FEBS Letters 586 (2012) 1397–1402

journal homepage: www.FEBSLetters.org

Review

Pirh2 RING-finger E3 ubiquitin ligase: Its role in tumorigenesis and cancer therapy

Yong-Sam Jung, Yingjuan Qian, Xinbin Chen *

Comparative Oncology Laboratory, University of California, Davis, CA 95616, USA

ARTICLE INFO

Article history:
Received 1 March 2012
Revised 21 March 2012
Accepted 22 March 2012
Available online 3 April 2012

Edited by Wilhelm Just

Keywords:
Pirh2
E3 ligase
Tumorigenesis
Cancer therapy

ABSTRACT

The ubiquitin-dependent proteasome system plays a critical role in many cellular processes and pathogenesis of various human diseases, including cancer. Although there are a large number of E3 ubiquitin ligases, the majority are RING-finger type E3s. Pirh2, a target of p53 transcription factor, contains a highly conserved $C_3H_2C_3$ type RING domain. Importantly, Pirh2 was found to regulate a group of key factors dedicated to the DNA damage response, such as p53, p73, PolH, and c-Myc. Interestingly, Pirh2 was upregulated or downregulated in different types of cancers. These suggest that Pirh2 is implicated in either promoting or suppressing tumor progression in a tissue-dependent manner. This review will focus on the major findings in these studies and discuss the potential to explore Pirh2 as a cancer therapeutic target.

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1. Introduction

The ubiquitin–proteasome system is one of the critical mechanisms controlling protein turnover and thus maintains cellular protein homeostasis. Although protein ubiquitination is catalyzed by a highly ordered enzymatic cascade, including ubiquitin-activating enzyme E1s, ubiquitin-conjugating enzyme E2s, and ubiquitin ligase E3s, the last of which primarily determine the substrate specificity [1]. E3 ubiquitin ligases contain three major groups, RING (the real interesting new gene) finger domain containing E3s, HECT (the homologous to E6-AP carboxyl terminus) domain E3s, and U-box proteins. Intriguingly, the majority of identified E3 ubiquitin ligases contain a RING-finger domain. Evidence showed that RING-finger E3 ubiquitin ligases target substrate proteins involved in many cellular processes, such as cell proliferation, differentiation, DNA repair, apoptosis, and metabolism [2]. As a result, aberrant activities of RING-finger E3 ubiquitin ligases are correlated with the pathogenesis of various human diseases, including cancer. For example, in multiple cancers, decreased expression of the p53 tumor suppressor is correlated with amplified expression of its ubiquitin ligases, such as Mdm2 and COP1 [3,4]. Therefore, understanding how E3s are implicated in tumorigenesis will provide clues for developing anti-E3s based cancer therapeutics. Indeed, small molecular inhibitors of Mdm2 have shown to be a promising treatment for tumors with elevated Mdm2 but decreased p53 [5–7]. However, the importance of Pirh2, a target and a ubiquitin E3 ligase of p53, in tumorigenesis is emerging. It appears that in addition to p53, Pirh2 regulates multiple other factors, including p73, p27, PolH (DNA polymerase eta), and c-Myc [8–12]. In this review, we will provide an overview of current findings on Pirh2 and discuss the potential to develop Pirh2 as a new target for cancer therapy.

2. Pirh2 and its isoforms

Human Pirh2 (p53-induced RING-H2 protein), also known as Rchy1 (RING-finger and CHY-zinc-finger domain-containing protein 1), is encoded by the RCHY1 gene which contains nine exons and located on the chromosome 4p21.1. To date, p53 is the only transcription factor known to directly activate the promoter of the RCHY1 gene [13]. Two p53 homologous, p63 and p73, share high sequence and structure identity with p53 and regulate some p53 target genes [14–16]. Therefore, p63 and p73 are likely to regulate Pirh2 expression. Evidence also showed that at least five isoforms of Pirh2 protein, named as Pirh2A, B, C, C′ (also called Pirh2b), and D, are generated by alternative splicing (Fig. 1). Pirh2A (full-length Pirh2) is composed of 261 amino acids and contains the N-terminal CHY-Zn-finger domain, the central RING-finger domain, and the C-terminal domain (CTD) (Fig. 1A). Due to alternative splicing, Pirh2B lacks exon 7, which encodes amino acids 171–179 of the RING domain [17] (Fig. 1B). Due to the usage of a second donor site in intron 7 and generation of a premature stop codon, Pirh2C lacks the last seven amino acids (180–186) of the RING domain and the entire downstream C-terminal sequence [17] (Fig. 1B). Due to the usage of an alternative 5' splice site in exon 8 and a 38-nucleotide deletion in the 5' end of exon 8 along with a premature stop codon, Pirh2C' contains identical amino acids to

* Corresponding author.
E-mail address: xbchen@ucdavis.edu (X. Chen).

