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News and Commentary

Strategies for therapeutic targeting of the p53 pathway in cancer

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The *TP53* gene is inactivated by point mutation in a large fraction of human tumors. p53 function is disrupted by indirect mechanisms in many wild-type *TP53*-carrying tumors as well. Loss of wild type p53 function allows apoptosis evasion and further selection of more malignant variants during tumor progression. Mutant *TP53*-carrying tumors show increased resistance to commonly used chemotherapeutic agents and radiotherapy. Therefore, p53 is an appealing target for novel anticancer therapeutic strategies. Several strategies for reactivation of the p53 pathway have been designed and tested during the last few years, such as *TP53* gene therapy and small molecules that reactivate mutant p53 or prevent Mdm2-mediated degradation of wild-type p53. Restoration of the p53 tumor suppressor pathway should trigger massive apoptosis, allowing rapid elimination of the tumor. The growing number of p53-targeting strategies raises hope for more efficient cancer therapy in the future.

After its discovery as a cellular SV40 large T antigen-binding protein in 1979, p53 has established itself as a key tumor suppressor, potent apoptosis-inducer, and prognostic marker in cancer (see Vousden and Lu[1] for a review). Strikingly, the *TP53* gene is mutated in approximately half of all human tumors (see www-p53.iarc.fr). This mutation frequency exceeds by far that of most other cancer-related genes, and emphasizes the central role of p53 and the p53 pathway in regulation of cell growth and survival. In contrast to other tumor suppressor genes, *TP53* is typically inactivated by single missense mutations, which is accompanied by loss of the remaining wild-type allele. The amino-acid substitutions cluster in the p53 core domain (residues 100–300) that recognizes p53-binding motifs in DNA (reviewed in Olivier *et al.*[2], McKinney and Prives[3]). As a rule, mutant p53 proteins are deficient for specific DNA binding. This argues that DNA binding and transcriptional regulation of target genes are critical functions for p53-mediated tumor suppression.

In addition to inactivating the normal function of p53, the mutations may also endow mutant p53 with so called gain-of-function activities (reviewed in Sigal and Rotter[4]). Such activities may include for example illegitimate DNA binding and transactivation of genes that promote tumor growth, for example, the *MDR1* gene, *MYC*, and *VEGF*. Furthermore, mutant p53 may hetero-oligomerize with the p53 family protein p73, resulting in disruption of p73-induced apoptosis, and possibly with other cellular proteins.

The p53 pathway is almost certainly dysfunctional also in a majority of wild-type *TP53*-carrying tumors. This could occur through for example overexpression of the p53 antagonist Mdm2, loss of the Mdm2 inhibitor $p14^{ARF}$ via homozygous deletion of the *INK4a* locus, or expression of the human papilloma virus E6 protein that triggers p53 degradation (reviewed in Asker *et al.*[5]). It is clear, therefore, that reactivation of p53-induced apoptosis is a plausible and important therapeutic goal in many tumors regardless of *TP53* status.

Clinical studies have provided compelling evidence to support the notion that *TP53* mutations are associated with poor prognosis (see Olivier *et al.*[6] and the review by Royds and Iacopetta in this issue). This has been particularly well studied in breast and colon cancer. Mutations that reside in the L2 and L3 loops in the core domain and affect Zn binding and direct DNA contacts seem to be associated with the worst prognosis. This illustrates the fact that prognosis depends not only on the presence or absence of *TP53* mutation, but also on the exact localization of the mutation and the amino-acid substitution. The frequent p53 mutations in tumors and the fact that *TP53* mutation increases resistance to currently used radiotherapy and chemotherapy makes p53 and the p53 pathway an appealing target for novel cancer therapeutic strategies. Restoration of the p53 pathway should induce massive apoptosis and rapidly eliminate the tumor. Over the past few years, several exciting novel approaches for either activating p53 in wild-type *TP53*-carrying tumors or restoration of wild-type p53 function in mutant *TP53*-carrying tumors have been presented.

