Role of post-translational modifications in regulation of tumor suppressor p53 function

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Abstract: As an important tumor suppressor, the inactivation and mutation of p53 is discovered in more than 50% of cancers. Repression of tumor progression by p53 is mainly through its function as a common transcription factor for regulation of its target genes, involved in cell growth regulation, DNA damage repair and apoptosis process. There are multiple types of post-transcriptional modifications (PTMs) on p53 protein, including phosphorylation, acetylation, mono- and di-methylation, ubiquitylation, sumoylation and so on. These modifications usually do not function alone; they always interplay with other PTMs and collectively regulate p53 function mainly through regulation of p53 stability and transactivity. This paper reviews the function and mechanism of major posttranslational modifications of p53 and the interaction between these posttranslational modifications.

Keywords: p53; post-translational modifications; transactivity

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Introduction

It has been widely accepted that p53 is an important tumor suppressor and TP53 is mutated in about 50% of all tumors. p53 germline mutation can lead to Li-Fraumeni syndrome, patients susceptible to various types of cancer (1). p53 knockout mice, with a higher incidence of cancer (mostly lymphoma), demonstrates the function of p53 as a tumor suppressor (2). In a wide range of human cancers, TP53 undergoes abnormally high frequency mutations. For example, TP53 mutations were identified in 50% to 60% of spontaneous human tumors such as the lungs, breast, bladder, colon, esophagus, stomach, liver, brain, bone, prostate, ovaries and lymphatic system tumors (3,4). p53 is also an important transcription factor that regulates the transcription of many downstream genes, such as p21 involved in cell cycle checkpoints, GADD45 involved in cell growth regulation and DNA damage repair, NOXA involved in the process of apoptosis (5,6). Therefore, p53 plays an essential role in regulating cell growth, DNA damage repair and apoptosis. The regulation of p53 transcriptional activity is important for its function as tumor suppressor. Research on p53 transcriptional activity is also essential for the treatment of p53 mutations-induced tumors. p53 can protect cells from the malignant development of tumors and play an important role in the process of aging, differentiation and fertility, as well as in neurodegenerative diseases, diabetes and myocardial infarction (7).

