PI3K-PKB/Akt Pathway

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Cold Spring Harbor Perspectives in Biology

Identification of the phosphoinositide-3-kinase–protein kinase B/Akt (PI3K-PKB/Akt) pathway and activating receptor tyrosine kinases (RTKs) began in earnest in the early 1980s through vigorous attempts to characterize insulin receptor signaling (for review, see Alessi 2001; Brazil and Hemmings 2001). These humble beginnings led to the identification of the components and mechanism of insulin receptor signaling via insulin receptor substrate (IRS) proteins to PI3K and consequent PKB/Akt-mediated activation by 3-phosphoinositide-dependent protein kinase 1 (PDK1). With the discovery of the potent contribution of PI3K and PKB/Akt activation to tumorigenesis, intense research into the regulation of this pathway led to the discovery of the negative regulators, the protein phosphatase 2 (PP2A), phosphatase and tensin homolog (PTEN), and the PH-domain leucine-rich-repeat-containing protein phosphatases (PHLPP1/2). More recently, the elusive PKB/Akt hydrophobic motif kinases—i.e., the mammalian target of rapamycin (mTOR), when associated with the mTOR complex 2 (mTORC2), and the DNA-dependent protein kinase (DNA-PK)—were identified, as was the ability of Ras to affect the PI3K-PKB/Akt pathway via PI3K, completing our current model of the PI3K-PKB/Akt pathway.

The PI3K-PKB/Akt pathway is highly conserved, and its activation is tightly controlled via a multistep process (as shown in Fig. 1) Activated receptors directly stimulate class 1A PI3Ks bound via their regulatory subunit or adapter molecules such as the insulin receptor substrate (IRS) proteins. This triggers activation of PI3K and conversion by its catalytic domain of phosphatidylinositol (3,4)-bisphosphate (PIP_2) lipids to phosphatidylinositol (3,4,5)-trisphosphate (PIP_3). PKB/Akt binds to PIP_3 at the plasma membrane, allowing PDK1 to access and phosphorylate

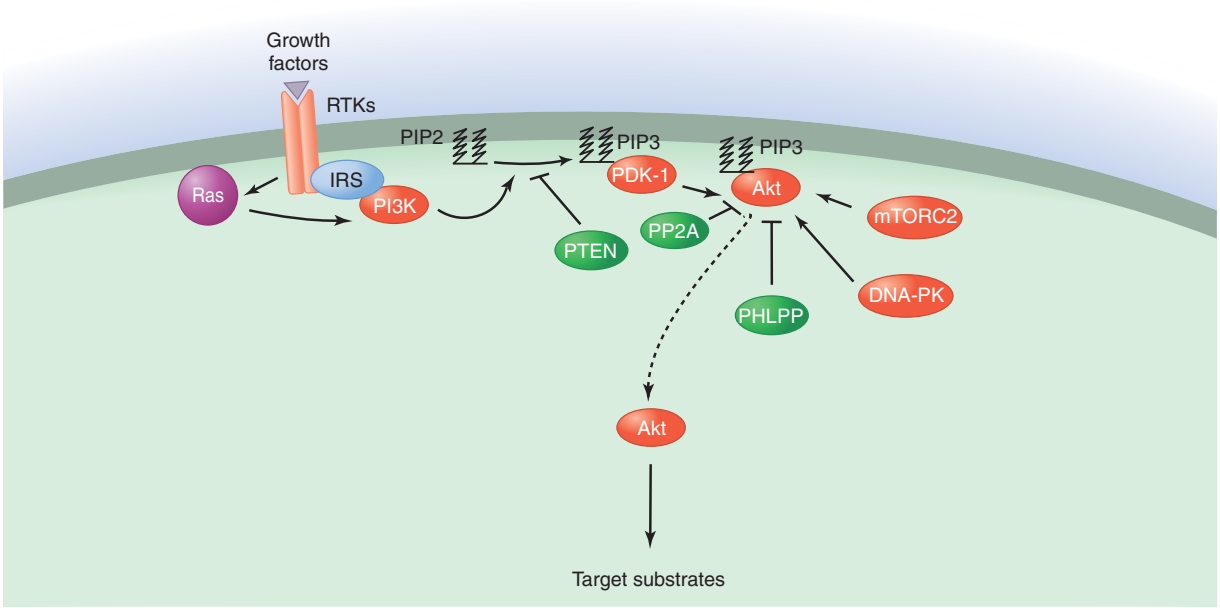

Figure 1. PKB/Akt activation downstream of RTKs via the P13K pathway.

