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REVIEW ARTICLE

Tumor suppressor p53 cross-talks with TRIM family proteins

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Abstract p53 is a key tumor suppressor. As a transcription factor, p53 accumulates in cells in response to various stress signals and selectively transcribes its target genes to regulate a wide variety of cellular stress responses to exert its function in tumor suppression. In addition to tumor suppression, p53 is also involved in many other physiological and pathological processes, e.g. anti-infection, immune response, development, reproduction, neurodegeneration and aging. To maintain its proper function, p53 is under tight and delicate regulation through different mechanisms, particularly the posttranslational modifications. The tripartite motif (TRIM) family proteins are a large group of proteins characterized by the RING, B-Box and coiled-coil (RBCC) domains at the N-terminus. TRIM proteins play important roles in regulation of many fundamental biological processes, including cell proliferation and death, DNA repair, transcription, and immune response. Alterations of TRIM proteins have been linked to many diseases including cancer, infectious diseases, developmental disorders, and neurodegeneration. Interestingly, recent studies have revealed that many TRIM proteins are involved in the regulation of p53, and at the same time, many TRIM proteins are also regulated by p53. Here, we review the cross-talk between p53 and TRIM proteins, and its impact upon cellular biological processes as well as cancer and other diseases.

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Introduction

p53 plays a central role in tumor suppression, and disruption of p53 function leads to the initiation and/or progression of human cancers.[1–5] The *p53* gene is mutated in more than 50% of human cancers, and in almost every type of human cancers.[1,3,5,6] It has been estimated that p53 function is impaired in majority of human cancers.[7] Indeed, in addition to p53 mutations, the p53 signaling is often attenuated through different mechanisms in human cancers. For example, many DNA tumor viruses encode proteins that directly bind to p53 and inactivate it, such as the large T-antigen of simian virus 40 (SV40), the E6 oncoprotein of human papilloma virus (HPV) types 16 and 18, and the E1B-55 kDa protein of human adenovirus type 5.[8,9] Furthermore, overexpression of many negative regulators of p53, such as MDM2, MDM4 (also known as MDMX), and PPM1D (also known as Wip1), can inactivate p53 in human cancers.[1,10,11]

As a transcription factor, p53 functions as a homotetramer and binds to the p53-responsive elements in p53 target genes to transcribe these genes in cells.[12,13] The p53-responsive element is composed of two decamers separated by a spacer of 0—14 nucleotides: RRRCWWGYYY (spacer) RRRCWWGYYY, where R is a purine, W is A or T, and Y is a pyrimidine.[9,12,13] So far, a large number of protein-coding genes have been identified to be direct p53 target genes. In addition, p53 also transcriptionally regulates non-coding genes, such as microRNAs (miRNAs) and long non-coding RNAs (LncRNAs), to exert its function in tumor suppression.[14–17] Through transcriptional regulation of select target genes in a highly context-dependent manner, p53 regulates a wide variety of important cellular processes, including cell cycle arrest, senescence, DNA repair, apoptosis, autophagy, ferroptosis, metabolism, and antioxidant defense, to maintain genomic integrity and tumor suppression[2–5,18,19] (Fig. 1). In addition to tumor suppression, studies have demonstrated that p53 is also involved in many other biological and pathological processes, including anti-infection, immune response, maternal reproduction, development, metabolic diseases, neurodegeneration, aging, etc.[4,5,20–26]

The tripartite motif (TRIM) proteins belong to a large protein family, which is characterized by the presence of a conserved N-terminal RBCC module consisting of a Really Interesting New Gene (RING) domain, one or two B-Boxes (B1/B2) and a coiled-coil (CC) domain.[27–29] So far, more than 80 TRIM family members have been identified in humans. These TRIM proteins have been reported to be involved in a variety of important biological processes including transcription, signal transduction, cell proliferation, apoptosis, DNA repair, cell differentiation, stemness, antiviral infection and immune response.[27–31] Alterations of functions and/or levels of TRIM proteins have been linked to different diseases including infectious diseases, developmental diseases, neuropsychiatric disorders, cardiovascular diseases, as well as cancers.[27,28,31–33]

Interestingly, recent studies have reported that many TRIM proteins regulate p53 levels and activity, and at the same time, p53 regulates expression of some TRIM proteins.[34,35] The cross-talk between the p53 signaling pathway and TRIM family proteins plays an important role in regulating cellular biological processes and impacts cancer and other diseases. In this review, we summarize recent advances in studies on the cross-talk between the p53 signaling pathway and TRIM family proteins.