p53 is involved in many biological processes, and there are many questions required to be answered about the regulation mechanisms of p53 activity. How was a protein with so many important functions located at the right place at the right time? What mechanism is involved in regulating the various functions of p53? The regulation of p53 occurs...
Phosphorylation of p53 occurs mainly at serine and threonine residues of N-terminal and C-terminal. After the cells are stimulated, most of the phosphorylation occur at once. Also, there are some sites phosphorylated in normal situation and undergo dephosphorylation induced by DNA damage (12). p53 was identified as a phosphorylated protein shortly after its discovery, and the first identified phosphorylation sites were murine Ser312 and Ser389 (13). In 1992, Lees-Miller et al. found that DNA-activated protein kinase DNA-PK was able to phosphorylate Ser15 and Ser37 at the aminoterminal transactivation domain of p53 (14). After that, studies have reported that phosphorylation at Ser15 of p53 induced MDM2 dissociation with p53, leading to the stabilization of p53 protein (15). These are the earliest assumptions about the post-translational modifications of p53. A milestone discovery is that phosphorylation at Ser15 is essential for cell stress independent on DNA damage. In the glucose-induced response, Ser15 can be phosphorylated by the AMPK (AMP-activated protein kinase) pathway and mediates the metabolic cell cycle G1/S block (16). Ser6 and Ser9 were originally discovered as substrates for CK1δ and CK1ε, members of the protein kinase CK1 family, and were phosphorylated at treatment with multiple genotoxic and non-genotoxic agents. The phosphorylation at Ser6 and Ser9 is important for tumorigenesis and metastasis induced by TGF-β, activated Ras and mutant p53 (17). Phosphorylation at the two loci also plays crucial role in the mesodermal development of xenopus (18). Phosphorylation at Ser46 mediated by p38 MAPK, HIPK2, DYRK2, MDM4 (19) and possibly other kinase can exert apoptotic cell death, one possible mechanism is that phosphorylation at Ser46 induces amphiregulin expression and its target microRNA (20). The transactivation domain of p53 is capable of forming two domains with similar structure, TAD1 (1–40 residues) and TAD2 (41–83 residues). The TAD2 domain of p53 is capable of interacting with the p62 subfamily of the universal transcription factor TFIIH, which is important for the p53-initiated transcription events after loosening of the chromatin structure of the promoter region. Phosphorylation at Thr55 mediated by transcription factor TAF1 (TAFII250), as well as phosphorylation at Ser46 can trigger the interaction of TAD2 with pleckstrin homology (PH) region of p62 (21). Phosphorylation of p53 at position 392 can be induced by DNA damage and plays a role in activating the sequence-specific DNA binding capacity of p53. Phosphorylation may also stabilize the formation of p53 tetramers, which is important for its activity, so phosphorylation modification is essential for p53 to play suitable activity (22).
inducing its conformational changes (23,24). K320 of p53 can be acetylated by another histone acetyltransferase p300/CBP-related factor PCAF (KAT2B) (25). The acetylation of p53 promotes the recruitment of transcriptional activators, such as CBP and PCAF complexes, in the promoter region of p53 downstream genes and activation of p53 downstream genes (26). Acetylation of p53 is important for its ability to inhibit the cell cycle progression of G2 phase, which is achieved by NF-Y-p53-dependent inhibition of G2 phase response gene (27,28). The effect of deletion of one or more sites may be compensated by other acetylation sites (29,30). Deacetylase HDAC1 could deacetylate most acetylation sites of p53 in vitro and cultured cells (31,32). Deacetylase SIRT1 is capable of interacting with p53 in the nucleus, specifically deacetylating the K382 acetylation of p53 (33). Depsipeptide, an inhibitor of HDAC, significantly induces acetylated p53 at K373/K382 binding to the regulatory region of p21 and increases the expression of p21 (23,34). Different stimulus signals can induce acetylation at K305 of p53 mediated by p300 in vivo and in vitro (35), which is important in regulating the transcriptional activity of p53 (35). K120, in the DNA binding domain of p53, can be acetylated by Tip60/hMOF (a MYST family HAT, independent of p300/CBP or PCAF) and the mutation of this site is of frequent recurrence in the process of tumor development (36). Acetylation at K120 induced by DNA damage significantly changes the effect of salt concentration on the specificity of its DNA binding capacity (37). p53 with K120 acetylation preferentially locates at the promoter region of the critical gene promoting apoptotic, rather than the promoter region of those genes involved in cell cycle arrest (38). Chronic myeloid leukemia (CML) is a disease that causes abnormal hematopoietic stem cell function due to the expression of BCR-ABL, which increased the acetylation at K317 of p53 and promoted the translocation of p53 to cytoplasm and activation of BAX after DNA damage. Acetylation at K320 (human p53)/K317 (mouse p53) plays an important role in the regulation of p53 shuttle between nucleus and cytoplasm and the p53-dependent BAX-mediated apoptosis following DNA damage (39). Recent research also revealed that in intestinal adenoma formation deacetylation of p53 was pivotal for the induction of autophagic flux (40).

In the absence of stimuli, p53 is at a low level of expression, mainly in the form of monomer. p53 protein has the most effective function in the form of tetramer because the DNA binding affinity of tetramer p53 is high (41). Oligomerization of p53 occurs prior to acetylation, and oligomerization could provide a docking site for acetyltransferase (42). Studies have shown that lysine acetylation modification of p53 C-terminal is of much higher efficiency in p53 tetramer than the dimmer and acetylation almost cannot occur on the p53 monomer. Acetylation at p53 C-terminal lysine residue also prevents the ubiquitination at the same lysine residue site induced by MDM2, further stabilizes the tetramer, enhances the DNA binding ability of p53 to specific sequence, and also promotes the recruitment of transcriptional activators (42).

