinity of mut p53 to MAR DNA was approximately 1,000-fold higher than that of wt p53 [Müller et al., in press].

## STRUCTURAL REQUIREMENTS FOR MAR-DNA BINDING BY MUTANT P53

Wt p53 contains two separate domains for its interaction with nucleic acids: the central core domain, mediating sequence-specific binding to p53 consensus DNA elements, and a domain located in the C-terminal region of p53, which directs the non-sequence-specific interactions of p53 with ds and ss DNA and RNA (see Fig. 1). Antibody interference analysis indicated that the C-terminal nonspecific DNA binding domain is involved in MAR binding, as MAR binding of mut p53 was blocked by the monoclonal antibodies PAb421 and PAb122, mapping to overlapping epitopes within this region. In addition, the p53 oligomerization domain, localized within the p53 C-terminus, most likely is functionally important in mediating MAR binding by mut p53. However, the C-terminus of p53 is not the sole mediator of this binding activity. By antibody interference, MAR binding also was blocked by PAb240, binding to an epitope within the core region of p53. Furthermore, our analyses of truncated p53 fragments clearly established that the p53 C-terminus, although absolutely required for MAR binding, by itself is not sufficient for exerting this activity. Instead, MAR binding in addition requires the central core domain of p53. In accordance with our claim that MAR binding is an activity specific for mut p53, this central core domain must contain a mutation in order to be active in MAR binding [Müller et al., in press]. As neither the isolated C-terminus nor the isolated mut p53 core domain by itself was able to bind MAR-DNA elements, we conclude that these domains must interact for MAR binding. As a model compatible with our data, we suggest that both domains are directly involved in binding to distinct sequence/structure elements on the MAR DNA, thereby conferring high affinity MAR binding properties to mut p53. As outlined in the first section, it is becoming more and more evident that the core domain of wt p53 is able to interact with nucleic acids in quite different ways. Thus, an involvement of the conformationally opened core domain of mut p53 in MAR binding is compatible with the unique properties of this unusual DNA binding domain. In line with this model, it has been demonstrated that the C-terminal region of p53, binding to nucleic

acids in a non-sequence-specific manner, can interact with the core domain of wt p53 in DNA binding, leading to high affinity binding of wt p53 to bulges in damaged DNA [Lee et al., 1995]. We propose that the altered conformational structure of the mut p53 core domain creates a new DNA binding motif, recognizing distinct structural determinants on MAR-DNA elements, whereas the C-terminal of mut p53 contributes to MAR binding via non-sequence-specific DNA binding, possibly to single-stranded regions of MAR DNA.

MAR elements are characterized by a high level of adenosine/thymidine (A/T)-rich DNA stretches. These A/T clusters are responsible for the high flexibility of these DNA elements. A/T richness also is responsible for DNA bending, a property characteristic for MAR-DNA elements [Bode et al., in press; Boulikas, in press]. Such structural determinants facilitate loop formation, which in turn would facilitate the binding of different motifs of MAR DNAs at the core domain and at the C-terminus on a p53 molecule. Consequently, oligomerization of p53 could provide multiple attachment points which would contribute to the high affinity binding of MAR/SAR elements by mut p53. This effect could even be enhanced by the recently described ability of the p53 core domain to interact with other p53 core domains via stacking, thereby leading to multimerization of p53 molecules on bound DNA [Stenger et al., 1994]. Clearly this model needs further experimental support which requires more knowledge also on the structural determinants of MAR DNA elements for their interaction with mut p53.

## BIOLOGICAL IMPLICATIONS OF MAR-DNA BINDING BY MUTANT P53

MAR elements organize the cellular chromatin into topologically independent loops, providing a structural basis for the independent spatial and temporal regulation of gene expression and initiation of DNA synthesis. Such a regulation is thought to form a higher order regulatory mechanism for controlling development and differentiation [Berezney, 1991; Bode et al., in press; Boulikas, in press; Gasser and Laemmli, 1987; Herbomel, 1990]. Experimental support for a regulatory role of MAR elements has been provided by transfection experiments, which demonstrated that MAR elements promote elevated and position-independent expression of genes in stably transfected cells [Bode et al., in press; Boulikas, in press]. Furthermore, there is evidence that the MAR element of the immunoglobulin κ gene locus plays a crucial role in the promoter switch and the overexpression of the translocated *c-myc* gene in Burkitt's lymphoma cells [Polack et al., 1993]. The importance of MAR elements in such fundamental regulatory processes renders these elements important targets for regulatory proteins by providing the possibility to modulate chromatin organisation. This in turn will affect gene expression and/or replication and thus cell function via long-range chromatin alterations. So far, however, virtually nothing is known about the possible regulation of gene expression via regulatory interactions of proteins with MAR elements, as most proteins so far identified to bind MAR elements are ubiquitous structural proteins, possible involved in anchoring MAR elements to the nuclear matrix [Bode et al., in press; Boulikas, in press]. Recently, however, a MAR-DNA binding protein, SATB1, has been described, which indeed might exert a regulatory role by binding to MAR elements [Dickinson et al., 1992], as it is primarily expressed in thymocytes, indicating a cell-type specific function for this protein. As p53 is a regulatory molecule, the binding of mut p53 to MAR elements should also be of regulatory rather than of structural nature. Mut p53 thus might be the first representative of a new and exciting class of oncoproteins which exert their oncogenic functions via long-range alterations of chromatin structure.

