Review Article
New insights into regulation of p53 protein degradation

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Abstract: The tumor suppressor p53 is a multi-functional protein, its functions covering cell cycle control, apoptosis, senescence, genome integrity maintenance, metabolism, cellular reprogramming and autophagy. Regulation of p53 stability is a central process in controlling these p53 functions. Multiple E3 ligases that mediate p53 degradation through the ubiquitination proteasome pathway have been well studied, studies also suggest p53 can be degraded through the ubiquitination-independent pathway and the proteasome-independent pathway. This review discusses these mechanisms involved in p53 protein degradation aims at establishing a better understanding on regulation of p53 protein.

Keywords: p53, protein degradation, ubiquitination, proteasome pathway

Introduction

Since the discovery of p53 in 1979 [1, 2], various studies have been conducted related to its functions and regulatory mechanisms. Previous research has confirmed that p53 is a critical regulator of cell fate, particularly under conditions of stress [3-5]. p53 functions as a node for organizing whether the cell responds to various types and levels of stress with apoptosis, cell cycle arrest, senescence, DNA repair, cell metabolism, or autophagy [6, 7]. As a key transcription factor that both activates and represses a broad range of target genes, p53 demands an complicated network to control and responses to the various stress signals. Several levels of regulation of p53 have been described, including control of transcription and translation. The principal mechanism of p53 regulation is by controlling the stability of the p53 protein [8], and p53 is regulated by an array of posttranslational modifications [9]. Classical models for the regulation of p53 stability focus on the ubiquitin-dependent pathway, especially Mdm2-dependent ubiquitination proteasome pathway. However, as discussed in this review, the astonishing progress has been made in our understanding of the abundant regulation pathways of p53 degradation over the past few years. These progress challenge the importance of the traditional regulatory events of p53 degradation.

p53 degradation through ubiquitination-dependent proteasome pathway

The mechanism of p53 degradation has been intensively studied. Various pathways are involved in the regulation of p53 protein degradation (**Figure 1**). The ubiquitin-dependent pathway may be the most classical mechanism. In this manner, ubiquitin is added at a lysine residue of p53 as a growing chain or monomeric unit, which leads to degradation of p53 by the proteasome complex or modifies activity of p53 [10]. The process of ubiquitination involves E1 activating enzymes, E2 conjugating enzymes and E3 ubiquitin ligases, these enzymes could attach an ubiquitin molecule to a lysine residue on a target substrate. Ubiquitin could be added to lysine residues of the target substrate directly (mono-ubiquitination) or to another ubiquitin protein (poly-ubiquitination) though a covalent isopeptide bond. Mono-ubiquitination serves as an important signaling event for the regulation of proteins, poly-ubiquitination at least 4 ubiquitins serves as a signal for degradation by the 26S proteasome [11, 12].
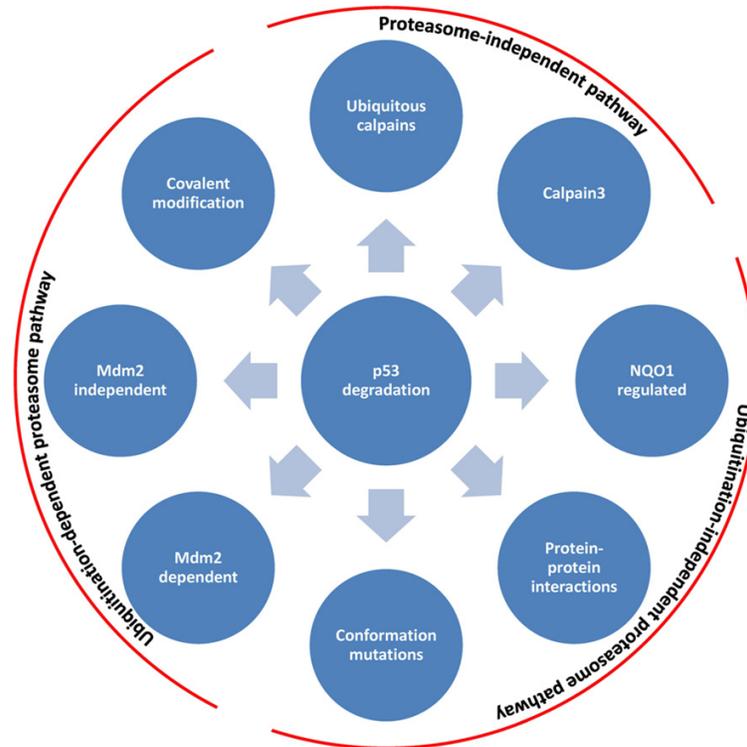
Figure 1. The schematic mechanisms involved in p53 protein degradation.

