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An update on post-translational modifications of p53 from molecular mechanisms to therapeutic opportunities in cancer



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Highlights:

- This review summarizes how the combinatorial post-translational modification code shapes p53 function through dynamic crosstalk among writers, erasers and reader proteins.
- Post-translational modifications drive allele-specific biological outcomes for hotspot p53 mutants and can silence wild-type p53 activity in the absence of TP53 coding mutations.
- Targeting p53 post-translational regulatory networks offers promising anti-tumor strategies while multiple pre-clinical and translational obstacles still limit clinical implementation.

Abstract: p53 activity is orchestrated by a sophisticated combinatorial network of post-translational modifications (PTMs), which fine-tune protein stability, DNA binding affinity, subcellular trafficking, co-regulator assembly, and downstream transcriptional output. Beyond well-characterized phosphorylation and acetylation, an expanding repertoire of PTMs including methylation, ubiquitination, ubiquitin-like conjugation, and metabolism-coupled modifications constitutes a context-dependent PTM code that dictates p53-driven biological outcomes. This modification code governs chromatin engagement, DNA repair fidelity, transcriptional target selectivity, and diverse cell-fate programs in both wild-type and hotspot-mutant p53. A major conceptual advance in the field is the appreciation that p53 function arises not merely from individual modification events, but from dynamic PTM-PTM crosstalk mediated by dedicated PTM writers, erasers, and reader proteins. In this review, we synthesize current knowledge of p53 PTM-dependent regulatory circuits, allele-specific mutant p53 gain-of-function biology, and emerging translational opportunities. We further discuss outstanding bottlenecks limiting clinical translation of PTM-targeted strategies across wild-type and mutant p53-driven cancers.



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Keywords: p53; post-translational modifications; protein stability; DNA binding; non-canonical functions; targeted therapies

1. Introduction

As a master stress-responsive transcription factor, p53 sits at the core of cellular homeostatic surveillance. It integrates diverse stress cues ranging from genotoxic injury, oncogenic hyperactivation to metabolic perturbation and redox imbalance [1,2]. Its tumor-suppressive capacity extends far beyond a canonical DNA-damage checkpoint. p53 coordinates a broad, context-sensitive transcriptional program, and biological outputs are jointly shaped by the type of cellular insult and intrinsic tissue-specific context [1,3]. Accordingly, p53-governed processes span cell-cycle arrest, apoptosis, genome-wide DNA repair, metabolic rewiring, and persistent cell-fate decisions such as senescence. Accumulating work demonstrates that temporal p53 signaling dynamics and post-translational status are tightly coupled. Early p53 activation pulses preferentially trigger apoptotic or senescence-related gene sets, while sustained signaling favors DNA repair and homeostatic restoration [4]. Post-translational modifications (PTMs) constitute the primary molecular machinery encoding such context-dependent p53 responses, rather than serving as secondary, fine-tuning modifications. While phosphorylation and acetylation are well-established drivers of p53 stabilization, nuclear retention and transcriptional competence, a growing catalog of reversible PTMs including ubiquitination, methylation, SUMOylation, NEDDylation, O-GlcNAcylation, adenosine diphosphate (ADP)-ribosylation, hydroxylation, and β -hydroxybutyrylation exert site- and stress-dependent regulatory effects on p53 function (Figure 1) [1,5]. Importantly, these marks do not operate in isolation. Dedicated PTM writers install chemical moieties, erasers remove these modifications, and reader proteins interpret combinatorial PTM signatures to reshape p53 interactomes and transcriptional selectivity. This conceptual framework redefines p53 as a dynamic PTM-governed signaling hub and opens new avenues for therapeutic intervention. Successful therapeutic strategies aim to remodel, exploit or decode distinct PTM profiles. Such strategies can reactivate dormant wild-type p53, drive degradation of oncogenic mutant p53 variants, or rewire downstream oncogenic signaling. In this review, we provide an updated overview of the expanding landscape of p53 PTMs. We discuss how PTM circuits drive tumorigenesis, mediate functional reprogramming for both wild-type and mutant p53, and summarize preclinical advances and translational challenges for PTM-targeted cancer therapeutics.

2. Post-translational modifications of p53 in regulatory mechanisms and functional reprogramming

PTMs of p53 act not merely as fine-tuning mechanisms, but as a regulatory framework that governs its function. In wild-type contexts, PTMs determine whether p53 executes tumor-suppressive transcriptional programs, while in mutant settings, they promote protein stabilization and enable oncogenic rewiring into functional dependencies [5–9]. Thus, PTMs regulation forms a central mechanistic axis in tumorigenesis, setting the stage for the following discussion on how specific PTMs govern wild-type p53 activity, drive mutant p53 stabilization and gain-of-function (GOF), modulate non-canonical roles, and provide actionable targets for therapeutic intervention (Figure 2).

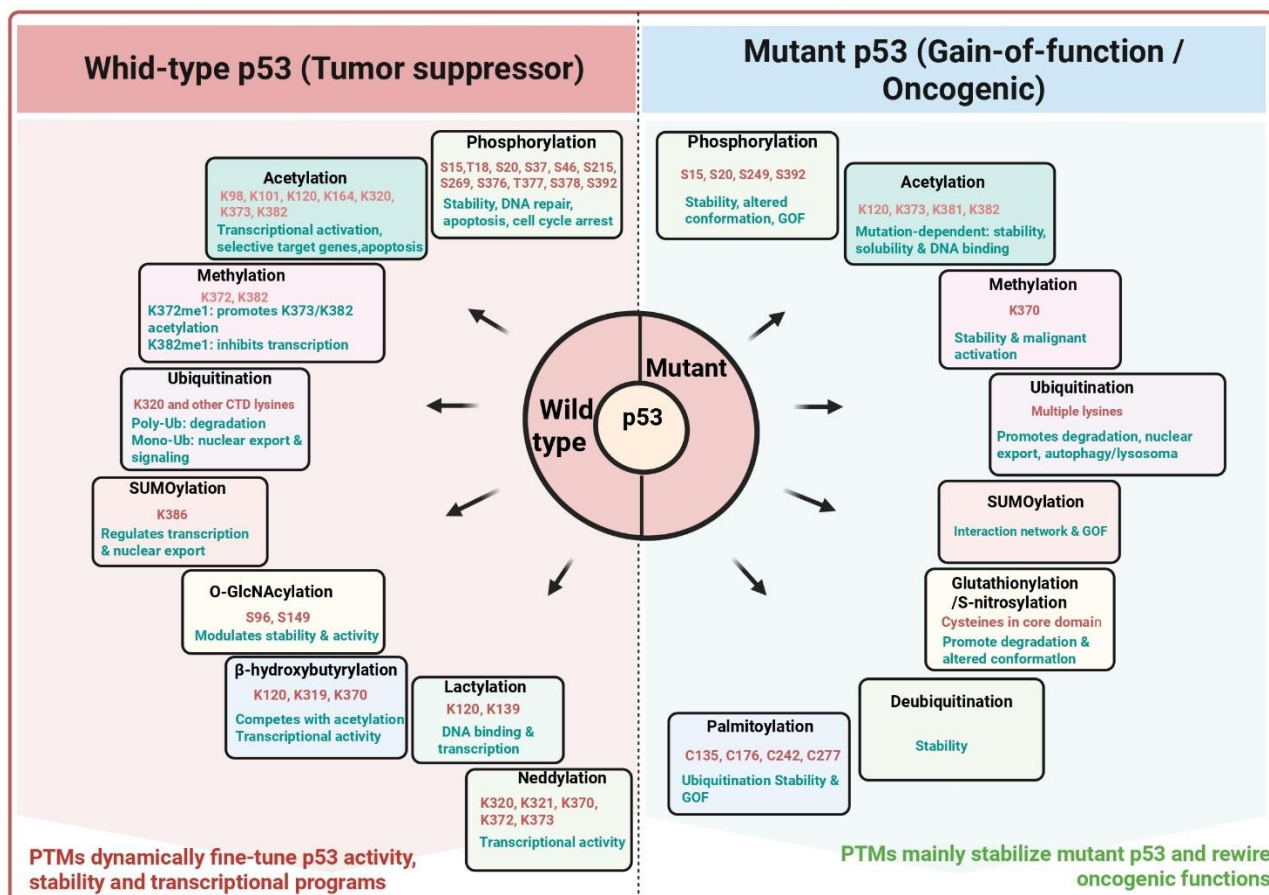


Figure 1. PTMs networks regulating p53 in wild-type and mutant contexts. This figure was created in BioRender (<http://app.biorender.com>).

