Journal of Cell Signaling
ISSN: 2576-1471
Tong et al., J Cell Signal 2017, 2:3
Commentary
Open Access

Proline Isomerase Pin1 is a critical Regulator for Retinoblastoma Protein Phosphorylation in Control of Cell Cycle and S-phase Check-point Upon DNA Damage

Ying Tong*, Yuhuang Li and Zhi-Xiong Xiao

Center of Growth, Metabolism and Aging, Key Laboratory of Biological Resources and Ecological Environment of Ministry of Education, College of Life Sciences and State Key Laboratory of Biotherapy, Sichuan University, Chengdu, Sichuan, China

***Corresponding author:** Ying Tong, Center of Growth, Metabolism and Aging, College of Life Sciences and State Key Laboratory of Biotherapy, Sichuan University, Chengdu, 610064 China, Tel: (+86) 8541-5509; Fax: (+86) 8541-5509; E-mail: tongying@scu.eud.cn

Received date: June 07, 2017; **Accepted date:** June 16, 2017; **Published date:** June 26, 2017

Commentary

Protein phosphorylation represents an universal regulatory mechanism in cellular signalling. Pin1-catalyzed isomerization of phospho-protein plays a pivotal role in this regulatory network. Through binding to specific phosphorylated Ser/Thr-Pro bonds, Pin1 induces conformational change of its targets, therefore affecting many diverse cellular events. Reports from us and others demonstrate that Pin1 can activate cyclin D1, resulting in hyperphosphorylation of Rb and facilitating G1-S transition. Meanwhile, Pin1 can directly bind to Rb to inhibit its PP2A-mediated dephosphorylation upon γ-irradiation. Deregulation of Pin1 can lead to disruptive S-phase checkpoint control. Present commentary aims to briefly discuss the significance of Pin1-Rb signaling in cell cycle control and S-phase checkpoint control.

Pin1 is an unique peptidyl-prolyl cis/trans isomerase conserved from archaea to mammal. Pin1 binds to phosphorylated Ser/Thr-Pro motifs to isomerize peptidyl-proline bonds from cis to trans or vice versa [1]. Phosphorylation is the prerequisite for Pin1 binding to its substrates. Thus, Pin1-catalyzed conformation switch represents a pivotal phosphorylation-dependent mechanism in regulation of cellular signaling [2,3].

By twisting the conformation of target proteins, Pin1 can modulate their stability, activity, cellular localization, phosphorylation status and/or protein-protein interactions. Up till now, more than 60 proteins have been identified as Pin1 substrates, which function in a wide spectrum of cellular events including cell cycle progression, proliferation, survival, differentiation, tumorigenesis and morphogenesis [4,5]. Pin1 coordinates cell division in cycling cells by targeting Cyclin D1, ErbB2/Ras, Wnt/β-catenin, and NF-κB signaling pathways [6-9].

Specifically, Pin1 contributes exclusively to tumorogenesis and cancer progress by isomerizing a series of proline-directed kinases, such as glycogen synthase kinase 3 beta, cyclin-dependent kinases and MAP kinases [4,5,10]. Pin1 has been also shown to participate in cellular response to genotoxic stress through interaction and activation of phosphorylatd p53 [11,12]. In addition, several reports revealed an important function of Pin1 in the modulation of self-renewal, pluripotency and differentiation of stem cells through pluripotent factors such as Nanog and Oct4 [13,14].

Retinoblastoma protein (Rb), the first identified tumor suppressor protein, is an essential regulator of cell cycle progression, apoptosis, senescence and differentiation. Regulation of Rb phosphorylation is the major mechanism for the modulation of Rb activity. Hypophosphorylated Rb interacts with E2F, a transcription factor involved in cell cycle progression and survival. Conversely, hyperphosphorylated Rb is unable to bind E2F proteins, thereby allowing E2F to promote cell cycle progression. Cyclin/Cyclin-dependent kinase (CDK) complexes are primarily responsible for phosphorylation of Rb, while protein phosphatase 1 (PP1) and protein phosphatase 2A (PP2A) are responsible for dephosphorylation of Rb [15].