transcriptional activation [16]. And some study also found MdmX could stimulate Mdm2-mediated ubiquitination and degradation of p53 [17]. ATM and c-Abl inhibit Mdm2 activity via the phosphorylation of Ser395 and Tyr394, whereas phosphorylation of Ser166 and Ser186 promote its E3-ligase activity. WIP1 could dephosphorylate Mdm2 and stabilize Mdm2 and facilitate p53 ubiquitination and degradation. CBP/p300-mediated acetylation could inhibit the activity of Mdm2 so that increase p53 levels [10]. PCAF, has been shown to have ubiquitination function and can directly ubiquitinate Mdm2, thus stabilize p53 [18]. USP2a, deubiquitination enzymes, was shown to deubiquitinate Mdm2 and promote Mdm2-dependent p53 degradation [19].

Regulation of p53 degradation through Mdm2-dependent ubiquitination proteasome pathway

E3-ubiquitin ligase is the key element in the ubiquitination process, Mdm2 was identified as a critical E3 ubiquitin ligase for p53 and mediates p53 ubiquitination through its RING domain [13]. As Mdm2 can both mono- and poly-ubiquitinate p53 depending on Mdm2 protein levels, only the poly-ubiquitinated form of p53 is associated with p53 destabilization and proteasomal degradation [14]. On the other hand, p53 could regulate the expression of Mdm2, thus the increased level of p53 will upregulates Mdm2 expression resulting in downregulation of p53 and activation creating a negative feedback loop [10].

There are multiple proteins could regulate the p53 degradation through regulating Mdm2. ARF, a tumor suppressor, could enhance p53 activity by inhibiting the function of two E3 ligases, Mdm2 and ARF-BP1, and stabilize p53 by binding Mdm2 and keep it in the nucleolus [15]. A regulator of the Mdm2-p53 interaction is MdmX, a Mdm2 homolog. However, MdmX was shown to mainly repress p53-mediated

Regulation of p53 degradation through Mdm2-independent ubiquitination proteasome pathway

