Review

The p53 functional remodeling axis: Molecular mechanisms from mutant inactivation to functional restoration and implications for tumor therapy

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Abstract

Cellular tumor antigen p53(p53) is a core tumor suppressor protein essential for maintaining genomic stability and cellular stress responses, and represents one of the most frequently mutated key molecules in human malignancies. Unlike the inactivation of most tumor suppressor genes via deletion or truncation, tumor protein 53(TP53) mutations predominantly manifest as missense mutations, resulting in the abnormal

stabilization, conformational distortion, impaired DNA binding, and transcriptional network reprogramming of the p53 protein. Certain mutant p53 not only loses its canonical tumor-suppressive function but also acquires tumor-promoting activities, manifested by facilitating tumor proliferation, invasion and metastasis, metabolic reprogramming, immune evasion, and therapeutic resistance. In recent years, research on mutant p53 has gradually shifted from “suppressing the aberrant protein” to “restoring tumor-suppressive functions”, thereby establishing a novel conceptual framework of the “p53 functional remodeling axis”. This framework emphasizes that aberrant p53 can be redirected from a tumor-promoting state to a tumor-suppressive state through approaches such as conformational correction, protein homeostasis regulation, interaction network rebalancing, downstream transcriptional program reconstruction, and combination therapy sensitization. In particular, the structural restorer rezatapopt targeting the TP53 Y220C mutation has demonstrated preliminary efficacy signals in clinical studies, suggesting that mutation-specific functional remodeling possesses realistic translational potential. Starting from the biological basis of p53 imbalance, this article systematically reviews the theoretical connotations, primary molecular mechanisms, pharmacological intervention strategies, relationship with the tumor immune microenvironment, and current status of clinical translation of the p53 functional remodeling axis, and provides prospects for its future application in precision oncology.

Keywords: P53, mutant p53, functional remodeling, conformational restoration, tumor therapy, precision medicine

INTRODUCTION

The Cellular tumor antigen p53(p53) protein is a core tumor suppressor that maintains genomic stability, coordinates stress responses, and determines cell fate, playing a pivotal role in DNA damage repair, cell cycle arrest, cellular senescence, apoptosis, metabolic homeostasis, and tumor immune regulation[1]. The tumor protein 53(TP53) gene is also one of the most frequently mutated genes in human malignancies. Its

aberrations are widespread across diverse solid and hematological tumors, and are closely associated with enhanced tumor aggressiveness, therapeutic resistance, and poor prognosis. Unlike many classic tumor suppressor genes that are primarily inactivated through deletion or truncation mutations, TP53 more frequently manifests as missense mutations within the DNA-binding domain. This type of mutation not only leads to the loss of wild-type p53 tumor-suppressive functions but also causes abnormal protein stabilization and accumulation, potentially conferring tumor-promoting activities in specific contexts[2-4].

Traditionally, TP53 mutations have been largely regarded as irreversible loss-of-function events; however, rapid advances in structural biology, chemical biology, and translational medicine in recent years are reshaping this paradigm. Accumulating evidence suggests that certain mutant p53 is not entirely “irreparable,” but rather holds the potential to regain wild-type-like functions through approaches such as structural stabilization, conformational correction, disruption of aberrant protein-protein interactions, and reconstruction of downstream transcriptional programs[1,5,6]. Notably, the TP53 Y220C mutation has emerged as the most representative model for “mutation-specific functional restoration,”as it creates a druggable cavity within the core domain of p53; The emergence of the corresponding small-molecule reactivator rezatapopt (PC14586) has further marked a pivotal step in transitioning p53 from an “undruggable target” to a “precisely targetable intervention”[6].

In this context, merely evaluating whether p53 is mutated is no longer sufficient to fully elucidate its complex biological behaviors and therapeutic implications in cancer. More importantly, mutant p53 is not a single, static endpoint of inactivation, but rather a dynamic functional spectrum collectively shaped by distinct conformational states, protein homeostasis dependence, aberrant interaction networks, differential transcriptional outputs, and microenvironmental effects[7]. Therefore, this article proposes and adopts the concept of the “p53 functional remodeling axis” to summarize the continuous process ranging from the destabilization, inactivation, and

gain-of-function acquisition of mutant p53, to its redirection toward a tumor-suppressive state upon pharmacological or pathway intervention. This concept emphasizes not only the “restoration of the p53 protein per se” but also the “restoration of the p53-dominated tumor-suppressive network”.

