

Oncogenic Mutations of the p53 Tumor Suppressor: The Demons of the Guardian of the Genome

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Abstract

The p53 guardian of the genome is inactivated in the majority of cancers, mostly through missense mutations that cause single residue changes in the DNA binding core domain of the protein. Not only do such mutations result in the abrogation of wild-type p53 activity, but the expressed p53 mutant proteins also tend to gain oncogenic functions, such as interference with wild-type p53-independent apoptosis. Because p53 mutants are highly expressed in cancer cells and not in normal cells, their reactivation to wild-type p53 function may eliminate the cancer by apoptosis or another p53-dependent mechanism. Several studies that embarked on this quest for reactivation have succeeded in restoring wild-type p53 activity to several p53 mutants. However, mutants with more extensive structural changes in the DNA binding core domain may be refractory to reactivation to the wild-type p53 phenotype. Therefore, understanding the structure and functions of oncogenic p53 mutants may lead to more potent reactivation modalities or to the ability to eliminate mutant p53 gain of function.

Introduction

The process of carcinogenesis involves the gain of oncogene activity and the loss of tumor suppressor gene function. A key tumor suppressor gene often lost is *p53*, which can induce temporary growth arrest and DNA repair, irreversible growth arrest, terminal differentiation, or apoptosis in response to potentially oncogenic cellular stress such as DNA damage (1, 2). p53 can mediate some of its functions in a transactivation-independent manner (3). However, its induction involves the direct or indirect activation of multiple genes involved in apoptosis, growth arrest, the cytoskeleton, growth factor regulation, and cell adhesion and the repression of genes involved in cell metabolism (4). Some common missense mutations in the DNA binding core domain (amino acids 102–292) simultaneously lead to both the loss of the tumor suppressor function of p53 and to the accumulation of a mutant p53 protein, which has an oncogenic life of its own.

The p53 tumor suppressor gene is mutated in over 50% of human cancers. Seventy-four percent of these mutations are missense, which result in full-length, albeit mutant, proteins. This fraction of missense mutations is much higher than in other tumor suppressor genes (5) and implies that p53 mutant proteins confer some selective advantage in carcinogenesis. One important feature of the oncogenic activity of p53 mutants is their ability to interfere with p53-dependent apoptosis by a dominant negative mechanism and, with p53-independent apoptosis, by a yet unknown mechanism that may involve transactivation. Because evasion of programmed cell death offers a strong selective advantage to cancer cells in metastasis and during chemotherapy, the antiapoptotic function of p53 mutants may be especially devastating.

Unlike wild-type p53, which under normal conditions has a short half-life curtailed when it is targeted by Mdm2 for degradation, mutant p53 proteins are outside this negative feedback loop and accumulate to high levels in cancer cells (6–8). Hence, given the high mutant p53 expression levels, reactivation of the wild-type function of p53 mutants offers the possibility of differentially targeting such transformed cells for apoptosis. A recent study (9) showed that compounds that restore wild-type p53 function can be injected *in vivo* with low toxicity and are effective in controlling tumors with mutant p53. Moreover, a different approach that used a peptide derived from the COOH terminus of p53 showed that reactivation of wild-type p53 function induces apoptosis in cells that express mutant p53 or high levels of wild-type p53 but not in cells that express low (perhaps physiological) levels of p53 (10). An understanding of the oncogenic gain of function of p53 mutants as well as the important structural regions and interactions of these proteins is therefore important to optimize reactivation approaches as well as to circumvent this gain of function of p53 mutants, perhaps even with existing treatment modalities.

Oncogenic Effects of p53 Mutants

Involvement of p53 mutants in cancer progression is associated with either *trans*-dominant suppression of wild-type p53 or a wild-type p53-independent oncogenic gain of function. The dominant negative effect of p53 mutants has been characterized in a variety of physiological processes that involve wild-type p53. These include: the repression of wild-type p53-mediated development and differentiation (11–14); apoptosis (15, 16); growth arrest (11); constitutive p21 expression (17); genomic stability (18, 19); resistance to H-1 parvovirus infection (20); immortalization (21); and inhibition of *ras* transformation of rat embryo fibroblasts (22).

