

Structure, Dysfunction, and Therapeutic Targeting of the p53 Tumor Suppressor in Human Cancer

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ABSTRACT: *TP53* is the most frequently mutated gene in human cancer, and its protein product, p53, serves as the cell's primary defense against cancer proliferation. Targeting p53 therapeutically has proven remarkably difficult, since p53 dysfunction cannot be pinpointed to a single problem. Therapies targeting p53 must be matched to specific dysfunction categories, such as loss of function, gain of function, or negative regulator overexpression. This review investigates how the diversity of p53 mutations necessitates targeted therapy by analyzing p53 structure, mutation types, and current therapeutic approaches, using evidence from experimental cancer models and clinical trials. By analyzing current treatment options, we show how p53 therapy relies on understanding mutation mechanisms. Structural mutants require reactivation drugs like APR-246 to refold the protein, while gain-of-function mutants require degradation strategies such as the Hsp90 inhibitor 17-AAG. Using the two interchangeably could render treatments ineffective or worsen outcomes by stabilizing oncogenic activity. This review argues that the effectiveness of p53-targeted therapy depends on specific, categorized treatment options. Matching the right therapy to the right mutation reduces treatment failure, improves clinical design, and could help save the lives of cancer patients with p53-altered tumors.

KEYWORDS: Cellular and Molecular Biology, Genetics; Cancer, Treatment, Therapeutic Strategies, Drugs, Tumor Suppression, Protein p53.

■ Introduction

The p53 protein is a central tumor suppressor that maintains genetic stability in most somatic cells and is commonly known to be a regulator of intracellular functions. Its loss of function due to a mutation in the *TP53* gene that allows for the proliferation of faulty DNA.^{1,2} It is important to understand the structure and behavior of p53 when considering the development and progression of cancer, as p53 plays a crucial role in regulating the cell cycle in response to stress signals.² The presence of mutant p53 (mutp53) varies among cancer types, with certain cancers exhibiting higher mutation rates than others. Small cell lung cancer, colorectal cancer, ovarian cancer, and endometrial cancer all have mutation frequencies of over 50%. Genomic instability and increased resistance to therapies often occur as a result of high p53 mutation frequencies.³ This can be shown through research that explores how high mutp53 expression in cancer patients is correlated with reduced overall patient survival.³ Globally, approximately 20 million new cancer cases and 9.7 million cancer deaths were recorded in 2022 alone.⁴ Given that *TP53* mutations are present in over 50% of all human tumors, this translates to an estimated 10 million new p53-mutant cancer diagnoses annually.^{4,5} These findings emphasize the importance of understanding the role and behavior of p53 when considering cancer development and progression.

Under normal conditions, p53 protein levels are kept under control by one of its primary negative regulators, MDM2. MDM2 and p53 form an autoregulatory feedback loop that targets p53 for degradation, ensuring activity remains low in healthy cells.⁶ Upon activation, p53 induces the expression of genes such as p21 that mediate p53-induced G1 cell cycle

arrest by inhibiting cyclin-dependent kinases (CDKs). This prevents RB phosphorylation, which halts entry into the S phase. As a result, cells are given more time to repair damaged DNA or undergo apoptosis.⁷ Additional studies have shown that p53 controls many “non-classical” pathways, including metabolic homeostasis, senescence, stem cell differentiation, angiogenesis, and DNA repair. Wild-type p53 (wtp53) also influences metabolic processes through transcriptional activation or by repressing target genes. p53 can suppress the expression of glucose transporters like GLUT1 and GLUT4 to reduce glucose uptake, which protects cells from oxidative stress. p53 promotes mitochondrial respiration by upregulating genes that promote oxidative phosphorylation, electron transport chain activity, and efficient ATP production. By increasing the expression of genes that promote fatty acid oxidation (FAO), p53 helps fatty acids enter the mitochondria, where they are broken down to produce ATP.^{6,8}

This paper will discuss how mutations in p53, such as regulatory expression by negative modulators, aberrant protein-protein interactions, and structural missense mutations, can contribute to cancer development and progression. We will go over how such mutations can be therapeutically targeted through different strategies such as reactivation therapies, inhibition of MDM2 and MDMX (also known as MDM4), and deletion or degradation of mutp53 proteins. The main therapeutic focus will be on small-molecule-based therapies that aim to reactivate mutp53 to a functional state and stabilize wtp53. Despite extensive research, p53 remains one of the most difficult tumor suppressor proteins to target.¹ Recent research shows that treating p53 dysfunctions the same regardless of the specific mutation category is not effective, nor is it accurate.