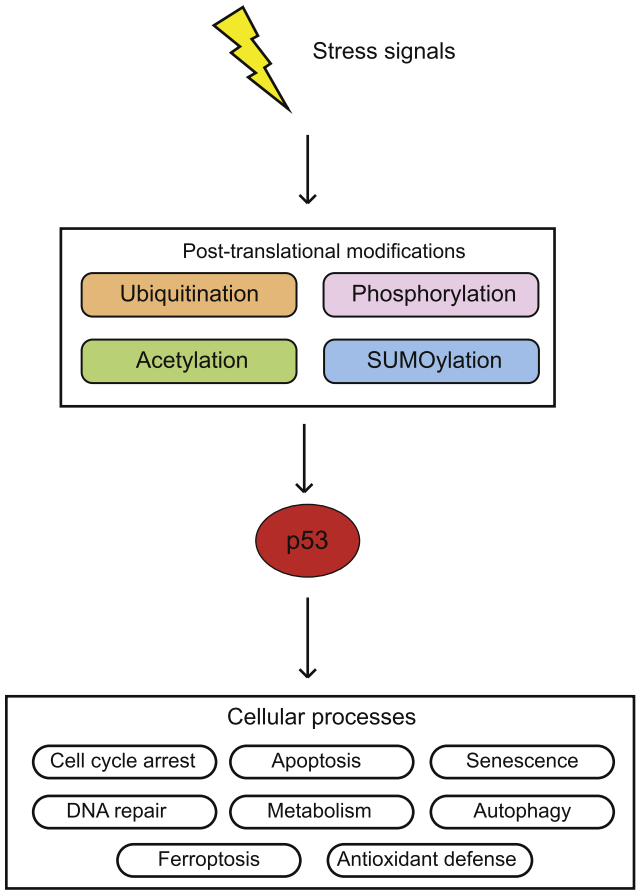

Figure 1 The p53 signaling pathway. In response to stress signals, p53 protein is accumulated and activated to transcribe select target genes to regulate a wide variety of cellular processes, including cell cycle arrest, senescence, DNA repair, apoptosis, autophagy, ferroptosis, metabolism, and antioxidant defense. The posttranslational modifications of p53, including ubiquitination, phosphorylation, acetylation and SUMOylation, etc., play a critical role in regulation of p53 protein levels and activity in cells.

p53 and its regulation

Given the critical function of p53 in tumor suppression and many other fundamental biological processes, p53 protein levels and activity are under tight scrutiny and regulation in cells. Usually, under non-stressed conditions, p53 protein has a very short half-life and its levels are maintained at low in normal cells and tissues. In response to a wide variety of stress signals, including DNA damage, hypoxia, nutritional deprivation, impaired ribosome biogenesis, activation of oncogenes, etc., p53 protein half-life is increased and p53 protein accumulates in cells, leading to

the activation of p53 transcriptional program to initiate various above-mentioned cellular responses.[2,4,18] Many different mechanisms have been reported to regulate p53, among which the post-translational modifications are known to be the most critical and efficient mechanism to regulate the level, conformation, localization and activity of p53.[4,36–39] These post-translational modifications include ubiquitination, phosphorylation, acetylation, SUMOylation, methylation, neddylation, etc.[4,36–39] Many proteins are involved in the regulation of p53, including E3 ubiquitin ligases, deubiquitinases, kinases, phosphatases, acetyltransferases, deacetylases, enzymes involved in SUMOylation and deSUMOylation, methylases, etc.[4,36–39] (Fig. 1).

Ubiquitination is one of the most important post-translational modifications for p53. Ubiquitination, which conjugates ubiquitin to the lysine (K) residues of substrate proteins, plays an important role in protein regulation, including protein degradation via the proteasome, regulation of the localization and activity of proteins, and modulating protein–protein interactions.[40] Ubiquitin can be interlinked via any of its lysines (K6, K11, K27, K29, K33, K48 and K63). K48-linked ubiquitination usually induces proteasomal degradation of substrate proteins, whereas K63-linked polyubiquitin often affects the activity or localization of substrate proteins, or their abilities to interact with other proteins.[40] Ubiquitination is a dynamic process catalyzed by E1 ubiquitin-activating enzymes, E2 ubiquitin-conjugating enzymes, and E3 ubiquitin ligases that are responsible for recognition of substrate proteins.[40] E3 ubiquitin ligase MDM2 is the most critical negative regulator of p53, which directly binds to and ubiquitinates p53 and leads to proteasomal degradation of p53.[10,11] *MDM2* is also a p53 target gene, which is transcriptionally induced by p53. Thus, MDM2 and p53 forms a negative feedback loop to keep p53 levels under fine-tuned control in cells.[10,11] MDM2 knockout in mice results in embryonic lethality due to uncontrolled activation of p53 and p53-mediated apoptosis, which can be rescued by p53 knockout, demonstrating the vital role of MDM2 in negative regulation of p53.[41,42] In addition to mediating proteasomal degradation of p53, MDM2 promotes p53 nuclear export to inhibit p53 transcriptional activation of its target genes.[43,44] In addition to MDM2, MDM4 is a protein sharing structural homology with MDM2 and functions as another important negative regulator of p53.[10,11] Although MDM4 has no detectable E3 ubiquitin ligase activity, it promotes MDM2-mediated ubiquitination and degradation of p53.[10,11] Like MDM2, MDM4 knockout in mice results in the embryonic lethality, which can be rescued by p53 knockout, indicating its critical role in negative regulation of p53 *in vivo*.[45] MDM2 and MDM4 are frequently amplified and/or overexpressed in different types of human cancers, and their overexpression is often mutually exclusive with p53 mutations in many human cancers, supporting the important roles of MDM2 and MDM4 in tumorigenesis through negative regulation of p53.[1,10,11]

