BBA - Reviews on Cancer 1868 (2017) 404–411

Contents lists available at ScienceDirect

BBA - Reviews on Cancer

journal homepage: www.elsevier.com/locate/bbacan

Review

p53 stability is regulated by diverse deubiquitinating enzymes

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ARTICLE INFO

Keywords:
Anti-cancer
Deubiquitination
DUB
E3 ligase
Ubiquitination

ABSTRACT

The tumor suppressor protein p53 has a variety of roles in responses to various stress signals. In such responses, p53 activates specific transcriptional targets that control cell cycle arrest, DNA repair, angiogenesis, autophagy, metabolism, migration, aging, senescence, and apoptosis. Since p53 has been identified as the most frequently altered gene in human cancers, regulation and stabilization of its normal functions are important. Stability of p53 is regulated by the ubiquitin-proteasome pathway (UPP). Furthermore, it is readjusted by deubiquitination via deubiquitinating enzymes (DUBs) that can eliminate ubiquitin from p53. Diverse DUBs directly or indirectly affect the ubiquitination of p53 and, consequently, regulate various cellular processes associated with p53. As maintenance of p53 is regulated by a variety of DUBs, the interaction of DUBs and p53 can affect diseases such as cancer. Currently, DUBs have a central role in our understanding of various cancers, and some have potential in the development of effective therapeutic strategies. This review summarizes the current knowledge of p53 and of the interconnection between p53 and DUBs.

1. Introduction

DNA damage, oncogenes, and hypoxia are leading causes of cellular damage. In several cellular processes, p53, known as a tumor suppressor protein, has essential roles including roles in cell cycle arrest, DNA repair, angiogenesis, autophagy, migration, aging, senescence, and apoptosis (Fig. 1) [1,2]. Through these cellular processes, p53 suppresses tumors and has a central role in maintaining genomic stability and preventing the organism from developing diseases such as cancer [3]. Moreover, p53 protects cells from cancer cell proliferation and tumorigenesis by controlling many stress signals [4,5]. Based on previous reports, mutated p53 is observed in more than 50% of human cancers, indicating that maintenance of the functions of normal p53 is important, as those functions can modulate cell cycle and repair in tumor cells, thereby triggering inhibition of diseases including cancers [6]. In addition, previous studies have indicated that modulation of the ubiquitin-proteasome pathway (UPP) results in regulation of p53 degradation [7,8]. Several deubiquitinating enzymes (DUBs) target p53 ubiquitination and directly remove ubiquitin chains. Furthermore, some DUBs have been shown to regulate E3 ligases of p53. These DUBs have a vital influence on targeting p53 ubiquitination directly or indirectly (Table 1). DUBs can regulate the p53 signaling pathway via different mechanisms within different cellular compartments in response to different stresses [9]. In eukaryotic cells, most proteins, including p53, are mediated by ubiquitination and deubiquitination pathways. In these pathways, DUBs have key roles in various cellular mechanisms related to homeostasis. Herein, we review the currently available information on p53 ubiquitination and summarize the interaction between various DUBs and p53.

2. Ubiquitination and deubiquitination pathways

Ubiquitination is a part of the post-translational modification (PTM) process. Ubiquitination affects proteins in various ways, but its main functions are to signal protein degradation via the 26S proteasome, modify cellular location of proteins, affect protein activity, and promote or prevent protein-protein interaction [10]. Ubiquitination is a process in which ubiquitin-tagged target proteins are degraded by means of the