Currently, several pivotal research avenues have emerged in the field of p53 functional remodeling, including: the development of mutation-specific conformational restorers[5,8]; broad-spectrum reactivation of mutant p53[2]; release of wild-type p53 mediated by Murine Double Minute 2(MDM2)/Murine Double Minute X(MDMX) inhibition[9]; selective degradation of aberrant mutant p53 accumulation[10,11]; and combination therapeutic strategies based on replication stress, DNA damage response, and tumor immune microenvironment reprogramming[12,13]. Notably, a 2025 study in Cancer Discovery systematically elucidated the structural and functional restoration of Y220C mutant p53 by rezatapopt, while subsequent research in 2026 further revealed the mechanisms of acquired clinical resistance to this class of drugs, indicating that p53-targeted therapy has transitioned from proof-of-concept to a stage of “mechanistic deepening and clinical optimization”[5].

Based on these insights, this review aims to systematically summarize the conceptual connotations, key molecular mechanisms, drug development strategies, tumor immunity associations, and clinical translational progress of the “p53 functional remodeling axis,” starting from the biological basis of p53 imbalance. This is intended to provide novel theoretical foundations and research perspectives for the precise intervention of mutant p53 and personalized cancer therapy.

BIOLOGICAL BASIS OF P53 FUNCTIONAL IMBALANCE

Canonical biological functions of wild-type p53

Under normal physiological conditions, intracellular p53 protein levels are typically maintained at low levels, primarily relying on MDM2-mediated ubiquitination and subsequent proteasomal degradation[14,15]. Upon exposure to DNA damage, replication

stress, oncogene activation, or other stress stimuli, ATM/ATR and their downstream CHK pathways are rapidly activated, which attenuates the negative regulation of p53 by MDM2, thereby promoting p53 stabilization and nuclear translocation[16,17]. Upon activation, p53 functions as a key transcription factor to regulate the expression of diverse target genes. On the one hand, it induces cell cycle arrest mediated by molecules such as p21, thereby providing time for DNA damage repair[18]; On the other hand, it promotes genomic damage repair by activating repair-related molecules such as GADD45[19]; When cellular damage exceeds the reversible threshold, p53 can also upregulate pro-apoptotic genes such as BAX, PUMA, and NOXA, thereby inducing programmed cell death[20]. Furthermore, p53 is also extensively involved in diverse biological processes, including the maintenance of metabolic homeostasis, regulation of autophagy, modulation of ferroptosis, and balancing of inflammatory responses[1,2,21]. Therefore, p53 serves not only as a core integrator of cellular stress responses but also as a crucial molecular hub determining cell fate.

In addition to its classical transcription-dependent functions, p53 also possesses important transcription-independent functions[22]. Studies have shown that under severe or acute stress conditions, p53 can directly localize to the mitochondrial outer membrane and promote the increase in mitochondrial membrane permeability and the release of cytochrome c by regulating the activity of BCL-2 family proteins, thereby rapidly initiating mitochondria-mediated apoptosis[22,23]. For this reason, p53 serves not only as a transcriptional regulator of stress signaling but also as a direct regulatory executor of cell death programs. Once its function is compromised, it not only impairs the cellular defense against genomic damage but also exerts profound impacts on multiple levels, including uncontrolled cell proliferation, evasion of apoptosis, and tumor progression[24-26].

Aberrant forms of mutant p53

The biological consequences of TP53 mutations are not merely a simple “loss of function,” but rather exhibit pronounced multi-level characteristics and heterogeneity.

Overall, the aberrant forms of mutant p53 can be broadly categorized into three types. The first is loss of function (LOF), wherein mutations lead to the loss of p53's transcriptional activation capacity for classical tumor-suppressive target genes, thereby compromising its core roles in cell cycle control, DNA damage repair, and apoptosis induction[7]. The second type is the dominant-negative effect (DNE), wherein mutant p53 forms tetrameric complexes with residual wild-type p53 to inhibit its normal transcriptional activity, further amplifying the biological consequences of p53 pathway inactivation[27]. The third type is gain of function (GOF), wherein certain mutants not only lose their original tumor-suppressive roles but also actively promote tumor cell proliferation, invasion, metastasis, metabolic adaptation, and therapeutic resistance through mechanisms such as aberrant protein-protein interactions, transcriptional network reprogramming, and microenvironmental regulation[4,28].