In addition to MDM2, many other E3 ubiquitin ligases have been reported to ubiquitinate p53 for proteasomal degradation, such as Pirh2, Cop1, ARF-BP1, CHIP, UBE2T, RBCK1, and SYVN1.[4,36–38] Like MDM2, some of these E3 ubiquitin ligases are also p53 target genes, such as *Pirh2* and *Cop1*, which form negative feedback loops with p53. Moreover, some E3 ubiquitin ligases, including MDM2, WWP1 and MSL-2, can promote nuclear export of p53 through mono-ubiquitination of p53, removing p53 from the nucleus where p53 functions as a transcription factor to reduce its transcriptional activity.[4,36–38] On the other hand, some deubiquitinases can bind to p53 and remove ubiquitin on p53. For instance, deubiquitinases USP7 (also called HAUSP), USP15 and USP49 deubiquitinate p53 to stabilize p53.[36,46–48] UPS10 deubiquitinates p53 to stabilize p53 and also reverses MDM2-induced p53 nuclear export, leading to p53 activation.[49] Interestingly, the deubiquitinase Otub1 abrogates p53 ubiquitination to stabilize p53 by inhibiting the MDM2 cognate ubiquitin-conjugating enzyme (E2) UbcH5 independently of its deubiquitinating enzyme activity.[50] Furthermore, USP7 can either deubiquitinate p53 to stabilize it or deubiquitinate MDM2 to promote MDM2-mediated ubiquitination and degradation of p53 depending on the cellular context.[51]

In addition to ubiquitination, phosphorylation, acetylation and SUMOylation also play important roles in regulation of p53 levels and activity. In response to DNA damage, ATM and Chk1/2 kinases phosphorylate p53 at serine 15 and serine 20, respectively, and protect p53 from degradation by MDM2 to stabilize and activate p53.[52,53] On the contrary, PPM1D[54] and PP1 (protein phosphatase 1)[55] inactivate p53 by dephosphorylating p53. PPM1D is frequently amplified and/or overexpressed in cancers, and its overexpression is often mutually exclusive with p53 mutations in cancers.[1] The transcriptional coactivators CBP/p300 acetylate p53 at several lysines to activate p53 transcriptional activity.[56,57] Some histone acetyltransferase (HAT) proteins, such as Tip60, MOF and MOZ, can promote p53 acetylation to increase p53 transcriptional activity.[57–60] In contrast, some histone deacetylases (HDACs), such as HDAC1 and HDAC8, deacetylate p53 and inhibit p53 transcriptional activity.[61,62] p53 can also be modified by SUMOylation, the reversible modification of proteins by the small ubiquitin-like modifiers (SUMOs), which affects the stability, localization, activity and interaction of proteins.[63] However, the biological consequence of p53 SUMOylation is still not clear, which might be affected by the SUMOylation site, cell and tissue types, stress signals, cellular microenvironment, and even experimental models and conditions.[36,37,64] The SUMOylation modification of p53 was reported to enhance p53 transcriptional activity, or suppress p53 transcriptional activity and promote p53 nuclear export.[36,37,64] Further studies are required to better understand the effect of the SUMOylation modification on p53.

p53 is also regulated by many non-coding genes, such as miRNAs and LncRNAs, which form a new layer of regulation for p53 in cells.[14–17] For instance, some miRNAs target p53 or its positive regulators to decrease p53 protein levels and activity.[15,65–68] In contrast, some miRNAs target negative regulators of p53, such as MDM2 and MDM4, to increase p53 protein levels and activity.[15,17,65,68] Similarly, LncRNAs can exert inhibitory or activating effects on p53 through targeting p53 and its regulators.[14,16] Thus, like these above-mentioned proteins, many miRNAs and LncRNAs function as negative or positive regulators for p53 and its signaling pathway.

TRIM family proteins and diseases

While most TRIM family proteins in humans possess the conserved N-terminal RBCC domains, TRIM proteins in humans can be subclassified into 11 subfamilies based on the differences in their C-terminal domain structure.[27–29] The RING domain, a specialized type of zinc finger that binds a pair of zinc atoms and is involved in mediating protein–protein interactions, is present in many E3 ubiquitin ligases to confer E3 ligase activity.[40] Through the RING domain, many TRIM proteins have the E3 ubiquitin ligase activity and are able to ubiquitinate substrate proteins to regulate their degradation, cellular locations, activities, and/or interactions with other proteins.[27–29] In addition to the ubiquitination modification, some TRIM proteins can catalyze SUMOylation and ISGylation modifications of substrate proteins by ubiquitin-like modifiers SUMOs and ISG15 (Interferon-stimulated gene 15), respectively, to regulate the stability, localization, activity, or function of substrate proteins.[27–29] The B-box domain of some TRIM proteins also contain zinc-binding motifs similar to the RING domain, which has been shown to modulate higher-order self-assembly, E3 ligase activity, and interaction with other proteins.[69] For instance, TRIM16, which does not possess the RING domain, still has the E3 ubiquitin ligase activity due to a RING-like fold in its B-box domain.[70] The coiled-coil domain can mediate oligomerization of TRIM proteins. Many TRIM proteins can form homodimers, and some TRIM proteins can form heterodimers (e.g. TRIM19-TRIM27, TRIM19-TRIM24, TRIM24-TRIM33 and TRIM24-TRIM28), and even heterotrimers (e.g. TRIM24-TRIM33-TRIM28).[69,71] These dimerizations and higher-order assemblies of TRIM proteins may allow the TRIM proteins to perform different tasks and maintain the flexibility to adapt these structures to different intracellular and extracellular stimuli.[69] The C-terminal region of TRIM proteins is responsible for the substrate recognition.[72]