The generally accepted mechanism behind mutant p53 *trans*-dominant suppression is the shutdown of wild-type p53 function because of heteromerization with mutant p53. Wild-type p53 forms a tetramer to perform its tumor suppressor activity, and this oligomerization is mediated by the oligomerization region (residues 319–360). This region is fully functional in core domain mutants (23, 24). It appears that in complex the mutant has the ability to drive wild-type p53 into a mutant or perhaps inactive conformation. Thus, when wild-type and mutant p53 were cotranslated, wild-type p53 lost the epitope recognized by the PAb1620 antibody and became reactive with the mutant specific PAb240 (25). It is not surprising, therefore, that the 273 (R to H) mutant, which seems to retain almost all of the wild-type conformation (98% folding of wild-type p53; see Table 1), has a very weak dominant negative activity (24). Heteromerization decreases the ability of wild-type p53 to bind to its various specific DNA target sequences (22–24, 26, 27) and transactivate downstream genes (27). Interestingly, the half-life of wild-type p53 increases dramatically when it is bound to mutant p53 (22, 28), probably the result of a sharp decrease in Mdm2 induction. A fragment of p53 termed DD that consists of amino acids 1–4 and 315–390, which

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Table 1 Comparison of structure and some functions of commonly studied p53 mutants

All mutants protected to a similar extent against cisplatin-induced apoptosis.

	273 (R to H)	248 (R to W or Q)	249 (R to S)	143 (V to A)	175 (R to H)	Ref. no.
Frequency of mutation at residue	7%	7%	3%	0.5%	4.5%	88
Mutation type	DNA contact	DNA contact	Conformational	Conformational	Conformational	70
% folded	98	86	85	31	30	102
Structural changes (NMR) ^a	Local	Local	Local	Extensive	ND ^b	72
Protection from apoptosis ^c	Low	Low	ND	ND	High	41
Spindle checkpoint disruption	ND	No	ND	Yes	Yes	73

^a NMR, nuclear magnetic resonance. Relative to wild-type p53.^b ND, not done.^c Etoposide-induced p53-independent apoptosis.

includes the oligomerization domain, was as effective as the full-length murine p53 135(A to V) mutant in cooperating with *ras* to transform rat embryo fibroblasts by eliminating wild-type p53 function (22).

There is evidence that p53 retains some tumor suppressor activity and transactivation ability as a monomer (29, 30). Interestingly, mutant p53 and the fragment DD can repress this transactivation. p53 Δ 324–355, which is unable to oligomerize because of the deletion in the oligomerization domain, is still able to transactivate the p21 promoter. This transactivation is suppressed by core domain mutants (30). This may indicate that the dominant negative effect of these mutants is attributable to their ability to squelch out factors required for wild-type p53 function and especially for transactivation (for review, see Ref. 31).

Although *trans*-dominance of p53 core domain mutants may not be surprising, the ability of p53 mutant proteins to exert wild-type p53-independent oncogenic effects is more unexpected. This effect was first reported in murine L12 pre-B cells, a cell line null for p53 that induced local tumors in mice that later regressed (32). However, L12 cells that expressed the murine p53 mutant 132(C to F) caused lethal tumors (32). Such mutant p53-mediated increased tumorigenicity was also demonstrated in (10)3 cells (33, 34) and T-cell acute lymphoblastic leukemia cells (35).

The gain of function of p53 mutants has been characterized further. Core domain p53 mutants were shown to increase mutation frequency (36), block differentiation (37), and increase metastatic potential (35, 38). A striking finding was that p53 mutants could interfere with wild-type p53-independent apoptosis induced by growth factor removal (39, 40), various types of DNA damage in myeloid and H1299 lung adenocarcinoma cells (40, 41), and the combination of HBV-X expression and tumor necrosis factor- α (42). This function of p53 mutants may be left over from cryptic wild-type p53, inasmuch as low levels of wild-type p53 have been shown to protect cells from apoptosis in a growth arrest independent manner (43, 44). p53 mutants also interfered with apoptosis, growth suppression, and p21 transactivation induced by p73 (45–47). This gives rise to the hypothesis that mutant p53 has a gain of function because it acts as a dominant negative for p53 family members p73 and perhaps p63. The oligomerization domains of p53 and p73 have been shown not to associate (48), which casts doubt on a dominant negative interaction between mutant p53 and p73, at least by a mechanism that involves heteromerization through the oligomerization domain. However, it has been subsequently shown that p53 mutants do associate with p73 (46) and that this interaction occurs through the DNA binding domains of these mutants (47).

p53 is polymorphic at residue 72 (arginine/proline; Ref. 49). Interestingly, the association between p73 and the 143(V to A) mutant was stronger with the arginine than the proline isoform, and the arginine isoform abrogated the growth suppression effect of p73, whereas the proline isoform did not (46). Moreover, examination of the frequency of the arginine isoform in unrelated populations showed

a decrease as one approaches the equator, indicating that this isoform was selected out because of the potent p53 mutants it produces as a result of the higher levels of UV radiation (46).