The mechanism of p53 transactivation is variant on different promoters and acetylation modification plays an important role in the selective regulation of p53 function. The role of acetylation is dependent on the cellular environment.

Methylation

Methylation at lysine and arginine is also a reversible mechanism for the regulation of p53 function. K370, K372 and K382 at the carboxy terminus of p53 can be methylated and the effect to enhance (43,44) or inhibit (45) the function of p53 depends on the modified site. Jansson et al. reported that three arginine residues R333, R335 and R337 of the p53 oligomerization domain (TET) can be methylated by a class II methyltransferase PRMT5 (46).

Lysine methylation

SET7/9 can methylate p53K372 in the nucleus after DNA damage, which enhances the overall stability of p53 binding to chromatin, increases recruitment of p53 in regulatory regions of p21 and other downstream genes, promotes transcriptional activation of p21 and other downstream genes (47). On the other side, Smyd2-mediated monomethylation at p53K370 inhibits the transactivation of p53, which inhibits p53-mediated cell cycle arrest and apoptosis (48). A demethylase KDM1, demethylating Lys370, prevents the binding of p53 coactivator 53BP1 (43). The 370 locus is close to the 372 locus, suggesting that interactions may occur between methylation at these lysines. Under physiological conditions, SET9 prevents Smyd2 from binding to p53 (48). The SET7/9-mediated methylation at K372 can activate p53 function by inhibiting Smyd2-mediated methylation at K370 after DNA damage. The role of smyd2-mediated methylation at K370 is to inhibit p53-mediated transcriptional activation; therefore,
methylation at K370 after DNA damage repair is required to remove methylation at K372 so that the activity of p53 can be restored to the basal level. These results indicate that methylation at lysine is a dynamic post-translational modification in the complex regulation of p53 activity. However, p53K370 can also be dimethylated with the effect of positive regulation of p53 activity, one evidence is that after DNA damage p53 protein with K370me2 modification increased in the promoter region of p53 downstream gene. The demethylation process from activated dimethylation modification to inhibitory monomethylation is regulated by lysine-specific demethylase LSD1 (43). Researchers have identified another modification associated with p53 physiological function, monomethylation at p53K382 by SET8 in 2007, which reduces the transactivation of p53 to high response downstream genes (45). Different from the K382 monomethylation modification, the level of p53K382me2 increased after DNA damage and was recognized and bound by the tandem Tudor domain of 53BP1, which interacted with p53 by stabilizing the accumulation of p53 (49). In addition, studies have reported that G9a and Glp could mediate the dimethylation at p53K373, while the p53K373R mutants cannot be methylated. Different from the activation effect by K370me2 and K382me2 (mediated by interaction with 53BP1), p53K373me2 modification is a non-activated signal (50).

Arginine methylation

Arginine methylation can also modulate the activity of p53, which is an important regulatory mechanism in p53 response. When DNA is damaged, Strap is able to recruit PRMT5 to p53 and promote methylation of p53. The absence of PRMT5 changes the specificity of p53 binding in the promoter region and triggers apoptosis dependent on p53. Methylation by PRMT5 also has influence on the activity of p53 oligomerization (46). Under physiological conditions, the arginine methylation sites of endogenous p53 by PRMT5 were identified as Arg333, Arg335 and Arg337. Arg335 and Arg337 can be dimethylated by PRMT5 while Arg333 is monomethylated (51). Arginine methylation modulates the promoter binding specificity of p53, and PRMT5 siRNA reduces the protein level of p21, an important downstream protein of p53 involved in the regulation of cell cycle arrest. Whereas the proteins encoded by downstream genes of p53 involved in apoptosis, such as PUMA, NOXA, AIP1 and APAF1 (52) are little affected or unaffected. Importantly, mutations of Arg333 and Arg337 exist naturally, although seldom, which demonstrate the importance of p53 methylation. Mutation of Arg337 (normally mutated to cysteine or histidine), related with tumor development, changes biochemical characteristics of p53 (53) and causes tetramer of p53 dynamically unstable (54). Thus, the role of p53 arginine methylation in the regulation of p53 activity may be a mechanism for the effect of these mutations.

