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Mini Review

Akt and p53R2, partners that dictate the progression and invasiveness of cancer

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ABSTRACT

The serine/threonine kinase or the so-called "Akt" is a key regulatory molecule of signaling pathway that regulates various cellular processes. Many intracellular proteins are involved in the activation or inhibition of Akt signaling and the hyperactivation of Akt signaling pathway is found to be frequently involved in various types of human cancers. Furthermore, while p53R2, a p53-inducible peptide involved in the synthesis of dNTPs normally works toward suppression of cancer through elimination of reactive oxygen species (ROS), inhibition of MAPK/ERK pathway and providing dNTPs for DNA repair, the overexpression of p53R2 is reported to be associated with cancer progression and resistance to therapy. In this review article, we will discuss the situation in which cancer cells with hyperactive PI3K/Akt signaling can recruit p53R2 in favor of cancer progression and resistance to therapy. In the hyperactive state of PI3K/Akt signaling (which happens in the absence of deactivation or excess of activation), p53R2 can be used by cancer cells to promote proliferation. Therefore, the hyperactivity of PI3K/Akt pathway and elevated levels of p53R2 can give rise to highly invasive cancers.

Contents

1. PI3K/Akt signaling pathway

The serine/threonine kinase (Akt), also known as protein kinase B (PKB) is a key player of signaling pathways which regulates multiple cellular processes, such as cell growth/size and survival/death as well as tissue invasion and angiogenesis. Full activation of Akt is dependent on the phosphorylation in two regulatory residues (Ser-473 and Thr-308) by various kinases [1,2].

Phosphorylation of Akt is mediated through several mechanisms and mainly by the binding of specific ligands to their receptors at the cell surface (Fig. 1). Most common ligands include growth factors, hormones, cytokines and signals derived from receptors for extracellular matrix molecules such as integrins that upon binding to their receptors, phosphorylate Akt by triggering the activation of the phosphatidylinositol 3-kinase (PI3K) [3,4].

PI3K is a lipid kinase and contains two subunits, p85, a regulatory subunit, and p110, a catalytic subunit [5]. In the absence of stimuli, the p85 subunit inhibits the activity of p110 by binding to its catalytic site. After binding of ligands to the receptor, p85 is attracted to receptors, the p110 inhibition is lost and finally PI3K is activated [6]. Moreover, in a p85-independent manner,

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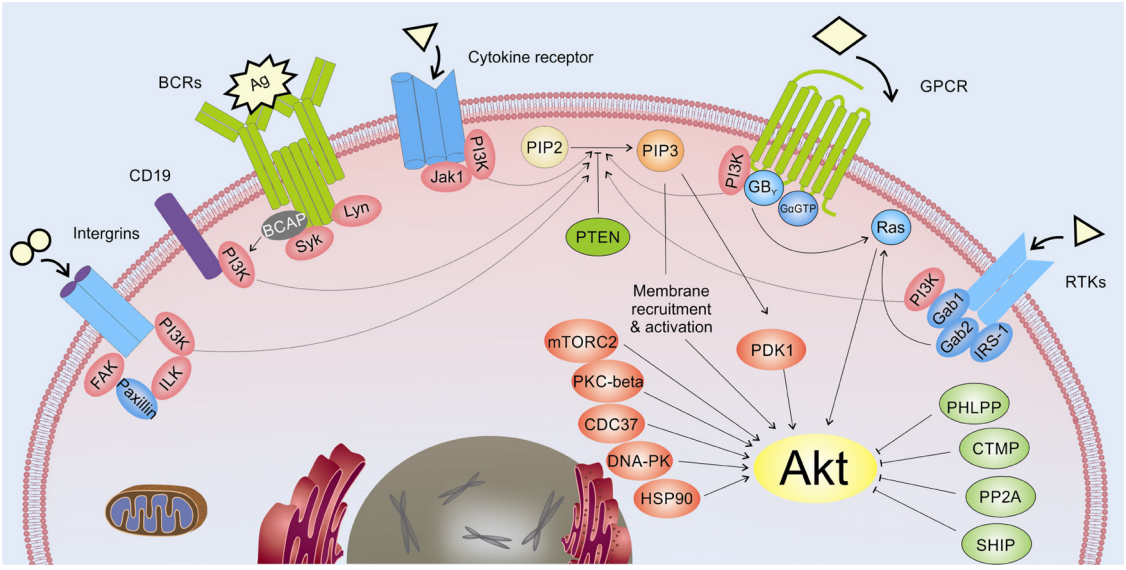

Fig. 1. Akt activation and/or inhibition mechanisms: Upon binding to RTK, growth factors induce the auto-phosphorylation of tyrosine residues on the intracellular domain of the receptor. The binding of PI3K to the phosphorylated receptor induces conformational changes in the catalytic domain of PI3K and eventuates in Akt activation. Other receptors such as GPCRs, Janus kinase- (1JAK1), integrins and B-cell receptors (BCR in B cells) also have the potential to activate PI3K by binding to their ligands. Afterwards, PI3K phosphorylates membrane bounded PIP2 to PIP3. The subsequent binding of PIP3 to Akt, results in kinase activation. Ras, while DNA-PK, CDC37 (cell division cycle-37), HSP90 (heat shock protein-90KD) and PKC-beta (protein kinase C-beta) as well as a variety of cellular stresses also phosphorylate Akt, PTEN (phosphatase and tensin homolog), SHIP (SH2-containing inositol phosphatase), protein phosphatase 2A (PP2A) and CTMP (carboxyl-terminal modulator protein) suppress Akt activity.

