CELL CYCLE
2020, VOL. 19, NO. 22, 2996–3003
https://doi.org/10.1080/15384101.2020.1838772

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REVIEW

HOPS and p53: thick as thieves in life and death

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ABSTRACT

The oncosuppressor protein p53 plays a major role in transcriptionally controlling the expression of a number of genes, which in turn regulates many functions in response to DNA damage, oncogene triggering, oxidative, and additional cell stresses. A developing area of interest in p53 is the studies related to its cytoplasmic function(s). Many investigations revealed the significant role of p53 in the cytoplasm, acting in a transcriptional-independent manner in important processes related to cell homeostasis such as; apoptosis, autophagy, metabolism control, drug, and oxidative stress response. The studies on cytoplasmic p53 have shown intricate mechanisms by which posttranslational modifications allow p53 to perform its cytoplasmic functions. A number of ubiquitins, deubiquitins, and small ubiquitin-like proteins, have a pivotal role in controlling cytoplasmic stability and localization. Recently, HOPS/TMUB1 a novel small ubiquitin-like protein has been described as a vital molecule stabilizing p53 half-life, directing it to the mitochondria and favoring p53-mediated apoptosis. Furthermore, HOPS/TMUB1 competing with importin-α lessens p53 nuclear localization, thereby increasing cytoplasmic concentration. HOPS/TMUB1 as p53 modifiers could be attractive candidates to elucidate apoptosis or other important transcriptional-independent functions which are key in cancer research in order to develop new therapeutic approaches.

ARTICLE HISTORY
Received 13 July 2020
Revised 22 September 2020
Accepted
24 September 2020

KEYWORDS
Hepatocyte Odd Protein Shuttling (HOPS); Transmembrane and ubiquitin-like domain containing 1 (TMUB1); Ubiquitin–Like Protein; p53; Apoptosis; Mitochondrial Apoptosis; Nucleophosmin (NPM)/p19 Arf; Tumor Suppressor Gene; Liver regeneration

Introduction

p53 is certainly one of the most studied proteins in biology and pathology. p53 governs the pathways that suppress cancer-cell growth by mediating cell-cycle arrest, apoptosis, and senescence [1,2]. p53 mutations are present in more of 50% of all cancers and inactivation of the p53 pathway is found in a high percentage of tumors derived from all tissues [3]. The majority of p53 functions are played by its transcription factor activity, which in turn transcribes a number of genes that determine the p53 oncosuppressor activity. Indeed, other important roles have been attributed to p53 in the control of cell homeostasis such as autophagy, metabolism, and antioxidant activity [4]. Other than transcriptional activity, a growing number of studies is describing important p53 functions independent of its transcriptional ability, differentiating between nuclear and cytoplasmic effects [5,6] (Figure 1).

Cytoplasmic p53

The nuclear transcriptional activity of p53 is well studied, less is known about its cytoplasmic role. Many studies indicate p53 accumulation in the cytoplasm is essential to perform its functions. p53 ubiquitination and degradation occur in the cytoplasm. Here, p53 mainly induces apoptosis *via* MOMP, allows centrosome duplication, and has an important role in controlling cell autophagy [7,8]. Many studies have shown that, following stress stimuli, p53 moves from nucleus to cytoplasm via nuclear-export receptor CRM1 upon activation of FOXO3a [9]. To perform its cytoplasmic functions, p53 – as an oligomeric protein – is subjected to a number of posttranslational modifications allowing its distribution in different regions of the cytoplasm [10]. The p53 destiny in the cytoplasm is complex and, presently, not well defined. p53 posttranslation modifications such as phosphorylation, conformational modifications, acetylation, or ubiquitylation are fundamental to