Virus-based Therapeutic Strategies for Mutant *TP53*-Carrying Tumors

Wild-type *TP53* reconstitution in mutant *TP53*-carrying or *TP53* null tumors can be accomplished by gene therapy, that is, introduction of an intact cDNA copy of the *TP53* gene using a suitable viral vector, typically one based on adenovirus (Adp53). *TP53* gene therapy has been tested in clinical trials in patients with lung cancer, head and neck cancer, and other tumors. Such studies have demonstrated a significant clinical effect with stabilized tumor growth or even tumor regression in at least a fraction of the treated patients, and no major toxicity (reviewed in Bykov and Wiman[7]). For example, a phase I study with Adp53 in patients with recurrent head and neck cancer (HNSCC) revealed low toxicity and clinical effect in around 50% of the patients.[8] Another phase I trial in patients with advanced non-small cell lung cancer showed disease stabilization in 16 of 25 evaluable patients and a significant

reduction in tumor size in two patients.[9] Subsequent studies demonstrated that combination of Adp53 with conventional chemotherapeutic drugs (cisplatin) or radiation may have even better clinical efficacy.[10,11] Adp53 gene therapy has so far been limited to local administration, that is, intratumor injection, in most studies. Systemic administration will be required for effective treatment of patients with disseminated disease. However, this is complicated by the lack of methods for efficient delivery to tumor cells and the possibility of neutralizing antibodies against viral antigens. Novel approaches for tumor targeting upon systemic administration and improved viral vectors for higher expression of wild-type p53 in tumor tissues would greatly improve the clinical utility of Adp53 therapy in cancer patients.

Another virus-based strategy exploits the fact that adenovirus blocks p53 in order to replicate and produce viral progeny. ONYX-015, a mutant adenovirus that lacks the E1B 55K gene whose protein product forms a complex with p53, was shown to replicate and lyse tumor cells lacking wild-type *TP53* but not those that retained wild-type function (Bischoff *et al.*[12]; see also Royds and Iacopetta, this issue). Further animal studies demonstrated that ONYX-015 inhibited tumor growth *in vivo* upon systemic administration, and the antitumor effect was enhanced by combination treatment with chemotherapeutic drugs.[13] The ONYX-015 concept has remained controversial, however. Other studies have shown that ONYX-015 replication in human tumor cells is independent of *TP53* status,[14,15] or that wild-type p53 function is, in fact, required for productive adenovirus infection and efficient adenovirus-induced cell death.[16,17]

Clinical trials in patients with recurrent head and neck cancer, metastatic colorectal cancer or pancreatic cancer have shown that ONYX-015 is safe and has significant antitumor effect in at least a fraction of the patients, alone or combined with chemotherapy.[18–23] Analysis of post-treatment tumor biopsies revealed tumor-selective viral replication and mutant p53-dependent tumor necrosis.[18,19] Unfortunately, the clinical effect of ONYX-015 has varied substantially and many patients have responded poorly. Similarly, tumor cell lines show great variation with regard to their susceptibility to ONYX-015. The observed variation in the response to ONYX-015 may be related to the fact that E1B 55K has other funcitons in addition to targeting p53, such as viral RNA export and inhibition of host protein synthesis, and that tumor cells may provide these functions to a variable extent. Interestingly, recent data indicate that heat shock can rescue viral RNA transport and sensitize tumor cells to ONYX-015 replication and lysis.[24]