Ubiquitination

In normal non-stimulated cells, p53 renews quickly and the expression of p53 remains low level. MDM2 is an important factor for maintaining p53 levels, which promoted the polyubiquitination of p53 and the degradation by proteasome pathway, thereby inhibiting p53-mediated transactivation (55). The major ubiquitination sites of p53 mediated by MDM2 are six lysines at the carboxy terminus (K370, K372, K373, K381, K382, and K386) (56). The expression of MDM2 is also regulated by p53, indicating a negative feedback of p53 expression. So that an increase in p53 level can induce MDM2 expression, leading to a decrease in p53 expression and activity (57). Moreover, several lysines of the DNA binding domain of p53 are also target for ubiquitination (58). MDM4 is similar to MDM2 and inhibits p53-mediated transactivation. The induction of p53 can result from its release from these negative regulatory factors. Inhibits and/or rapidly degradations of MDM2 and MDM4 cause rapid accumulation of p53 and activate its transcription function (59,60). Ubiquitination prevents p53 from binding to the downstream gene in the nucleus, leading to apoptosis and cell cycle arrest (61,62).

A number of E3 ligases involved in MDM2-independent p53 ubiquitination have been identified, such as Pirh2, ICP0, COP1, TOPORS, ARF-BP1, CHIP, Ubc13, synoviolin, EF41, CARP2, WWF1, MSL2, E6-AP, TRIM2454 and MKRN1 (63). Ubc13, WWF1, E4F1 and MSL2 are E3 ligases mediating proteasome-independent ubiquitination of p53. Besides these E3 ligases, MDM2 at low level also mediates mono-ubiquitination of p53, resulting in proteasome-independent p53 ubiquitination (64).

Different types of p53 ubiquitination result in different effects of p53 function. Several E3 ligases, in addition to MDM2, can mediate K48-linked polyubiquitination of p53 and target it to the 26S proteasome for degradation. Other types of ubiquitination, including mono- or K63-linked polyubiquitinations, affect p53 stabilization by regulating nuclear export and cytosolic localizations of
p53. Ubiquitination also disrupts p53 from binding to the promoter of target genes as a transcription factor in the nucleus that results in apoptosis and cell cycle arrest (65).

**Other post-translational modification**

In addition to the modifications described above, there are some other types of modifications of p53 which have already been identified, such as SUMO-1 and SUMO-2/3-mediated sumoylation (66), neddylation (NEDD8) (67), etc. Moreover, O-linked N-acetylglucosamine, ADP-riboylation and prolyl isomerization modifications can also regulate p53 activity (68). Recently, p53 β-hydroxybutyrylation, a new PTM, has been identified by Wenhui Zhao in 2019, which is catalyzed by CBP and results in lower levels of p53 acetylation, thereby attenuates p53 activity (69).

We have summarized the various PTMs of p53 and their effect on cellular functions (Table 1).

**Crosstalk between p53 post-translational modifications**

Hupp et al. proposes an allosteric model depending on post-translational modifications of the p53 C-terminus that activates p53 function as a DNA-binding protein, that the C-terminal of p53 can act as a negative regulator, maybe by binding to the core DNA binding region of p53 and make it form an inactive conformation (74). A variety of studies have supported this allosteric model (75,76). Some alterations, such as post-translational modifications and binding of single-strand DNA or antibody can disrupt the interaction between the C-terminal domain and the core domain of p53, allowing the DNA binding domain to form an activated conformation (23,75,76). Importantly, there is close interaction between post-translational modifications of p53 and these modifications participate in the regulation of p53 activity cooperatively.