Notably, GOF is not a universal attribute of all TP53 mutations, but rather exhibits significant mutant specificity and context dependence. In recent years, increasing studies have supported that certain hotspot missense mutations indeed possess relatively independent tumor-promoting activities, although their manifestation is influenced by multiple factors, including mutation type, tissue origin, co-occurring genetic alterations, and experimental model variations[4,29]. Therefore, mutant p53 should not be simply regarded as a static endpoint of inactivation, but rather understood as a dynamic spectrum of aberrant states encompassing loss of function, wild-type suppression, and gain of novel functions. It is precisely this complexity that provides a crucial theoretical basis for the subsequent proposal of the concept of "p53 functional reprogramming".

Hotspot mutations and their structural basis

TP53 hotspot mutations are predominantly located in the DNA-binding domain, with common sites including R175H, G245S, R248Q/W, R249S, R273H/C, and Y220C[1,7,30]. These mutations are not only highly prevalent in tumors but also highly representative in terms of protein structural stability, DNA-binding capacity, and functional output. Based on their impacts on the structure and function of the p53 protein, they are

generally broadly classified into two major categories: “conformational mutants” and “contact mutants”. Conformational mutants, such as R175H and Y220C, primarily compromise the spatial stability of the core domain, leading to aberrant protein folding and reduced thermodynamic stability, which predisposes p53 to destabilization and misfolding[31]; Contact mutants, such as R248Q and R273H, primarily impair the direct contacts between p53 and DNA response elements; although their overall protein backbone is relatively preserved, they are largely unable to effectively execute normal transcriptional regulatory functions[29].

These structural and functional differences dictate the significant heterogeneity among different mutants in their biological behaviors and therapeutic responses, thereby constituting an important basis for current precision stratified interventions. Of particular note, the Y220C mutation can induce a hydrophobic cavity on the surface of the p53 core domain, thus providing a definitive “small-molecule druggable pocket”[31]. This structural feature renders Y220C one of the most representative targets in current research on the conformational restoration of mutant p53, and also lays an important foundation for the subsequent development of mutant-specific structural stabilizers and functional reactivators.

CONCEPT AND CONNOTATION OF THE “P53 FUNCTIONAL REPROGRAMMING AXIS”

The “p53 functional reprogramming axis” is not a single molecular event, but rather a multi-level reconstruction process that spans protein structure, proteostasis, transcriptional networks, cell fate, and therapeutic responses. At its core, p53 dysregulation is not a static endpoint, but a plastic functional state spectrum that can be modulated, reversed, and reprogrammed. Therefore, the so-called “unctional reprogramming” refers not only to the partial restoration of wild-type-like activity in mutant p53, but also to the systematic correction of its aberrant stability, aberrant interactions, and aberrant outputs[2].

Structural reprogramming

For certain mutants, the essence of their functional inactivation is not complete protein loss, but rather primarily stems from the decreased thermodynamic stability and aberrant folding of the core domain. Based on this characteristic, the near-wild-type spatial conformation can be restored under certain conditions through small-molecule binding, covalent modification, or local structural stabilization strategies, thereby reestablishing DNA-binding capacity and downstream transcriptional activation functions. Therefore, structural reprogramming constitutes the most direct and most promising avenue for drug development in current research on p53 functional restoration. Existing studies indicate that the active metabolite of APR-246 can interact with cysteine residues in the p53 core domain, thereby promoting conformational restoration in certain mutants; In contrast, rezatapopt, developed for the Y220C mutation, enhances protein thermal stability and restores transcriptional activity by occupying the mutation-induced structural pocket, representing a typical paradigm for mutant-specific functional reprogramming[2].

Proteostatic reprogramming

Unlike wild-type p53, which typically undergoes rapid turnover, many mutant p53 proteins can accumulate aberrantly in tumor cells due to protection by HSP90, HDAC6, and associated molecular chaperone networks[10]. This aberrant proteostasis not only enables the sustained persistence of mutant p53 but also provides the basis for the maintenance and amplification of its gain-of-function. Therefore, p53 functional reprogramming should be understood not only as “repairing aberrant proteins”, but also as disrupting the proteostasis of mutant p53 aberrant accumulation, thereby attenuating its pro-tumorigenic outputs.

For rescuable mutants, the goal of reprogramming is to restore their normal activity; For hard-to-rescue mutants, their aberrant accumulation levels can be reduced by intervening in the molecular chaperone network, regulating the ubiquitin-proteasome pathway, or employing selective degradation strategies. In recent years, this

"destabilization" strategy has gradually emerged as an integral component of broad p53 functional reprogramming[28].