Different types of mutations in p53 lead to different cancer behaviors that should not be treated interchangeably, which raises the issue of certain therapies failing as they are unable to account for the specific p53 mutation situation. Recent studies in biology and pathway analysis show there is an urgent need to distinguish between loss-of-function (LOF) and gain-of-function (GOF) mutations and to identify when p53 should be neutralized or reactivated.⁹ Understanding and addressing these points is crucial for developing new therapies and advancing oncology for p53-driven cancers in general.

■ Discussion

Structure and Normal Function of p53:

p53 functions as a sequence-specific transcription factor that uses stress signals to indicate issues such as DNA damage, oncogene activation, ribosomal stress, and nutrient deprivation. In response to these signals, it regulates genes that control whether the cell repairs damage, stops division, or undergoes apoptosis.¹⁰ In humans, the *TP53* gene is located on the short arm of chromosome 17 at position 13.1, and encodes p53 with 393 amino acid residues. The 393 amino acids that p53 consists of make up its domains, which enable tumor-suppressing functions.¹¹ p53 functions as a homotetramer because individual monomers bind DNA weakly; thus, tetramer formation is essential for sequence-specific DNA binding.¹² Studies show that the tetramerization domain (TD) in the C-terminal region and the DNA binding domain (DBD) act together to make p53 a functional transcription factor capable of regulating genes.¹¹ Tetramer formation is essential for DNA binding and for ensuring p53 can be properly regulated to effectively activate its target genes in response to stress.^{13,14} Furthermore, studies show how minor disruptions in tetramer formation can severely impair gene regulation.¹⁵

The p53 protein relies mainly on domains for its tumor-suppressing functions. These domains allow for the binding of p53 to other cofactors, also known as “helper proteins,” that are crucial for p53 to be able to activate or suppress genes. When these domains are missing or mutated, p53’s tumor-suppressing function is weakened, which can lead to cancer formation and growth.¹⁶ The N-terminal region of p53 is primarily responsible for activating target gene expression. This region contains two transcriptional activation (transactivation) domains located within residues 1–61. TAD1 (residues 1–40) and TAD2 (residues 40–61) both help initiate the transcription process.^{17,18} TADs also interact with one of p53’s negative regulators, MDM2, an E3 ubiquitin ligase that marks p53 for degradation under normal conditions, ensuring p53 levels stay low when cells are not stressed.¹⁹ Additionally, the DNA-binding domain makes connections with both TADs by folding back and contacting parts of the same p53 molecule. These contacts help p53 identify target DNA sequences.²⁰

The proline-rich domain (PRD, residues ~63–94) has a unique flexible structure that helps stabilize p53 by regulating interactions with proteins such as MDM2. Through studies, it has been demonstrated that the PRD influences how p53 binds to DNA and how effectively it activates or represses different target genes. Unlike the DNA-binding domain, which

is frequently mutated in cancer, the PRD is rarely mutated.²¹ The central DNA-binding domain (DBD, residues ~102–293) is the most critical region for p53 activity as a transcription factor and tumor suppressor. The DBD is organized around an antiparallel β -sheet scaffold and contains several flexible loop regions, including the L1, L2, and L3 loops, which help with DNA recognition. These loop regions make sequence-specific contacts with DNA by inserting into the major and minor grooves of the DNA helix.²² The DBD functions as part of a tetrameric complex, with four p53 monomers assembling to bind DNA cooperatively (Figure 1). The three-dimensional fold of the DBD is maintained by a zinc ion, which is coordinated by conserved cysteine and histidine residues.²³ Most cancer-associated mutations occur in the DBD, with over 80% of p53 mutations found in tumors located in this domain.²²

The C-terminal regulatory domain (CTD, residues 363–393) modulates how, when, and how strongly p53 binds DNA and activates target genes. Flexibility and lack of three-dimensional structure in the CTD enable it to interact with multiple binding partners and respond better to regulatory signals.²⁴ It is one of the p53 domains that is subject to extensive post-translational modifications, including phosphorylation, acetylation, and ubiquitination.²⁵ These modifications change p53’s interaction with DNA and are crucial for determining whether p53’s ability to bind to target sequences will be enhanced or inhibited. Ensuring all five domains work together coordinately is essential for ensuring p53 does its job as a tumor suppressor effectively, with each domain contributing differently to how p53 senses stress, binds DNA, and activates gene expression programs.