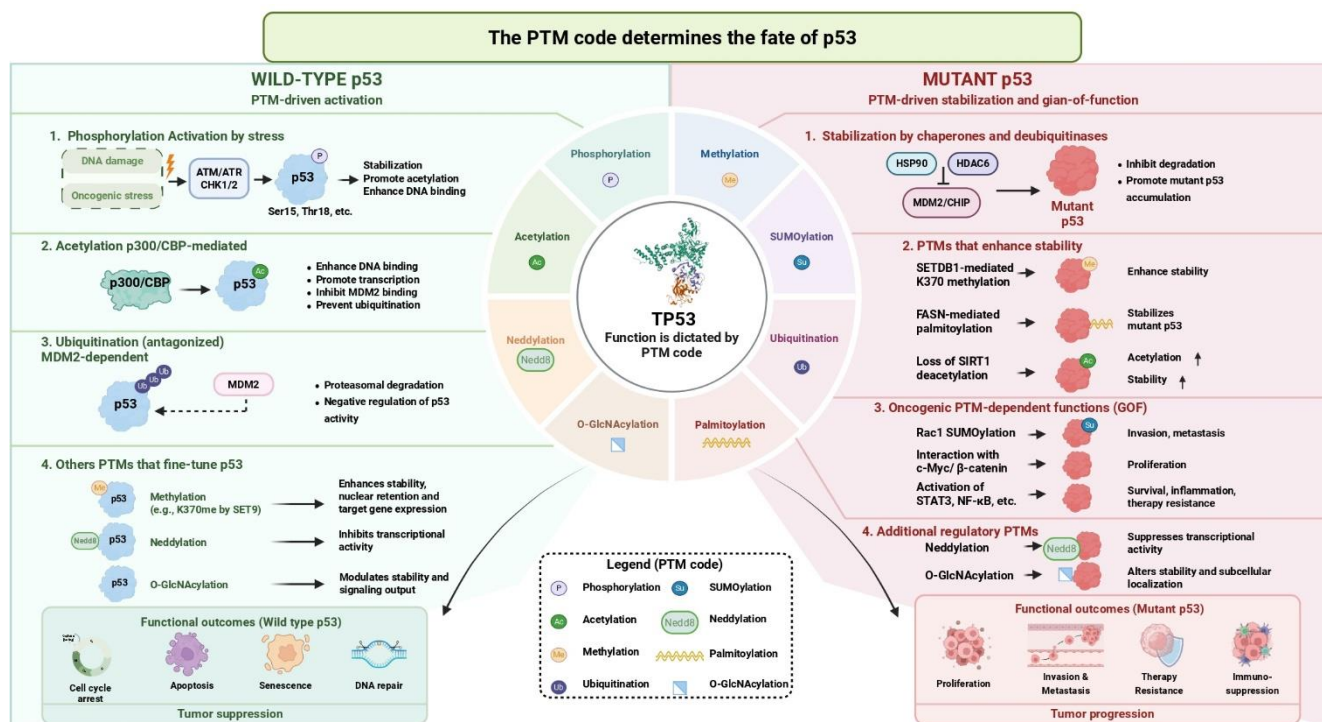


Figure 2. The impact of PTMs on the functional regulation of p53 protein. This figure was created in BioRender (<http://app.biorender.com>).

2.1. Dysregulation of p53 and functional inactivation of wild-type p53

In many TP53-intact cancers, p53 is functionally silenced by PTMs rewiring, often through loss of mis-specified phosphorylation and acetylation. Although the protein remains present, it cannot efficiently bind target promoters or activate transcription. Phosphorylation serves as the initial layer translating damage sensing into p53 activation, with highly site-specific effects. For example, the DNA damage response converges on the N-terminus of p53, inducing phosphorylation p53 at Ser18 and Ser23 (human Ser15/Ser20). These phosphorylation events play pivotal and synergistic roles in activating the p53-dependent apoptotic program, as evidenced by the profound impairment of IR-induced apoptosis in p53 S18/23A thymocytes [10]. Aurora A-mediated phosphorylation at Ser215 or Ser315 disrupts DNA binding and suppresses transcription of p21 and PTEN, while also promoting MDM2-dependent destabilization [11,12]. Similar misregulation by kinases such as PAK4 and CDK16 converts activating phosphorylation into inhibitory signals [13,14].

In normal cells, p53 activation follows a coordinated sequence of phosphorylation followed by acetylation, which is essential for DNA binding, transcriptional activation, and protection from MDM2-mediated repression [15–17]. Disruption of this cascade in cancers retaining wild-type TP53 compromises tumor suppression. For instance, adipose triglyceride lipase (ATGL) regulates p53 acetylation and phosphorylation via the peroxisome proliferator-activated receptor alpha (PPAR α)/p300 pathway, and imbalances inhibit cell cycle arrest and DNA repair while promoting apoptosis, increasing hepatocellular carcinoma sensitivity to genotoxic agents [18]. Acetylation also shapes a combinatorial ‘PTM code’ by regulating interactions with co-factors such as SET, VPRBP (DCAF1), DAXX, and PELP1, controlling promoter selectivity and transcription complex assembly [19–21]. Tumor-associated disruption of this code attenuates p53 activity and redirects its transcriptional output [22–24]. Beyond phosphorylation and acetylation, additional PTMs such as lysine methylation, neddylation, and O-GlcNAcylation modulate p53 stability and transcriptional output [25–28].

2.2. PTM-dependent stabilization and GOF of mutant p53

Most TP53 missense mutations generate full-length mutant p53 proteins that lose the canonical tumor-suppressive functions of wild-type p53 and acquire oncogenic GOF properties. These aberrant activities drive tumor proliferation, invasion, metastasis, metabolic reprogramming, and chemotherapy resistance. Notably, the stability and GOF phenotypes of mutant p53 are not inherent outcomes of TP53 mutations. Instead, they are dynamically and precisely governed by PTMs in a mutation-specific and context-dependent manner. Distinct hotspot mutant p53 variants exhibit unique PTM patterns, stability profiles, and downstream functional outputs. To systematically summarize the allele-specific regulatory effects of diverse PTMs on mutant p53 stability and function, we have compiled representative modification sites, biological consequences, mutant specificity, and current research advances in Table 1. As a classic conformational hotspot mutant, R175H p53 is tightly modulated by site-specific PTMs. Ser392 phosphorylation regulates the conformation, protein half-life, and oncogenic potential of R175H p53, while dephosphorylation at this site further exacerbates malignant transformation and drug-resistance [29,30]. Moreover, C-terminal lysine acetylation improves the solubility of misfolded R175H p53, relieves protein aggregation, and partially restores its DNA-binding capability. This acetylation also re-exposes R175H p53 to ubiquitination and subsequent proteasomal degradation,

thereby constraining its oncogenic activity [31]. In contrast, R273H is a typical DNA-contact mutant whose stability is controlled by the valosin-containing protein (VCP)-FBXO42-CCDC6-USP28 regulatory axis. VCP binding to R273H p53 disrupts the mutant p53-MDM2 interaction, abrogating MDM2-mediated ubiquitination and proteasomal degradation. Pharmacological VCP inhibition reverses this regulatory effect, promotes R273H ubiquitination, reduces endogenous mutant p53 abundance, and suppresses the proliferation of pancreatic cancer cells [32]. The R158G mutant displays strict allele-specific PTM-dependent regulation. Inhibition of histone deacetylase (HDAC) or sirtuin induces acetylation within the DNA-binding domain of R158G p53, which partially rescues impaired protein dimerization and transcriptional activity, thereby upregulating TRAF-interacting protein (TRAIIP) expression. Elevated TRAIIP further suppresses NF- κ B signaling and sensitizes R158G-harboring tumor cells to cisplatin. Importantly, this PTM-mediated tumor-suppressive effect is unique to R158G variant and is not observed in R175H, R248Q, or R273H mutants, highlighting the remarkable diversity of PTM regulation patterns among different p53 mutants [33]. Other hotspot p53 mutants further validate the conserved yet divergent PTM regulatory paradigms. The R249S mutant participates in multiple proteasome-associated oncogenic GOF programs shared by various p53 mutants. In comparison, the stability of R282W p53 relies heavily on HSP90 chaperone support, and this mutant fails to trigger STAT3-dependent oncogenic signaling activated by R248W p53. These discrepancies further demonstrate the distinct biological characteristics of individual mutant p53 variants [34,35]. Accumulating evidence demonstrates that oncogenic GOF of mutant p53 primarily depends on sustained protein stabilization rather than TP53 mutation alone [36–38]. PTMs serve as the core regulatory machinery that maintains mutant p53 stability by broadly restraining ubiquitin-dependent proteolytic degradation. The HSP90-HDAC6 chaperone complex stabilizes mutant p53 by blocking MDM2- and CHIP-mediated degradation, with HDAC6 reinforces HSP90 chaperone activity. Meanwhile, mutant p53 directly sequesters the acidic domain of MDM2. This interaction further disrupts MDM2-mediated degradation and maintains its own stability [37,39–42]. Multiple site-specific PTMs have been confirmed to drive mutant p53 stabilization and oncogenic activation. SETDB1-mediated K370 dimethylation, CDK4-triggered S249 phosphorylation, and fatty acid synthase (FASN)-dependent palmitoylation all contribute to the stabilization and malignant activation of mutant p53 [43–46]. Notably, FASN-mediated palmitoylation acts as a universal stabilizing modification, masking structural defects in multiple hotspot mutants including R175H, G245S, R248Q/W, R273H, and R282W. This pathway represents a mutation-independent PTM mechanism for sustaining mutant p53 stability [45]. Of note, identical PTMs exert bidirectional, context-dependent regulatory effects on mutant p53, rather than uniformly stabilizing or destabilizing protein function. The R181C mutant serves as a typical example of this unique regulatory pattern. The R181C mutation impairs SIRT1-p53 binding affinity, leading to defective deacetylation and sustained hyperacetylation at the K382 site. K382 hyperacetylation blocks MDM2 recruitment and ubiquitination, prolonging R181C protein half-life and enhances its oncogenic GOF activity [46]. This indicates that acetylation can stabilize specific mutant p53 variants, contrary to its canonical degradation-promoting role in other p53 mutants. Similarly, phosphorylation also exhibits allele-specific regulation of mutant p53 homeostasis. Ataxia telangiectasia mutated (ATM)-dependent S15 phosphorylation favors mutant p53 monoubiquitination and inhibits MDM2-induced polyubiquitination [47]. Moreover, S392 phosphorylation specifically modulates the stability of R175H but not R248W p53, further verifying the heterogeneous PTM regulatory landscape across distinct p53 mutants [30]. Beyond phosphorylation and acetylation, different types of PTMs exert opposing functions on mutant p53 stability.

