FEBS Letters 586 (2012) 1390–1396

journal homepage: www.FEBSLetters.org

Review

Mdm2 and MdmX partner to regulate p53

Xinjiang Wang [a,*], Xuejun Jiang [b]

[a] Department of Pharmacology & Therapeutics, Roswell Park Cancer Institute, Buffalo, NY 14263, USA
[b] Cell Biology Program, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA

ARTICLE INFO

Article history:
Received 6 February 2012
Revised 27 February 2012
Accepted 28 February 2012
Available online 8 March 2012

Edited by Wilhelm Just

Keywords:
Mdm2
MdmX
MDM4
p53
E3 ligase
Ubiquitination
Regulation
Degradation
Stress response

ABSTRACT

Mdm2 regulates the stability, translation, subcellular localization and transcriptional activity of p53 protein. Mdm2-dependent p53 inhibition is essential in regulating p53 activity during embryonic development and in adult tissues. MdmX, an Mdm2 homolog, is also essential for p53 inhibition in vivo. Recent advances in the field from biochemical and genetic studies have revealed an essential role for the MdmX RING domain in Mdm2-dependent p53 polyubiquitination and degradation. Mdm2 on its own is a monoubiquitin E3 ligase for p53, but is converted to a p53 polyubiquitin E3 ligase by MdmX through their RING–RING domain interactions. MdmX acts as an activator as well as a substrate of Mdm2/MdmX E3 complex. The insufficiency of Mdm2 for p53 polyubiquitination also demands other p53 E3 ligases or E4 factors be incorporated into the p53 degradation arena. Deubiquitinases nullify the effects of E3 actions and reverse the ubiquitination process, which permits a diverse and dynamic pattern of p53 stability control. Unsurprisingly, stress signals target MdmX to disengage the p53/Mdm2 feedback loop for timely and appropriate p53 responses to these stresses.

Published by Elsevier B.V. on behalf of the Federation of European Biochemical Societies.
Open access under CC BY-NC-ND license.

1. Background: the tumor suppressor p53

p53 suppresses tumor development through multiple activities including induction of growth arrest, apoptosis, senescence, and autophagy [1,2]. Beyond tumor suppression, p53 also regulates fecundity, metabolism, quiescence, and aging [3–8]. p53 remains dormant in unstressed cells owing to its inherent instability via fast degradation mechanisms. However, the short-lived p53 protein is stabilized and activated by many types of abnormal conditions including genotoxic stress, non-genotoxic such as hypoxia, low pH, heat shock and ribosomal stress, and by aberrant growth signals, among others [8–10]. Activation of p53 leads to transcriptional up-regulation of various p53 target genes [3]. To engage p53 under these various stress conditions, a complex regulatory network has evolved for precise p53 regulation. This regulatory network prevents accidental p53 activation, which is potentially lethal to many cell types, but initiates a rapid p53 response when stress signals are sensed. The key molecule in the p53 regulatory network is Mdm2, an E3 ubiquitin ligase with potentially oncogenic activity. Dynamic fine-tuning of the Mdm2-centered network dictates the proper rapidity, intensity, and duration of a p53 response, resulting in the appropriate biological outcomes [11].

p53 is modified by many types of posttranslational modifications. Among these, ubiquitination by E3 ligases has, perhaps, the most significant impact on p53 biology [12,13]. Many cellular E3 ligases capable of mediating p53 ubiquitination have been identified. The founding member of HECT domain E3 ligases that target p53 for degradation is E6AP, a protein that ubiquitinates p53 only in the presence of the human papillomaviruses E6 protein [14,15]. Mdm2 E3 ligase appears to be the physiological and primary E3 ligase regulating p53, and is thus the best studied in the field. Several recent reviews provide a comprehensive updates on our current understanding of Mdm2 [8,10,16,17]. This review will focus on recent advances in the regulation of Mdm2 E3 ligase activity by MdmX, and the significance of MdmX for p53 regulation, as summarized in Fig. 1.

