

Minireview Article

Upstreaming and downstreaming regulators and regulations of AKT/PKB: A molecular gateway to developmental carcinoma

Abstract

AKT or protein kinase B, the serine/threonine-specific protein kinase, is found in three analogous isoforms in cells of human and animal body. AKT is regulated and activated via various upstream regulators including GPCR (G protein-coupled receptor), RTK (Receptor tyrosine kinase), SYK (spleen tyrosine kinase), JAK (Janus kinase), and RAS lead to the further activation of multiple coordinated downstream cascades. The dysregulation of these pathways affects the cell cycle and cell proliferation, resulting in the development of carcinoma. Therefore, the study aimed with the objectives to explore all the major upstreaming and downstreaming regulators and signaling pathways of AKT as an approach for further detailed studies or clinical management of tumors or cancers.

Keywords: AKT signaling; AKT signal transduction; downstream regulators; developmental carcinoma; upstream regulators.

1. Introduction

Cancer is one of the most fatal diseases for both humans and animals in the present world. According to the global cancer statistics 2020, 2.21 million people were affected by lung cancer, 2.26 million by breast cancer, 1.93 million by colorectal, 1.41 million by prostate cancer, 1.20 million by skin cancer (non-melanoma) and 1.09 million in stomach cancer in 2020 (WHO, 2020). Cancer was the prime cause of death worldwide among the other deadly diseases in 2020, responsible for around 10 million deaths (WHO, 2020). The number was 0.4 million less in 2018 (9.6 million), exhibiting a rate of growth (WHO, 2019). The deaths from cancer are also anticipated to increase by 72% by 2030, reaching 13 million (IARC, 2022).

Comment [MF 1]: I suggest to support the introduction with additional references that clear the recent work in AKT genetically and biochemically in various type of cancers

AKT kinases are a group of cell signaling molecules responsible for the regulation of the cell cycle, cell survivability, metabolism, and proliferation[1]. AKT had been found to be linked to nearly 40% of prostate, ovarian, breast, and gastric cancers. Dysregulation of AKT upstream and downstream regulators including PI3K, PTEN, Receptor Tyrosine Kinases, NF κ B, MDM2, Foxo, mTOR, Nur77, and others as well as their signaling transduction pathways cause the misproportion of cell proliferation and apoptosis [2]–[8].

Therefore, the study aimed with the objectives to explore all the major regulators and associated signaling pathways of AKT/PKB as an approach for more advanced studies or better clinical management for developmental carcinoma.

2. AKT/PKB and its associated upstreaming regulators and regulations

AKT or Protein Kinase B can be found in several isoforms such as AKT1/ PKB α , AKT2/ PKB β , AKT3/ PKB γ and biochemically consists of pleckstrin homology (PH) domain, a short glycine-rich region, catalytic domain (CD) and regulatory domain (RD)[9]. CD is located at the center of the protein while PH domain is located at N-terminus and RD at C-terminus. The PH domain has the potential to bind with phosphatidylinositol-3,4,5-triphosphate (PIP3) for its unique biochemical configuration. Considering the first isoform of AKT having two phosphorylation sites (T308 and S473), one is placed at CD and another in RD whereas T309 at CD and S474 at RD for AKT2, and T305 at CD, and S472 at RD for AKT3[10], [11].

2.1 GPCRs (G-Protein Coupled Receptors) and PI3K/AKT regulation

GPCRs are the largest protein family involved in several signal transduction pathways by coupling with a variety of ligands. GPCRs consist of seven transmembrane (TM) segments including TM1, TM2, TM3, TM4, TM5, TM6, TM7, that provide three extracellular loops (ECL1, ECL2, and ECL3) and three intracellular loops (ICL1, ICL2, and ICL3)[12]. It has an N (amino) terminus outside the cell and a C (carboxyl) terminus inside the cell. Signals are passed inside the cell with the help of a heterotrimeric G protein consisting of three subunits, alpha, beta, and gamma respectively. GPCRs can facilitate intracellular signaling using both G α and G $\beta\gamma$ subunits. Accordingly, G $\beta\gamma$ subunits can interact with and regulate PI3K, a kinase possessing either p110 β or p110 γ subunits[13]. Activation of PI3K then activates AKT and other AKT-induced downstreaming regulators. On the other hand, G α

was found to regulate PI3K/AKT through multiple intermediate receptor transduction pathways including which involves RTKs, integrins, and other growth factor receptors[13]–[15].

2.2 RTK (Receptor Tyrosine Kinase) and AKT regulation

RTK is also a transmembrane receptor with an extracellular domain and intracellular tyrosine kinase domain. The extracellular domain is responsible for binding to various ligands whereas, the intracellular domain functions as a kinase catalytic site [16].