Although Mdm2 was identified as a critical E3 ubiquitin ligase for p53 and mediates p53 ubiquitination, an increasing number of data suggested that Mdm2-independent ubiquitination may also be involved in p53 degradation. The predominant data shown that p53 is still degraded in vivo in mdm2 deficient mice [20]. The later studies shown a number of E3 ligases have been documented for p53, including Pirh2, COP1, TRIM24, ARF-BP1, CARP1/2, TOPORS, Synoviolin, CHIP, JFK, MKRN1, E4orf6 and E1B55K, ICP0, MSL2, WWP1, Ubc13, E4F1 and BZLF1 [21]. These E3 ubiquitin ligases have diverse effects on p53, including 26S proteasome-mediated degradation, nuclear export, and transcriptional activation. Among these E3 ubiquitin ligases, Pirh2, COP1, TRIM24, ARF-BP1, CARP1/2, TOPORS, Synoviolin, CHIP, JFK, MKRN1, E4orf6, E1B55K and BZLF1 are involved in p53 degradation, as these E3 ubiquitin ligases could mediate K48-linked poly-ubiquitination of p53, though 26S proteasome-mediated degradation pathway [21].
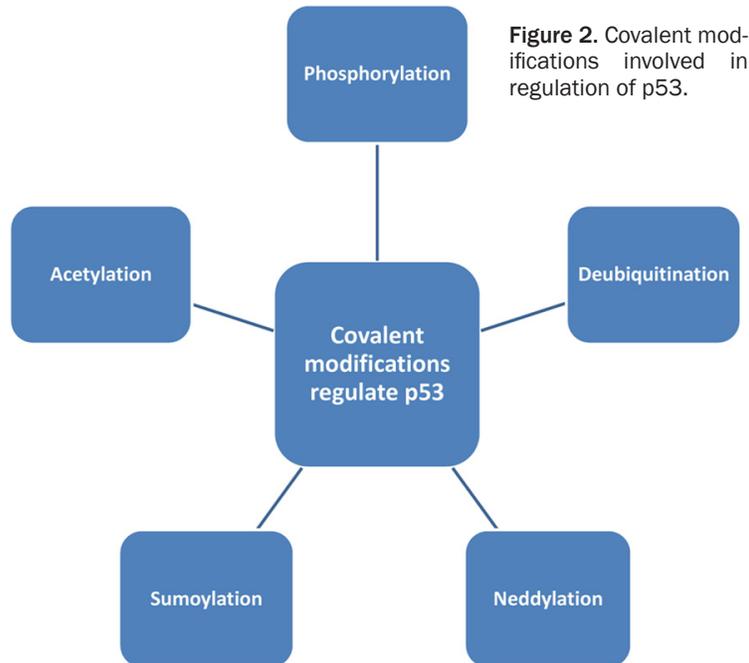
Figure 2. Covalent modifications involved in regulation of p53.

blocking the recruitment of Mdm2 to p53, which leads to p53 activation [23].

Deubiquitination enzymes (DUBs) have important influence on p53 degradation. USP7, also called Herpes-Specific Ubiquitin Specific Protease (HAUSP), was found to directly deubiquitinate and stabilize p53 [24]. On the other hand, it was also found that knockout of *hausp* in HCT116 cells caused a dramatic increase in p53 protein levels [25], suggesting that the effects of HAUSP on p53 were complex. Recent study found that USP10, a cytoplasmic DUB, could directly deubiquitinate p53, thus stabilize p53 [26].

Modifications of p53 regulates p53 degradation through ubiquitination-dependent proteasome pathway

Covalent modifications of p53 occur on more than 40 different amino acid residues and lead to different p53 activation. These modifications include phosphorylation, acetylation, methylation, ubiquitination, sumoylation, neddylation, glycosylation, ribosylation and O-GlcNAcylation [22] (**Figure 2**). Among these modifications, the ubiquitination of p53 is critical for maintaining appropriate protein levels, the key regulatory point for p53 function may be direct or indirect regulation of p53 stability through ubiquitin modification.

Phosphorylation of serine residues within the N-terminal p53 transactivation domain was among the first post-translational modifications of p53 identified. N-terminal phosphorylation at Ser15 and Ser20, after DNA damage and other types of stress by ATM, ATR, DNA-PK, Chk1 and Chk2, have been generally thought to stabilize p53 by inhibiting the interaction between p53 and Mdm2 [10].

Acetylation of p53 is important for stabilizing and activating the protein. Acetylation of p53 occurs at a number of key residues of p53 protein, but mainly occurs at the C-terminus. Acetylation of specific lysine residues on p53 abrogates Mdm2-mediated repression by