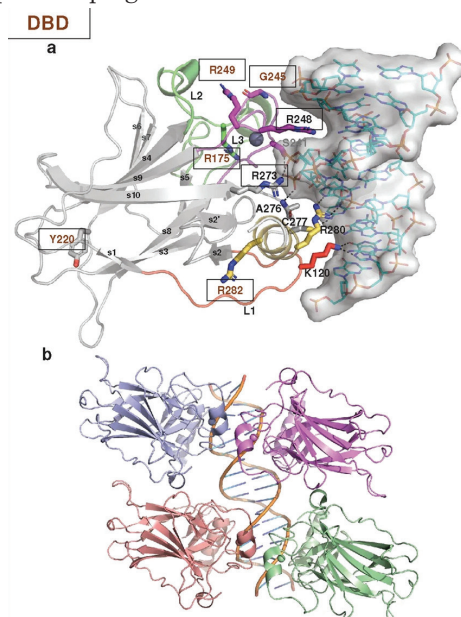


Figure 1: Structural organization of the p53 DNA-binding domain (DBD) and tetramer. a) three-dimensional structure of the DBD in complex with sequence-specific DNA, highlighting the β -sheet scaffold and loop regions (L1, L2, L3) that make direct contact with DNA bases. b) Full p53 tetramer bound to DNA, illustrating how four monomers assemble into two dimers that each recognize one DNA half-site. This tetrameric arrangement is essential for p53’s function as a transcription factor. Minor disruptions to this structure, such as those caused by structural hotspot mutations, can abolish tumor suppressor activity. Reproduced from Wang *et al.* 2023 under CC BY 4.0 license.¹

MDM2-mediated ubiquitination and proteasomal degradation are two post-translational mechanisms that work together to unfold and degrade the protein, keeping p53 levels low.²⁶ Upon cellular stress signals such as DNA damage, oncogene activation, or hypoxia, p53 undergoes post-translational modifications that disrupt the p53-MDM2 interaction. Stress-activated kinases, including ATM, ATR, and CHK1/CHK2, phosphorylate p53 at Ser15 and Ser20, disrupting the p53-MDM2 interaction and allowing p53 to accumulate.^{27,28} These modifications allow p53 to accumulate rapidly and form tetramers in the cell. Once in the nucleus, p53 must locate and bind to DNA-binding sites as a tetramer.¹²

Once stabilized, p53 activates target genes appropriate to the stress signal. For cell-cycle arrest, p53 strongly induces CDKN1A, a cyclin-dependent kinase inhibitor that codes for p21 and blocks cell cycle progression at the G1/S checkpoint. This halts the DNA replication process and gives cells time to repair damage before dividing.⁷ In the case of irreparable damage, p53 activates pro-apoptotic genes such as BAX and PUMA, which trigger mitochondrial membrane permeabilization and caspase-mediated apoptosis.²⁹ For DNA repair, p53 induces genes like GADD45A, which facilitate repair processes and assist in chromatin remodeling during repair. p53 also induces expression of DNA damage recognition proteins DDB2 and XPC, which recognize DNA lesions and help recruit repair machinery to sites of damage.³⁰ The structural and physiological integrity of p53 is crucial for it to carry out its functions. The DNA-binding domain must be properly positioned and structured to enable the recognition of target DNA sequences. Tetramer formation through the tetramerization domain provides the stability and structure required for proper DNA binding. Both the N-terminal and C-terminal regions allow these domains to integrate regulatory signals that fine-tune p53's activity (Figure 2).

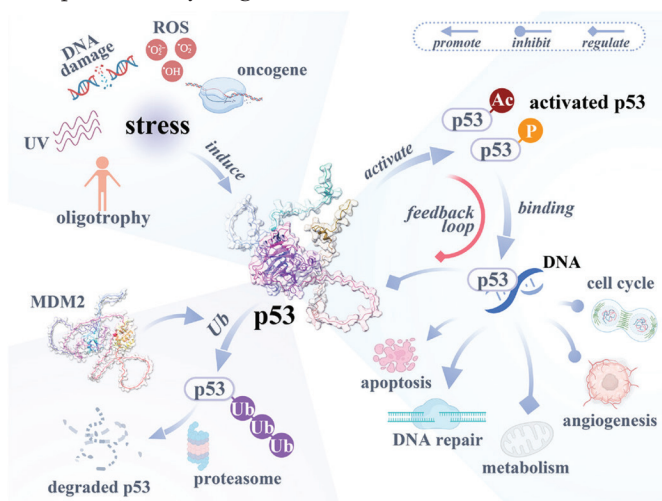


Figure 2: The p53 signaling pathway under normal and stress conditions. Under normal conditions, MDM2 ubiquitinates p53, targeting it for proteasomal degradation through a negative feedback loop. Upon stress signals, including DNA damage, ROS, UV radiation, and oncogene activation, p53 is stabilized through phosphorylation and acetylation. This allows it to bind DNA and activate programs including cell cycle arrest, apoptosis, DNA repair, angiogenesis, and metabolic regulation. Reproduced from Shen *et al.* 2023 under CC BY 4.0 license.³¹