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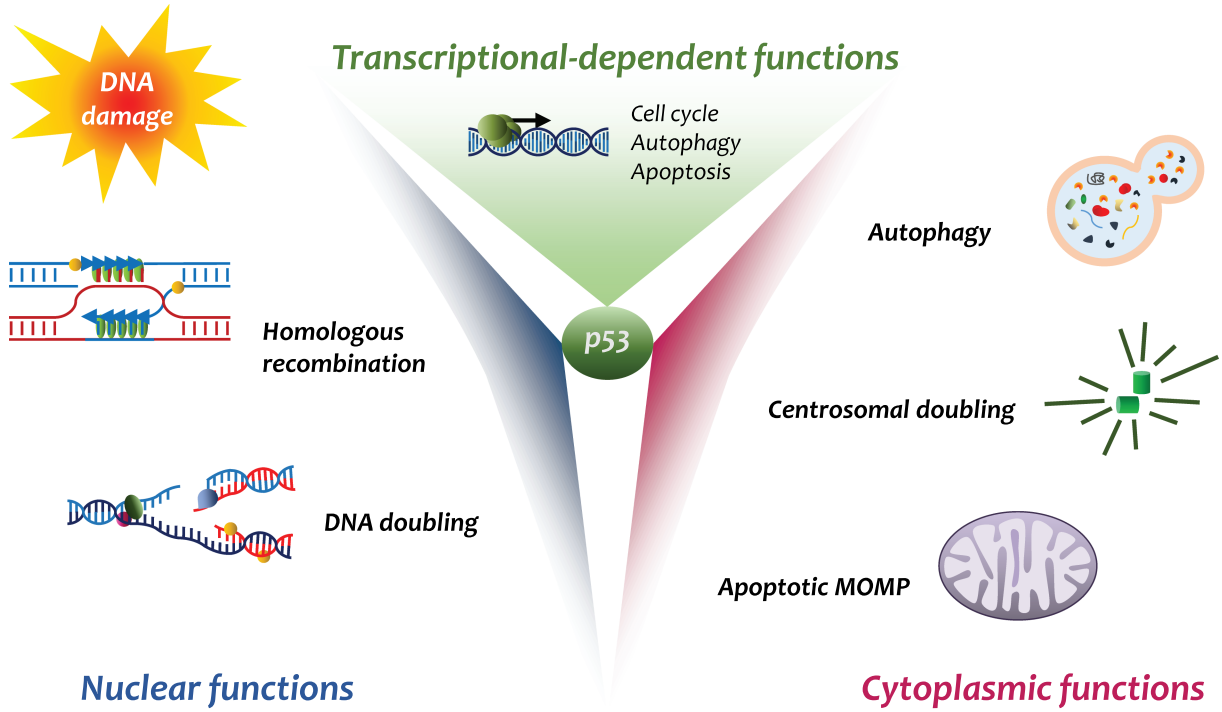

Figure 1. Schematic representation of the different activities of p53.
p53 regulates many cellular functions both at the transcriptional and not transcriptional levels. Together with the well-defined transcriptional activation of genes engaged in cell-cycle control and autophagic and apoptotic pathways, p53 acts in the nucleus and controls the proper DNA homologous recombination and doubling. At the cytoplasmic level, p53 is involved in autophagy outcome, directs centrosomal doubling, and activates mitochondrial apoptosis *via* MOMP.

sustain p53's cytoplasmic activities [11]. Many studies have highlighted p53 shuttling from the nucleus to cytoplasm and its subsequent increase in the cytoplasm and the mitochondria after DNA damage. DNA damage signaling triggers homeodomain-interacting protein kinase-2 (HIPK2), which in turn phosphorylates p53 on Serine46 [12]. This event has been well studied, the phosphorylation requires the recruitment of a phospho-specific prolyl-isomerase, Pin1, which binds phospho-p53 causing conformational changes that reduce p53-MDM2 affinity in the nucleus and the cytoplasm [13]. Modified p53 acquires the ability to bind MDM4 through BCL-2 activated MOMP [14]. Indeed, HIPK1 and Pin1 cooperate to promote translocation of p53 to the mitochondria to prompt direct apoptosis [15]. Notably, other important post-translational modifications, such as acetylation, appear to be significant in controlling p53 cytoplasmic functions [16]. Acetylated p53 at Lysine120 has been found in the mitochondria allowing mitochondrial apoptosis, demonstrating that p53 modifications are relevant in its transcription-independent functions [17,18].