Reactivation of p53 in Wild-type *TP53*-Carrying Tumors

Small molecules can be produced by large scale GMP synthesis using standardized protocols, they can be administered systemically in most cases, and they do not trigger an immune response that could reduce therapeutic efficacy. During the past few years, random screening of chemical libraries using different assays have led to the discovery of small molecules that can restore p53 function in tumor cells in various ways (Figure 1). As mentioned above, the p53 pathway is most likely disrupted also in a large fraction of wild-type p53-carrying tumors. Mdm2 is a critical regulator of p53 that is frequently overexpressed in wild type *TP53*-carrying tumors. Overexpression or dysregulation of *MDM2* may occur as a result of gene amplification,[25] or deletion of the *INK4a* locus that encodes $p14^{ARF}$ a negative regulator of Mdm2 (reviewed in Sherr and Weber[26]). Elevated levels of Mdm2 can also be due to a single nucleotide polymorphism (SNP) in the *MDM2* promoter which increases binding of the transcription factor Sp1.[27] Mdm2 is clearly an important therapeutic target. Different strategies for targeting Mdm2 and/or inhibition of p53-Mdm2 binding have been designed, including short p53-derived peptides (reviewed in Chene[28]). Although pharmacological disruption of protein–protein interactions is considered difficult, the interaction between p53 and Mdm2 seems particularly favorable for such strategies since the interacting surface on both proteins is small with only three participating amino-acid residues in p53.[29]

Vassilev and co-workers screened a diverse chemical library for substances that could interfere with p53-Mdm2 binding and identified a group of imidazoline compounds dubbed Nutlins that bind to the 'p53 pocket' on Mdm2. Nutlins mimick the three critical amino-acid residues in p53 that interact with Mdm2, that is, Phe-19, Trp-23, and Leu-26, as shown by X-ray crystallography analysis of a human Mdm2–Nutlin complex. They activate the p53 pathway in tumor cells at concentrations in the 1–3 μM range, resulting in cell cycle arrest and apoptosis. In contrast, treatment of normal cells triggers transient growth arrest but no apoptosis. Nutlins also inhibit xenograft tumor growth *in vivo* with no obvious toxicity.[30] RITA, another novel compound that activates wild-type p53 in human tumor cells, was identified in a screen of the Diversity set from the National Cancer Institute (NCI).[31]

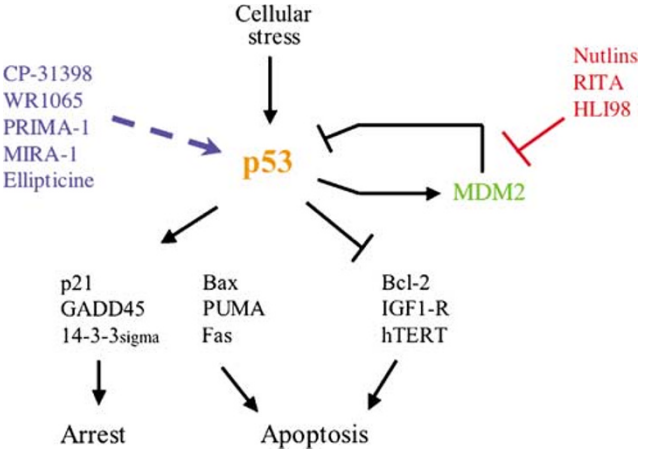

Figure 1 The p53 tumor suppressor pathway and novel small molecules that restore this pathway in human tumors. p53 regulates transcription of target genes including *p21/CDKN1A*, *BAX*, *FAS*, *PUMA*, *BCL-2* and *hTERT*, resulting in a biological response. Ellipticine, CP-31398, WR1065, PRIMA-1, and MIRA-1 have been shown to reactivate mutant p53 or induce cell death preferentially in mutant *TP53*-carrying tumor cells. Nutlins, RITA, and HLI98 target wild-type p53 or MDM2 and inhibit MDM2-mediated p53 degradation, resulting in activation of wild-type p53 and a p53-dependent biological response. For both groups of compounds, the therapeutic aim is reactivation of p53-dependent apoptosis to rapidly eliminate tumor cells

Further studies indicated that RITA could bind to the p53 N-terminus and cause a conformational change that prevents MDM2 binding, resulting in p53 accumulation and upregulation of p53 target genes. RITA induces apoptosis in human tumor cells in a wild-type p53-dependent manner, but has little effect on normal cells. However, expression of an activated oncogene like *C-MYC* increases the sensitivity of human fibroblasts to the compound. RITA has significant antitumor activity without any apparent toxicity in mice carrying human tumor xenografts.

