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Upstreaming and Downstreaming Regulators and Associated Signaling Transduction Pathways of AKT/PKB: A Molecular Gateway to Progressive Carcinoma

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Authors' contributions

This work was carried out in collaboration among all authors. Author AS designed and conceptualized the study, reviewed the literature, organized and wrote the final manuscript. Authors MHH and EI assisted in reviewing the literature and writing. Author MAA advised and revised the final manuscript. All authors read and approved the final manuscript for publication.

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Review Article

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ABSTRACT

AKT or Protein Kinase B, the serine/threonine-specific protein kinase, is found in three analogous isoforms in cells of human and animal bodies. 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

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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 associated signaling transduction pathways of AKT as an approach for further detailed studies or clinical management of tumors or cancers via targeted protein-based drug developments.

Keywords: AKT signaling; AKT signal transduction; downstream regulators; carcinoma development; 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).

AKT kinases are a group of cell signaling molecules responsible for the regulation of the cell cycle, cell survivability, metabolism, and proliferation [1]. By contributing to the angiogenesis and the staffing of inflammatory cytokines, the AKT signaling pathways also play vital roles in the progression of both tumors and cancers [2].

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, NFκB, MDM2, Foxo, mTOR, Nur77, and others as well as their signal transduction pathways causes the imbalance between cell proliferation and apoptosis [3]–[9].

In today's world, the establishment of multidrug resistance (MDR) and recurrence is one of the most critical challenges for the development and advancement of anticancer drugs [10]. Enhanced xenobiotic metabolic activity, high degree of drug efflux, growth regulators, expanded DNA repair potentiality, and hereditary variables (gene mutations, amplifications, and misepigenetic expressions are some of the leading underlying principles behind MDR [10]. In addition, using these medications poses a variety of pathophysiological alterations including decreased appetite, bowel problems, diarrhea, several haemopathies (e.g., anemia, thrombocytopenia, etc.), different neuropathies (such as delirium, depression, mood swing and so on), congestion, and many others [11]. As a consequence, researchers are mainly focusing on the development of immunotherapy, targeted protein-based drugs, and gene therapeutics. Targeting several upstream and downstream regulating proteins for AKT/PKB has become a central research area of potent anticancer drug developments. Moreover, the extensive research on AKT/PKB intracellular communication systems has recently prompted the discovery of several inhibitors for the related biomolecules. The identification of potent target inhibitors is very crucial for enhancing the longevity of cancer sufferers. Numerous AKT/PKB regulatory elements-binding blockers have been designed and discovered to this point; a few of which have already got approval for the clinical treatment and management of cancer patients [2].

Therefore, the study was aimed at exploring all the major regulators and associated signaling transduction pathways of AKT/PKB as an approach for more detailed insight and better clinical management of carcinoma development.

2. AKT/PKB AND ITS ASSOCIATED UPSTREAMING REGULATORS AND REGULATIONS

AKT or Protein Kinase B can be found in several isoforms such as AKT1/ PKBα, AKT2/ PKBβ, AKT3/ PKBϒ and biochemically consists of pleckstrin homology (PH) domain, a short glycine-rich region, catalytic domain (CD) and regulatory domain (RD) [12]. 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 [13,14].

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) [15]. 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 Gα and GβϒY subunits. Accordingly, GβϒY subunits can interact with and regulate PI3K, a kinase possessing either p110β or p110ϒY subunits [16]. Activation of PI3K then activates AKT and other AKT-induced downstreaming regulators. On the other hand, Gα regulates PI3K/AKT through multiple intermediate receptor transduction pathways including RTKs, integrins, and other growth factor receptors [16–18].

2.2 RTK (Receptor Tyrosine Kinase) and AKT Regulation

RTK is also a transmembrane receptor that contains an extracellular domain and an intracellular tyrosine kinase domain. The extracellular domain is responsible for binding to various ligands whereas, the intracellular domain functions as a kinase catalytic site [19].

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 [20].

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 [21]. PI3K activation makes AKT functional and initiates sequential cascades [22].

2.4 RAS

Another upstream regulator of AKT is activated RAS caused by growth factor binding to diverse RTKs [23].

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 [24]. Caspase-3 an effector protein of activated caspase-9 and caspase-8 is the promoter for ROS production [25]. Caspase-3 inactivation via AKT downstreaming leads to the ceasing of caspase cascades and apoptosis [26,27].

3.2 IκB/ NFκB Ceasing

Heterodimer of p50 and RelA or NFκB (Nuclear factor kappa B) 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 [28]. 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 NFκB inhibitors, degrades them, promotes cell survivability, and eventually induces tumorigenesis or carcinogenesis [29].