Abbreviations: UPP, Ubiquitin-proteasome pathway; DUB, Deubiquitinating enzyme; PTM, Post-translational modification; E1, Ubiquitin-activating enzyme; E2, Ubiquitin-conjugatng enzyme; E3, Ubiquitin ligase; RING, Really interesting new gene; HECT, Homologous to E6-AP carboxyl terminus; USP, Ubiquitin-specific proteases; UCH, Ubiquitin C-terminal hydrolases; MJD, Machado-Joseph disease protein domain proteases; OTU, Ovarian tumor proteases; JAMM, Jab1/Pab1/MPN metallo-enzyme motif proteases; MCPIP, Monocyte chemotactic protein-induced proteases; PPPDE, Permutated papain fold peptidases of dsDNA viruses and eukaryotes; Mdm2, Mouse double minute 2 homolog; MdmX, Murine double minute 4; UBE3A, Ubiquitin-protein ligase E3A; E6AP, Ubiquitin-protein ligase; COP1, Constitutively photomorphogenic 1; CARP, Caspase 8/10-associated RING domain protein; MSL2, Male-specific lethal 2; Parc, Parkin-like ubiquitin ligase; TRAF7, TNFR-associated factor; HAUSP, Herpes virus-associated ubiquitin-specific protease; PDCD5, Programmed cell death 5; ATX-3, Ataxin-3; SCA3, Spinocerebellar ataxia; USP9X, Ubiquitin-specific protease 9X-linked; HDACs, Histone deacetylases; CTCL, Cutaneous T-cell lymphomas; FAS, fatty acid synthase; TGF-β, Transforming growth factor beta

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http://dx.doi.org/10.1016/j.bbcan.2017.08.001
Received 27 April 2017; Received in revised form 21 July 2017; Accepted 5 August 2017
Available online 08 August 2017
0304-419X/

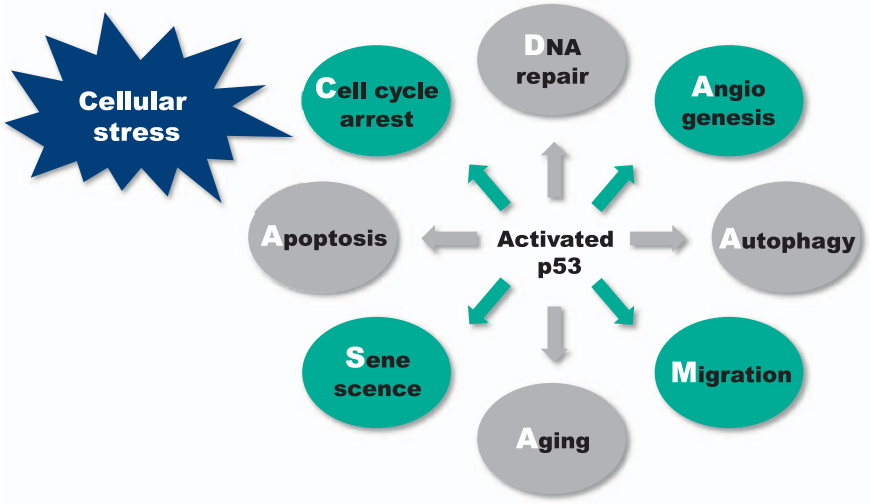
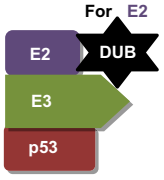
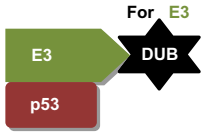


Fig. 1. p53 signaling in response to cellular stress
The cellular stress response signals activate a rapid signal transduction pathway, regulating cell fate based on the damaged cell condition. Activation of the p53 protein influences cell survival by inducing cell cycle arrest and apoptosis, whereas mutation of the p53 protein triggers tumorigenesis.

Table 1
Diverse DUBs influence p53 signaling.



E2	DUB	Ref
	OTUB1	(9, 55-59)



E3	DUB	Ref
Mdm2	USP2	(81)
Mdm2	USP2a	(31, 78)
MdmX		(30)
ARF-BP1	USP4	(79, 80)
Mdm2	USP7 (HAUSP)	(30, 46-54, 89)
Mdm2	USP15	(84, 85)
Mdm2	USP26	(86)