2. Mdm2-dependent p53 inhibition: canceling transcription or degrading the protein

Mdm2 was initially discovered as a p53 binding protein that possesses potent inhibitory effects on p53-mediated transcription [18]. The crystal structure of an Mdm2 N-terminal fragment bound with a p53 transactivation domain peptide demonstrated that the amino acids of p53 involved in binding to the Mdm2 cleft are

* Corresponding author.
E-mail address: xinjiang.wang@roswellpark.org (X. Wang).

0014-5793 Published by Elsevier B.V. on behalf of the Federation of European Biochemical Societies. Open access under CC BY-NC-ND license.
doi:10.1016/j.febslet.2012.02.049

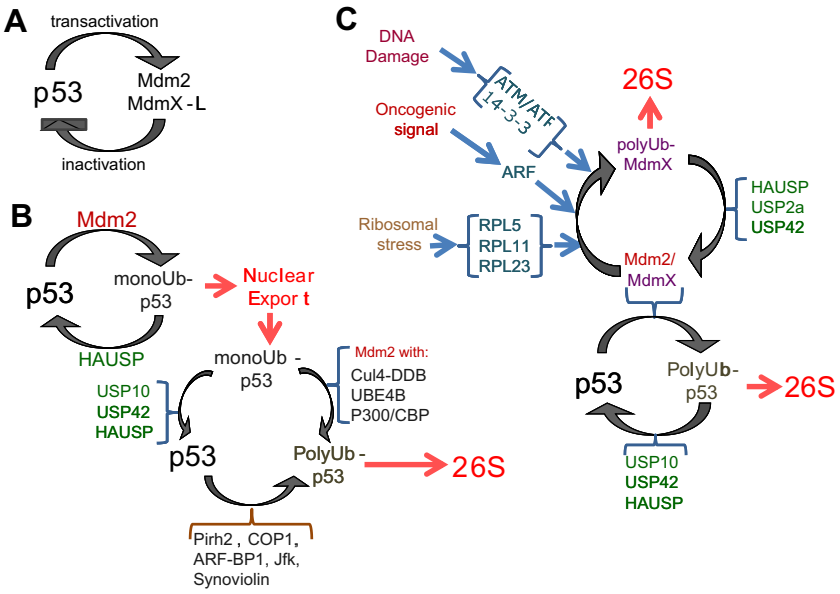

Fig. 1. Mdm2 and MdmX control p53 stability at multiple levels. (A) p53 and Mdm2 form a well-established autoregulatory feedback loop in which p53 transactivates *Mdm2* gene transcription and the subsequent increase in Mdm2 protein inactivates p53. Recently, the MdmX-L isoform has been shown to participate in a similar loop. (B) Mdm2 acting alone mediates monoubiquitination of p53 at multiple sites, facilitating p53 nuclear export to the cytoplasm. Other E3 ligases (such as Pirh2, etc.), or Mdm2 together with other E4 factors (such as UBE4B) or E4-like molecules (such as Cul4-DDB complex and p300/CBP) can polyubiquitinate p53 leading to its degradation by 26S. Deubiquitinases such as HAUSP, whose major substrates are ubiquitinated Mdm2 and MdmX, and USP10, whose major substrate is ubiquitinated p53, are involved in removal of ubiquitin moieties from their corresponding substrates and contribute to p53 stability control. (C) Mdm2/MdmX heterodimers formed via their RING domains mediate p53 polyubiquitination for efficient proteasomal degradation. Various stress signals trigger MdmX polyubiquitination by Mdm2/MdmX leading to degradation of MdmX, the activator component of Mdm2/MdmX E3 complexes, resulting in p53 stabilization and activation. Conversely, specific deubiquitinases exert dynamic regulation of p53, Mdm2, and/or MdmX by deubiquitinating these three proteins.