Many TRIM proteins have been reported to play important roles in the antiviral host response.[28,73] For example, TRIM28 inhibits integration of HIV-1 into the host genome via deacetylation of integrase.[74] TRIM25 and TRIM65 induce K63-linked polyubiquitination of the viral RNA sensors RIG-I and MDA5, respectively, to facilitate the antiviral innate immune response.[75,76] TRIM14 binds to cGAS and recruits USP14 to deubiqutinate and stabilize cGAS, enhancing the antiviral response against herpes simplex virus type 1 (HSV-1).[77] Furthermore, TRIM56 and TRIM32 induce K63-linked polyubiquitination of STING to facilitate the induction of the antiviral response.[78,79] In contrast, TRIM40 promotes K27- and K48-linked polyubiquitination and proteasomal degradation of both RIG-I and MAD5 to attenuate the antiviral immune responses.[80] TRIM29 induces K48-linked ubiquitination of STING and promotes its degradation to repress innate immune responses.[81]

Some TRIM proteins have been linked to developmental diseases and neurodegenerative diseases.[32] For instance, loss-of-function mutations in the *TRIM18* gene (also known as MID1) are responsible for the X-linked form of Opitz G/BBB Syndrome (XLOS), a disorder characterized by defects in the development of embryonic midline structures.[82] TRIM18 knockout mice display cerebellar development defects.[83] TRIM32 ubiquitinates and degrades dysbindin and plays an important role in preventing two developmental diseases, limb-girdle muscular dystrophy and Bardet-Biedl syndrome.[84] Mutations in the *TRIM37* gene cause muscle-liver-brain-eye (mulibrey) nanism, a rare prenatal-onset autosomal recessive growth disorder. TRIM37 interacts with and mono-ubiquitinates peroxisomal targeting signal receptor PEX5 protein, whose deficiency causes fatal human peroxisomal biogenesis disorders, leading to stabilization of PEX5 and promoting peroxisomal targeting signal protein import, to prevent muscle-liver-brain-eye (mulibrey) nanism.[85] TRIM2, which is highly expressed in the nervous system, binds to neurofilament light subunit (NF-L) and ubiquitinates it for degradation.[86] TRIM2 deficiency in mice leads to NF-L accumulation in the nervous system and neurodegeneration.[86] TRIM11 negatively regulates humanin, a neuroprotective peptide that specifically suppresses Alzheimer's disease-related neurotoxicity.[87] Increased α-synuclein expression has been linked to Parkinson's disease. TRIM41 is an E3 ubiquitin ligase for ZSCAN21, a transcription factor that induces α-synuclein expression in neuronal cells.[88] Furthermore, some rare genetic variants in *ZSCAN21* and *TRIM41* genes have been identified in patients with familial forms of Parkinson's disease, and their overexpression leads to the stabilization of the ZSCAN21 protein in neuronal cells.[88]

Interestingly, TRIM proteins are also involved in cardiovascular diseases.[33] For instance, TRIM63 and TRIM54, also known as the muscle RING-finger protein-1 and 3 (MuRF1 and 3), respectively, act as E3 ubiquitin ligases and mediate ubiquitination and proteasomal degradation of beta/slow myosin heavy chain (beta/slow MHC) and MHCIIa.[89] Mice deficient for TRIM63 or TRIM54 develop a skeletal muscle myopathy and hypertrophic cardiomyopathy characterized by subsarcolemmal MHC accumulation, myofiber fragmentation, and diminished muscle performance.[89] Furthermore, TRIM54 degrades four-and-a-half LIM domain (FHL2) and γ-filamin, and TRIM54 deficient mice are more prone to cardiac rupture after acute myocardial infarction.[90] Mutations in *TRIM55* gene (also known as MuRF2) have been associated with familial hypertrophic cardiomyopathy. TRIM55 can protect against diabetic cardiomyopathy through mono-ubiquitination of transcription factors PPARα and PPARγ1 to stabilize them in the heart of mice, and TRIM55 knockout in mice results in the exaggerated diabetic cardiomyopathy.[91]

More and more studies have also shown that TRIM proteins are involved in cancer; some TRIM proteins suppress tumorigenesis, whereas some TRIM proteins promote tumorigenesis through different mechanisms. Altered expression of many TRIM proteins have been observed in different types of cancers.[27,92,93] Furthermore, some TRIM proteins are also involved in chromosomal translocations and fused to other genes in cancers, resulting in the oncogenic gain-of-function.[27,92–94] For example, TRIM19 is fused to retinoic acid receptor-α in the t (15; 17) translocation of acute promyelocytic leukemia; TRIM24 is fused to FGFR1 in the t (7; 8) translocation of 8p11 myeloproliferative syndrome and to BRAF in the t (7; 7) translocation of liver cancer; TRIM33 and TRIM27 are fused to RET in the t (1; 10) and t (6; 10) translocation of papillary thyroid

carcinomas, respectively.[27,92–94] Interestingly, a growing body of studies have reported that many TRIM proteins cross-talk with p53 and its signaling pathway to impact cancer and other diseases,[34,35] which is summarized as follows.