How could MAR binding contribute to the oncogenic potential of mut p53? As outlined above, an active role of mut p53 in modulating gene expression is becoming more and more apparent. We propose MAR binding as a possible mechanism by which mut p53 can activate the expression of genes involved in cell proliferation and tumorigenesis. For example, mut p53–mediated DNA loop formation might allow *cis* acting regulatory elements cohabitating with MAR elements to come into close proximity to promoter structures of certain genes, resulting in their enhanced expression (Fig. 3). p53-mediated sublooping of chromatin loops for gene activation, as depicted in the model shown in Figure 3, not only is promoted by mut p53's ability to bind MAR DNA but also by its ability to tightly associate with the nuclear matrix by itself [Deppert and Haug, 1986]. As the N-terminal transactivator domain of mut p53 is required for mut p53–specific transactivation, mut

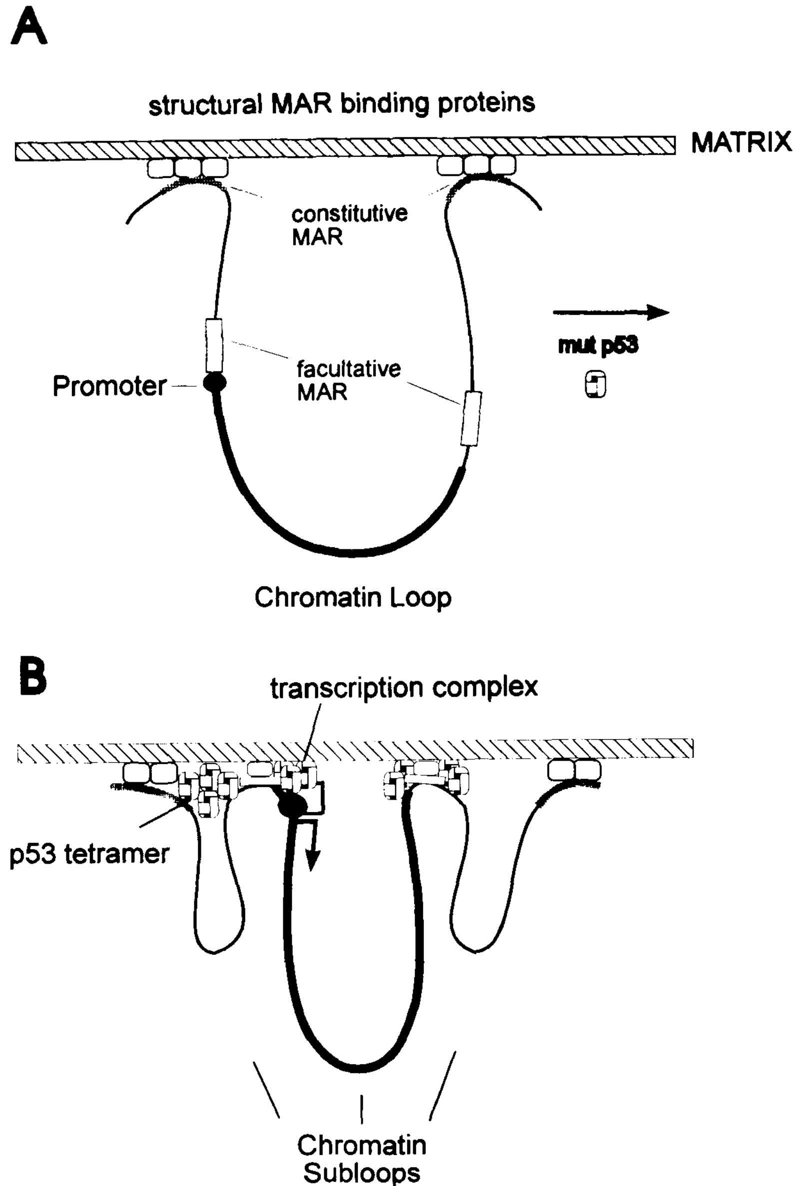


**Fig. 3.** Model for gene activation by mutant p53 by mediating the coordinated assembly of regulatory elements at the nuclear matrix. **A:** Model of an inactive gene (thick line) within an already opened chromatin loop, attached to the nuclear matrix via constitutive MAR elements and structural MAR binding proteins. This gene is flanked by facultative MAR elements, which become attached only to the nuclear matrix when transcription of the gene becomes activated. By binding of mutant p53 to constitutive and facultative MAR elements as well as to proteins of the nuclear matrix, sublooping of the chromatin is achieved (**B**). Regulatory *cis* elements, contained within or bordering the MAR elements, now are in close proximity, leading to the assembly of a transcriptional complex at the promoter. This results in activation of transcription (*arrow*).

p53 not only will serve to bring together the appropriate DNA elements but also to assemble transcriptional complexes on these DNA elements (Fig. 3). Alternatively, or in addition, binding of mut p53 to MAR elements might allow the creation of "active" chromatin domains, promoting the expression of otherwise silent genes. Such a model would account for the finding that the specificity of mut p53–mediated upregulation of gene expression is conferred by the cell itself. As the promoter/enhancer elements for a given gene are identical within a species, cell-specific gene expression is controlled both by the availability of the appropriate protein factors and by an appropriate chromatin structure. In this regard, mut p53's ability to induce alterations in chromatin structure leading to an opening of a chromatin domain

and thus to transcriptional activation by binding to MAR elements will critically depend on the accessibility of those MAR elements.

