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TRIM32 is a novel negative regulator of p53

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To ensure proper function, the tumor suppressor p53 is tightly regulated through different post-translational modifications, particularly ubiquitination. Recently, TRIM32 was identified as a p53-regulated gene and an E3 ubiquitin ligase of p53. Thus, TRIM32 and p53 form a novel auto-regulatory negative feedback loop for p53 regulation in cells.

Tumor suppressor TP53 (also known as p53) plays an important role in tumor suppression and many aspects of health and disease, such as metabolism, reproduction, longevity, neurodegenerative diseases, and diabetes.[1] p53 protein is maintained at low levels under non-stress conditions but can be rapidly stabilized and activated in response to various types of stress signals, including DNA damage, hypoxia, nutrition deprivation, and oncogene activation. p53 can be regulated by many different post-translational modifications, including ubiquitination, phosphorylation, acetylation, sumoylation, neddylation, methylation, and glycosylation, which regulate the stability, subcellular localization and/or DNA binding ability of p53.[1] Once activated, p53 regulates many stress response processes, including apoptosis, cell cycle arrest, senescence, DNA repair, and metabolism, through selective transactivation of target genes involved in different stress response pathways.[1]

Among these multiple post-translational modifications of p53, ubiquitination is the most important for regulation of p53 stability.[1] To date, more than 20 E3 ubiquitin ligases for p53 have been identified, including MDM2, RCHY1 (Pirh2), RFWD2 (COP1), STUB1 (CHIP), HUWE1 (ARF-BP1), Synoviolin, Cul1/4, RNF34 (CARP-1), RFFL (CARP-2), FBXO42 (JFK), and TOPORS, which promote p53 degradation through the proteasome degradation pathway.[1] Several of these ubiquitin E3 ligases, including MDM2, Pirh2, and COP1, are also p53 targets, and form auto-regulatory negative feedback loops to regulate p53. It remains unclear why so many E3 ubiquitin ligases are required to regulate p53 and how these E3 ubiquitin ligases crosstalk and cooperate with each other in this regulation. It is possible that these E3 ubiquitin ligases modulate p53 in a highly cell type-, stress signal-, and developmental stage-specific manner, which needs to be addressed by future studies. Some of these ubiquitin ligases, such as MDM2, Pirh2, and COP1, are frequently overexpressed in various types of human cancers, leading to reduced protein levels and function of p53 in tumor suppression.[1]

The TRIM (tripartite motif-containing) protein family that includes over 70 distinct members is defined by a shared tripartite motif consisting of a RING domain, 1 or 2 B-boxes, and a coiled coil domain. TRIM proteins are involved in many aspects of biological processes, including cell proliferation, differentiation, development, apoptosis, oncogenesis, and innate immunity. Some TRIM proteins, such as PML (TRIM19) and TRIM24, were reported to be linked to the p53 pathway. For example, PML, which is also a p53 target, recruits p53 into PML nuclear bodies and enhances p53 stability by protecting it from MDM2-mediated ubiquitination. TRIM24 was recently reported to be a p53-induced E3 ubiquitin ligase that mediates p53 ubiquitination.[2]

Our recent study identified TRIM32 as a novel p53 target and E3 ubiquitin ligase for p53.[3] In response to stress (e.g., DNA damage), p53 binds to the p53 DNA responsive element in the *TRIM32* promoter to transcriptionally induce TRIM32. In turn, TRIM32 interacts with p53 and degrades p53 through ubiquitination independently of MDM2. Thus, TRIM32 forms a novel negative feedback loop with p53 to negatively regulate p53 functions in mediating cell cycle arrest, apoptosis, and senescence in response to stress. TRIM32 is frequently overexpressed in different types of tumors.[3-5] TRIM32 overexpression promotes cell oncogenic transformation and tumorigenesis in a largely p53-dependent manner.[3] Our finding that TRIM32 negatively regulates p53, together with recent findings that TRIM32 ubiquitinates the NF-κB inhibitor PIASy and the tumor suppressor Abl-interactor 2 (ABI2), strongly suggests that overexpression of TRIM32 in cancer promotes tumorigenesis. Interestingly, recent studies also reported that TRIM32 degrades XIAP to induce tumor necrosis factor (TNF)-mediated apoptosis and, furthermore, facilitates degradation of N-myc (MYCN) on spindle poles and induces asymmetric cell division in human