Activation of p53 triggered by cell stress response is primarily regulated by post-translational modifications of p53, including phosphorylation and acetylation (77). For example, in the UV or radiation-induced response, the first modification induced in the N-terminus of p53 is phosphorylation at Ser33 and Ser37 and then phosphorylated p53 promotes acetylation at K373/K382 and K320 mediated by p300 and PCAF, respectively (78). Phosphorylation of p53 at the C-terminus induced by CHK1 and CHK2 in DNA damage response also regulates acetylation of the C-terminus (79). In the DNA damage response, both acetylation at K392 and phosphorylation at Ser392 of p53 increase the interaction between p53 and MDC1, which is an important linker protein capable of recruiting many proteins to DNA damage sites (80). Phosphorylation of the p53 C-terminus regulatory region (such as Ser392) catalyzed by casein kinase II (CK2) promotes binding of p53 with DNA and induces site-specific acetylation dependent on DNA and p300 (75). Phosphorylation of p53 amino terminal sites, including Ser15, Ser20, Ser33, Ser37, Ser46, Ser55 and Thr18 promotes the binding of p53 with p300/CBP and the transactivation of p53 (81). In addition, the biphosphorylation or polyphosphorylation events cooperatively increase the interaction of p53 and p300 by about 80-fold (82). Phosphorylation at these sites also prevents MDM2 binding, resulting in a decrease in p53 renewal (83).

Ubiquitination and acetylation are mutually exclusive events that have different effect on the regulation of p53 functions. With ubiquitination mediated by MDM2, p53 cannot be acetylated by p300/CBP, leading to rapid degradation through proteasome pathway (84). Interestingly, p300/CBP not only acetylated p53, but also acetylated MDM2, resulting in inhibition of p53 ubiquitination mediated by MDM2 (85). Acetylation of p53 inhibits its interaction with MDM2 and MDM4 (24,68). Recent studies have demonstrated that tripartite motif-containing protein 25 (TRIM25) might be a negative regulator of p53 acetylation and polyubiquitination as well as a positive modulator for p53 sumoylation, which modulates p53 nuclear export in prostate cancer cells (86).

There is also close relationship between methylation and acetylation at p53 lysine residues. Lysine methylation modification mainly occurs in response to DNA damage, which will promote (44,87) or even inhibit (48) the subsequent acetylation at other residues. For example, methylation at p53 K372 has the function to induce the subsequent acetylation modifications, thereby increase the stability and activity of p53 and result in upregulation of its target p21 gene and cell cycle arrest. p53 acetylation induced by DNA damage is also impaired in the absence of lysine methylation (87). Taken together, there is close and intricate relationship among post-translational modifications of p53, which is crucial for the function of p53 in cell stress and tumor suppression. Figure 1 has exhibited the crosstalk among post-translational modifications of p53 in response...
### Table 1 Molecular and cellular consequences associated with p53 PTMs