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) [30]. Through both OSR1/SPAK-dependent and independent cellular reactions, WNK signaling transduction controls a number of ion channels as well as indirect carcinogenesis [31]. 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-κB signaling pathways which is also correlated to carcinogenesis [32,33]. Nonetheless, several studies identified both tumor-suppressing and promoting effects of TGF-β in different cancer cells. TGF-β is a strong inducer of progressive arrest in initial carcinogenesis as well as benign epithelia. TGF-β signaling pathways, however, are profoundly downregulated in advanced malignancies. At advanced stages, it triggers progression rather than prevention of tumorigenesis or carcinogenesis [34].

3.4 AKT-CDK Regulation

AKT modulates the expression of multiple substrates, including such $p21^{waf1}$, $p27^{kip1}$, cyclin D, c-Myc, GSK-3β, cyclin D1, and FKHRL1 or phosphorylates them directly to control cellular proliferation at the G1-Synthesis and G2-Mitotic phases [35,36]. However, none of the downstreaming regulators of AKT were documented to affect the Synthesis-G2 phase [37]. 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 leads to progressive carcinoma [38].

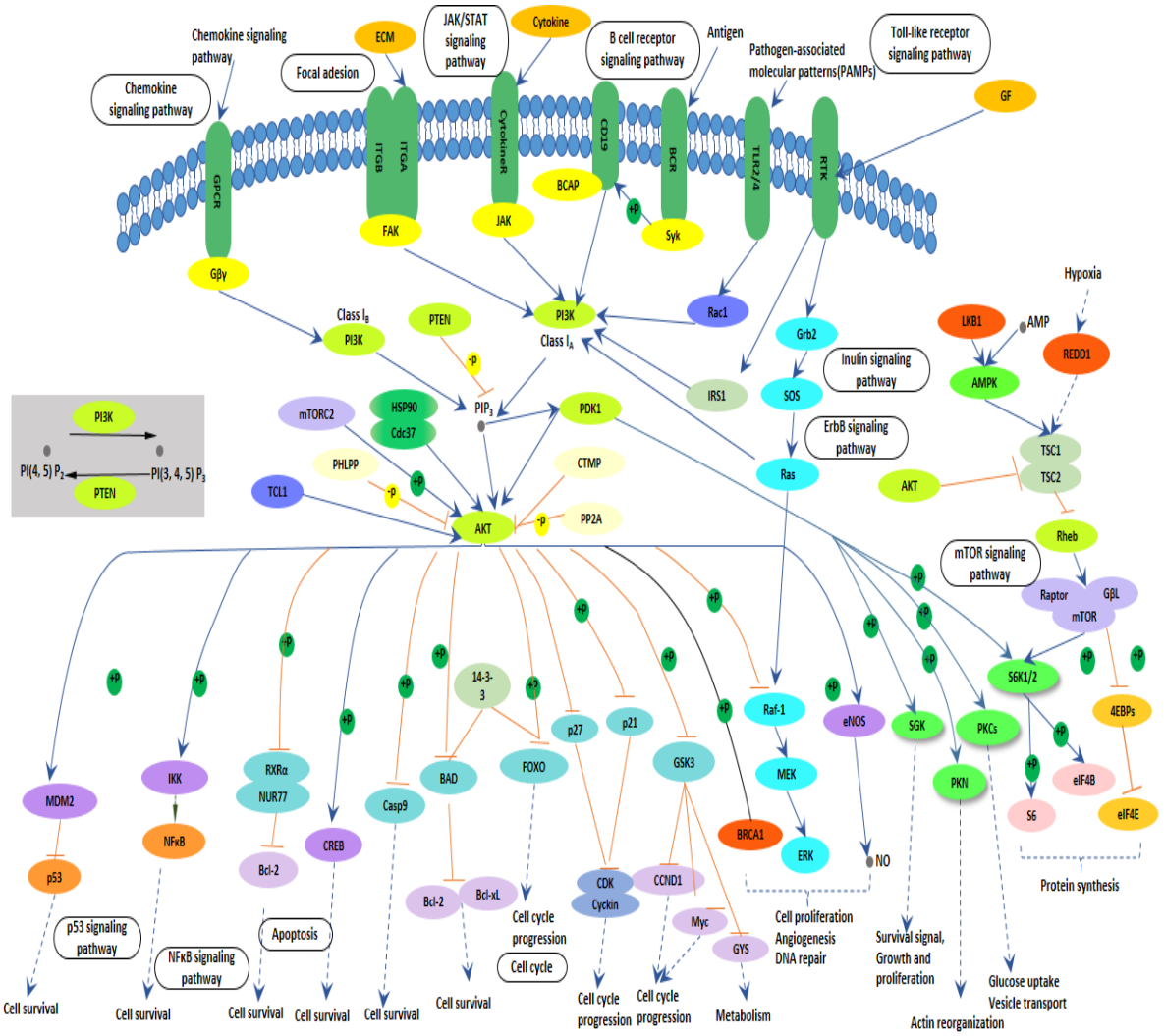

Fig. 1. Major upstreaming and downstreaming regulators and associated signaling transduction pathways of AKT/PKB [33]

3.5 AKT-MDM2-p53 and Carcinogenesis

Studies conducted in vitro have found that MDM2 (murine double minute 2) phosphorylation as a downstream regulator of AKT at Ser166 and/or Ser186 facilitates the translocation of MDM2 to the nucleus and diminishes p53-associated gene transcription [35]. The biochemically structured COOH terminus containing the RING finger domain with zinc moiety of MDM2 promotes a p53-specific E3 ubiquitin ligase activity [39]. 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 [40].

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 NFκB and p53 transcription [41]. AKT phosphorylates Nur77 in an inhibiting manner to suppress its activity which assists in the inducement of tumors or cancer [42].

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 [43]. 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 [44].

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 progressive 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 [45]. 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 [29]. 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 [46].