Instead of searching for molecules that prevent p53-Mdm2 binding, other investigators have screened for compounds that inhibit the E3 ligase activity of Mdm2. This approach led to the identification of a family of compounds designated HLI98.[32] The HLI98 compounds were shown to inhibit the E3 activity of human Mdm2, leading to stabilization of wild-type p53 and Mdm2, accompanied by p53-dependent transactivation and apoptosis. Further studies of their antitumor effect *in vivo* are needed. Nonetheless, this work provides proof of principle for the use of E3 ligase inhibitors to restore the p53 pathway in tumor cells.

Berkson *et al.*[33] screened the NCI Diversity set using an assay based on mouse fibroblasts expressing wild-type p53 and carrying a p53-responsive lacZ reporter. This assay allows identification of compounds that activate p53-dependent transcription in a cellular context. Two selected compounds induced wild-type p53 in human tumor cells (U2OS) in the absence of detectable DNA damage. At least one of the compounds, compound C, protects p53 from Mdm2-mediated degradation, and has only limited cytotoxic effect on normal primary fibroblasts. Both compounds show structural resemblance to the compound sangivamycin, a purine nucleoside analog which has several known activities including inhibition of protein kinase C. Sangivamycin was also able to induce p53 activity in the reporter assay used. It will be important to determine the molecular mechanism of action of these compounds, as well as their ability to inhibit tumor growth *in vivo*.

In summary, molecular scaffolds for activation of wild-type p53 in tumor cells through different mechanisms have been identified (Figure 1). The molecules do not seem to induce any major toxicity in normal cells at concentrations that are toxic to tumor cells. The existence of such a therapeutic window raises hope for the development of novel drugs for treatment of wild-type *TP53*-carrying tumors with less side effects than currently used chemotherapeutic agents.

Reactivation of Mutant p53

Several features of mutant p53-expressing tumor cells facilitate therapeutic targeting of mutant p53. First, mutant p53 is expressed at high levels in many tumors, due to lack of sufficient amounts of Mdm2 to trigger p53 degradation. In addition, extensive stress signalling in growing tumor cells as result of oncogene activation, hypoxia, and/or telomeric erosion may induce post-translational modifications of p53 that serve to activate p53 for DNA binding and transactivation of target genes. Therefore, pharmacological reactivation of mutant p53 in tumors cells should induce massive apoptosis, whereas normal cells that express low levels of wild-type p53 will be untouched. On the other hand, mutant p53 is a complex target, since it is not one protein but rather a wide range of proteins with different properties. Some mutant p53 proteins carry substitutions in amino-acid residues that contact DNA (e.g. Arg-248 and Arg-273) whereas others show a severely distorted structure (for instance Arg-175 and Gly-245) (reviewed in Bullock and Fersht[34]). Moreover, pharmacological refolding of an incorrectly folded mutant protein appears a more challenging undertaking than for example inhibition of a protein kinase domain or inhibition of protein–protein binding.

Previous studies in several laboratories have demonstrated that mutant p53 proteins can be reactivated for specific DNA binding, transcriptional transactivation, and even induction of apoptosis in human tumor cells, using monoclonal antibodies that recognize a C-terminal epitope in p53 or short synthetic peptides derived from the p53 C-terminus.[35–39] More recently, CDB3, a rationally designed 9-mer peptide derived from the p53-binding protein 53BP2 or ASPP, was shown to restore wild type conformation and DNA binding to mutant p53 in human tumor cells, followed by upregulation of p53 target genes.[40]