Is Mutant p53 Gain of Function Mediated by Transactivation?

The evidence for the appealing hypothesis that the gain of function of p53 mutants stems from their dominant negative inhibition of p53 family members is still controversial. An alternative or complementary hypothesis is that p53 mutants can transactivate or repress specific genes, and these genes mediate the various oncogenic effects of these mutants. Evidence for repression is still lacking, but there is convincing evidence from reporter assays that mutant p53 has the ability to transactivate specific target genes. Core domain p53 mutants were found to transactivate the MDR-1² gene promoter (33, 50), the *c-myc* promoter (51), the proliferating cell nuclear antigen promoter (52), the interleukin-6 promoter (53), the human heat shock protein 70 promoter (54), and the human epidermal growth factor receptor promoter (55) as well as the insulin-like growth factor-II promoter (42). Mutant p53 was also shown to transactivate the HIV-1 long terminal repeat promoter (56).

It appears that the same NH₂-terminal domain that mediates wild-type p53 transactivation is also necessary for the transactivation ability of p53 mutants, which argues that the transactivation is direct. Mutation of residues 22 and 23 (critical in wild-type p53 transactivation ability) in the transactivation domain of the 281(D to G) p53 mutant inhibited its transactivation of MDR-1 (50) and *c-myc* (51). In addition, the deletion of residues 1–58 in 281(D to G) p53 inhibited its transactivation of the proliferating cell nuclear antigen promoter, MDR-1 gene promoter, and the human epidermal growth factor receptor promoter (34). Although no consensus sequence has been found, mutant p53 has been shown to bind DNA of divergent sequences that have in common a tendency to adopt a non-B-DNA conformation (57).

Is transactivation the mechanism behind the gain of function of p53 mutants? Transactivation of MDR-1 seemed a promising candidate as the mechanism for mutant p53 antiapoptotic function, given that mutant p53 confers resistance against drugs such as etoposide and doxorubicin (40, 41). However, mutant p53-mediated resistance to γ -irradiation and growth factor removal-induced apoptosis (40) is not explained by this mechanism. Mutant p53-mediated resistance to cisplatin-induced apoptosis is also not explained, because cisplatin toxicity is MDR-1 independent. Although it is still unclear which gene or genes transactivated by mutant p53 are responsible for its gain of function, there are several lines of evidence that indicate that transactivation ability is essential. Mutation of NH₂-terminal residues 22 and 23, necessary for wild-type as well as mutant p53-mediated transactivation, caused a loss of the enhanced tumorigenicity conferred by the 281(D to G) p53 mutant to (10) 3 cells (50). Further-

² The abbreviation used is: MDR-1, multidrug resistance 1.

more, the murine 135(A to V) p53 mutant interfered with apoptosis induced by agents such as cisplatin and etoposide but not with apoptosis induced by actinomycin D, a powerful transcription inhibitor (40).

Combined Effects of *Trans*-dominance and Gain of Function of p53 Mutants

In carcinogenesis, the loss of wild-type p53 activity through mutant p53 *trans*-dominance and mutant p53 gain of function may occur simultaneously. Their effects can be additive and difficult to separate. In an effort to dissect their relative contributions, mice transgenic for the 135(A to V) p53 mutant were made on the background of mice with one functional wild-type p53 gene or null for p53. Mice that were hemizygous for wild-type p53 and contained the mutant transgene exhibited accelerated tumor development relative to hemizygous mice without the transgene. However, there was no difference in the rate of tumor development or survival of p53 nullizygous mice with and without the 135(A to V) mutant (58). This system shows that the gain of function effect of this p53 mutant is negligible relative to the effect of wild-type p53 loss, although it can be argued that p53 knockout mice may have an alternative tumor suppression mechanism (*e.g.*, see Ref. 59) that may render mutant p53 less efficient in carcinogenesis.