Editors: Lewis Cantley, Tony Hunter, Richard Sever, and Jeremy Thorner
Additional Perspectives on Signal Transduction available at www.cshperspectives.org

 doi: 10.1101/cshperspect.a011189
Cite this article as *Cold Spring Harb Perspect Biol* 2012;4:a011189

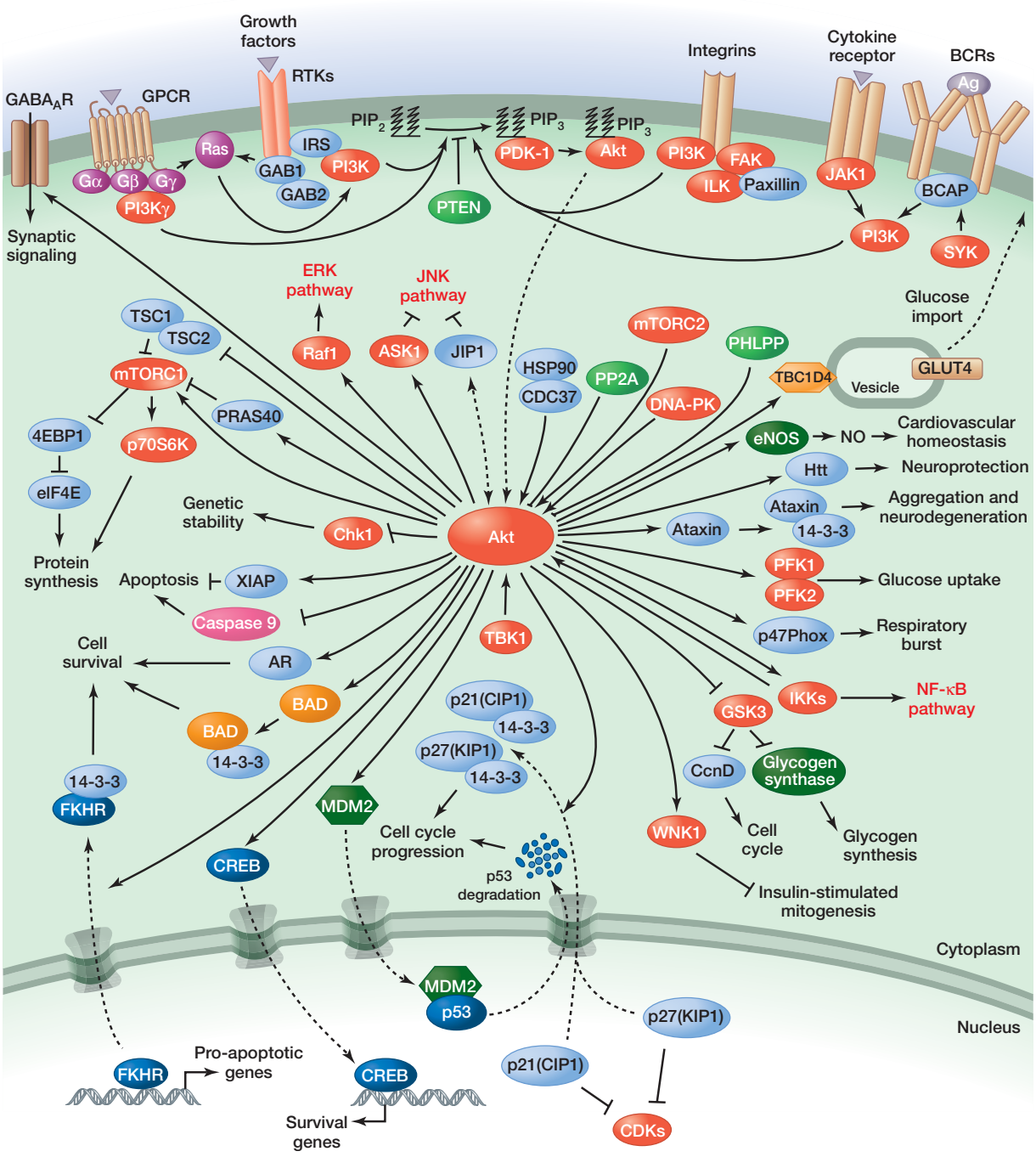

Figure 2. Signalling events activating PKB/Akt and cellular functions regulated by PKB/Akt.

T308 in the "activation loop," leading to partial PKB/Akt activation (Alessi et al. 1997). This PKB/Akt modification is sufficient to activate mTORC1 by directly phosphorylating and inactivating proline-rich Akt substrate of 40 kDa (PRAS40) and tuberous sclerosis protein 2 (TSC2) (Vander Haar et al. 2007). mTORC1 substrates include the eukaryotic translation initiation factor 4E binding protein 1 (4EBP1), and ribosomal protein S6 kinase, 70 kDa, polypeptide 1 (S6K1), which, in turn, phosphorylates the ribosomal protein S6 (S6/RPS6), promoting protein synthesis and cellular proliferation.Figure 1.

Phosphorylation of Akt at S473 in the carboxy-terminal hydrophobic motif, either by mTOR (Sarbassov et al. 2005) or by DNA-PK (Feng et al. 2004), stimulates full Akt activity.

Full activation of Akt leads to additional substrate-specific phosphorylation events in both the cytoplasm and nucleus, including inhibitory phosphorylation of the pro-apoptotic FOXO proteins (Guertin et al. 2006). Fully active PKB/Akt mediates numerous cellular functions including angiogenesis, metabolism, growth, proliferation, survival, protein synthesis, transcription, and apoptosis (as shown in Fig. 2). Dephosphorylation of T308 by PP2A (Andjelković et al. 1996), and S473 by PHLPP1/2 (Brognard et al. 2007), and the conversion of PIP_3 to PIP_2 by PTEN (Stambolic et al. 1998) antagonize Akt signaling.Figure 2.

Figures adapted, with kind permission, from Cell Signaling Technology (http://www.cellsignal.com.)

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Cold Spring Harb Perspect Biol 2012; doi: 10.1101/cshperspect.a011189