In parallel, screening efforts for small molecules that reactivate mutant p53 have led to the discovery of several structurally unrelated lead compounds (reviewed in Bykov *et al.*[41]; Figures 1 and 2). Rastinejad and co-workers used a protein assay to identify small molecules that prevent unfolding of the wild-type p53 core domain upon heating.[42] The hit molecule CP-31398 rescued wild type conformation and trancriptional transactivation of Ala-173 mutant p53, and inhibited xenograft tumor growth *in vivo* with no signs of toxic effects. Further studies have confirmed that CP-31398 treatment induces p53 reporter activity and p53 target genes, for example, *p21/CDKN1A* and *BAX*,[43–45] and demonstrated that CP-31398 activates the mitochondrial apoptosis pathway.[43] CP-31398 also stabilizes wild-type p53 by inhibiting its ubiquitination without affecting p53 phosphorylation or Mdm2 binding.[46] However, analysis by NMR did not detect any direct binding to the p53 core domain,[47] but it remains possible that CP-31398 binds to and affects folding of nascent p53. CP-31398 appears to induce both p53-dependent and

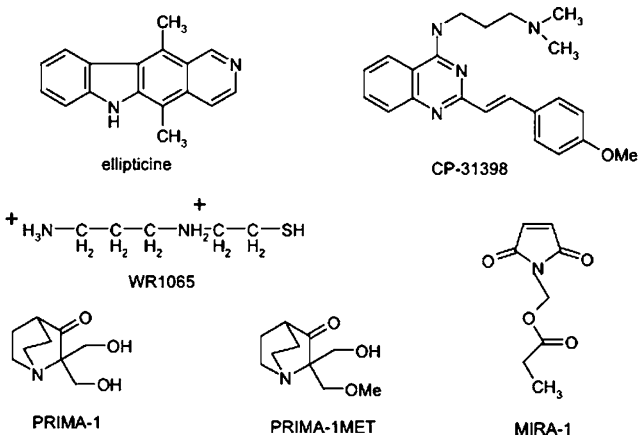

Figure 2 Chemical structures of identified small molecules that reactivate mutant p53 or induce cell death preferentially in mutant p53-expressing tumor cells

p53-independent cell death, indicating that it has other targets than p53.[44–46]

Ellipticine and derivatives thereof were shown to rescue as series of mutant p53 proteins, including His-175, Trp-248, Ser-249, and His-273 mutant p53, as assessed by induction of a p53-responsive luciferase reporter and the p53-responsive genes *p21/CDKN1A* and *MDM2*, as well as reactivity with conformation-sensitive antibodies PAb1620 and PAb240 and binding to a p53 motif in the *MDM2* gene.[48] In addition, upregulation of $p21^{WAF1}$ and Mdm2 was demonstrated in human tumor xenografts in ellipticine-treated nude mice. Certain ellipticine derivatives have previously shown moderate antitumor activity in phase I and II clinical trials but their clinical use has been limited by toxic side effects (for references, see Peng *et al.*[48]).

The molecule WR1065 is derived from the cytoprotective drug amifostine which is used as a radio- and chemoprotective agent in the clinic. WR1065 was first shown to reactivate mutant forms of p53 in a yeast transcription assay.[49] It can also reactivate Met-272 mutant p53 for DNA binding and transactivation of target genes in human esophageal carcinoma cells.[50] Subsequent studies showed that WR1065 activates wild-type p53 through a redox-dependent mechanism.[51] This raises the possibility that redox regulation has a role in mutant p53 reactivation by WR1065. The antitumor effect of WR1065 in mouse models has not yet been thoroughly tested.

In a screen of a chemical library from the National Cancer Institute, we identified a small molecule that induces apoptosis preferentially in mutant p53-expressing human tumor cells.[52] PRIMA-1 restores wild-type conformation and transcriptional transactivation to mutant p53 *in vitro*, and induces p53 target gene expression in a mutant p53-dependent manner. Systemic administration of PRIMA-1 (i.v. or i.p.) inhibits xenograft tumor growth in SCID mice. Our analysis of information in the NCI database confirmed that PRIMA-1 preferentially targets mutant p53-expressing tumor cells, in contrast to currently used chemotherapeutic agents like cisplatin and 5′-fluorouracil (5′-FU) which in most cases are more efficient in inducing cell death in wild-type *TP53*-carrying tumors.[53]