Neddylation and sumoylation are also important for p53 regulation. A number of ubiquitin-like protein (Ubl) such as SUMO (Small ubiquitin modifier) and NEDD8 (neural precursor cell-expressed developmentally downregulated-8) have been found covalently attached to their substrate in a manner similar to the ubiquitylation process. The neddylation pathway involves a set of enzymes working together to conjugate the NEDD8 protein to specific target proteins [27]. Mdm2 has been shown to neddylate K370, K372 and K373, which inhibit p53-mediated transcriptional activation. Moreover, Fbxo11 seems to have a similar effect on p53 function by neddylating K320 and K31. These data suggests that Neddylation appears to reduce the transcriptional activity and nuclear export [28]. There are four SUMO family members: SUMO-1, SUMO-2, SUMO-3 and SUMO-4. Most studies on p53 sumoylation have focused on SUMO-1, which has been shown to modify a lysine (K386) residue on the C-terminus of p53 results in modulating transcriptional activity of p53 [29]. However, the consequences of SUMO-1 modification of p53 activity are still unclear.

p53 degradation through ubiquitin-independent proteasomal pathway

The mechanism of p53 proteasomal degradation through poly-ubiquitination is well characterized. However, a number of recent studies

provided evidence for p53 proteasomal degradation regardless of its ubiquitination status in regulating process. The proteasome is a large, multi-catalytic protease that degrades proteins to small peptides, which containing a 20S proteasome subunit and two 19S regulatory cap subunits [30]. In contrast to the 26S proteasome, the core 20S proteasome lacks the 19S regulatory subunits that are responsible for recognizing poly-ubiquitinated proteins and for unfolding protein substrates [31]. The core 20S proteasome is considered to be capable of degrading unstructured proteins through ubiquitin-independent process [32]. As p53 is unstructured at both N- and C-termini [33], the degradation of p53 protein could be a ubiquitin-independent proteasomal manner. There are mainly 3 kinds of mechanisms for the p53 degradation by ubiquitin-independent process.

Regulation of p53 degradation through NQO1-regulated ubiquitination-independent 20S proteasome pathway

The first and the most studied one is NADH quinone oxidoreductase 1 (NQO1), which is a flavin-containing quinone reductase with a broad substrate specificity [34]. NQO1 is present in all tissues types and induced along with a battery of defensive genes in response to stresses including xenobiotics, antioxidants, oxidants, heavy metals, UV light and ionizing radiation [35], so that this gene provides necessary protection for cells against free radical damage, oxidative stress and neoplasia [36]. At first, researchers found that NQO1-null mice showed lower basal levels of tumor suppressor protein p53 in skin cells [37], and human colon carcinoma cells that overexpressed NQO1 accumulate elevated level of p53 [38]. It also has been shown that NQO1 activity regulates p53 stability by using an NQO1-specific inhibitor and overexpression of wild-type NQO1 or an inactive polymorphic NQO1 [39, 40]. DNA damage or oxidative stress can cause p53 stabilization because of inhibition of Mdm2 activity. Overexpression of NQO1 showed even higher p53 stabilization under these conditions and did not inhibit p53 degradation induced by overexpression of Mdm2. Furthermore, the degradation of p53 could occur even the pathway of protein ubiquitination is completely inhibited. These results suggested that p53 stabilization by NQO1 may not be mediated by inhibition of

Mdm2 activity and ubiquitination-dependent pathway [38, 40]. Further study suggested that NQO1 associates with the 20S proteasome, and that it prevents the degradation of proteins with unstructured regions, such as p53, p73 [33, 41], leads to stabilization of p53 and cellular protection [36].

Protein-protein interactions can protect p53 protein against ubiquitin-independent 20S proteasome pathway action

The second proposed mechanism is by formation of protein-protein complexes: protein-protein interactions can protect intrinsically unstructured proteins against 20S proteasomal action [42]. There are many proteins that interact with p53 [22, 43]. Most of the interacting proteins of p53 bind the unstructured N- or C-terminus. Usually the binding is convenient for complex functionality or p53 modification. After binding, the unstructured termini of p53 will acquire a specific structure, therefore preventing the 20S proteasomal-mediated degradation [44]. It has been documented that the SV40 Large T-antigen (LT) binds p53 and inhibits its degradation through ubiquitin-independent proteasomal pathway [40]. In addition, the interacting proteins such as HIF-1α, E2F-1, WT1 and Sin3a stabilize p53 [45-48]. The mechanism of this process of p53 stabilization has not yet been resolved.