Reprogramming of transcriptional networks and protein-protein interactions

The pathogenicity of mutant p53 lies not only in its loss of transcriptional activation of classical tumor suppressor target genes such as p21 and PUMA, but also in its ability to establish novel pro-tumorigenic transcriptional networks through aberrant interactions with p63, p73, NF-Y, SP1, SREBP, STAT3, and various chromatin regulators. This network reprogramming can drive multiple malignant phenotypes, including epithelial-mesenchymal transition, stemness maintenance, metabolic adaptation, inflammation amplification, and immune evasion[2,7].

Therefore, true functional reprogramming extends beyond merely restoring the conformation or expression status of p53; more importantly, it rectifies aberrant network outputs, redirecting cells back to a regulatory trajectory dominated by tumor-suppressive programs. Only when aberrant interactions are attenuated, pro-tumorigenic transcriptional programs are disrupted, and classical tumor-suppressive pathways regain dominance does p53 functional reprogramming hold systems biology significance.

Reprogramming of cell fate and therapeutic responses

The ultimate value of p53 functional restoration lies in altering the fate decisions of tumor cells. Upon reactivation of the p53 network, cells can re-enter cell cycle arrest, senescence, apoptosis, or other regulated cell death programs, and in certain cases, exhibit resensitization to radiotherapy, chemotherapy, or specific targeted therapies. Thus, p53 functional reprogramming extends beyond molecular-level "restoration", ultimately culminating in altered cellular behaviors and reestablished therapeutic responses.

Notably, p53 restoration is not a simple “all-or-nothing” event. p53 activation with varying intensities, durations, and cellular contexts may lead to distinct outcomes, including repair, arrest, senescence, or death. Therefore, the “p53 functional reprogramming axis” is better understood as a directional reprogramming process rather than a mere molecular switch[2].

MAJOR MOLECULAR MECHANISMS OF P53 FUNCTIONAL REPROGRAMMING

Conformational correction and restoration of wild-type-like folding

Conformational correction is currently one of the most intuitive and representative molecular mechanisms underlying mutant p53 functional restoration. For certain mutants, functional inactivation is driven not by complete protein loss, but rather by decreased stability of the core domain and conformational abnormalities. Based on this characteristic, certain small molecules can directly bind to the core domain of mutant p53, thereby enhancing its thermal stability and promoting its transition to a wild-type-like conformation, which partially restores its DNA-binding capacity and downstream transcriptional activation function[8].

Exemplified by the Y220C mutation, drugs can significantly enhance protein stability by occupying the mutation-induced structural cleft, thereby restoring p53-dependent transcriptional programs, upregulating target genes such as p21 and PUMA, and inducing tumor cell apoptosis[5]. This research avenue demonstrates that specific mutant p53 is not undruggable, but rather can be functionally reactivated through structure-guided small molecule design. In contrast, molecules such as APR-246 interact with cysteine residues within the core domain of p53 to partially promote the conformational restoration of certain mutants, representing another strategy of “broad-spectrum conformational correction”. Overall, conformational functional reprogramming is not only a crucial breakthrough in p53-targeted therapy, but also provides a structural biology basis for mutation-specific precision intervention.

Redox-dependent reactivation of mutant p53

In addition to direct conformational correction, redox-dependent functional reactivation is also one of the crucial mechanisms underlying mutant p53 intervention. APR-246 is the most representative molecule in this field, and its mechanism is not entirely confined to "restoring p53 conformation", but also encompasses multiple aspects, including the regulation of intracellular redox homeostasis, the remodeling of glutathione metabolism, and the enhancement of stress-induced cell death[32,33]. Therefore, APR-246 does not merely represent a simple "structural repair", but rather constitutes a composite intervention modality characterized by both protein reactivation and cellular stress remodeling.

Precisely because of the somewhat broad-spectrum nature of its mechanism of action, the clinical efficacy of APR-246 does not strictly correspond to specific TP53 mutation types[33,34]. Although the drug demonstrated some activity in early-phase studies, subsequent randomized phase III trials failed to meet the predefined primary endpoints, indicating that relying solely on the "pan-mutant restoration" strategy still faces practical challenges, including high patient heterogeneity, inadequate mutation stratification, and a lack of predictive biomarkers[34,35]. These findings have also, to some extent, propelled p53-targeted therapy to further shift from "broad-spectrum restoration" toward "mutation-specific precision stratification".

