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HIGHLIGHT

PHLPP phosphatase: a key mediator integrating multiple signaling pathways

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Cellular responses to bacterial or viral infections and to stress require rapid and accurate transmission of signals from cell-surface receptors to the nucleus (Karin and Hunter, 1995). These signaling pathways, relying on extensive protein phosphorylation events, lead to the activation of specific transcription factors that induce the expression of appropriate target genes. Among the activated transcription factors, nuclear factor κB (NF-κB) is essential for inflammation, immunity, cell proliferation and apoptosis. NF-κB requires a signaling pathway for activation. Such NF-κB-activating pathways can be triggered by a variety of extracellular stimuli, which lead to the phosphorylation and subsequent proteasome-mediated degradation of inhibitory molecules, the inhibitor of NF-κB (IκB) proteins (Karin and Ben-Neriah, 2000). Activated NF-κB migrates into the nucleus to regulate the expression of multiple target genes.

Two distinct NF-κB-activating pathways have emerged. The classical pathway is triggered by pro-inflammatory cytokines such as tumor necrosis factor α (TNFα) and leads to the sequential recruitment of various adaptors. This is followed by the recruitment and activation of the classical IκB-kinase (IKK) complex (Devin et al., 2000), which includes the scaffold protein NF-κB essential modulator (NEMO; also named IKKγ) (Yamaoka et al., 1998), IKKα and IKKβ kinases (Zandi, 1997). The alternative pathway is NEMO-independent and triggered by cytokines such as lymphotoxin β (Dejardin et al., 2002), B cell activating factor (BAFF) (Claudio et al., 2002) or the CD40 ligand (Coope et al., 2002) and by some viruses (Eliopoulos et al., 2003). This non-canonical signaling pathway relies on the recruitment of TNF receptor associated factor (TRAF) proteins to the membrane and on the NF-κB-inducing kinase (NIK) (Xiao et al., 2001), which activates an IKKα homodimer containing and inhibitory molecule p100 (Senftleben et al., 2001). Once phosphorylated by IKKα on specific serine residues located in both the N- and C-terminal regions (Xiao et al., 2004), p100 is ubiquitinated and cleaved to generate the NF-κB protein p52, which moves as heterodimer with RelB into the nucleus.

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In both cases, phosphorylation of the proteins in the circuits is essential for the activation of NF-κB. Dozens of kinases have been identified to be involved in the phosphorylation of the components in the pathway. However, the roles of phosphatases in NF-κB signaling remain less defined.

In this issue of *Frontiers in Biology*, an article by Wang and Zhang entitled “RNAi screen to identify protein phosphatases (PPs) that regulate the NF-κB signaling” applies a large-scale RNAi approach to identify PPs that regulate NF-κB activities. They found that PH domain leucine-rich repeat protein phosphatase (PHLPP) plays a critical role in TNFα-stimulated NF-κB transcriptional activation. Unexpectedly, this critical role is not achieved by the well-known mechanism of enhancing NF-κB/p65 nuclear import and retention. Instead, PHLPP promotes TNFα-induced phosphorylation at Ser276 on NF-κB/p65, indicating that PHLPP activates NF-κB pathway through a novel pathway. More intriguingly, knock-down of two important serine/threonine kinases, PKCα and Akt1, which are known targets of PHLPP (Brognard and Newton, 2008), drastically reduces the phosphorylation at Ser276 of NF-κB/p65. The results together suggest that PKC/Akt signaling pathways are communicated to NF-κB/p65 signaling through critical serine phosphorylation, among which PHLPP plays a key role. These findings highlight a highly integrated signaling network in cells that probably communicates signals to their destinations through various circuits, which may be more capable than our current transportation network.

References

Brognard J, Newton A C (2008). PHLiPPing the switch on Akt and protein kinase C signaling. Trends Endocrinol Metab, 19(6): 223–230

Claudio E, Brown K, Park S, Wang H, Siebenlist U (2002). BAFF-induced NEMO-independent processing of NF-kappa B2 in maturing B cells. Nat Immunol, 3(10): 958–965

Coope H J, Atkinson P G P, Huhse B, Belich M, Janzen J, Holman M J, Klaus G G B, Johnston L H, Ley S C (2002). CD40 regulates the processing of NF-kappaB2 p100 to p52. EMBO J, 21(20): 5375–5385

Dejardin E, Droin N M, Delhase M, Haas E, Cao Y, Makris C, Li Z W, Karin M, Ware C F, Green D R (2002). The lymphotoxin-beta receptor induces different patterns of gene expression via two NF-kappaB pathways. Immunity, 17(4): 525–535

Devin A, Cook A, Lin Y, Rodriguez Y, Kelliher M, Liu Z (2000). The distinct roles of TRAF2 and RIP in IKK activation by TNF-R1: TRAF2 recruits IKK to TNF-R1 while RIP mediates IKK activation. Immunity, 12(4): 419–429

Eliopoulos A G, Caamano J H, Flavell J, Reynolds G M, Murray P G, Poyet J L, Young L S (2003). Epstein-Barr virus-encoded latent infection membrane protein 1 regulates the processing of p100 NF-kappaB2 to p52 via an IKKgamma/NEMO-independent signalling pathway. Oncogene, 22(48): 7557–7569

Karin M, Ben-Neriah Y (2000). Phosphorylation meets ubiquitination: the control of NF-[kappa]B activity. Annu Rev Immunol, 18: 621–663

Karin M, Hunter T (1995). Transcriptional control by protein phosphorylation: signal transmission from the cell surface to the nucleus. Curr Biol, 5(7): 747–757

Senftleben U, Cao Y, Xiao G, Greten F R, Krähn G, Bonizzi G, Chen Y, Hu Y, Fong A, Sun S C, Karin M (2001). Activation by IKKalpha of a second, evolutionary conserved, NF-kappa B signaling pathway. Science, 293(5534): 1495–1499

Xiao G, Fong A, Sun S C (2004). Induction of p100 processing by NF-kB-inducing kinase involves docking IkB kinase a (IKKa) to p100 and IKKamediated phosphorylation. J Biol Chem, 279: 30099–30105

Xiao G, Harhaj E W, Sun S C (2001). NF-kappaB-inducing kinase regulates the processing of NF-kappaB2 p100. Mol Cell, 7(2): 401–409

Yamaoka S, Courtois G, Bessia C, Whiteside S T, Weil R, Agou F, Kirk H E, Kay R J, Israël A (1998). Complementation cloning of NEMO, a component of the IkappaB kinase complex essential for NF-kappaB activation. Cell, 93(7): 1231–1240

Zandi E, Rothwarf D M, Delhase M, Hayakawa M, Karin M (1997). The IkB kinase complex (IKK) contains two kinase subunits, IKKa and IKKb, necessary for IkB phosphorylation and NF-kB activation. Cell, 91: 243–252