The binding of ligands to the extracellular domain of two neighboring RTKs leads to the dimerization, and phosphorylation of the intracellular domain. The regulatory subunit P85 of PI3K then binds to the phosphorylated tyrosine residue on the activated receptor using its SH2 domain and recruits the catalytic subunit p110 to form PI3K. Since PI3K is conjugated with the subunits and activated, it turns PIP2 into PIP3 which further recruits AKT. Several membrane-bound proteins then phosphorylate the residues of AKT to activate it. PDK1 phosphorylates at threonine-308 residue while PDK2 and PDK3 phosphorylate Serine- 473 to make it completely functional. In addition, activated RAS induced by growth factor binding to RTK is another upstream regulator of AKT[17].

2.3 JAK (Janus Kinase)

Since the ligand binds to the Cytokine receptor, JAK induces phosphorylation to the receptor. SH2 domain-containing proteins including Grb2 or PI3K then attach to the phosphorylated receptor[18]. PI3k activation makes AKT functional and poses sequential cascades[19].

2.4 RAS

Another upstream regulator of AKT is activated RAS caused by growth factor binding to RTK[20].

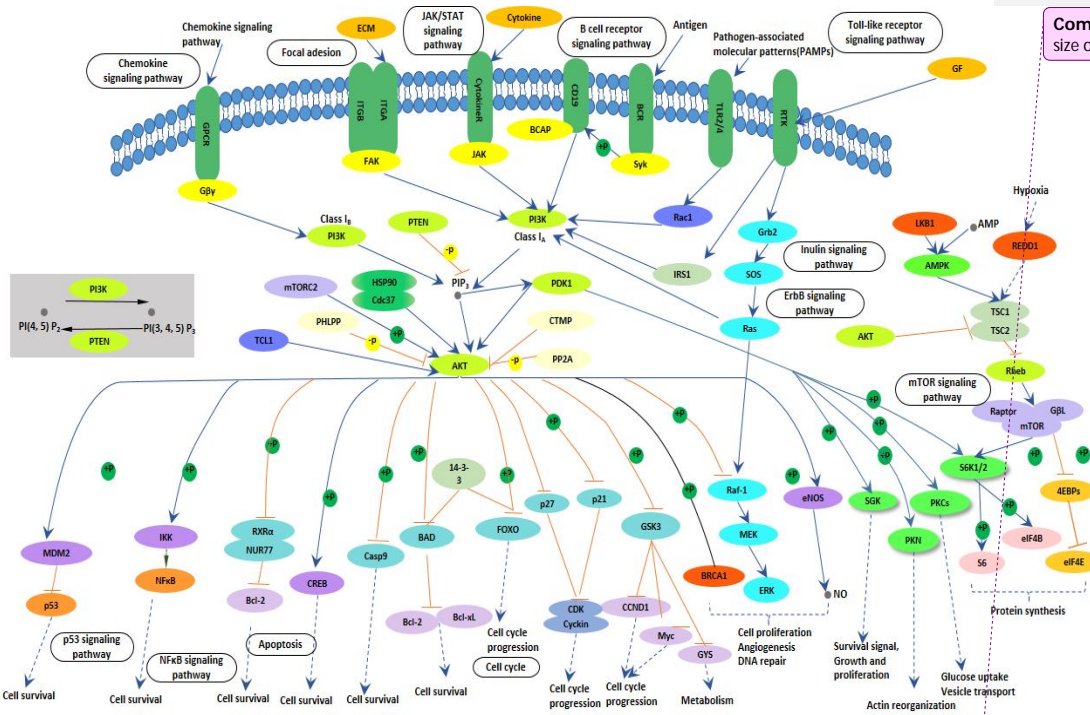


Figure 1. Upstreaming and downstreaming regulators and regulations of AKT [48]

3. Downstreaming regulators and regulations

3.1 Caspase cascades ceasing

AKT phosphorylates several caspases or cysteine-aspartate proteases as well as pro-apoptotic factors and allows those regulatory biomolecules to turn off [21]. Caspase-3 an effector protein of activated caspase-9 and caspase-8 is the promoter for ROS production [22]. Caspase-3 inactivation via AKT downstreaming leads to the ceasing of caspase cascades and apoptosis [23], [24].

3.2 IκB/ NFκB ceasing

Heterodimer of p50 and RelA or NFκB conjugating to IκBα remains inactivated in the cytosol. Several extracellular signals via cellular receptors activate the IκB kinase (IKK) leading to the phosphorylation of IκBα resulting in ubiquitination and dissociation from NFκB [25]. Being a transcription factor, NFκB binds to a specific domain of downstreaming DNA and alter cellular functions to expedite apoptotic

degradation of cell. AKT phosphorylates several NF κ B inhibitors, degrades them, promotes cell survivability, and eventually induces carcinogenesis[26].