Over 80% of cancer-associated p53 missense mutations occur within the DBD, primarily clustered at specific residue positions known as mutation hotspots.³ The six most frequently mutated residues are R175, G245, R248, R249, R273, and R282. These six residues account for a disproportionate amount of all p53 mutations across human cancers, as altering them disrupts p53 function, which gives cancer cells a survival advantage.³² These hotspot mutations can be classified into two major categories based on their mechanisms of inactivation. Contact mutations, which include R248 and R273, occur at residues that make direct physical contact with DNA bases or the DNA backbone. Mutations at these locations eliminate hydrogen bonds and electrostatic interactions that enable p53's sequence-specific recognition abilities.^{33,34} Structural mutations, which include R175H, G245S, R249S, and R282W, disrupt and destabilize the three-dimensional fold of the DBD, causing conformational changes or partial unfolding of the domain.^{3,33} R175, for instance, disrupts zinc-binding site interactions and impairs loop positioning critical for DNA recognition. It is important to note that not all mutations at the same residue have identical effects; some mutations can cause complete loss of function, while others retain partial activity.³ The high frequency of mutations specifically at these hotspots demonstrates the importance of these residues for p53's tumor suppressor activity and how their disruption promotes cancer progression.

p53 Mutations and Misregulation in Cancer:

Most *TP53* mutations are missense mutations, with over 80% involving single amino acid substitutions. This produces full-length proteins that are structurally altered instead of eliminating protein expression.^{3,35} The majority of these missense mutations cluster within the DNA-binding domain between codons 125 and 300.³⁶ The consequences of p53 mutations can be classified based on their functional effects. Mutations can lead to loss-of-function, where the protein loses its normal tumor-suppressing activities, or gain-of-function, where the mutant protein acquires new properties that actively promote cancer progression.^{35,37} Because p53 functions as a tetramer, mutant p53 proteins can exert dominant-negative effects by forming mixed tetramers with remaining wtp53 and blocking its function.³⁸

Loss-of-function mutations are the most common form of p53 inactivation in cancer. When p53 loses the ability to activate its target genes, cells lose access to the stress-response programs that would otherwise protect them from accumulating genetic damage. As a result, cells are no longer able to carry out processes such as inducing cell cycle arrest through p21, triggering apoptosis through BAX and PUMA, or repairing damaged DNA through genes like GADD45A, DDB2, and XPC.^{7,29,30} Without functional pathways, additional mutations can arise and go uncorrected. Loss-of-function mutations actively create conditions where genetically damaged cells continue to survive and replicate, further enabling cancer development.³

Unlike LOF mutations, which eliminate p53's normal tumor-suppressing abilities, GOF mutations give mutant p53

new cancer-promoting abilities. GOF mutp53 remains structurally stable and begins interacting abnormally with other proteins in the cell.^{35,38} One of the most commonly observed GOF mechanisms involves mutp53 binding to and blocking p63 and p73, two proteins from the same family as p53 that share a similar structure and function. By interacting with them, mutp53 prevents p63 and p73 from binding to their DNA targets, which blocks their ability to activate genes that suppress cell growth and trigger apoptosis.^{2,39} Gain of function mutp53 also binds with other transcription factors such as NF- κ B, ETS2, NF-Y, SREBP, and HIF-1 α . The mutp53 then changes which genes get turned on or off in ways that benefit cancer cells.² GOF mutp53 is also able to enhance the ability of cancer cells to invade surrounding tissue and spread to other parts of the body by turning on genes involved in cell movement and tissue breakdown.³⁸ It increases resistance to chemotherapy by activating proteins that either pump drugs out of cancer cells or break them down before they can work.³⁸ Additionally, by interfering with DNA repair and cell division checkpoints, GOF mutp53 can increase cell duplication and contribute to DNA damage.³⁸

The differences between LOF and GOF mutations make it clear that not all p53 mutations work the same way (Figure 3). Loss-of-function mutations prevent p53 from binding to DNA and activating the genes that protect against cancer. Typically, the protein will misfold, lose its ability to bind to DNA, or both. Gain-of-function mutations work differently. The mutant p53 will no longer be able to function as a normal transcription factor, but instead of becoming inactive, it begins interacting with other proteins in harmful ways.^{35,39} The two types also differ in protein stability. Loss-of-function mutants are often structurally unstable and may break down or co-aggregate inside cells. Gain-of-function mutants are typically very stable. They accumulate to abnormally high levels in cancer cells, often because chaperone proteins like HSP90 protect them from degradation.² Clinically, tumors with GOF mutations tend to be more aggressive, harder to treat, and associated with worse patient outcomes.³⁵ While LOF mutations eliminate p53's tumor-suppressive capacity, GOF mutations give the protein new oncogenic properties that contribute to tumor progression. Because of their prominent differences, making the distinction between these two mutation types is critical for understanding and treating p53-driven cancers.