P53 ubiquitin and modifier

Ubiquitylation represents one of the most important posttranslational modifications that occur to p53. Undoubtedly, p53 degradation happens in the cytoplasm by proteasome machinery, but posttranslational modifications, such as mono and multi mono-ubiquitylation, allow p53 to localize in different cytoplasmic compartments. MDM2 is the most important E3 in regulating p53 half-life [19,20] and has a preeminent role in regulating posttranslational modifications. The MDM2 level in the cell is crucial for p53 stability, low MDM2 levels enhance p53 half-life, while high MDM2 levels drive proteasome-mediated degradation [21]. Moreover, the role played by HAUSP in controlling mitochondrial p53 levels by deubiquitylation [22–24] must be considered. Indeed,

after the discovery of HAUSP, a number of deubiquitins regulating p53 has been described [25–30]. Indeed, the fine regulation of cytoplasmic levels of p53 is more complex than just MDM2-dependent concentration. Many functions exerted by p53 are directly related to its half-life in the cell and p53 protein stabilization is a determinant factor for its roles in the nucleus and cytoplasm. However, while the principal role of MDM2 as p53-E3 ubiquitin-ligase is clear, many studies have identified a number of molecules playing a role in p53 ubiquitylation. Among them, there are at least 15 proteins that can act as a MDM2-independent p53 E3-ligase. These p53-E3 ubiquitin ligases show different conformational structures and domains and some of them, such as E4F1 and UBC13, lack typical E3 domains [31]. Aside from the poly-ubiquitylation resulting in p53 degradation as a control mechanism of p53 stability, other molecules such as Ubiquitin-Like modifiers (UBL) are important not only in p53 stability, but also in its cytoplasmic localization [32]. Many investigations have revealed the role of Small Ubiquitin-like MOdifier (SUMO) in regulating p53 activity. SUMO proteins conjugated via an isopeptide bond to lysine 386 of p53 at its C-terminal regulatory domain. Some authors suggest that SUMOylation has a possible role in favoring p53 nuclear export to the cytoplasm, allowing p53 accumulation in physiological or pathological functions [33]. As of now, this is a point currently under debate. p53 SUMOylation in the nucleus has been described as a mechanism involved in lessening p53 transcriptional activity and allowing p53 enrichment in nuclear bodies. Moreover, p53 SUMOylation has been observed to have an important role in the pathogenesis of atherosclerosis [34]. Other than SUMO, another known p53 modification by UBL, Neural precursor cell Expressed Developmentally Downregulated protein 8 (NEDD8) has been defined [35]. Interestingly, NEDDylation on p53 utilizes different E3s depending on the lysine residues; when NEDDylation occurs at C-terminus lysines, K370, K372, K373 [36], it involves Mdm2, while FBXO11 promotes NEDDylation in lysines K320 and K321 [37]. p53 NEDDylation by Mdm2 or FBXO11 leads to a reduction in transcriptional activity.

HOPS/TMUB1 in brief

Recently, a novel UBL modifier, Hepatocyte Odd Shuttling Protein/Trans Membrane Ubiquitin 1 (HOPS/TMUB1) has been identified in controlling p53 stability and cytoplasmic accumulation [38]. As observed, HOPS seems to play a pivotal role in directing p53-mediated mitochondrial apoptosis in response to DNA damage, suggesting an involvement in the fine-tuning of p53 activity control (Figure 2). HOPS/TMUB1 (from hereinafter HOPS) is a ubiquitous shuttling protein characterized by a ubiquitin-like