An interesting possibility for modulating mut p53 functions when bound to MAR elements is mut p53's ability to interact with cellular proteins, like the replication protein RPA [Dutta et al., 1993] and the recombination protein Rad51 [Stürzbecher et al., 1995]. By binding these proteins, the activation of a certain chromatin domain by mut p53 might not affect transcription but rather result in the targeting of proteins involved in DNA replication (RPA) or recombination (Rad51), leading to the assembly of functional replication or recombination complexes. This hypothesis is compatible with the finding that mut p53 has been implicated in promoting cell proliferation [Dittmer et al., 1993] and unscheduled recombination [Xia et al., 1995]. Conversely, as binding of mut p53 to MAR elements is very tight, one could also envision a literal fixation of certain DNA loop structures by mut p53 bound to MAR elements. Fixation of the chromatin loop organization would have implications on the differentiation state of a cell, as gene expression, replication, and differentiation are thought to be coupled via chromatin organisation [Herbomel, 1990]. In this respect, it is an extremely interesting observation that enhancement of the tumorigenic phenotype of L12 cells by transfection of mut p53 correlates with a block in differentiation of these cells [Shaulsky et al., 1991].

## FUTURE AVENUES

The MAR concept of gene regulation by mut p53 is an appealing model for explaining the pleiotropic oncogenic activities of many mut p53 proteins. Further studies, however, aimed at determining the exact structural requirements of the DNA sequences recognized by the mut p53 protein and their in vivo functions in terms of p53-mediated gene regulation will have to prove this hypothesis. As a first indicator for assessing the relation of MAR binding to in vivo function, it will be interesting to determine whether the binding of various mut p53 to MAR elements correlates with their oncogenic properties. Furthermore, one would predict that mutant p53 molecules still displaying a wild-type conformation would exhibit reduced MAR binding activity, in accordance with the general notion that such mutant p53 molecules are only weakly oncogenic [Deppert, 1993; Zerrahn et al., 1992]. Analysis of MAR-DNA binding of mutant p53 thus could develop into a suitable test system for the classification of the oncogenic properties of mutant p53. Finally, I should like to address an issue which might be important for therapeutic considerations. If mut p53 functions as a dominant oncogene through long-range chromatin alterations and perturbation of chromatin structure at sites of the chromatin which are critical higher order regulatory elements for replication, gene expression, and recombination, then mut p53 is actively and constantly contributing to the progression of tumor cells to a more malignant phenotype. This in turn implies that elimination of mut p53 functions in tumor cells should be beneficial for cancer treatment. Understanding the interaction of mut p53 with MAR elements at the molecular level then might allow specific interference with MAR DNA binding of mut p53. This might provide a means for at least stabilizing the phenotype of a cancer cell (i.e., stop its progression), thereby considerably improving the means of therapeutic intervention. In an even more optimistic view, one could hope that elimination of mut p53's interaction with MAR elements of tumor cells might severely perturb replication and gene expression in these cells, leading to tumor cell death.

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