Relief of aberrant protein-protein interactions

The oncogenic effects of mutant p53 stem not only from its intrinsic loss of function, but are also closely associated with the aberrant regulatory networks established by "hijacking" other transcription factors or transcriptional cofactors. Previous studies have demonstrated that mutant p53 continuously drives pro-tumorigenic signaling by either suppressing p63/p73-mediated tumor-suppressive transcription or enhancing its binding to transcriptional complexes associated with inflammation, lipid metabolism, and stress[7,36]. Therefore, the relief of aberrant protein-protein interactions and the

dismantling of the mutp53-driven pro-tumorigenic transcriptional network constitute another crucial direction for functional remodeling.

Compared with merely repairing structural defects, this strategy more directly targets the oncogenic core of mutp53, namely its capacity for aberrant network output. Although such drugs and interventions are currently still under development, their theoretical appeal lies in the fact that they do not merely aim to “restore” mutp53 to its normal state, but rather achieve a deeper level of functional rectification by severing its aberrant interactions with key factors, thereby depriving tumor cells of their dependence on this pro-tumorigenic network[36]. From a systems biology perspective, this process essentially reflects a paradigm shift from “aberrant interaction-driven” to “tumor-suppressive network reconstitution”.

Functional rectification via mutant p53 degradation

For certain mutants that cannot be effectively restored through conformational correction, directly promoting their destabilization and degradation may represent a more feasible approach. The mechanistic basis lies in the fact that high levels of mutant p53 typically rely on specific molecular chaperone systems to maintain homeostasis; if this protective network is disrupted, aberrantly accumulated mutp53 can be rapidly cleared, thereby attenuating the survival dependence of tumor cells on it[2]. Therefore, targeting mutp53 for degradation is not merely a simple “removal of aberrant proteins”, but rather achieves functional rectification by relieving its continuous pro-tumorigenic driving effects.

Strictly speaking, this strategy does not restore the intrinsic wild-type activity of p53, but in a broader sense, it still falls within the scope of “p53 functional remodeling‘. Its essence lies in reverting the mutp53-driven pro-tumorigenic state of tumors back to a more vulnerable state that is highly susceptible to therapeutic interventions. In recent years, continuous advances in research targeting the HSP90/HDAC6 chaperone axis,

ubiquitination regulation, and the selective clearance of mutp53 based on its aberrant accumulation have indicated that “degradation of oncogenic mutp53” is gradually emerging as a crucial component of p53-targeted therapies[2,37].

THERAPEUTIC STRATEGIES FOR P53 FUNCTIONAL REMODELING

Mutation-specific restorers

The most representative successful paradigm currently is the use of mutation-specific restorers targeting specific mutant sites. Druggable mutations, exemplified by Y220C, provide a clear trajectory from structural recognition to clinical translation for p53-targeted therapies. Rezatapopt (PC14586) is currently the most representative molecule embodying this strategy. By specifically recognizing and stabilizing the structural pocket formed by the Y220C mutation, it restores the wild-type-like conformation and transcriptional activity of mutant p53, thereby achieving mutation-specific functional reactivation.

The significance of this strategy lies not only in demonstrating that specific mutant p53 can be directly targeted by pharmacological agents, but also in driving a paradigm shift in p53 therapeutic research from “broad-spectrum restoration” to “precision stratification”. Existing studies have demonstrated that rezatapopt exhibits preliminary single-agent antitumor activity in patients with advanced TP53 Y220C-positive solid tumors, with clinically meaningful objective responses and durations of response observed at the recommended dose levels[38]. Meanwhile, subsequent studies have also reported the acquired resistance mechanisms of these agents, including binding impairment and functional escape caused by *cis*-additive mutations, indicating that even the “precision restoration” strategy is subject to tumor evolutionary pressure[39]. Therefore, mutation-specific restorers represent not only a significant milestone in p53-targeted therapies, but also impose new requirements for the optimization of subsequent sequential therapies and combination strategies.

Inhibition of MDM2/MDMX in the wild-type p53 background

For tumors harboring wild-type TP53 but with the p53 pathway hyper-suppressed by MDM2/MDMX, relieving this suppression via MDM2 or MDMX inhibitors is also considered a crucial component of broad p53 axis remodeling. The rationale of this strategy lies in the fact that, in the wild-type TP53 background, p53 function is not truly lost, but rather remains in a state of continuous suppression by negative regulation; Therefore, disrupting the aberrant inhibitory interaction between MDM2/MDMX and p53 holds the promise of reactivating its endogenous tumor-suppressive activity.