TRIM proteins regulate p53 and its function

TRIM proteins that bind to and regulate p53

Studies have shown that quite a few TRIM proteins with the RING domain can bind to p53, such as TRIM24, TRIM39, TRIM32, TRIM59, TRIM31, TRIM71, TRIM69 and TRIM23, leading to ubiquitination and degradation of p53 (Fig. 2A). TRIM24, also known as transcription intermediary factor 1α (TIF1α), was the first reported TRIM protein that directly targetes p53.[95] TRIM24 binds to p53 and promotes its ubiquitination, leading to decreased p53 levels and transcriptional activity in a RING-dependent manner.[95] Furthermore, TRIM24 can be phosphorylated at serine 768 by ATM in response to DNA damage, leading to the degradation of TRIM24 and the subsequent stabilization and activation of p53.[96] Increased expression of TRIM24 was observed in many types of tumors, including breast cancer, prostate cancer and glioblastoma, which may contribute to p53 dysfunction in these tumors.[97–99] TRIM39 (also known as RNF23) can also bind to p53 and ubiquitinate p53 for degradation in a RING-dependent manner.[100] Interestingly, TRIM39 binds to p21, an important p53 target that mediates p53 function in inducing cell cycle arrest, and blocks p21 ubiquitination and degradation mediated by E3 ubiquitin ligase $CRL4^{Cdt2}$, which in turn contributes to the role of TRIM39 in tumor suppression.[101] TRIM32, TRIM59 and TRIM31 have also been reported to interact with p53 and ubiquitinate p53, leading to the proteasomal degradation of p53.[102–104] TRIM32 negatively regulates p53 levels to reduce the p53-dependent apoptosis, cell cycle arrest and senescence.[102] TRIM32 overexpression has been observed in different types of human cancers, including colorectal, lung, liver, and breast cancers, which promotes proliferation and chemoresistance of cancer cells and is associated with poor prognosis of cancer patients.[102,105–108] TRIM59 was reported to be overexpressed in human gastric tumors, leading to the decreased p53 levels and enhanced cell proliferation and metastasis.[103] TRIM31, which is up-regulated in the anchorage-deprived hepatocellular carcinoma (HCC) cells, enhances K48-linked poly-ubiquitination

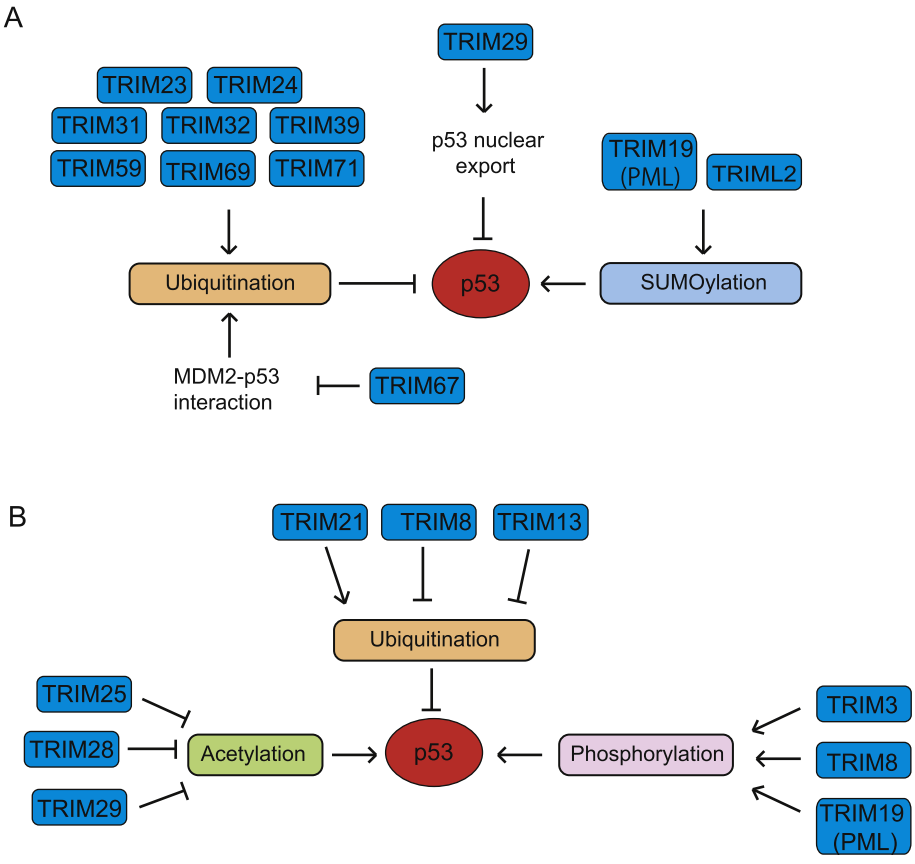

Figure 2 TRIM proteins regulate p53. **(A)** TRIM proteins that interact with p53 and directly regulate p53. TRIM23, TRIM24, TRIM31, TRIM32, TRIM39, TRIM59, TRIM69, and TRIM71 negatively regulate p53 through binding to and ubiquitinating p53, whereas TRIM19 (PML), TRIM67 and TRIML2 bind to and positively regulate p53. In addition, TRIM29 binds to and sequesters p53 in the cytoplasm to negatively regulate p53. **(B)** TRIM proteins that indirectly regulate p53 through regulating upstream p53 regulators. Through modulating the regulators for p53, TRIM3, TRIM8, TRIM13, and TRIM19 positively regulate p53, whereas TRIM21, TRIM25, TRIM28, and TRIM29 negatively regulate p53.