FASN-mediated palmitoylation inhibits mutant p53 ubiquitination to maintain protein stability, whereas glutathione modification promotes mutant p53 proteasomal degradation [45,48]. A variety of E3 ubiquitin ligases and deubiquitinases precisely tunes the turnover of distinct mutant p53 isoforms via proteasomal and lysosomal pathways. TRIM21 limits the cellular accumulation of R175H (mouse R172H) mutant p53 [49]. The USP15-lysosomal axis specifically governs R175H degradation [50]. The FBXO42-CCDC6-USP28 complex stabilizes R273H, R248Q, and R248W mutants [51]. In contrast, USP7 facilitates the dissociation and activation of Y220C p53, which is subsequently eliminated through CHIP-dependent degradation [52]. Pirh2 provides an additional ubiquitin-dependent route for mutant p53 disposal, as its induction restores proteasome-dependent degradation of mutant p53 and reduces its accumulation in cancer cells [53]. CHIP can also redirect aggregated mutant p53 toward autophagy-mediated degradation under hypoxic conditions, thereby linking ubiquitin-dependent quality control to autophagic clearance [54]. Redox-dependent glutathionylation further promotes proteasomal elimination of a broad spectrum of mutant p53 proteins, underscoring the ability of oxidative modification to destabilize mutant p53 across multiple allelic contexts [55]. Beyond protein turnover, SUMOylation can remodel mutant p53 signaling output by enabling gain-of-function mutant p53 to activate Rac1, thereby promoting tumor progression [56]. In summary, the stability and GOF of mutant p53 are not passive consequences of TP53 gene mutation, but active outcomes of tumor-specific proteostatic network remodeling. PTMs function as central regulatory hubs that integrate genetic mutation features, chaperone activity, and ubiquitin-autophagy degradation systems to shape the unique stability and functional profiles of different p53 mutants. Given the prominent allelic specificity and therapeutic vulnerability of PTM regulation, future mutant p53-targeted antitumor strategies must fully consider mutation-specific differences to achieve and effective therapeutic intervention.

Table 1. PTM and regulatory patterns of mutant p53 across different hotspot mutations.

PTM or regulatory layer	Representative sites or pathways	Major effect on mutant p53	Representative mutations	Characteristics of evidence	Representative references
Phosphorylation	Ser392, Ser15, Ser20	Modulates protein conformation, tetramerization status, protein half-life, and oncogenic GOF activities	R175H, R248W	Regulatory effects are site-dependent and cell context-dependent	[7,29,30]
Acetylation	K120, K373, K381, K382	Regulates mutant p53 solubility and clearance, blocks MDM2 recognition to modulate protein stability	R158G, R175H, R181C	Dual and controversial regulatory effects reported in different studies	[31,33,46]
Ubiquitination	MDM2, CHIP, TRIM21, TRIM71, Pirh2	Determines mutant p53 protein fate including proteasomal degradation, nuclear export, autophagy, and lysosomal clearance	Multiple hotspot mutations	Functional outcomes depend on ubiquitin chain types and binding partners	[41,49,53,54]
Deubiquitination	USP15, USP28	Preserves mutant p53 stability in an allele-specific manner	R175, R248Q/W, R273H	Strict allelic selectivity among different p53 mutants	[50,51]
Palmitoylation	C135, C176, C242, C277	Suppresses ubiquitination and extends mutant p53 protein half-life	Multiple hotspot mutations	Recently identified mutation-independent stabilizing mechanism	[45]
Oxidation and redox modifications	Glutathionylation	Alters mutant p53 protein folding and triggers proteasomal degradation	Multiple hotspot mutations	Further <i>in vivo</i> validation is still required	[48,55]
SUMOylation and other modifications	MDM2-related and Rac1-related pathways	Modulates protein interaction networks and oncogenic GOF, limited evidence supports its direct regulation on protein stability	Multiple hotspot mutations	Current evidence is relatively insufficient	[7,56]

2.3. PTMs regulation non-canonical p53 functions

PTMs also shape non-canonical mutant p53 functions, these modifications might alter mutant TP53 activity and contribute to a GOF leading to increased metastasis and tumor progression [7]. Stabilized mutant p53 integrates into pro-survival and oncogenic signaling circuits, such as STAT3-dependent proliferation in colorectal cancer [57].

Beyond signaling, PTMs link p53 to metabolism, ferroptosis, and autophagy. O-GlcNAcylation enhances nuclear stability [28,58], while β -hydroxybutyrylation competes with acetylation to inhibit activity [59]. Acetylation of K98/K101 represses SLC7A11, promoting ferroptosis [60], and CREB-binding protein (CBP)-mediated K382 acetylation regulates metastasis-related phenotypes [61]. Additional mechanisms include USP7-dependent reduction of H2Bub1 at SLC7A11, enabling ferroptosis independently of canonical transcriptional activation [62]. Autophagy is influenced by subcellular localization, cytoplasmic p53 inhibits, while nuclear p53 activates autophagy programs [63–65]. In this context, PTMs primarily influence p53 stability and trafficking rather than acting through a single autophagy-specific modification site [27,66,67]. Palmitoylation regulates nuclear import and stability via ZDHHC1 and FASN [45,67]. PTMs further affect tumor microenvironment interactions, such as CHK2- or MDMX-mediated phosphorylation influencing immunosuppressive signaling [68,69]. These findings extend PTM-regulated p53 function to the tumor microenvironment.

Overall, PTMs constitute a combinatorial regulatory code that governs both the magnitude and qualitative output of p53 signaling. In cancer, disruption of this landscape not only diminishes p53 activity but reprograms transcriptional specificity, reshaping cell fate decisions. Therapeutic strategies should aim to either disrupt PTM networks maintaining mutant p53 stability or reprogram its structural and signaling state to reduce oncogenic potential.

3. The expanding landscape of p53 post-translational modifications

PTMs constitute a central regulatory layer that governs p53 activity across diverse cellular contexts. Beyond simply modulating protein stability, PTMs dynamically control p53 conformation, subcellular localization, DNA binding, and transcriptional output. Increasing evidence indicates that p53 function is determined not by individual modifications, but by an integrated and context-dependent PTM landscape. PTM sites on p53 encode specific functional outcomes that dictate its activity in response to cellular stress. These modifications regulate p53's role in processes such as cell cycle control, apoptosis, DNA repair, and cellular metabolism. In this section, we first revisit classical PTMs, then summarize emerging modifications, and finally discuss how combinatorial regulation, spatial organization, and PTM-associated factors collectively shape p53 signaling (Figure 3).

3.1. Classical post-translational modifications of p53

(1) Phosphorylation

Among the earliest characterized PTMs, phosphorylation plays a key role in initiating p53 activation. p53 activity is regulated by phosphorylation and acetylation during activation, whereas ubiquitination and site-specific phosphorylation or dephosphorylation contributes to its attenuation and inactivation [20,21,70,71]. Phosphorylation sites are distributed throughout the protein of p53,

with the enrichment in the N-terminal transactivation domain and C-terminal regulatory region [6]. In response to DNA damage, ATM and ataxia telangiectasia and Rad3-related (ATR) kinases are activated and phosphorylate p53 as well as downstream effectors such as CHK2 and CHK1, thereby promoting cell cycle arrest, DNA repair, and apoptosis [72,73]. Notably, Ser15 of p53 represents one of the earliest phosphorylation events mediated by both ATM and ATR [74]. Phosphorylation at Ser15 and Ser20 reduces p53's interaction with its negative regulator, MDM2, promoting its activation and transcriptional function [75]. Phosphorylation at Ser46 is essential for the induction of pro-apoptotic genes such as p53-regulated Apoptosis-Inducing Protein 1 (p53AIP1) [76,77]. On the other hand, Ser269 destabilizes the p53 DNA-binding domain, driving a mutant-like conformation that reduces p53's normal functions [78]. Phosphorylation at Ser392 regulates p53 mitochondrial translocation and its role in transcription-independent apoptosis [79,80]. Phosphorylation of p53 at T18 creates a binding site for the FHA domain of Pellino1 (an E3 ubiquitin ligase), which increases their recruitment to the DNA damage site and activation of p21 transcription [81].