Overall, this strategy is more applicable to tumors harboring wild-type TP53 than to those with mutant TP53. In recent years, research efforts have continued to advance, and certain MDM2 inhibitors have demonstrated activity in clinical studies; however, dose-limiting toxicities such as myelosuppression remain a critical challenge limiting their further application. Furthermore, the substantial interpatient variability in sensitivity to these agents indicates that improving selectivity, optimizing dosing regimens, and identifying the most appropriate combination therapy scenarios remain critical to achieving clinical breakthroughs in this field[40,41].

Synthetic lethal combination strategies

TP53 mutations frequently impair the effective control of the G1/S checkpoint in tumor cells, thereby increasing their reliance on S-phase and G2/M checkpoints, mediated by ATR, CHK1, and WEE1, to maintain replication integrity and cell survival. Therefore, establishing synthetic lethal therapeutic strategies targeting these dependencies has emerged as a critical intervention for TP53-aberrant tumors. The core premise posits that, in the context of p53 dysfunction, tumor cells may sustain survival via alternative checkpoints, thereby concurrently exposing novel vulnerabilities.

Additionally, TP53 aberrations are frequently associated with increased replicative stress, enhanced dependence on DNA damage repair, and the emergence of metabolic vulnerabilities; consequently, combining p53 functional restoration with DNA damage repair inhibitors, replicative stress inhibitors, or specific metabolic inhibitors has a

strong theoretical rationale[42,43]. From a therapeutic strategy perspective, this combination is not merely "additive killing" but aims to exploit the biological compensatory dependencies arising from p53 deficiency to achieve more selective cytotoxicity. Future advancement in this field critically hinges on further elucidating the vulnerability profiles across diverse TP53 mutation backgrounds and thereby optimizing combination regimens and patient stratification.

Combination with radiotherapy, chemotherapy, and targeted therapy

Another important clinical value of p53 functional restoration lies in restoring tumor sensitivity to existing therapies. Many radiotherapy, chemotherapy, and certain targeted therapies ultimately depend on cellular recognition of DNA damage, integration of stress responses, and initiation of cell death pathways, whereas p53 deficiency constitutes a key molecular basis for the development of drug resistance. Therefore, restoration of p53 function may reactivate apoptotic pathways such as BAX, PUMA, and NOXA, thereby enhancing tumor response to platinum-based agents, topoisomerase inhibitors, radiotherapy, and certain targeted therapies[44,45].

From this perspective, the value of p53 functional restoration is not limited to the development of single targeted drugs but rather in its potential to serve as a "therapy sensitization platform", thereby enhancing the overall efficacy of traditional therapies and modern precision treatments. Consequently, p53 functional restoration is increasingly regarded as a critical hub connecting molecularly targeted therapy and comprehensive treatment. The key issue for the future is no longer merely "whether p53 function can be restored", but rather "under which therapeutic context restoring p53 function yields the greatest clinical benefit", which will directly determine its true translational value in combination therapy.

P53 FUNCTIONAL RESTORATION AND THE TUMOR IMMUNE MICROENVIRONMENT

In recent years, the relationship between p53 and tumor immunity has gained increasing attention. Wild-type p53 is involved not only in intracellular stress response and maintenance of genomic stability, but also in inflammatory homeostasis, antigen presentation, immune surveillance, and regulation of antiviral responses. In contrast, mutant p53 promotes immune escape through multiple mechanisms, including upregulation of PD-L1-related pathways, suppression of antigen presentation, alteration of chemokine profiles, remodeling of myeloid cell infiltration, and maintenance of an immunosuppressive tumor microenvironment. Existing studies have demonstrated that TP53 mutation status and its various subtypes are closely asso-ciated with immune escape phenotypes, and that different mutant variants exert distinct effects on shaping the tumor immune niche[46].

Notably, the impact of p53 functional remodeling may not be limited to alterations in intrinsic tumor cell fate, but rather extends to tumor-immune interactions. Some studies suggest that restoration of mutant p53 function not only induces intrinsic apoptosis in tumor cells but may also be accompanied by changes in immunogenicity. For example, when replication stress and DNA damage states are reshaped, this may further influence cGAS-STING signaling, interferon pathways, and immune checkpoint therapy responses. Studies in 2025 further demonstrate that different p53 mutants exhibit differential effects on replication initiation and cGAS-STING activation, and may consequently influence the efficacy of immune checkpoint inhibitor therapy[29]. Therefore, p53 functional restoration is likely not merely an intracellular therapeutic strategy but also a critical entry point for reshaping tumor-immune interactions and improving immune therapy responses.