Ras can interact with RBD (Ras-binding domain) of p110 subunit that results in its tethering to cell membrane and subsequent activation [7]. Activated PI3K converts phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-tri-phosphate (PIP3), a second messenger, which in turn recruits adaptor and effector proteins containing a Pleckstrin homology (PH) domain, such as Akt and phosphoinositide-dependent kinase-1 (PDK1) to the plasma membrane. After correct localization of Akt at the membrane via binding of PIP3, Akt can be phosphorylated by activating kinases, PDK1 (at Thr-308) and/or the mammalian target of rapamycin complex 2 (mTORC2) (at Ser-473) [4,8,9]. Akt can also be activated in response to many types of cellular stresses such as heat shock, hyperosmotic stress (limitation of blood flow and cell starvation), hypoxia (oxygen deficiency), UV irradiation and oxidative stress [10–13].

A counter-regulation by phosphatases has been revealed as an essential step to control PI3K signaling pathway. Phosphatase and tension homolog (PTEN) have a dual job as lipid and protein phosphatasing enzymes that negatively regulate Akt activation by dephosphorylation of the PIP3 at position 3 on the inositol ring [14]. The Akt activation can also be suppressed by other phosphatases such as SHIP-1 and SHIP-2 (Src homology domain-containing inositol phosphatases-1 and 2). These phosphatases are capable of removing the 5-phosphate from PIP_3 to yield PIP_2 [15]. On the other hand, there are many studies that show protein phosphatase 2A (PP2A), CTMP (carboxyl-terminal modulator protein) and PHLPP isoforms (PH domain and leucine rich repeat protein phosphatases) can also down-regulate Akt function [16–18].

Activation of Akt signaling pathway (Fig. 2) is found to be frequently involved in various types of human cancers [19]. The induction of Akt pathway provides cells with a survival signal that supports them to withstand the apoptotic stimuli. Akt also inhibits the pro-apoptotic factors BAD and procaspase-9 by their phosphorylation [20]. Besides, Akt phosphorylates and inactivates the FoxO, a transcription factor involved in expression of the pro-apoptotic genes, such as the Fas ligand gene [21]. Akt also activates IkB kinase (IKK), a positive regulator of NF-kB by direct or indirect phosphorylation of IKK inhibitor, which results in inactivation of NF-kB with subsequent transcription of anti-apoptotic genes [22]. Another role of Akt against apoptosis is phosphorylation and localization of MDM2 to the cell nucleus, where it mediates degradation of p53 and thereby antagonizes p53-mediated cell cycle checkpoints [23]. Akt activation promotes cell cycle progression by inhibition of the glycogen synthase kinase 3 (GSK3) activity. GSK3 phosphorylates and targets cyclin D for proteasomal degradation. Thus, inhibition of GSK3 by Akt leads to the accumulation of cyclin D [24]. Moreover, Akt directly or indirectly reverses the function of the cell cycle inhibitors $p21^{Waf1/cip1}$ and $p27^{Kip1}$ by phosphorylating them and brings about the cytoplasmic retention of these proteins [25]. Akt also phosphorylates and down-regulates Myt1 and Wee1 kinases

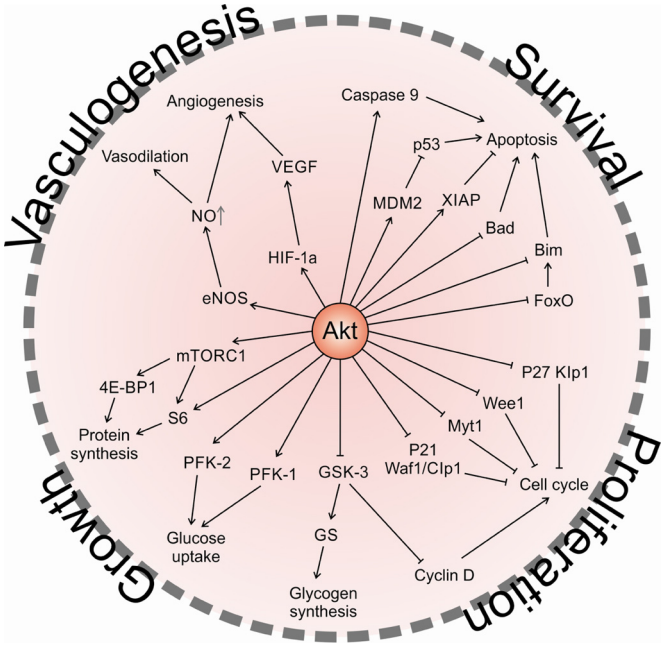

Fig. 2. Akt signal transduction pathway.