3.3 AKT-WNK-SPAK-TGF induced carcinogenesis

WNK (lysine deficient protein kinase 1) is an upstream and downstream regulator of PI3K/AKT pathway that affects AKT-mediated angiogenesis. The core configuration of the WNK pathway is the activated WNK kinases that phosphorylate and stimulate two major downstream substrate kinases OSR1 (oxidative stress-responsive kinase) and SPAK (Ste20/SPS1-related proline alanine-rich kinase)[27]. Through both OSR1/SPAK-dependent and independent cellular reactions, WNK signaling transduction controls a number of ion channels as well as indirect carcinogenesis[28]. The TGF-signaling pathway is directly inhibited by WNKs, although OSR1 and SPAK can induce TGF-signaling via Smad2/3 activation. Activated SPAK has a co-regulatory effect on NF- κ B signaling pathways which is also correlated to carcinogenesis^[29,48]. Nonetheless, several studies identified both tumor-suppressing and promoting effects of TGF- β in different cancer cells. TGF- β is a strong inducer of developmental arrest in initial carcinogenesis as well as benign epithelia. TGF- β signaling pathways, however, are profoundly downregulated in advanced malignancies. At advanced stages, it potentiates development and progression rather than preventing carcinogenesis [30].

3.4 AKT-CDK regulation

AKT modulates the expression of multiple substrates, including such p21^{waf1}, p27^{kip1}, cyclin D, c-Myc, GSK-3 β , cyclin D1, and FKHL1 or phosphorylates them directly to control cellular proliferation at the G1-Synthesis and G2-Mitotic phases[31], [32]. However, none of the downstream regulators of AKT were documented to affect the Synthesis-G2 phase [33]. AKT phosphorylates several CDKs (CDK family of Ser/Thr kinases) and assists in binding to several cyclin proteins to activate kinase activities and cell development and proliferation. The over-expression of AKT-CDK activities lead to carcinogenesis[34].

3.5 AKT-MDM2-p53 and carcinogenesis

Studies conducted in vitro have found that MDM2 (murine double minute 2) phosphorylation as downstream regulator of AKT at Ser166 and/or Ser186 facilitate the translocation of MDM2 to the

nucleus and diminishes p53-associated gene transcription[31]. The biochemically structured COOH terminus containing RING finger domain with zinc moiety of MDM2 possesses a p53-specific E3 ubiquitin ligase activity[35]. MDM2 predominantly modifies the COOH terminus of p53's lysine residues using monoubiquitin tagging for p53 monoubiquitin catalyzation. Most endogenous MDM2 dimerizes to the transcriptional co-regulator p300/CREB binding protein (CBP), and p53 ubiquitination is initiated in the nucleus. p300/MDM2 dimer has the potentiality for p53 polyubiquitination, whereas MDM2 alone can commence only p53 monoubiquitination in vitro. Thus p300/MDM2's E3 and E4 ubiquitin ligase activities assist in the reduction of p53 in the nucleus and the progression of carcinogenesis [36].

3.6 AKT-Nur77 downstreaming

Many prospective co-regulators and downstream regulators including genomic and nongenomic cascades can participate in the regulation of cancer development across Nur77. In some stages of molecular interactions, Considering genomic cascades, Nur77 was found to be acted as a promoter for NF κ B and p53 transcription[37]. AKT phosphorylates Nur77 in an inhibiting manner to suppress its activity that assists in carcinogenesis [38].

3.7 AKT and BCL 2 inhibition

AKT inhibits several downstreaming proteins belonging to the pro-apoptotic Bcl-2 family including forkhead transcriptional activators, Bad (BCL 2 associated with death promoter), and CREB (cyclic AMP response element-binding protein), and so forth by preventing the structural alterations[39]. Apoptotic regulatory signals enhance the pro-apoptotic proteins from the Bcl-2 family translocation from the cytoplasm to the membrane of mitochondria which results in sequential mitochondrial malfunctioning and exclusions of different degradable enzymes. The conformational changes turn the BCL-2 proteins to activate, translocate to the mitochondrial membrane and disrupt mitochondrial membrane integrity[40].