Reactivation of mutant p53 may increase sensitivity of tumor cells to chemotherapeutic drugs that preferentially kill wild-type *TP53*-carrying tumor cells. If so, novel molecules such as CP-31398 and PRIMA-1 would be expected to act synergistically with chemotherapeutic drugs. Combination treatment with CP-31398 and adriamycin or cisplatin has been tested in human tumor cells *in vitro*.[44] Whereas each drug alone triggered only cell cycle arrest, combined treatment caused cell death. We found that adriamycin, cisplatin and other chemotherapeutic drugs synergized with PRIMA-1MET (a methylated form of PRIMA-1 with similar activity profile and higher potency) as shown by various *in vitro* assays and also *in vivo* in SCID mice.[54] In addition, PRIMA-1 acted synergistically with fludarabine *in vitro* on tumor cells from patients with B-cell chronic lymphocytic leukemia (B-CLL).[55] As these chemotherapeutic drugs may further enhance mutant p53 levels in tumor cells, and since the effect of PRIMA-1 is dependent on the levels of mutant p53 expression, it is also possible and perhaps equally likely that treatment with chemotherapeutic drugs in fact increases sensitivity of tumor cells to PRIMA-1. This suggests that any agent that induces mutant p53 levels may synergize with PRIMA-1.

Work of other researchers has indicated that PRIMA-1 triggers apoptosis selectively in mutant p53-expressing colorectal carcinoma cells through a mechanism that involves the c-Jun-NH2-kinase pathway.[56] This study also demonstrated induction of the p53 target genes *p21/CDKN1A* and *GADD45* followed by G2 cell cycle arrest in mutant p53-expressing lung adenocarcinoma cells treated with PRIMA-1. No effect of PRIMA-1 was observed on the proapoptotic proteins Bax, Bcl-XL and Fas in these cells, and specific inhibitors of caspases 8, 9, and 3 did not inhibit PRIMA-1-induced cell death, suggesting that PRIMA-1 can trigger cell death in a caspase-independent manner. In another study, analysis of proteins that coimmunoprecipitated with mutant p53 upon PRIMA-1 treatment identified heat shock protein 90 (Hsp90) as a putative target for PRIMA-1. This suggests the possibility that Hsp90 mediates mutant p53 refolding in response to PRIMA-1 treatment.[57] Chipuk *et al.*[58] examined the effect of PRIMA-1 in enucleated cells (cytoplasts) and found that PRIMA-1 triggers p53-dependent apoptosis that involves caspase-activation. These results indicate that PRIMA-1 may reactivate transcription-independent functions of mutant p53 at mitochondria.

MIRA-1 represents a novel family of small molecules that target mutant p53.[59] These compounds are structurally different from PRIMA-1 but have similar potency and mutant p53 selectivity in cellular assays. However, MIRA-1 appears to reactivate a narrower range of mutants than PRIMA-1. Band shift assays revealed a significant stimulation of DNA binding of Gln-248, Tyr-176/Trp-248, His-175, and Trp-282 mutant p53. The MIRA compounds contain a maleimide group that could react with thiol and amino groups in proteins. The presence of a reactive 3–4 double bond in the maleimide group correlates with the mutant p53-dependent effect. It is well-known that wild-type p53 is subject to redox regulation (see Buzek *et al.*[60], Seo *et al.*[61]). This suggests that covalent modification of cysteine residues in mutant p53 by MIRA-1 has a role in conformational and functional rescue. Modification of thiol groups could for example prevent the formation of intramolecular or intermolecular disulfide bonds that would interfere with proper folding of the protein and/or produce inactive protein aggregates. Thus, at least two molecules shown to reactivate mutant p53, WR1065 and MIRA-1, may affect the redox status of p53. Further studies are needed to elucidate the role of redox regulation in mutant p53 reactivation.