3.9 AKT-FoxO Downstreaming

FOXO subfamily of forkhead transcriptional factors including 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) [47]. Phosphorylation of FOXO diminishes DNA binding potentiation and enhances the protein binding affinity for 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 which initiates a protein degrading mechanism [43]. 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 carcinoma development [48].

3.10 AKT-CDKIs 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 [49,50]. 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 (CDNK2A) 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 [51]. 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 the progression of tumors or malignancies.

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 tumor or cancer development, 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.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Chibaya L, Karim B, Zhang H, Jones SN. Mdm2 phosphorylation by AKT regulates the p53 response to oxidative stress to promote cell proliferation and tumorigenesis. Proc Natl Acad Sci USA. 2021;118(4):1–16.
2. He Y, Sun MM, Zhang GG, Yang J, Chen KS, Xu WW, Li B. Targeting PI3K/AKT signal transduction for cancer therapy. Signal Transduction and Targeted Therapy. 2021;6(1):1-7.
3. Testa JR, Bellacosa A. AKT plays a central role in tumorigenesis. Proc Natl Acad Sci USA. 2001;98(20):10983–5.
4. Zhou BP, Hung M-C. Novel targets of AKT, p21, and MDM2. Semin Oncol. 2002;29(3 Suppl 11):62–70.
5. Hemmings BA, Restuccia DF. PI3K-PKB/AKT pathway. Cold Spring Harb Perspect Biol. 2012;4(9).
6. Strozyk E, Kulms D. The role of AKT/mTOR pathway in stress response to UV-irradiation: Implication in skin carcinogenesis by regulation of apoptosis, autophagy and senescence. Int J Mol Sci. 2013;14(8):15260–85.
7. Tzivion G, Hay N. PI3K-AKT-FoxO axis in cancer and aging. Biochim Biophys Acta - Mol Cell Res [Internet]. 2011;1813(11): 1925. Available:http://dx.doi.org/10.1016/j.bbamcr.2011.08.014
8. Han YH, Cao X, Lin B, Lin F, Kolluri SK, Stebbins J, et al. Regulation of Nur77 nuclear export by c-Jun N-terminal kinase and AKT. Oncogene. 2006;25(21):2974–86.
9. Shukla S, MacLennan GT, Marengo SR, Resnick MI, Gupta S. Constitutive activation of PI3K-AKT and NF-κB during prostate cancer progression in