<table>
<thead>
<tr>
<th>PTM type</th>
<th>PTM residues</th>
<th>Molecular and cellular consequences</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphorylation</td>
<td>S6, S9</td>
<td>Regulation of tumorigenesis and metastasis; involves in mesodermal development</td>
<td>(17,18)</td>
</tr>
<tr>
<td></td>
<td>S15</td>
<td>Mediates cell cycle G1/S block; increases stabilization of p53 protein in cell stress response</td>
<td>(14,16)</td>
</tr>
<tr>
<td></td>
<td>S37</td>
<td>Promotes p53 activity in cell stress response</td>
<td>(14)</td>
</tr>
<tr>
<td></td>
<td>S46, T55</td>
<td>Exert apoptotic cell death</td>
<td>(20,21)</td>
</tr>
<tr>
<td></td>
<td>S392</td>
<td>Activates the sequence-specific DNA binding capacity of p53</td>
<td>(22)</td>
</tr>
<tr>
<td>Acetylation</td>
<td>K305, K370, K372, K386</td>
<td>Increase the sequence-specific DNA binding capacity</td>
<td>(23,24)</td>
</tr>
<tr>
<td></td>
<td>K120</td>
<td>Promotes p53-dependent apoptosis induced by DNA damage; regulates tumor development</td>
<td>(36)</td>
</tr>
<tr>
<td></td>
<td>K164</td>
<td>Regulation of p53-mediated cell growth arrest; promotes p53-dependent apoptosis induced by DNA damage</td>
<td>(24)</td>
</tr>
<tr>
<td></td>
<td>K320</td>
<td>Increases the sequence-specific DNA binding capacity, promotes the recruitment of transcriptional activators, affects p53 shuttle between nucleus and cytoplasm and the p53-dependent BAX-mediated apoptosis following DNA damage; induces cell cycle arrest</td>
<td>(25,26,39,70)</td>
</tr>
<tr>
<td></td>
<td>K373, K382</td>
<td>Promote its promoter-specific transactivity and apoptosis in the cellular UVB response; mediate p21 activation for G1 phase arrest; Deacetylation of K382 is catalyzed by HDAC1 and SIRT1</td>
<td>(31-34,70,71)</td>
</tr>
<tr>
<td></td>
<td>K381</td>
<td>Activates transcription and induces apoptosis</td>
<td>(72)</td>
</tr>
<tr>
<td>Methylation</td>
<td>K370</td>
<td>Represses the transactivation of p53, resulting in inhibition of p53-mediated cell cycle arrest and apoptosis; Demethylation of K370 is catalyzed by KDM1, prevents the binding of p53 coactivator 53BP1</td>
<td>(43,48)</td>
</tr>
<tr>
<td></td>
<td>K370me2</td>
<td>Positive regulation of p53 activity</td>
<td>(43)</td>
</tr>
<tr>
<td></td>
<td>K372</td>
<td>Enhances the overall stability of p53 binding to chromatin, increases recruitment of p53 in regulatory regions of p21 and other downstream genes</td>
<td>(47)</td>
</tr>
<tr>
<td></td>
<td>K373me2</td>
<td>Inactivation of p53</td>
<td>(50)</td>
</tr>
<tr>
<td></td>
<td>K382</td>
<td>Reduces the transactivation of p53 to high response downstream genes</td>
<td>(45)</td>
</tr>
<tr>
<td></td>
<td>K382me2</td>
<td>Increases the transactivation of p53</td>
<td>(49)</td>
</tr>
<tr>
<td></td>
<td>R333, R335me2</td>
<td>Regulation of sequence-specific DNA binding capacity and oligomerization of p53</td>
<td>(46,52)</td>
</tr>
<tr>
<td></td>
<td>R337me2</td>
<td>Modulates the promoter binding specificity of p53, changes biochemical characteristics of p53 and causes tetramer of p53 dynamically unstable; regulates tumor development</td>
<td>(52-54)</td>
</tr>
<tr>
<td>Ubiquitination</td>
<td>K370, K372, K373, K381, K382, K386</td>
<td>Mediates degradation of p53, inhibits p53-mediated transactivation leading to apoptosis and cell cycle arrest</td>
<td>(55,56,61,62)</td>
</tr>
<tr>
<td>Sumoylation</td>
<td>K386</td>
<td>Represses transcription activity and binding to the endogenous p21 gene of p53</td>
<td>(73)</td>
</tr>
<tr>
<td>β-hydroxybutyrylation</td>
<td>K120, K319, K370</td>
<td>Results in lower levels of p53 acetylation, thereby attenuates p53 activity</td>
<td>(69)</td>
</tr>
</tbody>
</table>

PTM, post-transcriptional modification.
of DNA damage.

