

Regulation of Skp2 levels by Pim-1 Protein Kinase

Jasmine Ooi

The Pim-1 protein kinase plays an important role in regulating both cell growth and survival and enhancing transformation by multiple oncogenes. The ability of Pim-1 to regulate cell growth is mediated, in part, by the capacity of this protein kinase to control the levels of the p27, a protein that is a critical regulator of cyclin-dependent kinases that mediate cell cycle progression. To understand how Pim-1 is capable of regulating p27 protein levels, we focused our attention on the SCF^{Skp2} ubiquitin ligase complex that controls the rate of degradation of this protein. We found that expression of Pim-1 increases the level of Skp2 through direct binding and phosphorylation of multiple sites on this protein. Along with known Skp2 phosphorylation sites including Ser⁶⁴ and Ser⁷², we have identified Thr⁴¹⁷ as a unique Pim-1 phosphorylation target. Phosphorylation of Thr⁴¹⁷ controls the stability of Skp2 and its ability to degrade p27. Additionally, we found that Pim-1 regulates the anaphase-promoting complex or cyclosome (APC/C complex) that mediates the ubiquitination of Skp2. Pim-1 phosphorylates Cdh1 and impairs binding of this protein to another APC/C complex member, CDC27. These modifications inhibit Skp2 from degradation. Marked increases in Skp2 caused by these mechanisms lower cellular p27 levels. Consistent with these observations, we show that Pim-1 is able to cooperate with Skp2 to signal S phase entry. Our data reveal a novel Pim-1 kinase-dependent signaling pathway that plays a crucial role in cell cycle regulation.

紹介論文

Regulation of Skp2 levels by Pim-1 Protein Kinase

Cen. B, et. al. & Kraft, AS. (Medical University of South Carolina, Wake Forest University School of Medicine, North Carolina, University of California)

JBC, 285, 29128-29137 (2010)

要旨

Studies have identified that Pim-1 kinase regulates Skp2 levels through the Pim-1 kinase activity, reduces APC/C^{Cdh1} E3 ligase activity and thus protects Skp2 from degradation. The Pim-1 protein kinase is abnormally elevated in human cancers, regulated by growth factors, and collaborates with other oncogenes to induce cell transformation. The ability of this enzyme to modulate the activity of both the SCF^{Skp2} and APC/C^{Cdh1} and thus control p27 levels is likely to be essential to the biological activities of this protein kinase.

参考論文

A small molecule inhibitor of Pim-1 protein kinases blocks the growth of precursor T-cell lymphoblastic leukemia/lymphoma

Blood, 115, 824-833 (2009)