and degradation of p53, which in turn promotes resistance of HCC cells to anoikis, a form of programmed cell death that occurs in anchorage-dependent cells when they detach from the surrounding extracellular matrix.[104] TRIM71 (also known as LIN41) binds to p53 and degrades p53 through ubiquitination to antagonize p53-dependent pro-apoptosis and pro-differentiation during stem cell differentiation.[109] TRIM69 interacts with p53 and induces its ubiquitination and degradation in human lens epithelial cells, and inhibition of TRIM69 expression leads to p53 activation and cataract formation.[110] TRIM69 expression is up-regulated in pregnancy-associated breast cancer, suggesting its potential role in this type of cancer through inhibition of p53 function.[111] Additionally, TRIM23, which is overexpressed in colorectal cancer and associated with poor prognosis of colorectal cancer patients, interacts with p53 and results in the ubiquitination and degradation of p53, thereby promoting cancer cell proliferation.[112]

In addition to ubiquitination, TRIM proteins also modify p53 with SUMO. TRIM19, also known as promyelocytic leukemia protein (PML), is essential for the formation of the subnuclear structure known as PML nuclear bodies (PML-NBs), which are thought to be sites of transcription, DNA repair and viral replication. TRIM19 directly binds to p53 and induces its SUMOylation at lysine 386, leading to stabilization and enhanced transcriptional activity of p53.[113,114] Similarly, TRIML2 was reported to bind to p53, promoting the SUMOylation of p53 and leading to transactivation of pro-apoptotic p53 target genes.[115] Interestingly, TRIML2 was reported to be overexpressed in oral squamous cell carcinoma and triple-negative breast cancer,[116,117] suggesting that the positive regulation of p53 by TRIML2 may be cancer type specific.

TRIM29, also known as ataxia telangiectasia group D-complementing (ATDC), is a TRIM protein without the RING domain. TRIM29 interacts with p53 and sequesters p53 in the cytoplasm, which in turn inhibits p53 transcriptional activity in colorectal cancer cells.[118] Interestingly, TRIM29 was reported to be overexpressed in multiple types of human cancers, including colorectal cancer and gastric cancer,[119–121] but downregulated in HCC and head and neck squamous cell carcinomas,[122,123] suggesting the tissue and tumor type specific function of TRIM29. In addition, TRIM67, which is frequently downregulated in colorectal cancer, binds to p53 to inhibit MDM2-mediated p53 ubiquitination and degradation. Knockout of TRIM67 accelerates colorectal tumorigenesis in $Apc^{Min/+}$ mice and chemical carcinogen azoxymethane-induced colorectal cancer in mice.[124]

TRIM proteins regulating p53 indirectly

In addition to binding to p53 to regulate p53 directly, some TRIM proteins also indirectly regulate p53 levels and activity (Fig. 2B). Several TRIM proteins have been reported to regulate p53 through modulating MDM2. TRIM13, also known as ret finger protein 2 (RFP2) or LEU5 (leukemia associated gene 5), forms a complex with MDM2, leading to ubiquitination and degradation of MDM2 in a RING-dependent manner, which in turn stabilizes p53 and induces apoptosis.[125] TRIM13 is induced by γ-irradiation, which may contribute to the accumulation of p53 protein in cells and p53-mediated apoptosis in response to γ-irradiation.[125] TRIM13 is deleted in some B-cell chronic lymphocytic leukemia, and its expression is decreased in breast cancer and non-small-cell lung carcinoma, suggesting that loss of TRIM13 may contribute to p53 dysfunction in these cancers.[126–128] TRIM8 stabilizes p53 by degradation of MDM2 in a RING-dependent manner, leading to cell cycle arrest and inhibition of cell proliferation.[129] The expression of TRIM8 is decreased in clear cell renal cell carcinomas and gliomas.[130,131] Further, the downregulation of TRIM8 expression in gliomas is associated with poor prognosis of cancer patients.[131]

Some TRIM proteins have been reported to regulate p53 activity through modulating the phosphorylation and acetylation modifications of p53. PML (TRIM19) recruits p53 into the PML-NBs, mediating the p53 phosphorylation by HIPK2 at serine 46 and thus facilitating p53 acetylation by CBP at lysine 382, which enhances p53 transcriptional activity and induces growth arrest and apoptosis of cells.[132] PML also recruits Chk2 and CK1 kinases into the PML-NBs, enhancing p53 phosphorylation at serine 20 and threonine 18, respectively, in response to DNA damage, which in turn inhibits MDM2-mediated ubiquitination and degradation of p53.[133,134] Furthermore, PML mediates p53 acetylation at lysine 120 and lysine 382 by recruiting MOZ/KAT6A, enhancing p53 transcription activity and p53-mediated senescence.[135]