Mutant p53 proteins can also cause additional damage by mixing with wtp53 tetramer subunits and disrupting their function, also known as the dominant-negative effect. In cells that carry one mutant and one normal copy of *TP53*, both types of p53 protein are produced and can combine into the same tetramer.⁴⁰ This means that even one mutant copy of p53 can impair and affect the function of the remaining wtp53. Studies have shown that cells with equal amounts of mutant and wild-type p53 display less than 50% of normal p53 DNA-binding activity. This further suggests that mutp53 dominant negative effects are disproportionately damaging.⁴¹ This has been confirmed in animal studies where mice carrying one mutant *TP53* gene and one normal *TP53* gene behave similarly to mice completely lacking p53 when exposed to DNA-dam-

aging agents.^{40,42} This helps explain why the Li-Fraumeni syndrome causes cancers at very high rates and unusually early ages, even though they still carry one functional p53 allele.⁴¹ It is important to understand that the dominant-negative effect is not equally strong for all mutations and varies depending on the specific mutation or cell type. Over 91% of p53-mutant cancers ultimately lose both p53 gene alleles, which indicates evolutionary pressure on the cancer cells to fully remove p53 function rather than relying on partial removal through the dominant-negative effect.⁴³

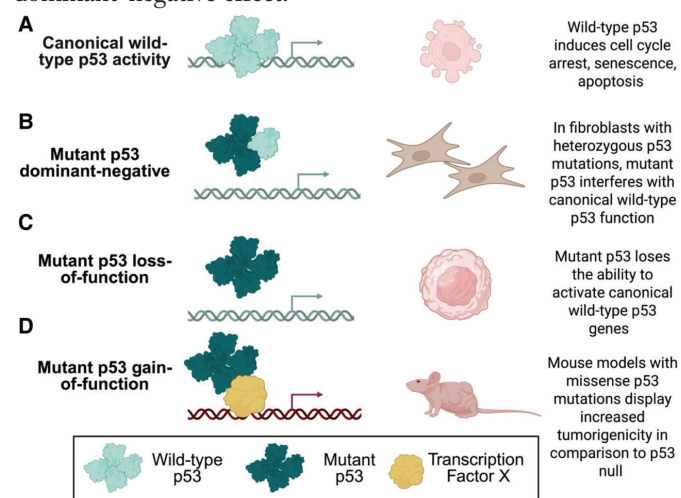


Figure 3: Functional categories of mutant p53 and their mechanisms of tumor suppressor inactivation. Wild-type p53 activates target genes that suppress cancer growth. Loss-of-function (LOF) mutations prevent p53 from binding DNA, eliminating its tumor-suppressive capacity. Gain-of-function (GOF) mutations give the mutant protein new cancer-promoting interactions with transcription factors. The dominant-negative effect occurs when mutant and wild-type p53 combine into mixed tetramers, impairing the remaining functional protein. Each category represents a fundamentally different molecular problem requiring a distinct therapeutic strategy. Reproduced from Efe *et al.* 2026 under CC BY 4.0 license.³⁷

p53 can also be functionally silenced in cells with a completely normal, unmutated gene. One of the most common ways this happens is through the overexpression of MDM2 or its related protein MDMX. In normal cells, MDM2 and p53 exist in a balanced feedback loop that keeps p53 levels low when cells are healthy. In certain cancers, however, the genes encoding MDM2 or MDMX are amplified or overexpressed. As a result, these proteins are produced in excess and continuously suppress p53 activity even when the cell is under stress.^{44,45} High-risk human papillomaviruses like HPV-16 and HPV-18 produce a protein called E6 that directly degrades p53 through a pathway distinct from MDM2, achieving the same functional effect as a mutation.^{46,47} p53 can also be impaired when the cellular machinery responsible for activating it is disrupted. For example, if the kinases that phosphorylate p53 at S15 and S20 in response to DNA damage are lost or mutated, p53 cannot be properly activated. This leaves cells functionally p53-deficient despite having a completely intact *TP53* gene.⁴⁴ These non-mutational mechanisms demonstrate that p53 dysfunction can occur through multiple pathways, each of which may require a different therapeutic approach.