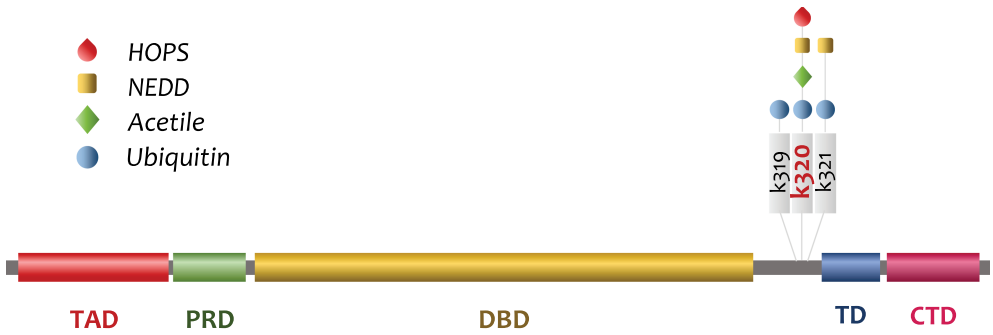

Figure 2. HOPS crosstalk with other p53 modulators.

Ubiquitylation, NEDDylation, and acetylation occur at K320 balancing p53 levels and activation. HOPS interacts with p53 at K320 thus generating an effective crosstalk with other posttranscriptional modifiers. **TAD** – Transactivation Domain; **PRD** – Proline-rich Domain; **DBD** – DNA Binding Domain; **TD** – Tetramerization Domain; **CTD** – C-Terminal Domain

(UBL) domain, three transmembrane segments, with proline-rich and C-terminus leucine-rich regions [39]. *Hops* transcribes a single mRNA, which codifies for three proteins with different molecular weights. HOPS localization in cells is primarily in the nucleus, but during proliferation or after stress stimuli, such as genotoxic or oxidative agents, HOPS migrates to the cytoplasm. *Hops* has been isolated in liver regeneration together with other novel genes [40,41]. In normal livers, HOPS is mostly present in the nucleus in quiescent hepatocytes, but after partial hepatectomy, it rapidly migrates in the cytoplasm where it remains until the end of the first M-phase. It has been demonstrated that cAMP or EGF are the major factors involved in HOPS shuttling. Similar results have been obtained in hepatoma cells induced to proliferate or arrested with serum deprivation. HOPS contains a Nuclear Export Signal (NES) domain that allows the export outside the nucleus through the exportin Chromosome Region Maintenance 1 (CRM-1) [42].

Interestingly, it has been demonstrated that in the cytoplasm, HOPS plays a role in mitotic spindle assembly and centrosome duplication and its reduction in the cell leads to altered mitosis figures with multipolar spindle and cytokinesis failure [43]. HOPS has been found to participate in the ERAD pathway, playing an important role in the control of cholesterol biosynthetic enzyme HMG-CoA reductase [44]. HOPS is abundantly expressed in the brain, where it plays a role in the regulation of basal synaptic transmission [45,46]. Notably, HOPS has been shown to interact and control the stabilization of the tumor suppressor $p19^{Arf}$. It has been demonstrated that HOPS not only acts as a stabilizer of $p19^{Arf}$, but regulates its nucleolar localization and mediates the interaction with the oncosuppressor protein nucleophosmin (NPM) [47]. Moreover, it has been demonstrated that $p19^{Arf}$ stabilization by HOPS results in p53 overexpression. However, the presence of a UBL in the HOPS structure supports the idea of direct involvement of UBL as a modifier in $p19^{Arf}$ survival (*Manuscript in preparation*).

Recently, the HOPS-Knockout mouse model has been developed. $Hops^{-/-}$ mouse is viable at birth, even if they present a slightly reduced Mendelian frequency with respect to $Hops^{+/+}$ mouse [38].