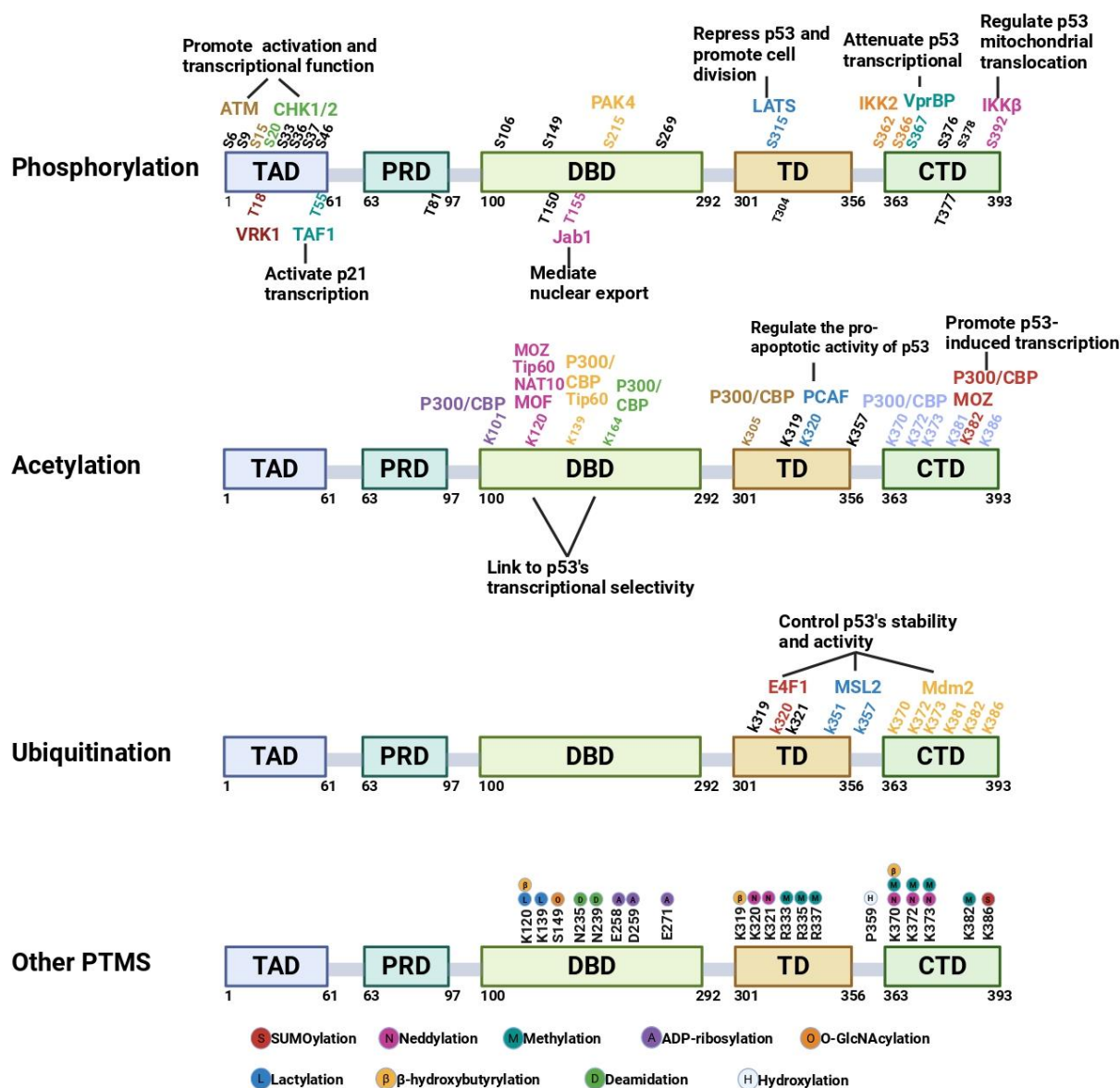


Figure 3. The major modification sites of p53, partial modifying enzymes and representative functions were plotted. This figure was created in BioRender (<http://app.biorender.com>).

(2) Acetylation

In parallel with phosphorylation, acetylation represents another major activating modification of p53. Acetylation regulates both canonical p53 functions, such as cell cycle arrest and apoptosis, and noncanonical processes including metabolism and ferroptosis [21]. Mechanistically, acetyltransferases such as p300/CBP, PCAF, Tip60, and MOF modify multiple lysine residues on p53, enhancing transcriptional activity and protecting p53 from ubiquitination-mediated degradation [82–85]. Acetylation-regulated interaction between p53 and SET reveals a widespread regulatory mode [19]. Acetylation plays a critical role in p53's transcriptional activity and its decision to promote either cell cycle arrest or apoptosis in response to stress. Acetylation at Lys120 and Lys164 is linked to p53's transcriptional selectivity, with Lys120 particularly involved in apoptotic transcription [86,87]. Acetylation of these sites also links p53 to immune modulation, further highlighting its broad role in tumor suppression and immune response [88].

(3) Ubiquitination and ubiquitin-like modifications

In contrast to activating modifications, ubiquitination primarily functions to restrain p53 activity. Under physiological conditions, p53 levels are maintained at low levels through MDM2-mediated ubiquitination and proteasomal degradation [89,90]. Ubiquitination of p53, primarily through MDM2, targets the protein for proteasomal degradation, controlling its stability and activity under normal conditions. However, p53 poly-ubiquitination facilitates proteasomal degradation, while mono-ubiquitination promotes p53 translocation to the cytoplasm [91–93]. Beyond ubiquitination, ubiquitin-like modifiers such as SUMO and NEDD8 further expand this regulatory layer. Neddylation, mediated by MDM2 and FBXO11, suppresses p53 transcriptional activity, whereas SUMOylation modulates both transcription and nuclear export [94–96]. Neddylation of p53 at specific lysine residues (K320, K321, K370, K372, K373) by HDM2 and FBXO11 suppresses p53 transcriptional activity without affecting its stability [27,96]. Similarly, SUMOylation at Lys386 regulates both p53-dependent transcription and its nuclear export [97,98].

3.2. Emerging and noncanonical p53 modifications

While classical PTMs establish the core regulatory framework, an expanding set of noncanonical modifications further diversifies p53 regulation (Figure 4).

(1) Methylation

Methylation provides an additional layer of site-specific control. SETD8-mediated monomethylation at K382 suppresses p53 transcriptional activity and may contribute to early tumorigenesis [99,100]. Similarly, other methyltransferases such as Set7/9 regulate p53 target gene expression in a site-dependent manner [26].

(2) ADP-ribosylation

In response to DNA damage, PARP1-mediated ADP-ribosylation enables rapid recruitment of p53 to DNA lesions [101–103]. Moreover, this modification links p53 to metabolic regulation through NAD⁺ consumption and shifts toward oxidative phosphorylation [104,105].

(3) Redox-related modifications

In addition, redox-dependent modifications such as glutathionylation and S-nitrosylation alter key cysteine residues within the p53 core domain, disrupting DNA binding and transcriptional activity even in the absence of genetic mutation [106,107].

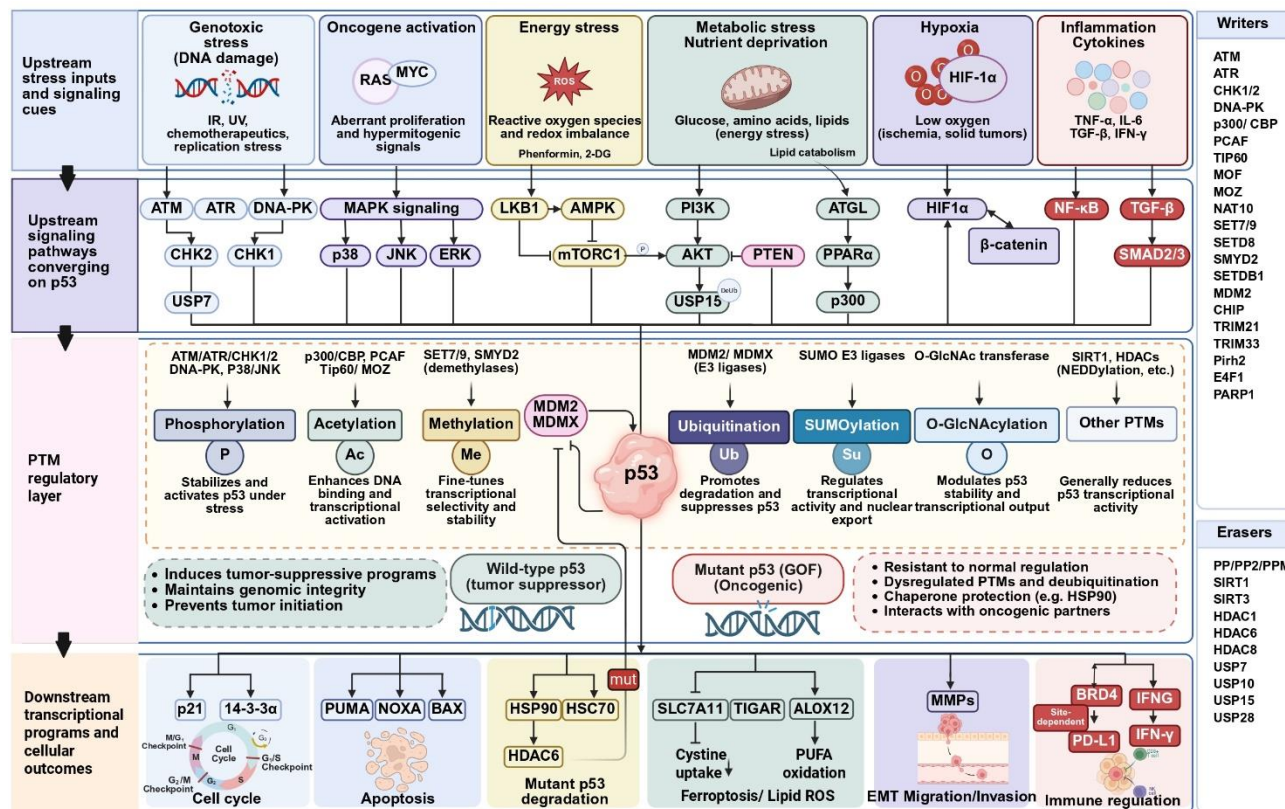


Figure 4. Schematic overview of p53 PTM regulatory network with major modifications, regulators and PTM-PTM crosstalk. This figure was created in BioRender (<http://app.biorender.com>).

3.3. Metabolic sensing modifications

Metabolic sensing modifications on p53 integrate cellular metabolic states with p53's tumor-suppressive functions. These modifications allow p53 to dynamically respond to changes in nutrient availability, oxidative stress, and energy balance, which are often altered in cancer [108].

(1) O-GlcNAcylation

O-GlcNAcylation is a key nutrient-sensing modification of p53. This modification, typically occurring at Ser149, stabilizes p53 by reducing its interaction with MDM2, thus promoting its transcriptional activity. During calorie restriction, increased O-GlcNAcylation supports gluconeogenesis, while reduced O-GlcNAcylation enhances p53's activity under nutrient deprivation [8,28,109,110].

(2) Lactylation

Lactylation of p53, particularly at lysines K120 and K139, is linked to lactate metabolism and promotes tumorigenesis. This modification is catalyzed by lactate and facilitates tumor cell adaptation

to hypoxic and low-oxygen conditions. In lung cancer, lactylation promotes metastasis and immune evasion, demonstrating how metabolic reprogramming can alter p53 function [111,112].

(3) β -hydroxybutyrylation

β -hydroxybutyrate induced by ketogenesis, occurs at lysines K120, K319, and K370 on p53. This modification reduces p53 acetylation, which in turn lowers its transcriptional activity, particularly under conditions of metabolic stress such as fasting. β -Hydroxybutyrylation decreases p53's ability to induce apoptosis and cell cycle arrest [59].

(4) Deamidation

Deamidation of p53 occurs at glutamine residues, particularly at N235 and N239, and is catalyzed by carbamoyl phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase (CAD). This modification suppresses p53 transcriptional activity, contributing to p53 inactivation in tumors. Inhibition of CAD restores p53 function, indicating that deamidation may be a potential therapeutic target for enhancing p53 activity in cancer treatment [113].