Whatever the mechanism behind mutant p53 oncogenicity, there is convincing evidence from Li-Fraumeni syndrome families that missense mutations in the core DNA binding domain of p53 are indeed oncogenic. Seventy-one percent of families with Li-Fraumeni and 22% of families with Li-Fraumeni-like syndrome have p53 germline mutations in one of the p53 alleles. A comparison between families with core domain missense mutations and mutations that led to no expression or truncation of p53 showed that the former had a significantly higher incidence of cancer, and the age of cancer onset was earlier (60).

Several clinical studies correlated mutant p53 expression and enhanced angiogenesis. It was shown that mutant p53 decreased the expression of the angiogenesis inhibitor thrombospondin-1 (61), up-regulated the vascular endothelial growth factor (62, 63), and up-regulated the basic fibroblast growth factor (64). This up-regulation of angiogenesis was at least partly attributable to the dominant negative action of mutant p53, inasmuch as the exogenous expression of wild-type p53 was shown to inhibit angiogenesis (65) and specifically the vascular endothelial growth factor (66).

Similarly, clinical studies assessing the effect of doxorubicin chemotherapy in breast cancer (67), cisplatin chemotherapy in advanced ovarian carcinoma (68), and general survival (69) found that mutant p53 expression resulted in significantly worse prognoses.

Different Mutants Vary in Their Oncogenicity

p53 mutations in the core domain are classified into two types. Mutations such as those at the mutational hotspots 248R and 273R occur in the DNA contact areas on either the L3 loop or the nearby loop-sheet-helix motif of p53 (70) and are termed class I mutations. However, other mutations, like those at 175R, occur in areas important for the conformational stability of p53 protein, such as the L2 loop in the zinc region, and lead to conformational changes that expose the mutant-specific epitope of the PAb240 antibody and result in the loss the wild-type-specific epitope detected by PAb1620 (25, 70, 71). These are termed class II mutations. This categorization, although useful, may be oversimplifying the situation, because the contact mutants may also evince some local conformational changes (72) and may vary in their degree of folding (see Table 1). The conformational mutations were shown to be more oncogenic than the DNA binding mutations in several systems. The conformational mu-

tants 175(R to H) and 249(R to S) resulted in immortalization of mammary epithelial cells, whereas the DNA contact mutants 248(R to W) and 273(R to H) did not (21). The conformational mutants 175(R to H) and 179(H to Y) had a marked protective effect against etoposide-induced apoptosis, whereas contact mutants 248(R to W) and 273(R to H) had a much milder effect (41). The same study showed, however, that there was no difference between 175(R to H) and 273(R to H) in the protective effect of these mutants against cisplatin-induced apoptosis. Conformational mutants 175(R to H), 245(G to D), 143(V to A), and 281(D to G) disrupted the spindle checkpoint and resulted in polyploidy in Colcemid-treated Li-Fraumeni fibroblasts, whereas the contact mutant 248(R to W) did not (73). The contact mutant 273(R to H) has shown additional evidence of wild-type p53 function. When tumor-derived cell lines with missense p53 mutations were examined for wild-type p53 transcriptional activity, lines with the 273(R to H) mutant possessed it, whereas lines with mutants 156(R to P), 175(R to H), 248(R to W), 248(R to Q), and 280(R to K) did not (74).

Success in the restoration of the wild-type p53 phenotype to cells with p53 mutants may also follow the general pattern outlined above if physiological criteria such as apoptosis, tumor regression, and inhibition of colony formation and proliferation are used. By these criteria, successful restoration to wild-type p53 function of mutants was shown thus far for mutations 273(R to H; Refs. 10, 75, 76), 273(R to C; Ref. 76), 280(R to K; Ref. 10), 241(S to F; Ref. 9), 248(R to Q; Ref. 75, 76), and 249(R to S, Ref. 9). All of these mutations except the last are contact mutations, and the 249(R to S) has been shown to cause only local structural changes and has a degree of folding similar to p53 proteins mutated at 248R (Table 1).