autochthonous transgenic mouse model. Prostate. 2005;64(3):224–39.
10. Meegan MJ, O'Boyle NM. Special issue "anticancer drugs". Pharmaceuticals. 2019;12(3):134.
11. Nussbaumer S, Bonnabry P, Veuthey JL, Fleury-Souverain S. Analysis of anticancer drugs: A review. Talanta. 2011;85(5):2265-89.
12. Elghazi L, Balcazar N, Bernal-Mizrachi E. Emerging role of protein kinase B/AKT signaling in pancreatic β-cell mass and function. Int J Biochem Cell Biol. 2006;38(2):157–63.
13. Martelli AM, Tabellini G, Bressanin D, Ognibene A, Goto K, Cocco L, et al. The emerging multiple roles of nuclear AKT. Biochim Biophys Acta - Mol Cell Res [Internet]. 2012;1823(12):2168–78. Available:http://dx.doi.org/10.1016/j.bbamcr.2012.08.017
14. Hanada M, Feng J, Hemmings BA. Structure, regulation and function of PKB/AKT - A major therapeutic target. Biochim Biophys Acta - Proteins Proteomics. 2004;1697(1–2):3–16.
15. Hilger D, Masureel M, Kobilka BK. Structure and dynamics of GPCR signaling complexes. Nat Struct Mol Biol [Internet]. 2018;25(1):4–12. Available:http://dx.doi.org/10.1038/s41594-017-0011-7
16. New DC, Wu K, Kwok AWS, Wong YH. G protein-coupled receptor-induced AKT activity in cellular proliferation and apoptosis. FEBS J. 2007;274(23):6025–36.
17. Lappano R, Maggiolini M. GPCRs and cancer. Acta Pharmacol Sin [Internet]. 2012;33(3):351–62. Available:http://dx.doi.org/10.1038/aps.2011.183
18. Schneider J, Korshunova K, Musiani F, Alfonso-Prieto M, Giorgetti A, Carloni P. Predicting ligand binding poses for low-resolution membrane protein models: Perspectives from multiscale simulations. Biochem Biophys Res Commun [Internet]. 2018;498(2):366–74. Available:https://doi.org/10.1016/j.bbrc.2018.01.160
19. Karpov OA, Fearnley GW, Smith GA, Kankanala J, McPherson MJ, Tomlinson DC, et al. Receptor tyrosine kinase structure and function in health and disease. AIMS Biophys. 2015;2(4):476–502.
20. Azad T, Rezaei R, Surendran A, Singaravelu R, Boulton S, Dave J, et al. Hippo signaling pathway as a central mediator of Receptors Tyrosine Kinases (RTKS) in tumorigenesis. Cancers (Basel). 2020;12(8):1–22.
21. Yamaoka K, Saharinen P, Pesu M, Et V, Iii H, Silvennoinen O, et al. Protein family review The Janus kinases (Jaks); 2004.
22. Ibrahim SSA, Huttunen KM. Orchestrated modulation of rheumatoid arthritis via crosstalking intracellular signaling pathways. Inflammopharmacology [Internet]. 2021;29(4):965–74. Available:https://doi.org/10.1007/s10787-021-00800-3
23. Downward J. Targeting RAS and PI3K in lung cancer. Nat Med. 2008;14(12):1315–6.
24. Li D, Ni S, Miao KS, Zhuang C. PI3K/AKT and caspase pathways mediate oxidative stress-induced chondrocyte apoptosis. Cell Stress Chaperones. 2019;24(1):195–202.
25. Wu Y, Wang D, Wang X, Wang Y, Ren F, Chang D, et al. Cellular Physiology Biochemistry and Biochemistr y Caspase 3 is Activated through Caspase 8 instead of Caspase 9 during H 2 O 2 -induced Apoptosis in HeLa Cells. Cell Physiol Biochem [Internet]. 2011;100084. Available:https://www.karger.com/Article/PDF/329955
26. Kermer P, Klöcker N, Labes M, Bähr M. Insulin-like growth factor-I protects axotomized rat retinal ganglion cells from secondary death via PI3-K-dependent AKT phosphorylation and inhibition of caspase-3 *in vivo*. J Neurosci. 2000;20(2):722–8.
27. Brentnall M, Rodriguez-Menocal L, De Guevara RL, Cepero E, Boise LH. Caspase-9, caspase-3 and caspase-7 have distinct roles during intrinsic apoptosis. BMC Cell Biol [Internet]. 2013;14(1):1.
28. St.-Germain ME, Gagnon V, Parent S, Asselin E. Regulation of COX-2 protein expression by AKT in endometrial cancer cells is mediated through NF-κB/IκB pathway. Mol Cancer. 2004;3:1–11.
29. Ghoneum A, Said N. PI3K-AKT-mTOR and NFkB pathways in ovarian cancer: Implications for targeted therapeutics. Cancers (Basel). 2019;11(7).
30. Nishida H, Sohara E, Nomura N, Chiga M, Alessi DR, Rai T, et al. Phosphatidylinositol 3-kinase/AKT signaling pathway activates the WNK-