Therapeutic Targeting of p53 Alterations:

p53 is one of the most common targets in cancer therapy, given its tumor-suppressing role in the cell cycle and the high frequency of its dysfunction in human cancers. However, due to its lack of typical drug target features such as well-defined binding pockets, p53 was considered an “undruggable” protein for many years.⁴⁸⁻⁵⁰ The challenge is further complicated by the fact that p53 dysfunction in cancer does not follow a single pattern. Some tumors carry LOF mutations, while others carry GOF mutations. wtp53 is also commonly suppressed by regulatory mechanisms like MDM2 overexpression.⁵¹ Each scenario presents a different problem that cannot be addressed by the same therapeutic approach. As a result, p53 targeted therapies can be sorted into different categories. The most current major approaches include reactivation of misfolded mutp53 proteins, inhibition of negative regulators like MDM2 and MDMX, degradation of GOF mutp53 proteins, and small-molecule strategies that can be tailored to specific mutation contexts (Table 1).¹

Overexpression of MDM2 or MDMX presents the therapeutic goal of releasing and stabilizing the functional p53 that is already present, since this type of dysfunction cannot be directly categorized as a mutation. MDM2 suppresses p53 by blocking target gene activation, marking p53 for degradation, and exporting p53 out of the nucleus.⁵² However, MDMX works differently. Instead of degrading p53 directly, it binds to the same transactivation domain as MDM2 and suppresses p53's transcriptional activity. MDM2 and MDMX form heterodimers to increase the efficiency of p53 ubiquitination and degradation.⁴⁴ Small molecules serve as a therapeutic solution for this by binding to the p53-binding pocket of MDM2, which physically blocks it from interacting with p53. The most well-studied examples are the Nutlin family of compounds, including Nutlin-3 and its clinical derivatives RG7112 and idasanutlin (RG7388). These small molecules occupy MDM2's hydrophobic binding cleft by mimicking three of p53's key binding residues (Phe19, Trp23, and Leu26). MDM2 is blocked from suppressing p53 as a result, allowing p53 levels to accumulate and its function to be restored.⁵³

Despite their initial clinical promise, MDM2 inhibitors have not achieved widespread therapeutic success. This is due to many factors, such as toxicity, side effects that limit patient tolerance, and rapid development of resistance through acquired p53 mutations. A phase I clinical trial of RG7112 (a first-generation Nutlin compound) showed responses in AML patients, but all patients experienced adverse events, including dose-limiting thrombocytopenia, neutropenia, diarrhea, and gastrointestinal toxicity.⁵⁴ Another RG7112 trial in 20 patients with MDM2-amplified liposarcoma demonstrated 70% stable disease with increased p53 expression, but late hematological toxicity remained a significant concern.⁵⁵ Resistance studies revealed that prolonged treatment with idasanutlin (RG7388, a second-generation MDM2 inhibitor) led to the emergence of p53-mutated resistant cell populations, demonstrating that these inhibitors provide limited cancer cell elimination and select for p53 LOF mutations.⁵⁶ Additionally, MDM2 inhibitors cannot fully activate p53 in tumors where MDMX

is also overexpressed. The study of dual MDM2/MDMX inhibitors and combination strategies that target both proteins simultaneously has increased in popularity as a result.⁵⁷ These approaches are only effective in tumors where p53 remains structurally intact.

For tumors carrying missense p53 mutations, the therapeutic goal involves fixing the protein directly. Many missense mutations, particularly structural ones like R175H and R249S, cause the DNA-binding domain to lose its proper shape without destroying the protein entirely. The protein is still there and stable, but it is misfolded, which prevents DNA binding. If a small molecule can restore the protein back into its proper shape, it might regain the ability to bind DNA.⁴⁸ The most advanced drug in this category is APR-246 (also known as eprenetapopt or PRIMA-1MET), which is a methylated derivative of the earlier compound PRIMA-1. Inside cells, APR-246 converts to an active compound called methylene quinuclidinone (MQ). MQ works by forming covalent bonds with cysteine residues on the p53 surface, particularly Cys124 and Cys277. These bonds stabilize the mutant protein and shift its shape back toward a wild-type-like structure that can bind DNA and turn on target genes.¹

Early clinical trials demonstrated remarkable promise in patients with *TP53*-mutant myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). In a phase Ib/II trial, APR-246 was combined with azacitidine, the first FDA-approved treatment of MDS. The combination achieved an overall response rate of 71% with 44% complete remission (CR) in 55 patients with *TP53*-mutant MDS or AML.⁵⁸ A similar French phase II study confirmed these results, reporting a 62% overall response rate in MDS patients with a median overall survival of 12.1 months.⁵⁹ The subsequent phase III trial, however, did not provide statistical significance even though the complete remission rate was 53% higher in the eprenetapopt plus azacitidine arm (33.3%) compared to azacitidine alone (22.4%).⁶⁰ Another phase II trial evaluating APR-246 plus azacitidine as post-transplant maintenance therapy in *TP53*-mutant MDS and AML patients achieved a median relapse-free survival of 12.5 months and median overall survival of 20.6 months, a substantial improvement compared to historical controls showing approximately 30% one-year relapse-free survival and median overall survival of 5-8 months after transplantation.⁶¹

A related approach uses zinc metallochaperones. Structural mutations such as R175H prevent the mutant protein from properly coordinating the zinc ion that is essential for correct DNA-binding domain folding. Therapeutic Zinc metallochaperones like ZMC1 (NSC319726) are synthetic molecules that transport zinc into the cell, allowing it to bind to the zinc-binding site of mutp53, restoring zinc coordination and allowing the protein to refold into its normal functional shape.⁶² These results demonstrate that mutp53 reactivation is achievable through stabilization approaches like APR-246 and zinc metallochaperone strategies like ZMC1. Ongoing trials continue to evaluate these therapies in different contexts and new strategies for targeting missense mutations.