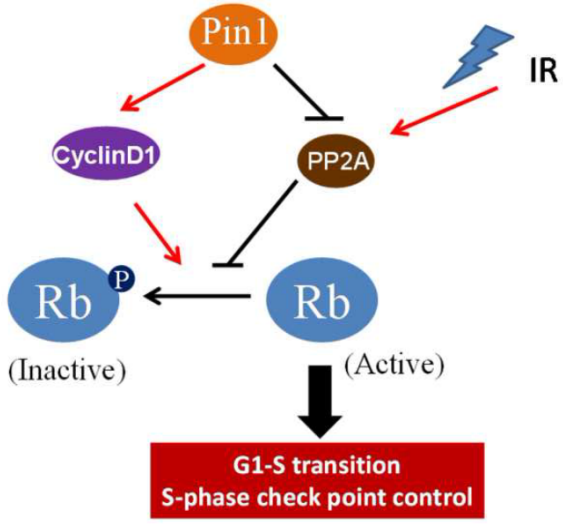

Figure 1: Pin-1 is a critical regulator for Rb phosphorylation in cell cycle and S phase check-point control.

We have previously demonstrated that Pin1 deficiency leads to a decrease in Cyclin D1 expression, resulting in reduced Rb phosphorylation. IGF-1 can induce Pin1 protein expression which promotes cyclin D1-dependent Rb phosphorylation and cell cycle S-phase entry [16].

In our recent study, we found that Pin1 can directly bind to Rb to modulate its phosphorylation. Pin1 WW domain binds to Rb C-pocket. G1-S Cyclins promote Rb phosphorylation and facilitates Pin1-Rb interaction, leading to inhibition of PP2A-mediated Rb dephosphorylation. Importantly, we found that overexpression of Pin1 leads to hyperphosphorylated Rb and defective S-phase checkpoint control in response to γ-irradiation. Thus, deregulation of Pin1

expression can disrupt S-phase checkpoint control upon DNA damage, which may contribute to genomic instability important for tumorigenesis. Consistent with this notion, we found that Pin1 overexpression is closely associated with Rb hyperphosphorylation in human breast cancer biopsies, suggesting an important pathological role for Pin1-Rb signaling in cancer development [17].

In summary, our studies demonstrate that Pin1 is a critical regulator of Rb activity (Figure 1). On one hand, Pin1 activates cyclin D1 to facilitate Rb hyperphosphorylation. On the other hand, Pin1 directly binds to Rb and inhibits PP2A-mediated Rb dephosphorylation in response toγ-irradiation. By both ways, hyperphosphorylated Rb loses its function in cell cycle control at G1-S transition and disrupts S-phase check point control.

Pin1-mediated regulation of Rb phosphorylation adds a fine switcher for the modulation of Rb function. This is consistent with a previous report that phosphorylation of Ser608/612 in Rb spacer domain facilitates Pin1-Rb binding and further boosting Rb phosphorylation at S780. Pin1 knockdown leads to G1 arrest and reduced proliferation rate in T98G glioblastoma cells [18]. Abnormally high expression of Pin1 accompanying with increased Rb phosphorylation was discovered in many types of tumors [17,19,20]. In the near future, major challenges will include a better understanding of the molecular regulation of Pin1-Rb signaling in response to physiological and pathological growth stimuli, and more comprehensive studies investigating Pin1-Rb signaling in governing cellular proliferation, apoptosis, senescence and differentiation.

Acknowledgement

This work was supported by the National Key Basic Research Program (973 Program) of China (2012CB910700).