(5) Hydroxylation

Hydroxylation of p53, catalyzed by JMJD6, inhibits p53 acetylation and represses its transcriptional activity. Hydroxylation at P359 promotes p53 stability by facilitating its interaction with deubiquitinases USP7 and USP10, which prevent p53 degradation. Notably, depletion of JMJD6 enhances p53 activity and sensitizes cells to DNA damage-induced apoptosis, suggesting its role in regulating p53 response under stress [114,115].

(6) Lipid metabolism-regulated PTMs

Beyond the metabolism-associated p53 PTMs discussed above, lipid catabolism serves as another key regulator of p53 signaling. p53 acetylation acts as a central regulatory node connecting lipid peroxidation and ferroptosis. For example, acetylation at K101 and other residues maintains the tumor-suppressive activity of p53 via TIGAR/SLC7A11 [60]. Notably, p53 exerts context-dependent bidirectional control over ferroptosis. p53 promotes ferroptosis by repressing SLC7A11 and activating ALOX12-dependent PUFA oxidation [116,117], while it can also limit lipid reactive oxygen species (ROS)-induced cystine starvation via p21 to suppress ferroptotic cell death [118]. Accumulating evidence highlights tight crosstalk between cellular lipid metabolism and the p53 PTM landscape. Lipolytic activity remodels the balance of p53 acetylation and phosphorylation through the PPAR α /p300 signaling axis. This metabolic-PTM circuit reshapes p53-dependent transcription, fine-tunes DNA-damage responses, and dictates tumor cells sensitivity to genotoxic therapies. This regulatory cascade was first identified in hepatocellular carcinoma, in which ATGL-driven lipolysis reprograms cellular metabolic by inducing PPAR α /p300-dependent p53 acetylation and later studies confirmed its role in modulating responses to genotoxic drugs [18,119].

3.4. Decoding the PTM crosstalk and context-dependency

(1) The combinatorial PTM code

Phosphorylation at the N-terminal transactivation domain (TAD) of p53 often initiates a cellular response, which then triggers acetyl modifications in the C-terminal domain (CTD), collectively

controlling p53's transcriptional activation [91]. The interplay between acetylation and ubiquitination at overlapping lysine sites in the CTD regulates p53's transactivation and stability. Phosphorylation at Thr377 and Ser378 reduces acetylation at Lys373 and Lys382, suggesting that these sites function in a competitive manner to modulate p53 activity [120]. Mutations at these sites can alter this balance, influencing the functional output of p53 [121]. Additionally, the ubiquitination of Lys320 by E4F1 inhibits acetylation at the same site, specifically affecting the transcriptional program related to cell cycle arrest [122]. Methylation of p53 at Lys372 by Set7/9 is a key modification for subsequent acetylation at Lys373 and Lys382, stabilizing and activating p53 in response to DNA damage [123]. This methylation is essential for Tip60 binding to p53, further promoting its acetylation. Disruption of Set7/9 methylation impairs p53 activation and predisposes cells to oncogenic transformation [26]. Some p53 PTMs propagate their effects indirectly by recruiting or activating chromatin-modifying enzymes, which establish secondary PTM patterns on target chromatin and associated factors. For example, p53-associated p300/CBP promotes histone acetylation, while p53-SET1C cooperation promotes H3K4me3 at the p21 promoter [124,125].

(2) Cell type and stress-specific PTM signatures

Different stress conditions and cell types generate unique PTM signatures on p53. For example, phosphorylation of Ser46 and proline isomerization by Pin1 are critical for linking damage signaling to mitochondrial apoptosis [126]. DNA damage and ROS production activate ATM-CHK2 signaling, which in turn phosphorylates USP7 at S168 and T231. This phosphorylation is crucial for USP7's deubiquitinating activity, stabilizing p53 and contributing to DNA repair [127]. In U2OS and HEK293 cells, TGF- β promotes the translation of USP15. Upregulated USP15 deubiquitinates p53 to stabilize it [128]. O-GlcNAcylation also plays a role in stress responses, especially during pyroptosis. Reduced O-GlcNAcylation at p53's Ser96 and Ser149 enhances its transcriptional activity, promoting apoptosis and activation of the caspase-3-GSDME pathway [109]. Acetylation at K120 promotes apoptotic transcription and transcription-independent mitochondrial death, while acetylation at K101 and K98 is essential for ferroptosis and residual tumor suppression, particularly through targets such as SLC7A11 [21,116,129].

(3) PTM-mediated DNA damage response

p53 PTMs act cooperatively and dynamically to fine-tune DNA damage responses, whereby distinct modification sites coordinate rather than function independently to govern DNA repair and cell fate decisions. ATM/ATR-mediated synergistic phosphorylation of p53 at Ser37 and Ser46, together with DNA-PK-dependent RPA32 phosphorylation, dissociates the p53-RPA complex and sustains homologous recombination (HR). Notably, this regulatory effect cannot be achieved by either single modification alone [130]. Under replicative stress, ATR-induced p53 Ser15 phosphorylation, coupled with RPA binding, restrains excessive RAD51 foci formation and overactive HR, while preserving the repair capacity of crosslinker-triggered double-strand breaks (DSBs) [131]. Thus, the regulatory role of p53 Ser15 in HR is highly dependent on the type of DNA damage [132]. Following base or cleavage-type DNA damage, ATM-mediated p53 Ser15 phosphorylation promotes p53 recruitment to γ H2AX-labeled chromatin foci. Mutations of p53 at Ser15 and Ser18 disrupt foci assembly, p21 induction, and efficient DSB processing [133]. In addition to phosphorylation, p53 methylation and acetylation cooperate to stabilize DNA repair complexes. Methylation at K382 is recognized by the Tudor domain of 53BP1, facilitating p53 stabilization and multi-complex assembly upon DNA damage [134]. Mechanistically,

K382 acetylation synergizes with Ser392 phosphorylation to strengthen p53-MDC1 interaction [135]. p53 phosphorylation at Ser392 also promotes the recognition of aberrant DNA structures and Holliday junctions, whereas phosphorylation at Ser376 and Ser378 alleviates p53-mediated repression of BLM- and WRN-dependent Holliday-junction resolution [136,137]. Beyond HR and DSB repair, p53 PTMs also modulate nucleotide excision repair (NER) and base excision repair (BER). p53 enhances global NER by transcriptional upregulation of DDB2 and p48, and by directly recruiting DDB1 to DNA-lesion sites [103,138]. BER efficiency is regulated in cell-cycle-dependent manner. G0/G1-phase cells exhibit enhanced BER capacity, while G2/M-phase cells preferentially undergo apoptosis upon DNA damage. This cell fate switch is governed by coordinated p53 Ser15 phosphorylation and Ser376 dephosphorylation [139,140].

(4) Spatial regulation

PTMs also influence p53's localization within the cell. Deubiquitinases such as HAUSP/USP7 regulate the p53–MDM2 axis by stabilizing p53 and promoting its nuclear localization [66,141].

(5) Structural insights

Recent structural studies have revealed how PTMs affect p53 function in full complexes, including p53 bound to nucleosomes, RNA polymerase II, and BCL-xL at the mitochondria [142–144]. The studies have revealed how PTMs affect p53 conformation and DNA engagement. For instance, phosphorylation at Thr55 suppresses p53's ability to bind promoters, while acetylation at the CTD weakens its interaction with DNA, thus modulating the specificity of DNA binding [71,145,146].

4. Novel regulators and effectors of p53 PTMs

(1) Phosphorylation and dephosphorylation of p53

Enzymatic writers and erasers of PTMs play a pivotal role in regulating p53's activity (Figure 4). For example, TAF1 phosphorylates p53 at Thr55 to promote its degradation under normal growth conditions [147]. Other kinases, such as IKK β , phosphorylate p53 at Ser392, facilitating its activation in response to stress [148]. Additionally, Jab1 stimulates phosphorylation at T155 to mediate p53 nuclear export [149]. Computational analysis and experimental validation have identified NEK2 as a novel kinase that phosphorylates p53 at Ser315, which represses p53 activity and promotes cell division [150]. Similarly, phosphorylation at Ser367 by VprBP attenuates p53's transcriptional and growth-suppressive functions, contributing to tumor progression [151]. Dephosphorylation is equally important for terminating p53's response after damage is repaired, ensuring that sustained p53 activation does not harm the cell. This process is regulated by Ser/Thr phosphatases from three families (PP, PP2, and PPM), which control p53 dephosphorylation and reset its activity [152].

(2) Acetyltransferases and deacetylases of p53

Six acetyltransferases, grouped into two classes-p300/CBP/PCAF and Tip60/MOF/MOZ-acetylate p53 at distinct lysine residues. Acetylation at K370, K372, K373, K381, K382, and K386 in the C-terminal domain is primarily mediated by CBP/p300 [153]. Additionally, acetylation at K101, K139, K164, and K305 is catalyzed by p300/CBP [17,60]. PCAF acetylates p53 at K320, inhibiting its pro-apoptotic activity [154,155]. Tip60 acetylates p53 at K120, which is crucial for p53-mediated apoptosis after DNA

damage [84]. The K139 site of p53 is also acetylated by Tip60 [156]. Similarly, MOZ acetylates K120 and K382, enhancing p53-induced transcription, particularly in regulating p21 expression [157,158]. MOF acetylates p53 at Lys120, and this modification is implicated in both the transcription-dependent and transcription-independent apoptotic pathways induced by p53 [129]. NAT10 plays a key role in p53 activation by acetylating p53 and counteracting MDM2, facilitating p53's role as a cellular stress sensor [159]. Acetylation equilibrium is maintained by histone deacetylases (HDACs), including HDAC1 and SIRT1 [160–162]. Other HDACs, such as SIRT3 and HDAC8, also deacetylate p53, with HDAC6 selectively removing acetylation at K381/382 [163–165]. Inhibition of HDAC6 increases acetylated p53 levels, enhancing its pro-apoptotic activity [165].