Another reactivation strategy involves COTI-2, an orally available third-generation thiosemicarbazone compound. The drug reshapes mutp53 back into wtp53 while also independently triggering DNA damage responses that push cancer cells toward apoptosis.⁶³ This means COTI-2 can eliminate tumor cells through both p53-dependent and p53-independent pathways, which is a significant advantage in tumors where restoring p53 function alone may not be enough to stop cancer cell survival.⁶³ Preclinical studies in head and neck cancer showed that COTI-2 also increases the effectiveness of cisplatin and radiation when used together, suggesting potential combined therapeutic approaches.⁶³ A Phase I clinical trial evaluating COTI-2 in patients with recurrent gynecologic cancers found it to be generally safe and well tolerated, with the most common side effects being nausea, fatigue, and gastrointestinal symptoms.⁶⁴ However, like other therapeutic approaches, COTI-2 is not a universal solution, and its effectiveness varies depending on the specific mutation present.^{1,63}

Under normal conditions, p53 must be present in the nucleus to carry out its tumor-suppressing functions, but a protein called XPO1 acts as a nuclear export receptor that physically transports p53 out of the nucleus and into the cytoplasm.⁶⁵ In cancer, XPO1 is frequently overexpressed, causing excessive export of p53 and other tumor suppressor proteins away from their targets, contributing directly to cancer progression.⁶⁵ This problem is compounded by MDM2, which not only marks p53 for degradation but also actively facilitates its nuclear export.²⁶ Nuclear targeting strategies address this by blocking XPO1 directly, trapping p53 inside the nucleus where it can function.⁶⁶ The most clinically advanced drug in this category is Selinexor (KPT-330), an orally available XPO1 inhibitor. Studies in gastric cancer found that XPO1 was overexpressed in tumor tissue compared to normal tissue and was associated with poor patient survival, and that blocking XPO1 with Selinexor effectively caused p53 to accumulate in the nucleus.⁶⁶ Selinexor also provides opportunities for combination approaches, with greater anti-tumor effects shown when combined with standard chemotherapy compared to either treatment alone.⁶⁶ Nuclear targeting is particularly relevant for tumors where p53 is structurally intact but kept inactive through regulatory suppression, making it a complementary approach to other reactivation drugs like APR-246, ZMC1, and COTI-2.^{1,65,66}

Gain-of-function mutp53 presents a different problem. Restoring wild-type shape through drugs like APR-246 will most likely be of no help here because the main problem is not the absence of tumor suppression, but the promotion of cancer through aberrant protein interactions.⁶⁷ One major strategy for GOF mutants is promoting degradation. In cancer cells, chaperone proteins, including Hsp40, Hsp70, and Hsp90, bind to and shield mutant p53 from the normal ubiquitin-proteasome degradation machinery.⁶⁷ Disrupting these interactions will re-expose mutp53 to degradation, reducing its levels and eliminating its oncogenic activity. The Hsp90 inhibitor 17-AAG (tanespimycin) has been shown to destabilize mutp53 in cancer cells, with preclinical studies that demonstrate reduced mutp53 levels and tumor growth inhibition.⁶⁷ Combining it with MDM2 inhibitors like nutlin-3a produces synergistic ef-

fects that destabilize mutp53 while activating any remaining wtp53.⁴⁴ However, this combination has not yet been tested in clinical trials.

The chaperone-associated E3 ubiquitin ligase CHIP (the C-terminus of Hsc70-interacting protein) is also a possible solution for targeting mutp53 for degradation. It recognizes misfolded proteins such as mutp53 and directly ubiquitinates them for proteasomal degradation. CHIP activity is not transcriptionally regulated by p53, meaning it can function even when the p53-MDM2 feedback loop is broken. While this could prove to be an effective therapy method, direct CHIP activators do not currently exist, and this approach remains in early preclinical stages.⁶⁷ Another emerging strategy involves disrupting the specific GOF mutant protein-protein interactions. Mutant p53 binding to transcription factors such as p63, p73, and NF- κ B enables GOF mutant activity. Small molecules that interfere with these interactions could potentially block GOF activity without having to restore wild-type function or degrade the protein. This approach is still in earlier stages of development compared to other therapies, but it presents a more targeted way to address specifically GOF mutations.⁶⁷