**Summary and outlook**

Different stimuli lead to different post-translational modifications of p53, making p53 a protein that can be dynamically regulated, and play the corresponding function quickly and accurately in various stress responses and physiological processes. As the most frequently inactivated tumor suppressor in human cancers, the inactivation and mutation of p53 has been reported in more than 50% of cancers (88). It has been widely accepted that regulation on cell cycle progression is one of the major mechanisms by which p53 inhibits tumor cell growth (89). As an important transcription factor, p53 facilitates cell cycle arrest mainly through upregulation of the expression of its target genes involved in cell cycle progression, such as p21, GADD45 and Cdc25C (90). Since PTMs of p53 play essential roles in regulation transactivity of p53, cell cycle progression mediated by p53 is also regulated by these modifications. We have summarized the effect of various p53 PTMs on cell cycle progression (*Table 2*). Interaction between post-translational modifications makes the regulation of p53 function complex and delicate. All of the post-translational modifications of p53 are reversible. PTM-removal enzymes are important for cells to recover from stress response and play an essential role in establishing thresholds for p53 activation, thereby preventing p53 from improper activation. Furthermore, some modifications are mutually exclusive, so PTM-removal enzymes are required to change the state of modification, in particular for the activation of p53 to promote its function. These PTM-removal enzymes can affect the development of tumors, which may serve as a potential target for new antineoplastic drugs. Considering that p53 also inhibits the expression of many genes, the role of post-translational modifications in p53-mediated transcriptional inhibition is also an interesting subject to research. Moreover, since p53 is an important tumor suppressor and is dysfunctional in a variety of cancers, does the post-translational modification, in addition to mutations in gene sequences, lead to abnormal activity of p53 in these cancers? Research on the function of p53 post-translational modifications, its underlying molecular mechanism(s) and interaction between these modifications are of great significance to provide new molecular basis for therapeutic strategy of p53 dysfunction associated cancers.

![Figure 1](https://example.com/figure1.png)

**Figure 1** Crosstalk between post-translational modifications of p53 in response of DNA damage.

<table>
<thead>
<tr>
<th>PTM type</th>
<th>Effect on cell cycle progression</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphorylation</td>
<td>ATM and ATR phosphorylate p53 (Ser6, -15, -37, and -392) in response to DNA damage mediate p21 activation for arresting the cell cycle at the G1-S checkpoint</td>
<td>(91)</td>
</tr>
<tr>
<td></td>
<td>Phosphorylation of p53 on Ser15 induced by AMPK activation initiates AMPK-dependent cell-cycle arrest (G1/S block)</td>
<td>(16)</td>
</tr>
<tr>
<td></td>
<td>Phosphorylation of p53 on Ser33 mediated by p38γ, p38δ and JNK2 causes a transient G1 arrest</td>
<td>(92)</td>
</tr>
<tr>
<td>Acetylation</td>
<td>Acetylation of p53 at K164, K320, K373 and K382 induce cell cycle arrest</td>
<td>(93-95)</td>
</tr>
<tr>
<td>Methylation</td>
<td>Methylation of p53 at R333, R335 and R337 enhance p53-dependent cell cycle arrest</td>
<td>(46,96)</td>
</tr>
<tr>
<td></td>
<td>Smyd2-mediated monomethylation at p53K370 inhibits p53-mediated cell cycle arrest</td>
<td>(48)</td>
</tr>
<tr>
<td></td>
<td>Methylation of p53K372 induces cell cycle arrest by upregulation of p53 target p21 gene</td>
<td>(47)</td>
</tr>
<tr>
<td>Ubiquitination</td>
<td>E3 ligase Pih2 mediated ubiquitination of p53 decreases p53-mediated cell cycle arrest</td>
<td>(97)</td>
</tr>
<tr>
<td></td>
<td>K48-linked ubiquitination of p53 mediated by E3 ligase MDM2 inhibits cell cycle arrest</td>
<td>(98,99)</td>
</tr>
</tbody>
</table>

PTM, post-transcriptional modification.
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**Footnote**

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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