	DUB	Ref
	USP5	(82, 83)
	USP7 (HAUSP)	(30, 51, 53)
	USP9X	(72, 73)
	USP10	(24, 28, 61-66)
	USP11	(62, 67, 68)
	USP24	(22)
	USP29	(69)
	USP42	(70, 71)
	OTUD1	(74)
	OTUD5	(75, 76)
	Ataxin-3	(77)

proteasomal system, thereby determining the fate of the target proteins (Fig. 2) [11]. The multisubunit 26S proteasome consists of one 20S core complex for proteolysis and two 19S regulatory complexes for protein recognition [11]. Proteasome-mediated ubiquitination involves consecutive actions in which three catalytic enzymes (ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2), and ubiquitin ligases (E3)) participate [12]. Initially, E1 stimulates ubiquitin via an ATP-dependent activity by generating a thiol ester bond between the carboxyl terminus of ubiquitin and the cysteine residue of E1 [12,13]. The E1-activated ubiquitin is then transferred to a target protein through the action of E2 [14]. Finally, E3 is promoted to catalyze the ligation of ubiquitin to a lysine residue of the target protein (Fig. 2) [14]. The E3 proteins can be broadly categorized on the basis of their catalytic domains, which include the really interesting new gene (RING) and homologous to E6-AP carboxyl terminus (HECT) domains [15,16]. RING domain E3 ligases act as a bridge between E2 and the target protein by directly transferring ubiquitin to the target protein, whereas the HECT domain E3 ligases proceed in a series in which ubiquitin from E2 is first transferred to E3 [15].

A target protein with attached ubiquitin can exhibit mono-ubiquitination, multiubiquitination, or polyubiquitination, and each of those types determines its cellular functions [17]. Monoubiquitination acts on protein transport, DNA repair, endocytosis virus budding, nuclear export, and histone regulation, while multiubiquitination influences endocytosis [17]. Polyubiquitination is involved in degradation through the 26S proteasome and regulation of cellular functions of target proteins [13,17]. Polyubiquitination relies on the seven lysine residues of ubiquitin (K6, K11, K27, K29, K33, K48, and K63) [18]. Usually, K48-linked polyubiquitination regulates proteasome-dependent degradation of target proteins, whereas K63-linked polyubiquitination affects cellular functions such as endocytosis, DNA repair, and signaling activation [18,19].

Balanced maintenance of ubiquitinated protein is enabled by deubiquitination [14], and deubiquitination is aided by DUBs, which have a key role in cleaving ubiquitin chains [20]. In addition, deubiquitination is associated with a DUB cysteine protease, which denotes the presence of a catalytic activity residue [21]. Catalytic activity of DUBs separates the isopeptide bond between the glycine site of ubiquitin and the lysine site of the target protein [22]. Based on their features, DUBs can be categorized into at least seven subfamilies: ubiquitin-specific protease (USP), ubiquitin C-terminal hydrolases protease (UCH), Machado-Joseph disease protein domain protease (MJD), ovarian tumor protease (OTU), Jab1/Pab1/MPN metallo-enzyme motif protease (JAMM), monocyte chemotactic protein-induced protease (MCPIP), and permutated papain fold peptidase of dsDNA viruses and eukaryotes (PPPDE) subfamilies [20]. The USP, UCH, OTU, MJD, MCPIP, and PPPDE subfamilies contain cysteine peptidase activity. Only the JAMM subfamily includes zinc metalloisopeptidase activity [12,20]. The USP subfamily represents approximately 55% of all DUB enzymes; thus USP is considered the largest DUB subfamily [20]. Various DUBs cleave the attachment of ubiquitin on ubiquitinated target proteins, thereby regulating cellular homeostasis. Therefore, the regulation of DUBs for ubiquitinated target proteins can determine cell fate.

3. Regulation of p53 via the ubiquitin-proteasome pathway

Studies into regulation of p53 via PTM processes that involve phosphorylation, acetylation, ubiquitination, SUMOylation, neddylation, and methylation are being increasingly reported [23,24]. Phosphorylation and acetylation of p53 stimulate p53-associated transcription factors [25,26], whereas ubiquitination, SUMOylation, and neddylation of p53 repress p53-related transcription factors and affect the nuclear export of p53 [25,26]. Lastly, methylation of p53 at K382