Table 1: Mutation-specific therapeutic strategies targeting p53 dysfunction. Structural mutants are targeted through reactivation drugs like APR-246 and zinc metallochaperones like ZMC1. COTI-2 offers an additional reactivation approach with a distinct mechanism. GOF mutants are addressed through degradation strategies, including 17-AAG and the CHIP pathway. Wild-type p53 suppressed by MDM2/MDMX is released through inhibitors like Nutlin-3a. Selinexor addresses nuclear export of p53 through XPO1 inhibition. Each strategy is matched to a specific type of p53 dysfunction, as applying the wrong approach to the wrong mutation context can worsen outcomes rather than improve them.

Method/Approach	Example Drugs	Clinical Status
Reactivation of structural mutant p53 to restore wild-type conformation	APR-246 (eprenetapopt), PRIMA-1MET	Phase III (MDS/AML)
Restoration of zinc coordination to structural mutants	ZMC1 (NSC319726)	Preclinical
Degradation of GOF mutant p53 using HSP90 inhibitors	17-AAG (tanespimycin)	Preclinical
Prevention of wild-type p53 degradation by blocking MDM2/MDMX	Nutlin-3a, RG7112	Phase I/II
E3 ubiquitin ligase-mediated degradation (CHIP pathway)	No direct activators available	Early preclinical
Reactivation of mutant p53 plus induction of DNA damage responses	COTI-2	Phase I
Nuclear retention/reactivation of p53 through XPO1 inhibition	Selinexor (KPT-330)	Phase I/II in p53-related solid tumors

p53 alterations are so diverse that effective therapies can only be developed if they are curated for specific types of dysfunction. Structural mutants like R175H that cause the DNA-binding domain to misfold are good candidates for reactivation strategies like APR-246, COTI-2, and zinc metallochaperones. Since these mutations disrupt protein structure rather than eliminating DNA-contacting residues, refolding the protein back into its proper shape can restore its normal abilities.⁶⁸ GOF mutants are best addressed through degradation strategies or disruption of their protein-protein interactions rather than reactivation. Simply trying to fix the protein may not eliminate its ability to hinder remaining healthy p53 or interact with other cancer-promoting proteins.⁶⁹ In contrast, tumors with wtp53 that are being suppressed through MDM2 or MDMX overexpression do not require structural repair. They instead

need MDM2/MDMX inhibitors to release p53 from suppression.⁷⁰ Tumors with intact p53 may also benefit from nuclear retention strategies such as XPO1 inhibition, which keeps p53 in the nucleus as a transcription factor.⁶⁶ Choosing the right therapeutic strategy based on the mutation context matters because using the wrong one can backfire. For example, using a reactivation drug like APR-246 on a GOF mutant may not be effective, since the primary problem is not misfolding but the mutant protein's aberrant interactions with transcription factors like p63 and p73, making degradation strategies like 17-AAG a more appropriate choice. Similarly, using MDM2 inhibitors in tumors with mutant p53 would stabilize the mutant protein instead of wild-type p53, potentially accelerating tumor growth.⁵⁷

■ Conclusion

The p53 protein is essential for maintaining genetic stability through cell cycle regulation. As this review has demonstrated, p53's function depends on its structural integrity. The distinction between LOF and GOF mutations is critical to maintain this. Loss-of-function mutations eliminate tumor-suppressing activity while gain-of-function mutations drive cancer progression through new oncogenic properties. Beyond mutations, the overexpression of MDM2 and the dominant negative effect can further complicate treatment.

Promising mutation-specific therapies have begun to emerge. Structural mutants can be treated through drugs like APR-246, which aim to reactivate mutp53 by binding to specific cysteine residues and restoring its wild-type conformation. GOF mutants require degradation strategies rather than reactivation, since only refolding will not eliminate oncogenic activity. Wild-type p53 suppressed by MDM2 needs inhibitors to release it from suppression. Using the wrong approach can compromise clinical efficacy. For example, MDM2 inhibitors in mutp53 tumors can inadvertently stabilize the mutant protein, potentially worsening outcomes.

While mutation-specific treatment is increasingly practiced in clinical oncology, continued progress depends on expanding the range of effective drugs available for each mutation category. This requires several key advances. First, while molecular testing is increasingly used in clinical trials, broader and more consistent implementation across all p53-driven cancer types remains an important priority to ensure that drug mechanisms are matched to specific mutations. Second, combination therapies should be an area of exploration to address multiple aspects, such as the primary mutation and resistance pathways. Finally, new drugs should be developed for mutation types that currently lack effective treatments, particularly contact mutants and GOF degradation strategies. Matching therapies to specific p53 mutation types is key to improving cancer treatment.

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