TRIM8 can enhance p53 phosphorylation at serines 15 and 20 through an unknown mechanism, leading to the transcriptional activation of p53 targets involved in cell cycle arrest and apoptosis.[129] In cervical cancer cells, TRIM3 activates p53 through regulating p38 MAPK signaling, which is known to phosphorylate p53 at serine 33.[136,137] The downregulation of TRIM3 expression has been reported in liver cancer and colorectal cancer and is associated with poor prognosis in cancer patients.[138,139] TRIM28, also known as KRAB-associated protein 1 (KAP1) or transcriptional intermediary factor 1 β (TIF-1β), binds to MDM2 and stimulates the formation of p53-HDAC1 complex and inhibits p53 acetylation, promoting p53 ubiquitination and degradation to inhibit cellular apoptosis.[140] In line with its role as a negative regulator of p53, overexpression of TRIM28 has been observed in lung, breast and cervical cancers.[141–143] TRIM29 (ATDC) binds to the acetyltransferase Tip60 and promotes its degradation to inhibit the acetylation of p53 at lysine 120 by Tip60, which in turn promotes cell proliferation and enhances transforming ability of cells in soft agar.[144] TRIM25 interferes with the formation of p53-MDM2-p300 complex, suppressing the acetylation of p53 to inhibit p53-dependent cell death and DNA damage response.[145] In addition, TRIM25 interacts with G3BP2 and promotes the G3BP2/RanBP2-mediated SUMOylation and nuclear export of p53 to inhibit p53 transcriptional activity, which in turn promotes cell proliferation and inhibits chemotherapeutic agent docetaxel-induced apoptosis of prostate cancer cells.[146] TRIM21 (also known as Ro52) regulates p53 via a mechanism involving USP7 and the guanosine 5′-monophosphate synthase (GMPS).[147] Under non-stress conditions, TRIM21 binds to and ubiquitinates GMPS and sequesters GMPS in the cytoplasm. Under stress conditions, GMPS is released from its

interaction with TRIM21 and translocates to the nucleus, where it transfers p53 from MDM2 to a GMPS-USP7 deubiquitination complex, leading to p53 stabilization and activation.[147]

Other TRIM proteins regulating p53

In addition to the above-mentioned TRIM proteins, some TRIM proteins have also been reported to regulate p53 with unclear mechanisms. For instance, TRIM66 and TRIM11 negatively regulate p53 protein levels.[148,149] TRIM66, also known as transcription intermediate factor 1δ (TIF1 δ), is a TRIM protein without the RING domain. TRIM66 is overexpressed in osteosarcomas.[148] TRIM66 suppresses the apoptosis of osteosarcoma cells by down-regulating protein levels of p53, and caspases 7 and 9.[148] TRIM11 is highly expressed in breast cancer, lung cancer, liver cancer and ovarian cancer.[149–152] TRIM11 negatively regulates p53 protein levels to promote proliferation, migration, and invasion of HCC cells.[149] However, the mechanisms by which TRIM66 and TRIM11 negatively regulate p53 protein levels remain unclear. In addition, TRIM52 was reported to promote the cell cycle progression of specific glioblastoma cell lines in a p53-dependent manner, suggesting that TRIM52 negatively regulates p53.[153] Currently, the precise effect of TRIM52 on p53 and its underlying mechanism are unclear, which need to be addressed by future studies.

TRIM proteins regulated by p53

While many TRIM proteins regulate p53 as summarized above, many TRIM proteins are also regulated by p53. Studies have shown that genes encoding some TRIM proteins are direct p53 target genes, and some TRIM proteins can be indirectly regulated by p53 through different mechanisms (Fig. 3). For example, TRIM24 and TRIM32, two TRIM proteins that ubiquitinate p53, are direct transcriptional targets of p53.[96,102] p53 binds to the p53-responsive elements in *TRIM24* and *TRIM32* genes and induces their expression in response to stress. At the same time, TRIM24 and TRIM32 can bind to p53 and ubiquitinate and degrade p53. Thus, like MDM2, TRIM24 and TRIM32 form negative feedback loops with p53 to regulate p53 levels and activity.[96,102] In addition to these two p53 negative regulators, *TRIM19* (PML), *TRIM3*, *TRIM8* and *TRIM67*, which positively regulate p53 levels and activity, are also direct p53 target genes.[124,129,154,155] Therefore, TRIM19 (PML), TRIM3 (BERP), TRIM 8, and TRIM67 form positive feedback loops with p53, which may amplify p53 signaling in response to stress signals in cells. As a p53 target, TRIM3 regulates the intracellular trafficking of GABA(A) receptors to the postsynaptic membrane, and TRIM3 deficient mice exhibit increased resistance to pentylenetetrazol-induced seizures, suggesting a potential role for p53 in the central nervous system.[154] In addition to the direct transcriptional regulation by p53, TRIM8 can also be regulated by p53 indirectly. N-MYC promotes expression of miR-17-5p and miR-106b-5p to negatively regulate TRIM8 in clear cell renal cell carcinoma and colorectal cancer.[156] It is known that N-MYC protein levels is downregulated by the miR-34a,[157] which is a transcription target of p53.[158] Thus, p53 indirectly induces TRIM8 expression via the miR-34a/N-MYC/miR-17-5p & miR-106b-5p pathway, and thereby forms a positive feedback loop with TRIM8 to regulate cell proliferation and therapeutic responsiveness.[156] TRIML2 is a direct target of p53, and interestingly, its expression is preferentially induced by a p53 variant with arginine at codon 72.[115] Since TRIML2 stabilizes p53 by SUMOylation, TRIML2 forms a positive feedback loop to activate p53 particularly in cells with the p53 variant with arginine at codon 72.[115] In addition, *TRIM22* (also known as Staf50) is also a p53 target gene; p53 induces TRIM22 expression.[159] Ectopic expression of TRIM22 reduces clonogenic growth of leukemic cells, suggesting that TRIM22 contributes to the tumor suppressive function of p53.[159] The downregulation of TRIM22 expression has been reported in breast cancer and Wilms tumors,[160,161] which may contribute to the dysfunction of p53 in these tumors.