indeed also required for binding to transcriptional machinery [19]. Therefore, Mdm2 binding conceals the transactivation potential of p53 by forming Mdm2/p53 complexes. Later, it was found that overexpression of Mdm2 also promotes proteasomal degradation of p53 [20,21]. Using GST-Mdm2 fusion protein to reconstitute p53 ubiquitination in vitro, it was demonstrated that Mdm2 is an E3 ligase and that Mdm2 belongs to the RING family of E3 ligases [22,23]. Several other p53 E3 ligases have since been identified. However, Mdm2 appears to be essential in restricting p53 activity during embryonic development as demonstrated by mouse genetic studies [13,24,25]. In addition to p53, Mdm2 E3 ligase has other substrates such as ribosomal protein L27 that regulates p53 translation [26]. Importantly, conditional loss of Mdm2 in several adult tissues causes p53-dependent cell death accompanied by p53 protein accumulation and activation of p53 target gene expression [10,16]. Since the p53 binding domain of Mdm2 resides in the N-terminus while the E3 ligase activity resides in the C-terminus, mutation of the Mdm2 RING domain allows one to differentiate between the effects of Mdm2 on inhibiting p53 transcription and the effects on p53 degradation in vivo. Surprisingly, RING domain point mutations like Mdm2C462A cause p53-dependent lethality in a manner similar to complete deletion of the whole *Mdm2* gene [27]. This observation implies that the binding of Mdm2 to the p53 transactivation domain has little effect while the E3 ligase activity within the RING domain is sufficient to account for Mdm2 mediated p53 inhibition [28]. Subsequent to these discoveries, the Mdm2 RING domain became the centerpiece of p53 regulation in vivo.

3. MdmX as a potent activator of Mdm2-dependent p53 degradation in vitro and in vivo

The mechanism underlying Mdm2-dependent p53 degradation is complicated by the discovery of MdmX, a RING finger-containing homolog of Mdm2 [29]. Genetic studies indicate that MdmX is as essential as Mdm2 for negative regulation of p53 during embryonic development because MdmX knockout also causes p53-dependent embryonic lethality in mice [30]. Genetic analysis suggests that MdmX-mediated p53 inhibition consists of two components, one that is dependent on Mdm2 and one that is not [31]. Conditional deletion of Mdm2 causes a significant increase in p53 protein levels in MEFs, while conditional deletion of MdmX in an Mdm2 heterozygous background causes only a moderate increase in p53 protein levels. This observation has led to the conclusion that Mdm2 regulates p53 mainly through protein degradation while MdmX regulates p53 mainly via modulation of its transcriptional activity [32]. MdmX is a potent inhibitor of p53 transcriptional activity [29,33]. However, how MdmX contributes to Mdm2-dependent p53 degradation has remained controversial for many years. There are several possible reasons for this: (1) Mdm2 was originally reported to be sufficient for p53 polyubiquitination in vitro in a concentration-dependent manner [34], suggesting other factors play only minor roles in the p53 ubiquitination process; (2) MdmX has little E3 ligase activity toward p53; (3) MdmX overexpression in cell culture has generated contradictory results with regards to p53 ubiquitination and degradation (see reference in [33]).

MdmX shares low overall similarity with Mdm2 at the level of amino acid sequence. However, both proteins have a nearly identical p53 binding domain at their N-terminus and a RING domain at their C-terminus. A RING domain is a well-established E2-interacting domain that confers E3 ligase activity to RING domain-containing proteins [35]. However, RING domains can also interact with RING domains of other proteins thus forming protein heterodimers [36]. Interestingly, the Mdm2 RING domain was found capable of interacting with the MdmX RING domain [37]. Although MdmX does not possess significant E3 ligase activity towards p53, MdmX autoubiquitination does occur in vitro [38,39]. The stimulatory ef-

Download English Version:

https://daneshyari.com/en/article/2048280

Download Persian Version:

https://daneshyari.com/article/2048280

Daneshyari.com