0014-5793/$36.00 Published by Elsevier B.V. on behalf of the Federation of European Biochemical Societies.
http://dx.doi.org/10.1016/j.febslet.2012.03.052

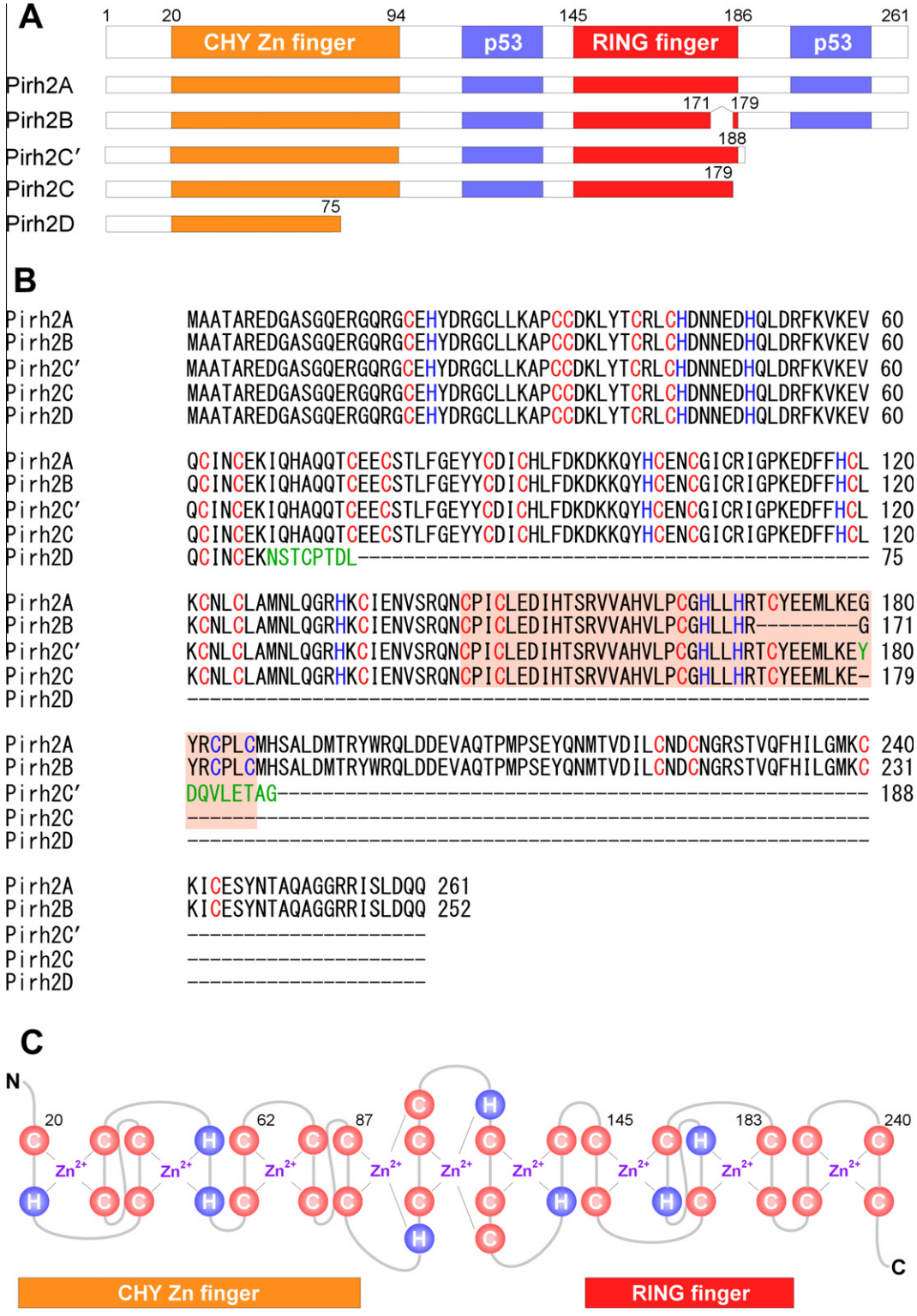

Fig. 1. Schematic representation of Pirh2 and isoforms. (A) The domains of the human Pirh2 protein and the binding sites of p53 are indicated. (B) Sequence alignment of full-length Pirh2 and its isoforms using ClustalW2 multiple sequence alignment program. Pirh2C' and Pirh2D have an additional unique amino acid (shown in green). (C) Secondary sequence organization of the CHY-zinc-finger/RING-finger domain. The cysteine and histidine are labeled as C and H, respectively. There are nine potential interleaved zinc binding sites.

Pirh2C plus additional 9 unique amino acids at the C-terminus [18] (Fig. 1B). Due to insertion of an "A" that shifts the reading frame and generation of a premature stop codon, Pirh2D only contains 75 amino acids from the N-terminal of Pirh2A plus 8 unique amino acids [19] (Fig. 1B). Pirh2 contains nine zinc binding sites, with six in the CHY-Zn-finger domain, two in the RING domain, and one in the CTD [20] (Fig. 1C). Since the consensus RING-H2 ($C_3H_2C_3$) finger domain is required for Pirh2 to act as an E3 ubiquitin ligase in vitro and in vivo [21], Pirh2B, Pirh2C, Pirh2C', and Pirh2D lack the intrinsic ubiquitin ligase function because of truncation or