HOPS and p53

Importantly, when the $Hops^{-/-}$ mice are treated with DNA damage drugs such as etoposide or camptothecin, they are resistant to apoptosis due to reduced activation of p53. A link between lack of HOPS and altered p53 response has been established through analyzing the reduced p53 response after etoposide treatment. In particular, a direct binding between p53 and the UBL domain of HOPS has been shown, which defines a prolonged half-life in p53. Mutational analysis in the terminal glycine of HOPS-UBL (G176) demonstrates the reduction in the ability of HOPS to sustain p53 stability. The decreased contribution of p53 in apoptosis in $Hops^{-/-}$ mouse has been analyzed *in vivo* and *in vitro* to understand the involvement of HOPS in apoptosis. As above described, HOPS is a shuttling protein that migrates to the cytoplasm, upon stress or in proliferation. After etoposide treatment, it has been found that HOPS and p53 migrate and their binding increases in the cytoplasm. Both proteins utilize the exportin CRM-1 to shuttle to the cytoplasm [38,42,48]. In particular, both proteins show accumulation in the mitochondria. Notably, comparing the p53 mitochondrial levels in $Hops^{-/-}$ mice after etoposide treatment, a reduced amount of p53 in the thymus was found in the spleen and testis; this indicates an important contribution of HOPS in maintaining the mitochondrial p53 levels which in turn directs apoptosis after DNA damage. When overexpressed HOPS not only increases p53 levels, but it competes with importin-α in binding to lysine-320 of the p53 NLS, restraining p53 import and promoting its accumulation in the cytoplasm [38] (Figure 3). Interestingly, as HOPS and p53 also bind in the nucleus, many investigations are directed toward understanding the contribution of HOPS in