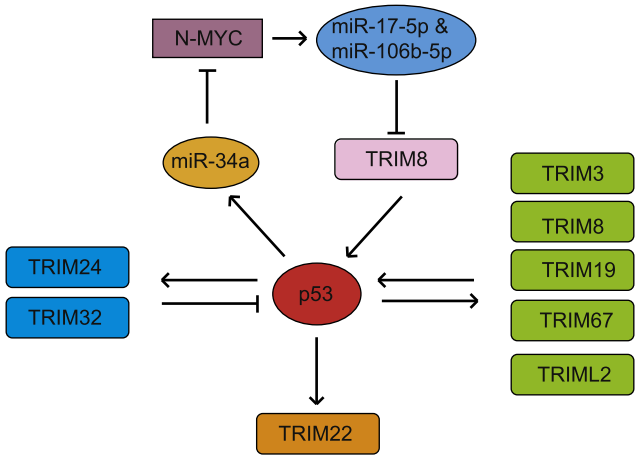

Figure 3 TRIM proteins regulated by p53. p53 transcriptionally regulates TRIM3, TRIM8, TRIM19, TRIM22, TRIM24, TRIM32, TRIM67, and TRIML2. At the same time, TRIM24 and TRIM32 negatively regulate p53 and form negative feedback loops with p53; TRIM3, TRIM8, TRIM19, TRIM67 and TRIML2 positively regulate p53 and form positive feedback loops with p53. In addition, TRIM8 is regulated by p53 through p53 target miR-34a, which forms a positive feedback loop with p53.

Conclusion and perspective

As summarized above, p53 plays a pivotal role in cell fate decision in response to various exogenous and endogenous stress signals. A wide variety of proteins and many different mechanisms have been reported to regulate p53 in a highly dynamic and context-dependent manner to maintain proper p53 levels and activity for accurately exerting its function in cell fate decision. Interestingly, recent studies have revealed that many TRIM proteins are negative or positive regulators for p53, and at the same time, many TRIM proteins are regulated by p53 to mediate p53 functions in cellular stress response and tumor suppression. This cross-talk between p53 and TRIM proteins adds a new layer of regulation to this already very complex p53 signaling pathway. While these findings bring TRIM proteins as exciting new players in the p53 signaling pathway, they also

raise some important questions which need to be addressed. For example, why do cells need so many TRIM proteins to regulate p53 when there are already so many other proteins, especially many other E3 ubiquitin ligases, involved in the p53 regulation? How is the cross-talk between p53 and TRIM proteins precisely regulated in different physiological and pathological processes? Can p53 be regulated by these TRIM proteins in cell, tissue and organ type-specific, stress signal-specific, and developmental stage-specific manners? While many studies on the cross-talk between p53 and TRIM proteins are derived from *in vitro* cell culture systems, it is unclear whether all of these regulations can be observed *in vivo* in animal models. These are vital and urgent questions to be solved by future studies, particularly studies with different TRIM transgenic animal models. In addition to tumor suppression, p53 has been known to regulate many other physiological and pathological processes, including anti-viral infection, metabolism, reproduction, neurodegeneration, and aging. While many studies on TRIM proteins have focused on the role of p53 in tumor suppression, future studies are needed to determine the contribution of TRIM proteins to the roles of p53 in the above-mentioned biological processes and diseases. For example, both p53 and TRIM proteins have been shown to play a critical role in anti-viral infection and immune response. However, it remains unclear how p53 and TRIM proteins cooperate to efficiently modulate the immune system to exert the anti-viral infection function. Similarly, while both p53 and TRIM proteins have been shown to be involved in neurodegenerative diseases, the impact of their cross-talk upon neurodegenerative diseases is largely unknown. Answering these questions will help us further understand the cross-talk between p53 and TRIM family proteins, and its impact upon biological and pathological processes, which will benefit the clinical application of targeting p53 signaling pathway and TRIM family proteins for therapies in cancer and other diseases including infection diseases and neurodegenerative diseases.

Conflict of Interests

These authors declare no conflicts of interest.

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