What emerges from this analysis is the view that there is a spectrum of p53 oncogenic mutations, where at one end there are mutants that are weaker in their mutant p53 function and more amenable to restoration of wild-type p53 function. At the very edge of this end is inactive (cryptic) p53, which is not a mutant but nevertheless demands activation in the form of modifications to the negative regulatory COOH-terminal domain to exhibit the tumor suppressor response (77–85). According to this view, what lies at the other end of the spectrum is a set of missense core domain mutations that cause widespread changes in the p53 protein (Table 1, Fig. 1). The resulting mutants are stable and would be refractory to attempts to restore them

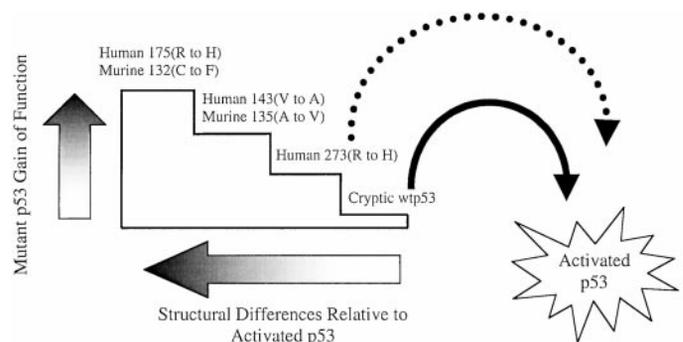


Fig. 1. The spectrum of p53 mutations. Examples of mutation archetypes are placed according to their structural changes relative to activated p53 and their stability. More extensive and stable mutants are more refractory to reactivation and possess increased oncogenic gain of function. The contact mutant 273(R to H) has the least structural changes among the mutants shown and is the most amenable to reactivation. The mutant 143(V to A), similar to the murine 135(A to V), has more extensive structural changes, but it is conformationally unstable and hence more sensitive to modifications that will interfere with its mutant conformation. The stable conformational mutant 175(R to H), similar to the murine 132(C to F), is expected to be most refractory to reactivation. Cryptic (inactive) p53 is also included, as the p53 species demanding the mildest structural changes, in the form of physiological posttranslational modifications upon cellular stress, to assume its activated form. Wild-type p53 (*wtp53*).

to wild-type p53 function. The conformationally unstable mutants such as the temperature sensitive 143(V to A), which has a mutant conformation at 38°C and a wild-type conformation at 32°C, are expected to be somewhere in between. An illustration is the difference between the murine temperature sensitive 135(A to V) and the stable murine 132(C to F). The former exhibits pronounced gain of function at 38°C (40),³ but this is completely lost upon modification of the extreme COOH-terminus, important for mutant p53 stability (see below) by alternative splicing³. The 132(C to F) mutant also exhibits pronounced gain of function, but it is not lost with alternative splicing of the COOH-terminus (86).

Molecular epidemiological data shows that mutations at R175, R248, R249, R273, R282, and G245 are the most common missense mutations of p53 (87). The most common is R273, although it seems to be selected against in leukemia (88). This may indicate that it was selected for on the basis of its oncogenic potency or even perhaps that mutants that are too oncogenic are detrimental to the survival of the cancer in the long term. However, other processes, such as the mode of action of the mutagenizing agent, may determine which mutants are formed (5, 89). An interesting example is aflatoxin B1, associated *in vitro* with G:C to A:T mutation in the third base of codon 249 (42).

Inactivation of p53 Mutants or Reactivation to a Wild-Type p53 Phenotype

Given the active role of p53 mutants in promoting carcinogenesis and their very common occurrence in cancer, efforts are being made to inactivate their function or, even better, to revert them to a wild-type phenotype. Both approaches depend on interfering with regions and interactions in the mutant p53 protein necessary for it to retain the mutant p53 phenotype. The possible candidates include: the NH₂ terminus necessary for mutant p53-mediated transactivation; the DNA binding domain, where the trouble begins; the oligomerization domain, important in the mutant p53 dominant negative effect; and the extreme COOH terminus that comprises approximately the last 30 amino acids, which is important for mutant p53 stability.

Evidence that the extreme COOH terminus is important for mutant p53 stability comes from data that showed that truncation of the COOH terminus of the murine 135(A to V) mutant caused it to become reactive with PAb246 and PAb1620, core domain antibodies specific for the wild-type conformation (25). Functionally, modification of the extreme COOH terminus resulted in a loss of mutant p53 transactivation potential in the 281(D to G) mutant (51) and a loss of wild-type p53-independent antiapoptotic gain of function in the 135(A to V) mutant.³ Furthermore, modification of the extreme COOH terminus caused some oncogenic p53 mutants to regain DNA binding to p53 specific elements and some even to regain the ability to transactivate wild-type p53 target genes (76, 90–94).