Conformational mutations of p53 can protect p53 protein against ubiquitin-independent 20S proteasome pathway action

The third mechanism is mutation mediated p53 conformational changes: p53 can possibly escape the ubiquitin-independent manner by conformational mutations that make the unstructured domains inaccessible to the 20S proteasome [44]. It shown that some of the hotspot mutants are less susceptible to degradation by ubiquitin-independent manner in cells as they bind NQO1 with higher affinity [49]. As this fact, some of the mutations disrupt p53 conformation and resist degradation by the 20S proteasome. On the other hand, the mutants may accumulate because unlike wild-type p53, they are poor in inducing Mdm2 expression and therefore escape Mdm2-dependent degradation [50].

p53 degradation through proteasome-independent pathway

Calpains are a family of calcium-dependent intracellular proteases that can be divided into two major groups: the ubiquitous calpains, and tissue-specific calpains [51]. As calpains activity can be regulated by autoproteolysis and the inhibitor protein calpastatin, suggesting that, like the proteasome, calpains are part of a regulatory proteolytic system [51].

Regulation of p53 stability through ubiquitous calpains mediated proteasome-independent pathway

Ubiquitous calpains recognize are usually considered exclusively cytoplasmic proteases, and cleave their substrates to only a limited extent. It has been reported that ubiquitous calpains can downregulate p53 stability [51, 52]. Ubiquitous calpain has been demonstrated involved in the proteolytic cleavage of p53. p53 protein can be cleaved by calpain in vitro to generate an N-terminally truncated protein, and inhibition of calpain correlated with enhanced stability of the p53 protein [53].

Regulation of p53 stability through Calpain 3 (CAPN3) mediated proteasome-independent pathway

The specific cysteine proteinase, Calpain 3 (CAPN3), is mainly expressed in the muscle [54] and localized in the nucleolus [55]. Def, a novel nucleolar factor, belongs to a novel protein family that is evolutionarily conserved from yeasts to humans and it is a component of the ribosomal small subunit (SSU) processome in the nucleolus [56, 57]. In recent study, Def has been demonstrated could induce degradation of the p53 protein in both human (MCF7 cell and HepG2 cell) and zebrafish, and this process is independent of the proteasome pathway but is dependent on a specific nucleolus localized cysteine protease, CAPN3 [55].

Conclusion

Now, it is clear that the regulation of p53 degradation is a complex process that is extremely sensitive to many forms of stress. Various pathways are involved in the regulation of p53 protein degradation. Among these pathways, Mdm2-dependent ubiquitination proteasome pathway is the most classical mechanism, and

Mdm2 was identified as a critical E3 ubiquitin ligase for p53. Recent studies shown a number of E3 ligases have been documented for p53, including Pirh2, COP1, TRIM24, ARF-BP1, CARP1/2, TOPORS, Synoviolin, CHIP, JFK, MKRN1, E4orf6, E1B55K and BZLF1 [21], these Mdm2-independent ubiquitination proteasome pathways also are involved in p53 degradation. Covalent modifications of p53, include phosphorylation, acetylation, methylation, ubiquitination, sumoylation, neddylation, glycosylation, ribosylation and O-GlcNAcylation [22], may directly or indirectly regulate p53 stability through ubiquitin modification. Moreover, the p53 protein level also could be regulated through NQ-O1-mediaed ubiquitination-independent 20S proteasome pathway [34]. Protein-protein interactions and conformational mutations of p53 can protect p53 protein against ubiquitin-independent 20S proteasome pathway action [42, 44]. In addition, ubiquitous calpains and CAPN3 mediated proteasome-independent pathway are also part of regulatory system of p53 protein degradation.

Disclosure of conflict of interest

None.

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