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The PI3K/AKT pathway in the pathogenesis of prostate cancer

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1. ABSTRACT

Despite recent advances in our understanding of the biological behavior of prostate cancer (PCa), PCa is becoming the most common malignancy in men worldwide. The phosphatidylinositol 3-kinase (PI3K)/AKT pathway has been implicated in prostate carcinogenesis. Inflammatory cytokines (CCR9, IL-6, and TLR3) regulate PI3K/AKT signaling during apoptosis of PCa cells, and PI3K/AKT signaling participates with androgen-, 1α,25(OH)2-vitamin D3-, and prostaglandin-associated mechanisms and is regulated by ErbB, EGFR, and the HER family during cell growth. During metastasis of PCa cells, the PI3K/AKT/NF-kappaB/BMP-2-Smad axis, PTEN/PI3K/AKT pathway, and PI3K/AKT/mTOR signaling regulates tumor cell metastasis and invasion. The present review focuses on the PI3K/AKT signal pathway and discusses the role of the PI3K/AKT signal pathway in PCa tumorigenesis.

2. INTRODUCTION

Prostate cancer (PCa) is one of the most significant health problems among men worldwide. In 2010 PCa resulted in 256,000 deaths, which was an increase from 156,000 deaths in 1990 (1). As of 2011, PCa is the second most frequently diagnosed cancer and the sixth leading cause of cancer deaths in males worldwide (2). In the United States alone, it is estimated that there will be 240 890 new cases and 33 720 deaths in 2011 (3). In 2013, an estimated 238,590 new cases and 29,720 cancer-related deaths are expected in the United States (4). Thus, PCa has become one of the most common malignancies in men worldwide, with varying rates of tumor progression and responses to treatment. The phosphatidylinositol 3-kinase (PI3K)/AKT pathway has been implicated in prostate carcinogenesis and castration resistance, although the precise function of the PI3K/AKT pathway remains to be fully elucidated. Thus, the modulation of PI3K/AKT signal transduction may offer promising new approaches to the treatment of PCa.

The PI3K enzymes are primarily involved in the phosphorylation of membrane inositol lipids, thus mediating cellular signal transduction (5). The PI3K pathway is usually activated by genomic aberrations across many cancer lineages. Data from the Sanger Institute Collaboration indicate that approximately 30% of patients with castration-resistant PCa harbor p110α mutations (6). Both receptor tyrosine kinases (RTKs) and non-RTKs lead to PI3K activation, resulting in the second messenger, phosphatidylinositol (3-5)-trisphosphate (PIP3), from phosphatidylinositol 4,5-bisphosphate (PIP2). PI3K activation recruits pleckstrin homology (PH) domain-containing proteins to the cell membrane, including the AKT/PKB kinases, driving the conformational changes and resulting in phosphorylation by the constitutively-active phosphoinositide-dependent kinase 1 (PDK1) at threonine 308 (7) and by PDK2 (mammalian target of rapamycin complex 2 (mTORC2)) at serine 473 (8). Activated AKT translocates to the cytoplasm and nucleus and activates downstream targets involved in survival, proliferation, cell cycle progression, growth, migration, and angiogenesis. The present review focuses on the PI3K/AKT signal pathway and discusses our current limited knowledge of the ontology of the PI3K/AKT pathway in the pathogenesis of PCa.

3. PI3K/AKT IN THE APOPTOSIS OF PROSTATE CANCER CELLS

Inflammation-related cytokine toll-like receptors (TLRs), CC chemokine receptor-9 (CCR9), and interleukin-6 (IL-6) are upstream regulators of the PI3K/AKT pathway (9-11). TLR3 signaling partially