(3) p53 PTM readers and complexes

p53 PTM reading involves a variety of reader proteins that interpret the modification patterns to regulate p53's downstream functions. The C-terminal lysine code of p53 is key to this process. For example, 53BP1 recognizes K382me2, while PHF20 binds to double methylated p53 (K370me2/K382me2), promoting stabilization and activation [166–168]. L3MBTL1 reads K382me1, mediating transcriptional repression [169], whereas acetylation often acts by displacing repressors bound to the unacetylated tail, especially SET and related acidic-domain proteins [19,170], with fewer firmly established acetyl-lysine readers such as PBRM1 BD4 [171]. Acetylated p53 recruits transcriptional cofactors through bromodomains: CBP recognizes acetylated p53, TAF1's tandem bromodomain recruits the transcription factor IID (TFIID) machinery preferentially through p53 K373ac/K382ac, and PBRM1 BD4 recognizes p53 K382ac within the PBAF complex. These interactions promote promoter occupancy and transcriptional activation, especially at CDKN1A/p21 [171,172]. p53 C-terminal acetylation relieves repression by disrupting acidic-domain proteins that preferentially bind its unacetylated, lysine-rich C-terminal domain. This mechanism is best established for SET and also applies to DAXX, VPRBP/DCAF1, and PELP1 [19,170,173].

(4) The role of phase separation

Phase separation adds another layer of regulation to p53 PTMs. PTMs influence the formation of nuclear and cytoplasmic condensates, with Ser392 phosphorylation favoring transcriptional condensates. Mutant p53, however, shifts to aggregated states, impairing its function. This phase separation modulates p53's ability to perform its functions by either promoting aggregation or recruiting p53 into functional condensates [174–177].

(5) PTMs crosstalk in the tumor immune microenvironment

p53 PTMs are tightly intertwined with the tumor immune microenvironment (TIME) and profoundly shape anti-tumor immune responses. In T cells, C-terminal p53 acetylation promotes *IFNG* transcription and establishes a positive p53–IFN- γ feedback loop. Genetic manipulation of endogenous p53 acetylation sites in T cells further supports this regulatory axis. Acetylation-deficient or acetylation-mimetic mutations respectively impair or potentiate CD8⁺ T cell-dependent antitumor immunity, providing solid genetic evidence linking site-specific p53 PTMs to distinct tumor immunophenotypes [178]. Lactylation is another immune-modulatory PTM that restricts p53 antitumor function. AARS1-mediated lactylation of p53 at K120 and K139 suppresses p53 DNA-binding activity and transcriptional competence [111]. In lung cancer bone metastases, the SLC2A3–lactate–p53 lactylation signaling cascade facilitates osteoclast differentiation, impairs CD8⁺ T cell function, and renders tumor lesions refractory to anti-PD-1

immunotherapy. Nevertheless, the precise causal relationship between site-specific p53 lactylation and TIME remodeling requires further validation [112]. Notably, p53 acetylation exerts dual, site-specific regulation of intrinsic PD-1 transcription in tumor cells. Acetylation at K120 and K164 upregulates cancer cell-intrinsic PD-1 expression, whereas C-terminal p53 acetylation disrupts BRD4–p53 interaction and represses PD-1 transcription [88,179]. Importantly, these tumor cell-autonomous regulatory pathways primarily modulate intrinsic tumor growth and are distinct from canonical T cell-derived PD-1/PD-L1 immune checkpoint signaling. Collectively, PTM-dependent p53 immune regulation represents an emerging and therapeutically promising research frontier in cancer biology.

5. Post-translational modifications of p53 as therapeutic targets

PTMs of p53 constitute a central regulatory layer controlling its stability, activity, and transcriptional specificity. Therapeutic strategies targeting p53 increasingly focus on modulating these PTMs rather than merely altering p53 abundance, as the functional state of p53 is determined by the combinatorial pattern of modifications. Effective interventions modulate key mechanisms including MDM2/MDMX-mediated repression, acetylation, phosphorylation, methylation, ubiquitin-mediated degradation, and interactions with PTM “reader” proteins which are discussed in each subsection below (Figure 5 and Table 2).

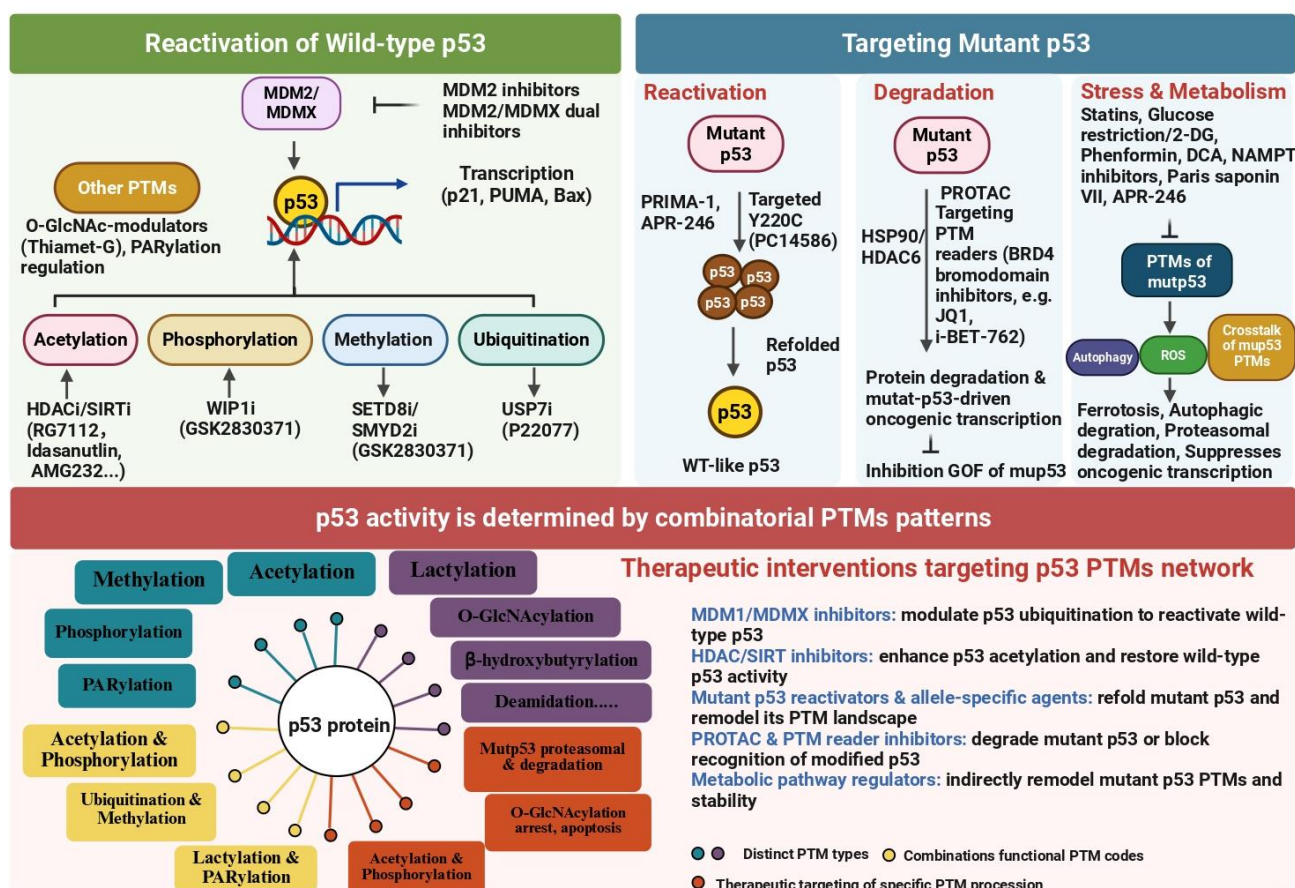


Figure 5. PTMs-centered therapeutic targeting of p53. This figure was created in BioRender (<http://app.biorender.com>).

Table 2. PTM-targeted therapeutic strategies for wild-type and mutant p53.