Conclusions and Future Perspectives

Reconstitution of the p53 tumor suppressor pathway is one of the most exciting novel concepts for improved cancer therapy. Adenoviral vectors can deliver intact *TP53* cDNA to tumor cells carrying mutant *TP53* or lacking *TP53*. This strategy has already been tested clinically and shown antitumor effect in a subset of patients. However, it needs further optimization, including improved methods for systemic therapy. ONYX-015, a modified adenovirus that lacks the E1B-55K protein, is an elegant strategy that has also shown some success in

clinical trials, but factors that determine viral replication in tumor cells are not completely understood. Small molecules that restore p53-dependent apoptosis in tumor cells have been identified using various approaches. Compounds that target wild-type *TP53*-carrying tumor cells prevent Mdm2-mediated p53 degradation in various ways, either through blocking p53-Mdm2 binding or inhibition of Mdm2-dependent p53 ubiquitination. Thus, the molecular mechanism of action is at least partially known for some of these substances. Novel compounds that target mutant *TP53*-carrying tumor cells can restore wild-type conformation and DNA binding to mutant p53, or target mutant p53-expressing tumor cells through more indirect mechanisms. The exact molecular mechanisms for mutant p53 reactivation are more obscure. Restoration of wild type p53 function may involve direct binding of a low molecular weight compound to mutant p53 in a way that promotes correct folding of at least a fraction of all mutant p53 protein molecules in a cell. As pointed out by Bullock and Fersht,[34] the mutant p53 core domain exists in an equilibrium between an unfolded and a correctly folded state. Any compound that binds to the native fold only will shift the equilibrium towards this state, resulting in restoration of wild type conformation. Conclusive data on the possible binding of mutant p53-reactivating compounds to the mutant p53 core domain or elsewhere in the protein will hopefully be obtained by NMR, X-ray crystallography, and/or mass spectrometry analysis. Alternatively, mutant p53-reactivating molecules could interfere with the binding of mutant p53 to other cellular proteins, for example p73, resulting in transcriptional activation of target genes regulated by both p53 and p73, and p73-dependent apoptosis. It is also possible that cellular chaperones like Heat shock protein 90 (Hsp90) are affected, as indicated above. More indirect mechanisms for mutant p53-dependent cytotoxicity may involve targeting of gene products illegitimately activated by mutant p53, for example c-myc and VEGF, in tumors cells that are dependent on their overexpression. A better understanding of the molecular mechanisms of mutant p53 reactivation is clearly an important goal, as this will facilitate the design of more potent and specific structural analogs or even entirely novel molecular scaffolds.

The list of p53-based therapeutic strategies under preclinical development is growing and oncologists may well possess several p53-targeting anticancer drugs in the future. At that point, molecular analysis of the exact mechanism for ablation of the p53 pathway in a tumor will become essential for selection of therapy. Evidently, it will be important to analyze not just p53 itself but the p53 pathway as a whole in order to select the most optimal drug or strategy. More efficient and affordable routine methods for analysis of the p53 pathway in tumor specimens, including DNA sequence analysis of the *TP53* gene itself, will be critical for the clinical use of novel p53-targeting drugs.

Novel p53-based therapeutic strategies may be combined with conventional cancer therapy. Clinical studies have shown a beneficial effect of the combination of Adp53 gene therapy and chemotherapeutic drugs or radiotherapy. Similarly, the observed synergy between novel experimental drugs such as PRIMA-1 and for instance cisplatin in various *in vitro* assays and in mice carrying human tumor xenografts indicates that combination therapy with standard chemotherapeutic agents and novel p53-targeting drugs may allow increased clinical efficacy with less unwanted side effects. Combination treatment will probably also be a key strategy for minimizing development of therapy resistance, a general problem in cancer therapy.

Despite the successful identification of p53-targeting small molecules in recent years, further screening of chemical libraries using protein-based and/or cellular assays should be carried out with the aim of identifying novel molecular scaffolds for targeting the p53 pathway in human tumors. This will increase chances of finding compounds with significant clinical antitumor effect and desirable pharmacodynamic and toxicity profiles. With several compounds already identified and further screening efforts underway, we can expect novel and even more potent compounds added to the arsenal of p53-targeting drugs during forthcoming years. Molecules targeting the p53 tumor suppressor pathway will hopefully become powerful weapons against cancer.

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