OSR1/SPAK-NCC phosphorylation cascade in hyperinsulinemic db/db mice. Hypertension. 2012;60(4):981–90.
31. Sie ZL, Li RY, Sampurna BP, Hsu PJ, Liu SC, Wang HD, et al. WNK1 kinase stimulates angiogenesis to promote tumor growth and metastasis. Cancers (Basel). 2020;12(3):1–20.
32. Gallolu Kankanamalage S, Karra AS, Cobb MH. WNK pathways in cancer signaling networks. Cell Commun Signal. 2018;16(1):4–9.
33. CUSABIO. PI3K-AKT signaling pathway; 2022. [Internet]
Available:PI3K-AKT signaling pathway - Cusabio.
34. Principe DR, Doll JA, Bauer J, Jung B, Munshi HG, Bartholin L, et al. TGF-β: Duality of function between tumor prevention and carcinogenesis. J Natl Cancer Inst. 2014;106(2):1–16.
35. Liang J, Slingerland JM. Multiple roles of the PI3K/PKB (AKT) pathway in cell cycle progression. Cell Cycle. 2003;2(4):336–42.
36. Kandel ES, Skeen J, Majewski N, Cristofano A Di, Pandolfi PP, Feliciano CS, et al. Activation of AKT / protein kinase B overcomes a G 2 / M cell cycle checkpoint induced by DNA damage. 2002;22(22): 7831–41.
37. Maddika S, Ande SR, Wiechec E, Hansen LL, Wesselborg S, Los M. AKT-mediated phosphorylation of CDK2 regulates its dual role in cell cycle progression and apoptosis. J Cell Sci. 2008;121(7):979–88.
38. Zhou C, Du J, Zhao L, Liu W, Zhao T, Liang H, et al. GLI1 reduces drug sensitivity by regulating cell cycle through PI3K / AKT / GSK3 / CDK pathway in acute myeloid leukemia. Cell Death Dis; 2021. [Internet]
Available:http://dx.doi.org/10.1038/s41419-021-03504-2
39. Zhou BP, Liao Y, Xia W, Zou Y, Spohn B, Hung MC. HER-2/neu induces p53 ubiquitination via AKT-mediated MDM2 phosphorylation. Nat Cell Biol. 2001;3(11):973–82.
40. Moll UM, Petrenko O. The MDM2-p53 Interaction. 2003;1(14):1001–8.
41. To SKY, Zeng JZ, Wong AST. Nur77: A potential therapeutic target in cancer. Expert Opin Ther Targets. 2012;16(6):573–85.
42. Masuyama N, Oishi K, Mori Y, Ueno T, Takahama Y, Gotoh Y. AKT inhibits the orphan nuclear receptor Nur77 and T-cell apoptosis. J Biol Chem. 2001;276(35): 32799–805.
43. Zhang X, Tang N, Hadden TJ, Rishi AK. AKT, FoxO and regulation of apoptosis. Biochim Biophys Acta - Mol Cell Res. 2011;1813(11):1978–86. [Internet]
Available:http://dx.doi.org/10.1016/j.bbamcr.2011.03.010
44. Yamaguchi H, Wang HG. The protein kinase PKB/AKT regulates cell survival and apoptosis by inhibiting Bax conformational change. Oncogene. 2001;20(53):7779–86.
45. Porta C, Paglino C, Mosca A. Targeting PI3K/AKT/mTOR signaling in cancer. Front Oncol. 2014;4:1–11.
46. Paplomata E, O'regan R. The PI3K/AKT/mTOR pathway in breast cancer: Targets, trials and biomarkers. Ther Adv Med Oncol. 2014;6(4):154–66.
47. Roy SK, Srivastava RK, Shankar S. Inhibition of PI3K/AKT and MAPK/ERK pathways causes activation of FOXO transcription factor, leading to cell cycle arrest and apoptosis in pancreatic cancer. J Mol Signal. 2010;5:1–13.
48. Gargini R, Cerliani JP, Escoll M, Antõn IM, Wandosell F. Cancer stem cell-like phenotype and survival are coordinately regulated by AKT/FoxO/bim pathway. Stem Cells. 2015;33(3):646–60.
49. Hickman ES, Moroni MC, Helin K. The role of p53 and pRB in apoptosis and cancer. Curr Opin Genet Dev. 2002; 12(1):60–6.
50. Harper JW, Elledge SJ. Cdk inhibitors in development and cancer. Curr Opin Genet Dev. 1996;6(1):56–64.
51. Hunter T, Pines J. Cyclins and cancer. II: Cyclin D and CDK inhibitors come of age [see comments]. [Review]. Cell. 1994; 79(4):573–82.

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