The DNA binding core domain was a second target for modification and initially investigated by introducing a second mutation in the DNA binding domain of p53 oncogenic mutants and screening for suppression of the oncogenic function of the mutants. Such suppressor mutations greatly decreased the number of colonies formed relative to cells expressing the single, oncogenic mutations. Also, suppressor mutations led to an increase in transactivation from wild-type p53 specific promoters and induction of death in BHK cells (76, 95, 96). A combination of suppressor mutation and COOH-terminal truncation yielded the best results (76).

A peptide derived from the COOH terminus (residues 361–382) was found to bind to both the COOH terminus and the DNA binding domain and presumably to interfere with the interactions between

these two regions (97). The presence of the peptide reestablished wild-type p53-specific DNA binding and transactivation (75, 97). When fused to the Antennapedia homeodomain to facilitate cell entry, it could also retard colony formation and induce apoptosis of cells expressing high levels of wild-type p53 or cells expressing high levels of mutant p53 (10, 75). This peptide did not, however, induce apoptosis in cells expressing normal levels of wild-type p53 (10). This approach, reminiscent in its thinking to the ONYX-015 virus-selective killing of cells not expressing wild-type p53 (98–101), relies on the high levels of mutant p53 normally expressed in cancers as the selective agent, which is then reactivated to wild-type p53 and causes apoptosis. The reason for the high levels of expression is that most p53 mutants are effectively outside the negative feedback loop of Mdm2. Unlike the wild type, p53 mutants do not transactivate the *mdm2* promoter, and hence insufficient Mdm2 is expressed to target the p53 for degradation (7, 8). Alternatively, p53 mutants may bind Mdm2 less efficiently or not at all, and this may prevent their degradation (6).

Recently, a large-scale screen found two compounds that could keep the DNA binding core domain of p53 stable in the wild-type conformation upon heating. This approach seems to depend not on mutant p53 reactivation *per se* but prevention of the nascent p53 protein from assuming the mutant conformation. The novelty of these compounds is that they are relatively stable *in vivo* and have no significant toxicity. When they were administered to nude mice xenografted with a human melanoma cell line that possessed the 249(R to S) mutant and a carcinoma cell line that possessed the 241(S to F) mutant, tumor growth of the xenografted cell lines was significantly suppressed (9).

Possession of mutated p53 at high levels may yet prove to be a double-edged sword for cancer cells. In the long term, transient restoration of wild-type p53 function to p53 mutants may develop into a powerful therapeutic modality that will enable the selective killing of cancer cells. However, given the differences between p53 mutations, it is probable that a significant number of the more stable conformational mutants will be refractory to such manipulations. Hence, an understanding of the effects and important functional regions of p53 mutants may lead to approaches that can neutralize the oncogenic activity of such mutants that cannot be restored to wild-type p53 function. Thus, the use of agents that can inhibit mutant p53 function may increase the efficiency of chemotherapy (Fig. 2). Mutant p53 inhibition, together with the induction of programmed cell death, can be a feature of the same agent as is the case with actinomycin D (40). The screening of the existing repertoire of chemotherapeutic agents for effectiveness against cancer cells with p53 mutants will result in the ability to tailor the chemotherapy to the particular p53 mutant involved in the cancer of an individual patient and in the more effective killing of the cancer cells.

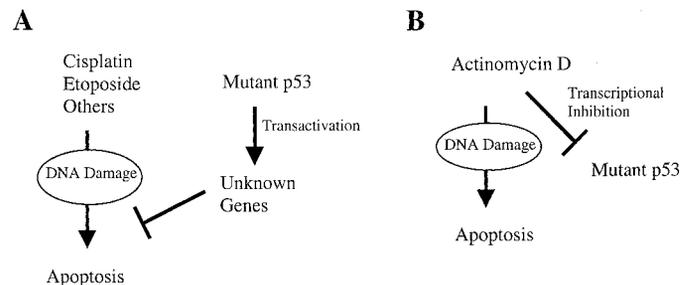


Fig. 2. Circumventing the antiapoptotic function of mutant p53; A, mutant p53 can interfere with apoptosis induced by multiple agents, including some used in chemotherapy; B, repression of mutant p53 antiapoptotic function, presumably through the inhibition of transactivation, with actinomycin D.

³ Sigal, A., Matas, D., Almog, N., Goldfinger, N., and Rotter, V. Anti-apoptotic activity of p53 mutants is dependent on the C-terminus, submitted for publication.

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