Context	Targeting Strategy	Key Mechanism	Representative Agents	Therapeutic Effect	Clinical development stage	Biomarker considerations	Mutation specificity	Major limitations of each strategy	References
Wild-type p53	MDM2/MDMX inhibition	Releases p53 from negative regulation	RG7112, Idasanutlin, AMG232, HDM201, APG-115, ALRN-6924	Reactivates transcription (p21, PUMA, Bax)	Phase I/II, several candidates with clinical stagnation	Requires functional wild-type p53, better response potential in MDM2-amplified tumors	Only active for wild-type TP53, ineffective for p53-mutant tumors	Dose-limiting toxicity, adaptive resistance, limited durability for single-agent treatment	[180–183]
	Acetylation enhancement (HDAC/SIRT inhibition)	Restores Lys120/Lys373/Lys382 acetylation	Depsipeptide, Tenovins, Inauhzin	Enhances stability and transcription	Pre-clinical/early clinical	Dependent on intact wild-type p53 expression	Wild-type-p53-dependent	Broad off-target epigenetic effects, low p53-specificity	[162,184–190]
	Isoform-specific HDAC targeting	Site-specific acetylation control	HDAC1, HDAC6, HDAC8 inhibitors	Restores apoptosis/stem cell targeting	Pre-clinical	Potential biomarkers: ARID1A mutation for HDAC6 inhibition, leukemia subtype for HDAC8 inhibition	Wild-type-p53-dependent	Lack of well-defined patient-stratification biomarkers	[161,191–194]
	Phosphorylation maintenance	WIP1 inhibition preserves phosphorylation	GSK2830371	Activates p53 targets	Pre-clinical	Tumors retaining stress-responsive wild-type p53	Wild-type-p53-dependent	Potential interference with broad kinase-signaling networks	[195]
	Deubiquitination targeting	Destabilizes HDM2, stabilizes p53	USP7 inhibitor (P22077)	Induces apoptosis	Pre-clinical	Requires intact USP7-HDM2-p53 axis	Wild-type-p53-dependent	Relatively narrow therapeutic window	[196]
	Methylation modulation	Inhibits SETD8/SMYD2	SETD8, SMYD2 inhibitors	Restores activity, chemosensitivity	Pre-clinical	Neuroblastoma and non-small cell lung cancer (NSCLC) may show preferential responses	Wild-type-p53-dependent	Insufficient site-specific <i>in-vivo</i> validation	[197–199]
Mutant p53	Other PTMs	O-GlcNAcylation/PARYlation regulation	Thiamet-G, PARP-related pathways	Enhances DDR signaling	Pre-clinical	DNA-damage-proficient tumors	Wild-type-p53-dependent	Indirect regulation of p53, low target specificity	[103,200]
	Structural reactivation	Refolding via cysteine targeting	PRIMA-1, APR-246	Restores WT-like function	Phase II/III	No fully validated predictive biomarkers available	Broad activity for structural p53 mutants	Hyperstable mutant p53 variants are refractory; heterogeneous patient responses	[201–203]
	Redox modulation, glutathione depletion, ferroptosis-related cell death	Glutathione depletion, oxidative stress	APR-246	Ferroptosis/apoptosis	Phase II/III	Oxidative-stress-sensitive tumor subsets	Broad for structural p53 mutants	Dual structural-rescue and redox-toxicity mechanism complicate biomarker interpretation	[204–207]
	PTM-dependent degradation	Disrupts HSP90–HDAC6 chaperone axis	HSP90, HDAC6 inhibitors	Promotes degradation	Pre-clinical	Tumors with high stabilized mutant-p53 abundance	Works for multiple stable mutant p53 variants	Systemic proteostasis-related toxicity, poor mutant-p53 selectivity	[208–211]
	Allele-specific targeting	Stabilizes mutation-induced pocket	PC14586 (Y220C)	Mutation-selective reactivation	Phase I/II	Tumor must harbor Y220C mutation	Strictly Y220C-allele specific	Extremely narrow mutation spectrum, only applicable to Y220C carriers	[212–214]
	Metalion restoration	Restores zinc coordination	Zn metallochaperones, arsenic trioxide	Structural rescue	Pre-clinical/early clinical	Zinc-deficient structural mutant p53	Restricted to zinc-loosing structural mutants	Variable rescue efficiency across different p53 alleles	[215–217]
	PROTAC-based degradation	Ubiquitin–proteasome targeting	Mutation-specific PROTACs	Selective degradation	Pre-clinical concept validation	Hot-spot-mutant-positive tumors	Design-dependent mutation selectivity	No mature <i>in-vivo</i> lead compound available for clinical use	[218,219]
	PTM reader targeting	BRD4 recognizes acetylated GOF mutant p53 and sustains oncogenic transcriptional reprogramming; BET inhibition disrupts this reader-writer axis	JQ1, i-BET-762	Suppresses mutant-p53-driven transcription; inhibits tumor growth in TNBC and colorectal models	Pre-clinical	Tumors with high BRD4 expression and acetylated GOF mutant p53	GOF mutant-p53-dependent	BET inhibitors have broad epigenetic off-target effects; no mutant-p53-specific clinical trial yet	[20,220,221]
Metabolic pathway targeting	Metabolic pathway targeting	Metabolic perturbation indirectly remodels p53 PTMs; modulates chaperone function, autophagy and ubiquitination to control mutant p53 stability	Statins, 2-DG, phenformin, DCA, NAMPT inhibitors	Destabilizes oncogenic mutant p53 and restrains tumor growth	Pre-clinical	Dependent on metabolic vulnerability of mutant-p53-driven tumors	Conformation- and allele-selective; preferential activity toward misfolded mutants	Lacks mutant-p53-specific biomarkers; challenging clinical implementation	[222–229]

5.1. Reactivation of wild-type p53 through PTM modulation

(1) Targeting the MDM2–MDMX axis

In tumors with wild-type TP53, functional suppression often occurs through overactive negative regulators, primarily MDM2 and MDMX. Pharmacologic disruption of MDM2-p53 interaction with small molecules such as RG7112, RG7388 (Idasanutlin), MK-8242, AMG232, SAR405838, DS-3032b, HDM201, NVP-CGM097, and APG-115, all of which have exhibited compelling anti-tumor activity in preclinical models and clinical setting, can restore p53 activity, leading to transcription of canonical targets such as p21, PUMA, and Bax [180–183]. Dual MDM2/MDMX inhibitors (e.g., ALRN-6924) demonstrate improved pharmacodynamic activity and disease-control rates with reduced thrombocytopenia [230]. Limitations of MDM2 inhibitors include dose-limiting toxicities, adaptive resistance, and limited response durability, highlighting the need for combinatorial approaches, such as USP2 inhibition or combination with immunotherapies, to potentiate p53 activation [231–234]. Common resistance mechanisms include MDM2 amplification upregulation of alternative repressors and cell-cycle checkpoint rewiring which further restrict single-agent clinical utility [235,236].

(2) Enhancing p53 acetylation through deacetylase inhibition

Targeting PTM regulators has emerged as a complementary strategy to enhance wild-type p53 activity. Acetylation is a key activating PTM of p53, regulating DNA binding, promoter selectivity, and transcriptional outcomes. HDACs suppress p53 function by removing activating acetylation marks and their inhibition restores p53 acetylation, stability, and transcriptional output [162,184,237]. HDAC inhibition restores activating acetylation marks, enhancing p53 stability and transcriptional output in a site-specific manner. For example, histone deacetylase inhibitors preferentially acetylate p53 at Lys373 and Lys382, inducing p21 expression and growth arrest without genotoxic stress [185–187]. SIRT inhibitors (cambinol, tenovins, inauhzin) specifically increase p53 Lys382 acetylation, triggering apoptosis and tumor growth suppression [188–190]. Isoform-specific HDAC inhibition further refines efficacy of p53. Inhibition of HDAC1 enhances acetylation of p53 at Lys120, restoring p53 pro-apoptotic function [161,191]. HDAC2 blockade promotes p53 acetylation, disrupts cell cycle and apoptosis signaling, and inhibits hepatocellular carcinoma progression [194]. HDAC6 inhibition restores p53 Lys120 acetylation in ARID1A-mutant ovarian cancer [193]. HDAC8 inhibition selectively impairs leukemia stem cells by elevating p53 acetylation [192]. It should be noted that most of these deacetylase-targeting observations are derived from pre-clinical studies. Pan-HDAC inhibitors exert broad off-target epigenetic effects rather than acting specifically on p53 and therapeutic efficacy is strictly dependent on intact wild-type p53 which narrows eligible patient populations [238,239].

(3) Additional PTM regulators beyond acetylation

Other PTM modulators also enhance wild-type p53 function. WIP1 inhibition (GSK2830371) preserves phosphorylation of p53 and activates downstream targets p21, PUMA, and Bax [195]. USP7 inhibition (P22077) destabilizes HDM2, stabilizes p53, and induces apoptosis selectively in cells with intact USP7-HDM2-p53 pathway [196]. Methylation-targeting strategies, such as SETD8 or SMYD2 inhibition, restore p53 activity and chemosensitivity in neuroblastoma and NSCLC models [197–199]. O-GlcNAcylation modulation (Thiamet-G) activates p53 signaling, whereas PARP-dependent modifications

regulate recruitment of p53 to DNA damage sites and influence repair pathway choice [103,200]. In contrast, although protein kinase C (PKC) has been implicated in regulating p53 phosphorylation and stability, its therapeutic targeting has not yet achieved the same mechanistic clarity or translational relevance [240,241].

5.2. Therapeutic targeting of mutant p53

Mutant p53 proteins frequently acquire GOF properties, actively contributing to tumor progression, metastasis, metabolic reprogramming, and therapeutic resistance [242–244]. Unlike simple loss-of-function variants, mutant p53 acts as an oncogenic driver, necessitating targeted strategies. Importantly, therapeutic responses cannot be predicted solely by TP53 mutation status, as the PTM landscape critically influences p53 functionality and drug sensitivity.

(1) Reactivation of mutant p53

Small molecules such as PRIMA-1, and APR-246 (eprenetapopt), that are converted into the biologically active compound, methylene quinuclidinone (MQ), covalently modify cysteine residues within the p53 core domain, promoting refolding and partial restoration of wild-type-like transcriptional activity [201–203]. APR-246, the most well-characterized agent, is converted intracellularly into methylene quinuclidinone, modifying Cys277 and Cys124 [202]. Early clinical studies demonstrated that APR-246 is well-tolerated and can induce apoptosis and p53 target gene expression [204,245–247]. Beyond structural rescue, APR-246 exerts redox-modulating effects, including oxidative stress induction and glutathione depletion, contributing to ferroptosis-related cell death [204–207]. The limitations of this strategy include structural heterogeneity of TP53 mutations and some mutant p53 proteins function as hyperstable oncogenic scaffolds and are less amenable to refolding [244,248].

(2) PTMs-dependent degradation of mutant p53

Targeting the PTM-dependent stability network of mutant p53 is another strategy, particularly via the HSP90-HDAC6 chaperone axis [37,208]. Disruption of proteostasis networks, including HSP90, HDAC6, DNAJA1, and the mevalonate pathway, promotes mutant p53 degradation [208–211]. HSP90-mediated chaperoning protects mutant p53 from MDM2- and CHIP-dependent degradation, resulting in its accumulation in tumors [41]. Combination strategies, such as PKC inhibition with MDM2 or MDM4 derepression, have shown preclinical efficacy, suggesting that PKC operates within a broader oncogenic state suppressing p53 rather than serving as a sole PTM target [249,250].