CLINICAL TRANSLATION ADVANCES

From broad-spectrum reactivation to mutation-specific stratification

One significant evolution in p53-targeted research is the gradual shift from early approaches of broad-spectrum restoration of all mutant p53 to a strategy of precise intervention targeting druggable mutations. APR-246 represents an early practical

implementation of the broad-spectrum reactivation strategy; its clinical studies have partially demonstrated the biological plausibility of mutant p53 functional restoration, yet also indicate that therapeutic efficacy may be readily diluted by tumor heterogeneity in the absence of precise stratification. In contrast, the development pathway of rezatapopt better exemplifies the application paradigm of precision oncology in the p53 field, wherein a specific structural pocket-forming Y220C mutation is first identified, followed by structure-guided design of a matched small molecule, and subsequent selective evaluation in patients harboring the specific mutation. This pathway significantly enhanced the credibility of p53 druggability and advanced the transition of p53-targeted therapy from proof-of-concept to precision stratification[38].

Current clinical evidence and limitations

To date, rezatapopt has demonstrated preliminary antitumor activity in patients with TP53 Y220C-mutated advanced solid tumors and has advanced to further clinical evaluation. Current evidence indicates that the drug has advanced to more targeted development in specific tumor types and molecular contexts, exhibiting promising translational potential. Meanwhile, studies have documented acquired resistance mechanisms, particularly drug binding impairment and functional escape resulting from additional mutations in cis, suggesting that even mutation-specific precision restoration strategies cannot fully circumvent the constraints imposed by tumor evolution.

On the other hand, the development of MDM2/MDMX inhibitors for wild-type TP53 tumors continues to advance; however, their clinical application remains limited by dose-limiting toxicities, insufficient biomarker screening, and poorly defined optimal patient populations[38,39]. Overall, current p53 functional restoration has advanced from a purely basic research concept to the clinical validation stage, but its further translation still relies on more precise patient stratification, more rational combination therapy design, and a more reliable efficacy evaluation system.

PRACTICAL CHALLENGES

Although p53 functional restoration demonstrates promising research prospects and translational potential, several key challenges persist prior to achieving clinical breakthrough.

First, TP53 mutations exhibit high heterogeneity. Different mutant variants exhibit significant differences in the extent of structural damage, residual functional retention, gain-of-function potency, and drug sensitivity, rendering a single drug insufficient to cover the entire mutation spectrum. This implies that the development of future p53-targeted therapies is unlikely to adhere to a universal approach for all TP53 mutations but rather necessitates a refined stratification system based on mutation types, structural characteristics, and functional status.

Second, standardized and reliable criteria for evaluating the extent of p53 functional restoration remain lacking. Current clinical and translational research predominantly employs TP53 mutation status as a key inclusion criterion; however, therapeutic efficacy may be determined not by the mutation per se but by the drug's ability to restore sufficient p53 transcriptional output, induce effective cell death programs, and correct critical aberrant interaction networks. Thus, reliance solely on changes in protein expression or genotyping remains insufficient to accurately reflect the true extent of functional restoration. Thus, the development of a biomarker system capable of dynamically assessing the depth of functional restoration remains an urgent unmet need in this field.

Third, acquired resistance has begun to emerge. Reactivators targeting the TP53 Y220C mutation have exhibited binding impairment and functional escape due to cis-acting mutations, indicating that even precision restoration strategies based on precise structural recognition cannot entirely circumvent the selective pressure for drug resistance imposed by tumor evolution. This observation indicates that p53 functional restoration does not represent a definitive therapeutic endpoint but rather necessitates

integration into sequential and combination therapy frameworks for comprehensive understanding and clinical application.

Finally, combination therapy strategies remain to be systematically optimized. The ultimate response outcomes following p53 restoration—whether cell cycle arrest, senescence, apoptosis, immune remodeling, or others—frequently depend on multiple factors, including tumor histotype, concomitant driver events, microenvironmental context, and treatment timing. Therefore, the focus of future research should not be confined to validating monotherapy efficacy but should prioritize identifying optimal combination scenarios across diverse biological contexts to maximize the clinical value of p53 functional restoration.