References

1. Finn G, Lu KP (2008) Phosphorylation-specific prolyl isomerase Pin1 as a new diagnostic and therapeutic target for cancer. Curr Cancer Drug Targets 8: 223-229.
2. Yaffe MB, Schutkowski M, Shen M, Zhou XZ, Stukenberg PT, et al. (1997) Sequence-specific and phosphorylation-dependent proline isomerization: a potential mitotic regulatory mechanism. Science 278: 1957-1960.
3. Lu KP, Finn G, Lee TH, Nicholson LK (2007) Prolyl cis-trans isomerization as a molecular timer. Nat Chem Biol 3: 619-629.
4. Litchfield DW, Shilton BH, Brandl CJ, Gyenis L (2015) Pin1: Intimate involvement with the regulatory protein kinase networks in the global phosphorylation landscape. Biochim Biophys Acta 1850: 2077-2086.
5. Zhou XZ, Lu KP (2016) The isomerase PIN1 controls numerous cancer-driving pathways and is a unique drug target. Nat Rev Cancer 16: 463-478.
6. Liou YC, Ryo A, Huang HK, Lu PJ, Bronson R, et al. (2002) Loss of Pin1 function in the mouse causes phenotypes resembling cyclin D1-null phenotypes. Proc Natl Acad Sci U S A 99: 1335-1340.
7. Wulf GM, Ryo A, Wulf GG, Lee SW, Niu T, et al. (2001) Pin1 is overexpressed in breast cancer and cooperates with Ras signaling in increasing the transcriptional activity of c-Jun towards cyclin D1. EMBO J 20: 3459-3472.
8. Ryo A, Nakamura M, Wulf G, Liou YC, Lu KP (2001) Pin1 regulates turnover and subcellular localization of beta-catenin by inhibiting its interaction with APC. Nat Cell Biol 3: 793-801.
9. Saegusa M, Hashimura M, Kuwata T (2010) Pin1 acts as a modulator of cell proliferation through alteration in NF-kappaB but not beta-catenin/TCF4 signalling in a subset of endometrial carcinoma cells. J Pathol 222: 410-420.
10. Ma SL, Pastorino L, Zhou XZ, Lu KP (2012) Prolyl isomerase Pin1 promotes amyloid precursor protein (APP) turnover by inhibiting glycogen synthase kinase-3beta (GSK3beta) activity: novel mechanism for Pin1 to protect against Alzheimer disease. J Biol Chem 287: 6969-6973.
11. Zheng H, You H, Zhou XZ, Murray SA, Uchida T, et al. (2002) The prolyl isomerase Pin1 is a regulator of p53 in genotoxic response. Nature 419: 849-853.
12. Zacchi P, Gostissa M, Uchida T, Salvagno C, Avolio F, et al. (2002) The prolyl isomerase Pin1 reveals a mechanism to control p53 functions after genotoxic insults. Nature 419: 853-857.
13. Nishi M, Akutsu H, Masui S, Kondo A, Nagashima Y, et al. (2011) A distinct role for Pin1 in the induction and maintenance of pluripotency. J Biol Chem 286: 11593-11603.
14. Moretto-Zita M, Jin H, Shen Z, Zhao T, Briggs SP, et al. (2010) Phosphorylation stabilizes Nanog by promoting its interaction with Pin1. Proc Natl Acad Sci U S A 107: 13312-13317.
15. Burkhart DL, Sage J (2008) Cellular mechanisms of tumour suppression by the retinoblastoma gene. Nat Rev Cancer 8: 671-682.
16. You H, Zheng H, Murray SA, Yu Q, Uchida T, et al. (2002) IGF-1 induces Pin1 expression in promoting cell cycle S-phase entry. J Cell Biochem 84: 211-216.
17. Tong Y, Ying H, Liu R, Li L, Bergholz J, et al. (2015) Pin1 inhibits PP2A-mediated Rb dephosphorylation in regulation of cell cycle and S-phase DNA damage. Cell Death Dis 6: e1640.
18. Rizzolio F, Lucchetti C, Caligiuri I, Marchesi I, Caputo M, et al. (2012) Retinoblastoma tumor-suppressor protein phosphorylation and inactivation depend on direct interaction with Pin1. Cell Death Differ 19: 1152-1161.
19. Bao L, Kimzey A, Sauter G, Sowadski JM, Lu KP, et al. (2004) Prevalent overexpression of prolyl isomerase Pin1 in human cancers. Am J Pathol 164: 1727-1737.
20. Rizzolio F, Caligiuri I, Lucchetti C, Fratamico R, Tomei V, et al. (2013) Dissecting Pin1 and phospho-pRb regulation. J Cell Physiol 228: 73-77.