(3) Allele-specific targeting of mutant p53

Allele-specific approaches have been developed for druggable mutants, such as Y220C, which forms a pocket in the DNA-binding domain. Small molecules like rezatapopt (PC14586) bind this pocket, stabilizing the mutant protein and restoring wild-type-like transcriptional activity [212–214]. PC14586 has entered early-phase clinical trials but is restricted exclusively to Y220C-positive tumors. While limited to specific mutations, these strategies demonstrate the feasibility of structurally targeted therapies. Additional approaches include arsenic trioxide for structural mutants and zinc metallochaperones that restore zinc coordination, further enabling functional rescue of p53 [215–217].

(4) Emerging strategies for targeting mutant p53

Emerging modalities include proteolysis-targeting chimeras (PROTACs) that selectively degrade mutant p53 or its regulators via the ubiquitin–proteasome system [218]. Mutation-specific PROTACs, such as aptamer-based designs targeting hotspot variants like R175H, illustrate the potential for selective degradation [219]. Targeting PTM “reader” proteins that interpret modification patterns offers a refined approach to modulate transcriptional outputs, potentially providing more precise control than simply altering protein levels [20]. Targeting PTM readers such as BRD4 and CBP/p300 bromodomains can disrupt oncogenic transcriptional reprogramming driven by acetylated gain-of-function mutant p53, yielding potent anti-tumor effects in preclinical solid tumor models [220,221]. Nevertheless, broad epigenetic off-target effects and the lack of mutant-p53-specific clinical trials remain major obstacles for further translational application. Combination therapies integrating redox modulation, PTM regulation, and immune signaling are being explored to enhance efficacy and overcome monotherapy limitations [251,252].

(5) Targeting metabolic pathways to modulate mutant p53

Among metabolic therapeutic strategies targeting mutant p53, inhibition of the mevalonate pathway is the most well-characterized approach. Statins suppress HMGCR, exerting anti-tumor effects against mutant p53 beyond canonical cholesterol reduction. Mechanistically, statin-mediated depletion of mevalonate-5-phosphate disrupts the DNAJA1-mutant p53 complex, triggering CHIP-dependent nuclear export, ubiquitination, and degradation of misfolded mutant p53. This intervention exhibits strict conformation and allele selectivity. Structural misfolded mutants including R175H, Y220C, and R156P are highly responsive to statin treatment, while contact mutants exemplified by R273H typically display resistance [222]. Beyond chaperone regulatory, mutant p53 cooperates with SREBP signaling to drive mevalonate-dependent oncogenic reprogramming, and pharmacological blockade of this pathway reverses mutant p53-associated malignant phenotypes and tumor progression [223]. Consistently, a fluvastatin-cisplatin nanoprodruge has been developed to combine mevalonate suppression with chemotherapy, effectively downregulating mutant p53 in NSCLC xenograft models, although translational limitations remain regarding scalable manufacturing, *in vivo* biodistribution, and safety profiles [224]. Glucose metabolic perturbation also modulates mutant p53 stability through PTM-dependent autophagic regulation. Glucose deprivation induces mutant p53 deacetylation, which enhances MDM2 binding and initiates Beclin-1-, ATG5-, and ATG7-mediated autophagic degradation, establishing a direct link between metabolic stress, p53 PTM remodeling, and mutant p53 homeostasis [225]. In contrast, 2-deoxyglucose treatment elevates intracellular superoxide, impairs autophagic flux, and triggers p62-dependent apoptosis in mutant p53-harboring tumors [253]. Combined phenformin with 2-deoxyglucose treatment induces energy stress, activates AMP-activated protein kinase (AMPK), represses mechanistic target of rapamycin (mTOR) and extracellular signal-regulated kinase (ERK) signaling, attenuates HSP90-HSC70 chaperone support, and ultimately promotes proteasome-dependent mutant p53 clearance [226]. NAD⁺ metabolism profoundly shapes mutant p53 function by modulating SIRT and proline-rich RNA-binding protein (PRRP)-dependent PTMs. Pharmacological inhibition of SIRT1/2 elevates p53 Lys382 acetylation, restricts MDM2-mediated p53 turnover, and restores wild-type p53 transcriptional activity [189,190]. Conversely, SIRT1 activation by YK-3-237 promotes mutant p53 deacetylation, reduces mutant p53 abundance, and rescues the expression of pro-apoptotic PUMA and NOXA in mutant p53-expressing breast cancer cells [227]. Targeting NAMPT or NMNAT further expands

this regulatory landscape. NAMPT inhibition reduces NAD-dependent SIRT1 and HSP70 chaperone activity, selectively destabilizing aggregation-prone p53-R175H, and enhancing p73-mediated tumor suppression in head and neck squamous cell carcinoma (HNSCC) models [254]. In gliomas, NMNAT-fueled NAD production promotes PARP1-mediated p53 PARylation, which diminishes p53 Lys382 acetylation and attenuates p53-dependent apoptotic responses [255]. Lactate-driven metabolic reprogramming represents an emerging metabolite-dependent p53 PTM regulatory mechanism. In lung cancer bone metastases, SLC2A3-mediated glucose uptake increases lactate accumulation and promotes p53 lactylation. Pharmacological inhibition of SLC2A3 by Paris saponin VII remodels lactate metabolism, suppresses metastatic progression, and potentiates anti-PD-1 immunotherapy in both organoid and *in vivo* models [112]. High glucose also impairs wild-type p53 function via O-GlcNAc modification. The glucose-O-GlcNAc-CK2 axis facilitates CRL4(COP1) complex assembly, accelerating p53 degradation. The investigational peptide P28 blocks COP1-p53 interaction and alleviates hyperglycemia-driven tumor growth in preclinical breast cancer models [256]. Multiple metabolic enzymes further fine-tune p53 PTMs and tumor-suppressive signaling. Under low 3-phosphoglycerate conditions, PHGDH interacts with AXIN and recruits HIPK2 and TIP60, thereby inducing p53 Ser46 phosphorylation and apoptotic activation [257]. ME2-derived 2-hydroxyglutarate stabilizes oncogenic mutant p53, while ME1/ME2 ablation restores wild-type p53 activity by reducing MDM2 levels and activating ROS-AMPK signaling [258,259]. PDK1 inhibition exerts context-dependent effect on mutant p53 stability. DCA-mediated PDK1 suppression stabilizes p53-R248Q via enhanced HSP90 chaperone activity, whereas combined DCA and 17-AAG treatment switches chaperone dependency toward HSC70-mediated autophagic degradation of mutant p53 [260]. In breast cancer, mutant p53 transcriptionally upregulates PDK1, and PDK1 depletion sensitizes R273H-mutant tumors to APR-246 therapy [261]. Notably, all metabolic targeting strategies described above are currently limited to preclinical evidence. In particular, glucose-restriction-based interventions face substantial practical obstacles for clinical translation.

6. Conclusion

A pivotal conceptual advance in p53 post-translational modification research lies not solely in the discovery of new modification sites, but in establishing p53 as a dynamic signaling hub controlled by coordinated PTM networks. PTM writers, erasers, and reader proteins cooperatively shape p53 function through multiple mechanisms. These proteins displace inhibitory repressors, assemble co-regulatory complexes, tune promoter-binding selectivity, coordinate DNA-damage repair programs, mediate metabolic adaptation, and control protein turnover and stability. This integrated regulatory model provides mechanistic insight into two key oncogenic scenarios. It explains how wild-type p53 becomes functionally silenced without TP53 coding-sequence mutations, and how hotspot mutant p53 acquires stable oncogenic GOF, beyond simple loss of tumor-suppressive activity. This PTM-centered paradigm lays out a multi-faceted roadmap for p53-directed anticancer therapeutics. Conventional strategies largely focus on disrupting the MDM2-p53 axis to reactivate wild-type p53. Meanwhile, next-generation interventions aim to precisely perturb PTM regulatory machineries. Interventions cover MDM2/MDMX inhibition, VPRBP-USP2 regulatory circuits, chaperone-mediated mutant p53 stabilization, and metabolism-driven PTM signaling. These approaches all highlight the necessity of context-specific predictive biomarkers. Nevertheless, multiple substantial translational bottlenecks persist. The majority of PTM-targeting approaches are supported only by pre-clinical evidence, with scarce clinical data verifying

safety and therapeutic efficacy. Outstanding obstacles include dose-limiting on-target and off-target toxicities, adaptive or acquired drug resistance, mutation-allele-dependent heterogeneous treatment across tumor entities, and the absence of robust, clinically validated biomarkers for patient stratification and response monitoring. Furthermore, multilayered PTM-PTM crosstalk together with cell-type and tissue-specific PTM signatures are still not fully deciphered, hampering predictable clinical manipulation of p53 activity. Taken together, the combinatorial PTM code determines the activation potential of wild-type p53, as well as protein stability and oncogenic GOF phenotypes of mutant p53, yielding multiple druggable nodes for cancer intervention. This PTM-centric framework unifies canonical p53 signaling with recent progress in ferroptosis regulation, tumor immune modulation, DNA-damage repair, and metabolic stress sensing. Future research priorities include untangling complex PTM-PTM crosstalk, developing highly selective, low-toxicity small-molecule modulators for PTM enzymes, and validating robust predictive biomarkers. Progress along these directions will enable the development of personalized, PTM-guided therapeutic regimens to improve clinical outcomes for patients bearing p53-mutant or functionally inactivated p53-driven malignancies.

Declaration of generative AI and AI-assisted technologies

Figures were created in BioRender (<http://app.biorender.com>). The authors did not use generative AI or AI-assisted technologies in the writing of this manuscript.

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Conflicts of interest

The authors declare no competing interests.

Authors' contribution

M.L.: writing—original draft preparation and writing—review and editing; S.W.: writing—original draft preparation and writing—review and editing; X.F.: writing—review and editing; R.Z.: supervision, writing—review and editing, funding acquisition and conceptualization. All authors have read and agreed to the published version of the manuscript.

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