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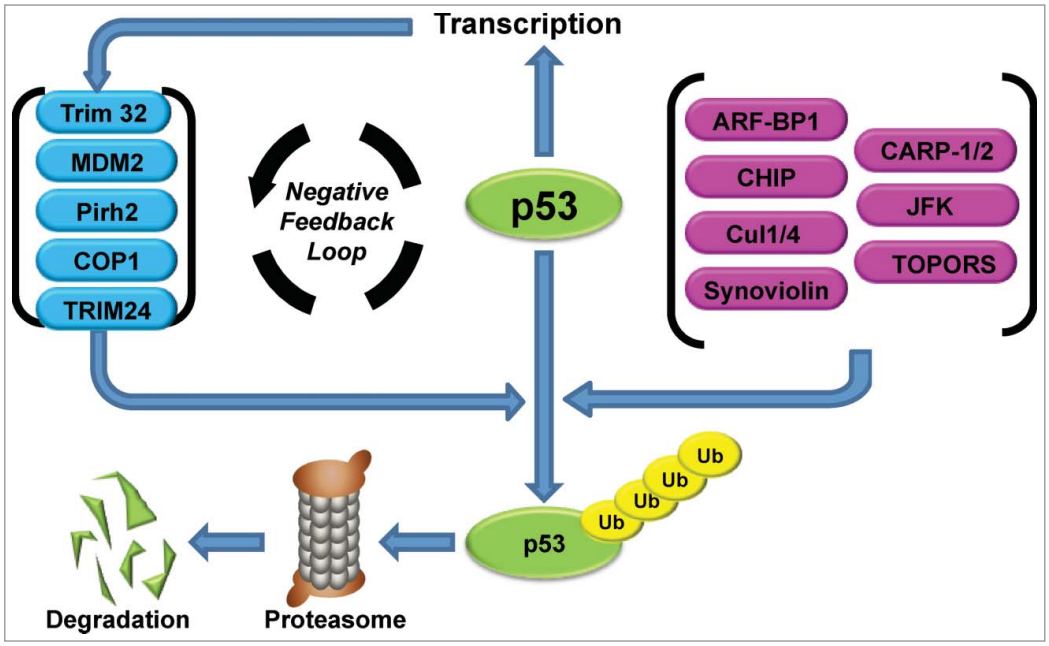

Figure 1. The regulation of p53 by E3 ubiquitin ligases. A group of E3 ubiquitin ligases, including TRIM32, MDM2, RCHY1 (Pirh2), RFWD2 (COP1), STUB1 (CHIP), HUWE1 (ARF-BP1), Synoviolin, Cul1/4, RNF34 (CARP-1), RFFL (CARP-2), TRIM24, and FBXO42 (JFK), ubiquitinate p53 and target it for degradation through the proteasome degradation pathway. Among them, p53 transcriptionally activates TRIM32, MDM2, Pirh2, COP1, and TRIM24, forming negative feedback loops for p53 regulation.

neuroblastoma cells, suggesting that TRIM32 may have tumor suppressive functions under certain contexts.[6] Currently, the defined roles of TRIM32 in different types of cancer remain unclear. It is possible that TRIM32 exerts different roles in tumorigenesis by regulating different proteins and mechanisms in a highly tissue- and cell type-specific manner. Interestingly, growing evidence has supported the concept that, in addition to its role as an oncogene mainly through negative regulation of p53, MDM2 has tumor suppressive functions in the appropriate context. Future studies with genetically engineered mouse models should provide further insights into this important question (**Fig 1**).

In addition to its role in cancer, TRIM32 regulates many other aspects of biological processes, for example neuronal and muscle cell differentiation. TRIM32 ubiquitinates dysbindin (DTNBP1), a protein associated with both skeletal muscles and neural tissues.[7] TRIM32 binds to argonaute-1 (AGO1), which plays a role in siRNA-mediated gene silencing, and induces activity of microRNAs involved in the regulation of neuronal differentiation.[8] TRIM32 was recently shown to interact with the p53 family member TAp73 and promote its degradation, which may contribute to neuronal development.[9] Similarly, point mutations in the *TRIM32* gene cause muscular dystrophy, indicating a role of TRIM32 in muscle development.[10] Our current understanding of TRIM32 is still very limited. Future studies should shed further light on the functions of TRIM32 under both psychological and pathological conditions. Considering that p53 has multiple functions in addition to tumor suppression, the regulation of p53 by TRIM32 may have different impacts on other aspects of biological processes and diseases related to p53 function in addition to tumor suppression. A better understanding of TRIM32 and other p53 E3 ubiquitin ligases will lead to the discovery of new targets and strategies in cancer therapy and other diseases, such as metabolic syndromes and neurodegenerative diseases.

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