Overall, the true challenge of p53 functional restoration lies not merely in whether p53 can be restored, but in achieving predictable, monitorable, and sustainable functional restoration within the context of complex tumor heterogeneity. This also dictates that the future trajectory of the field must transition from proof-of-concept validation to mechanism-based stratification, from single-agent exploration to combination therapy optimization, and from structural restoration to functional outcome-guided precision translational research.

PERSPECTIVES

With the continued advancement of structural biology, chemical biology, and precision oncology, p53 functional restoration is progressively transitioning from proof-of-concept to an actionable translational research pathway. In contrast to the traditional perspective that TP53 abnormalities represent irreversible inactivation events, current research increasingly underscores that mutant p53 is not merely a terminally defective molecule but resides in a dynamic functional state amenable to regulation, correction, and reprogramming. This paradigm shift provides a new theoretical foundation for p53-targeted therapy and expands “functional restoration” from a single molecular repair strategy to a comprehensive intervention framework encompassing

structural restoration, homeostasis regulation, network correction, and therapeutic sensitization.

In the future, the development of p53 functional restoration will increasingly rely first on the refinement of mutation subtyping and functional stratification. Different TP53 mutations exhibit significant differences in structural impairment, residual activity, gain-of-function, and drug sensitivity; therefore, the development of mutation-specific therapeutics targeting specific mutation sites will remain one of the most promising directions in this field. The success exemplified by Y220C demonstrates that only through the close integration of structural characteristics, functional status, and patient stratification can p53-targeted therapy truly enter the realm of precision medicine.

Second, the research focus of p53 functional restoration will shift from whether restoration is achieved to the extent of restoration and the resulting functional outcomes. Moving forward, there is an increased need to establish a comprehensive evaluation system capable of dynamically reflecting p53 transcriptional output, cell death effects, the extent of network reconstruction, and changes in microenvironmental responses, to overcome the current limitation of efficacy assessment based solely on mutation status or alterations in protein expression. Essentially, what is truly clinically significant is not merely the correction of p53 structure, but rather the effective reconstruction of its tumor-suppressive functional network and its ultimate translation into measurable therapeutic benefits.

Third, p53 functional restoration is unlikely to develop as a single-agent definitive therapy but is more likely to serve as a pivotal hub within combination therapy frameworks. Whether in combination with DNA damage repair inhibitors, replication stress inhibitors, immunotherapies, conventional radiotherapy, chemotherapy, or targeted drugs, the therapeutic significance of p53 functional restoration lies not only in direct tumor killing but rather in restoring the tumor's responsiveness to existing therapies. Therefore, a central objective in this field moving forward is to identify the

most biologically rational and clinically promising combination scenarios across diverse tumor types, mutation backgrounds, and treatment stages.

Additionally, the emergence of tumor evolution and acquired resistance indicates that p53 functional restoration should not be conceptualized as a static therapeutic strategy but rather should be integrated into a dynamic treatment management framework. As drug resistance mechanisms become increasingly elucidated, determining strategies to delay functional escape through sequential therapy, combinatorial blockade, or adaptive therapy will constitute a critical challenge for subsequent clinical translation. This further indicates that future p53 research must extend beyond the paradigm of merely "restoring a protein" to encompass the reconstruction of tumor cell equilibrium with stress responses, treatment sensitivity, and microenvironmental interactions at a higher systemic level.

Overall, p53 functional restoration represents a highly promising new direction in precision cancer therapy. Its true significance lies not only in providing a novel breakthrough for "undruggable" targets but also in shifting the therapeutic paradigm from the static assessment of "whether a gene mutation exists" to the dynamic conceptualization of "whether abnormal function can be reshaped". It can be anticipated that, as mutation-specific drugs, dynamic biomarkers, and combination therapy strategies continue to mature, p53 functional restoration will evolve from its current frontier exploration into an integral component of future precision oncology.

DECLARATIONS

Author's contributions

Drafted the manuscript: ZG.W and ZX.L;

Revised it: BG.X, Z.G, MB.W and SF.S

performed manuscript review: SL.S;

All authors read and approved the final manuscript.

Contributed equally to this work and are co-first authors: ZG.W and ZX.L.

Availability of data and materials

No datasets were generated or analysed during the current study.

AI and AI-assisted tools statement

Qwen3.7 and DeepSeek-V4 models were adopted for linguistic revision, grammatical verification and text polishing. All sections of this article were reviewed and confirmed by the authors, who take full responsibility for the accuracy and authenticity of all content contained herein.

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Conflict of interest

The authors did not report any conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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