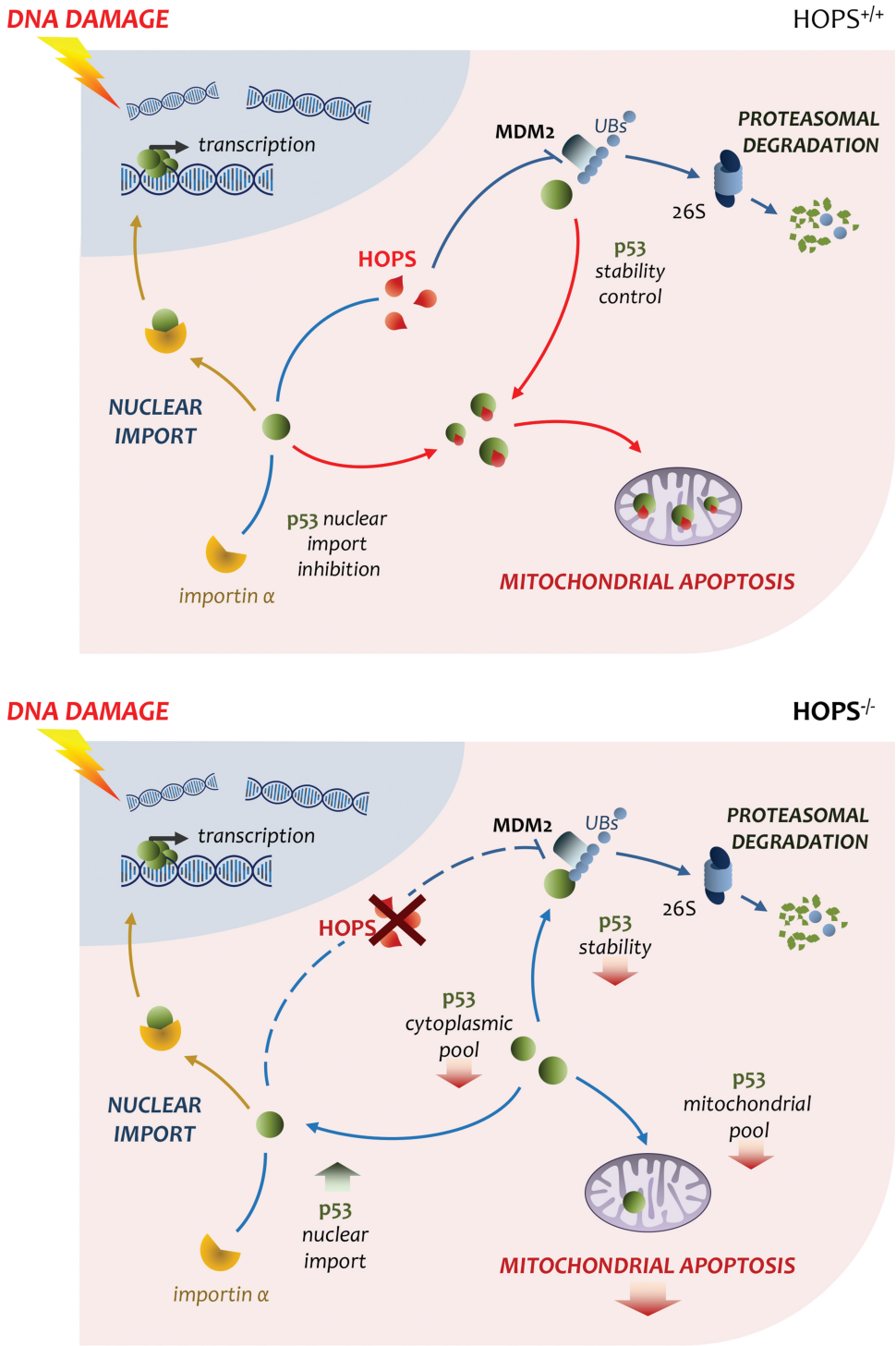

Figure 3. Overview of HOPS impact on p53 activity in the cellHOPS is concerned in lengthening of p53 half-life inhibiting MDM2 E3 ligase activity. Upon DNA damage stresses, HOPS enhances p53 stability sustaining p53 cytoplasmic pool. Cytoplasmic p53 is than available for mitochondrial translocation and MOMP induction for apoptotic outcome. Moreover, HOPS can modulate importin α binding to p53, responsible for p53 nuclear import, thus reducing p53 transcriptional activation (upper panel). In the absence of HOPS apoptotic response to DNA damage inputs is reduced. In HOPS$^{-/-}$ models p53 half-life is shortened leading to cytoplasmic pool drop and in turn reduced mitochondrial apoptosis. Importin α binding to p53 is not hampered by HOPS competition and nuclear import is increased (bottom panel).

regulating the transcriptional activity of p53; this would establish the role of HOPS in p53-related transcriptional dependent and independent apoptosis.

Conclusions

The discovery of the cytoplasmic role of p53 in apoptosis and other important systems such as autophagy and metabolism is critical for cancer therapeutics. Indeed, the transcriptional-independent role of p53 in apoptosis has been well studied, but controversial results have been observed in how p53 drives mitochondrial apoptosis. Many difficulties derive from the limited information regarding how p53 orchestrates its functions toward a specific pathway rather than another [49,50]. To this end, HOPS has been found not only to increase the p53 stability, but localizes p53 to the mitochondria to facilitate mitochondrial apoptosis.

HOPS similarly to other modifiers, such as SUMO and NEDD, seems to play an important role in controlling the cytoplasmic function of p53. The posttranslation modifications of p53 are of great and growing interest in cancer research to address deeper understanding of this function with the aim of utilizing them in therapeutic approaches. Many data indicate HOPS is an important regulator of p53 in cytoplasmic functions and adds another solid contribution to better understand the intricate and fascinating role of p53 in the cell.

Besides SUMOylation or NEDDylation, the HOPSylation may have a novel and significant function not only related to p53, but other HOPS targets are to be discovered to better understand the HOPS role in biology and pathology.

Acknowledgments

We wish to thank the members of our laboratory, Damiano Scopetti, Simona Ferracchiato, Nicola Di Iacovo, and Silvano Pagnotta for the fruitful discussions and support. The original studies in the authors' own laboratory were supported in part by Associazione Umbra Contro il Cancro-AUCC, Fondazione Cassa di Risparmio di Perugia-FCRP and Comitato Maria Grazia Frasconi. G.S. is recipient of a PRIN 2015 Project 20152CB22L_004.

Disclosure statement

No potential conflict of interest was reported by the author.

Funding

This work was supported by the Ministero dell'Istruzione, dell'Università e della Ricerca [20152CB22L_004]; Fondazione Cassa di Risparmio di Perugia(IT); Comitato Maria Grazia Frasconi; Associazione Umbra per la lotta Contro il Cancro.

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