3.8 AKT-mTOR downstreaming

mTOR (mammalian target of rapamycin) or FRAP1 (FK506-binding protein 12-rapamycin-associated protein 1), a serine/threonine protein kinase is a downstream regulatory molecule of AKT. AKT-mTOR is the most common regulating pathway found prevalently in several developmental carcinomas. mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) are two distinctive protein complexes containing other proteins with a core mTOR that lead to unique intracellular regulating functional phenomena[41]. mTORC1 is constituted of the proteins mLST8, Raptor, Deptor and AKT substrate 40 (PRAS40) and activated via AKT inhibition to tuberous sclerosis 1/2 (TSC1/2). TSC1/2 is further constituted with a heterodimeric form of tuberin with hamartin and acts as a suppressor for carcinogenesis via the kinetic activity of RhebGTP, an upstream regulator of mTORC1[26]. AKT phosphorylation at serine 939 and threonine 1462 locations of TSC2 assist in inhibiting TSC1/2. In addition to that, phosphorylation of PRAS40 by AKT occurs at the same time which induces mTORC1 activation. mTORC1 interacts with and promotes the bimolecular activity of 40S ribosomal protein S6 kinase 1 (S6K1), HIF-1, and suppresses the eukaryotic initiation factor 4E binding protein (4EBP1) expression by conjugating with the larger subunits [42].

3.9 AKT-FoxO downstreaming

FOXO subfamily of forkhead transcriptional factors include FOXO4/AFX FOXO3a/FKHRL1, and FOXO1a/FKHR are phosphorylated and activated via downstreaming kinetic activity of AKT. These factors regulate apoptosis and cell cycling via acting upon Bcl-6, Fas ligand, Bim, and CKI p27^{KIP1} (cyclin-dependent kinase inhibitor) [43]. Phosphorylation of FOXO diminishes DNA binding potentiation and enhance the protein binding affinity 14-3-3. Accordingly, 14-3-3FOXO complexes then exerted from the nucleus, disrupt FOXO-dependent transcriptional activation for FKHRL1, FKHR, and AFX and arrest the cellular apoptotic mechanisms. Due to the altered bimolecular configuration of 14-3-3FOXO complexes, ubiquitination runs up that initiates a protein degrading mechanism[39]. For example, the binding of FOXO 1 to SKP 2 induces polyubiquitination and subsequent degradation by ubiquitin-proteasome systems (UPSs). Additionally, PTEN (phosphatase and tensin homolog deleted on chromosome 10 or MMAC1 or TEP1) loss due to

hyperactivation of upstreaming regulation increases AKT and FOXO blocking. Both of the pathways have interrelation with AKT and progressive carcinoma[44].

3.10 AKT-CDKs interactions

Cyclin-dependent kinases (CDKs) are one of the protein kinases families involved in influencing different stages of the cell cycle and thus regulating the cell cycle. Among the CDKs protein family, CDK4/6 and CDK2 are two of the most significant proteins that control the cell cycle. Resting cells undergo cellular proliferation upon several stimuli via upregulating D- and E-type cyclins throughout G1 phase in the cell cycle. D-type cyclin binding to CDK4/6 and E-type cyclin binding to CDK2 then translocate to the nucleus and are phosphorylated by the CAKs (CDK Activating Kinases). These potential complexes further phosphorylate several proteins such as p130 (RBL2), p107 (RBL1), and pRB (RB1) from the retinoblastoma family[45], [46]. The E2F transcription factors can trigger the transcriptions and expressions of specific genes that control the doorway of the cell cycle from G1 to S phase since pRB phosphorylation inhibits it from interacting with the E2F transcription factors. Cyclin-CDKs inhibitors minimize or completely inhibit the phosphorylation of cyclin-CDKs to other proteins or substrates.

CDK inhibitors are grouped into two major classes. The first group inhibitors including p19INK4D (CDKN2D), p15INK4B (CDKN2B), p18INK4C (CDKN2C), and p16INK4A (CDKN2A) block cyclin-D-CDK4/6 complexes and the second group inhibitors including p21 (CDKN1A), p27 (CDKN1B), p57 (CDKN1C) which are commonly known as kinase inhibitor proteins (KIPs) block cyclin-A-CDK and cyclin-E-CDK complexes[47]. However, some KIP proteins are also found as an inhibitor for cyclin-D-CDKs complexes. P27 and p21 are sustained in the cytoplasm due to phosphorylation mediated by AKT, prohibiting the potentiation of it from blocking CDK2 in the nucleus. The turning on of AKT-induced CDK2 phosphorylation then promotes and regulates developmental carcinoma.

4. Conclusion

Overexpression of any stimulus responsible for AKT activation or any mutation of the proteins for regulating upstream and downstream cascades are the prime causes of dysregulation of

AKT signaling pathways that lead to progressive carcinoma. Since AKT and its associated regulators are the root cause of developmental carcinoma, further studying of AKT signaling pathways in depth with their interrelations, and determining the precise role of all the regulators in the signaling transduction pathways will contribute to the establishment of more appropriate and tailored therapeutic approaches for the patients.

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Comment [MF3]: References require updating, the present of recentness is 22.9 % only

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