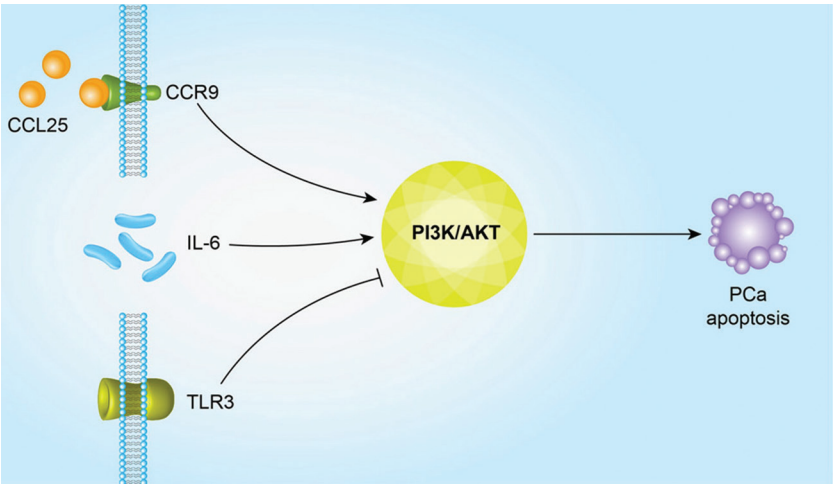

Figure 1. Inflammatory cytokines regulate PI3K/AKT signaling in the apoptosis of prostate cancer cells. CCR9 combined with its natural ligand, CCL25, and IL-6 are upregulators of the PI3K/AKT pathway, leading to PCa cell apoptosis resistance. TLR3 inhibits PI3K/AKT pathway activation and induces apoptosis.

triggers apoptosis and growth arrest of human PCa cell lines (LNCaP) *in vitro* through inactivation of the PI3K/AKT pathway (9). CCR9 and the natural ligand of CCR9, CCL25, interact to upregulate the PI3K/AKT pathway, resulting in decreased apoptosis (12). IL-6 is another upstream regulator of the PI3K/AKT pathway in surviving PCa cells (11). IL-6 has been shown to activate the PI3K/AKT pathway, then regulate cyclin A1 to resist PCa apoptosis. Thus, cyclin A1 has been identified as an important downstream target of the PI3K/AKT pathway (11). The CCR9-CCL25 axis and IL-6 are upregulators of the PI3K/AKT pathway, leading to PCa cell apoptosis resistance. In addition, TLR3 inhibits PI3K/AKT pathway activation and induces apoptosis (Figure 1). Inflammatory cytokines primarily act as promotors in anti-apoptosis, which suggests that chronic inflammation leads to apoptosis resistance, and results in tumorigenesis.

By targeting PI3K/AKT in PCa cells, ethanolic neem leaf extract (13) and phyllanthus (14) have been shown to induce apoptosis. Both ethanolic neem leaf and phyllanthus are plants that have anticancer properties. Two studies have identified the target of the plants, demonstrating the key role of PI3K/AKT in apoptosis of PCa cells. In addition, the neuropeptide, prosaposin, and the active domain of prosaposin, saposin C, are known to have potent neurotrophic activities and are involved in neuroembryologic development (15,16). Prosaposin promotes survival of PCa cells and prevents apoptosis via the PI3K/AKT-dependent pathway (17), suggesting a novel target for PCa therapy.

4. PI3K/AKT IN THE PROLIFERATION OF PCa CELLS

Long-term androgen ablation therapy for PCa impedes inhibition of the PI3K/Akt pathway, thus contributing to increased apoptosis resistance of tumor cells (18). Androgens and the cognate receptor of androgens, androgen receptor (AR), play an essential role in prostate development in the adult and promote PCa growth in patients (19). Thus, androgen is a target during PCa treatment. A study which focused on AR signaling targets, insulin-like growth factor I (IGF-I) and prostate specific antigen (PSA), showed that IGF-I/PI3K/Akt signaling combined with AR activation is essential for androgen-induced PSA expression, which is associated with PCa (20). This result suggested an association between androgen and PI3K/AKT signaling in PCa. A subsequent study showed that knocking down the cochaperone small glutamine-rich TPR-containing protein alpha (SGTA) leads to the suppression of androgen and PI3K/Akt signaling, resulting in PCa cell proliferation (21).

Antiproliferative effects result from 1α,25(OH)2-vitamin D3 (1,25(OH)2D3) in a variety of cancer cell types, including PCa cell lines (22,23). It has been demonstrated that 1,25(OH)2D3 inhibits prostate growth in primary prostatic cells from histologically normal prostate, benign prostatic hyperplasia, PCa specimens (24), multiple PCa cell lines (25–27), xenograft models of PCa (28,29), and the Dunning rat prostate model (30). Although classic actions of 1,25(OH)2D3 are mediated through the vitamin D receptor, a recent study showed that 1,25(OH)2D3 synergizes with inhibition of the PI3K/AKT pathway to induce G1 arrest and senescence and inhibit the growth of human PCa cell lines and primary human PCa strains (31).

Multiple genes involved in the prostaglandin (PG) pathway in PCa are regulated by 1,25(OH)2D (32). PGE and PGF are the major prostaglandins stimulating the proliferation of PCa cells (32). PGE acts through four different PGE receptor (EP) subtypes (EP1–EP4), while PGF activates the FP receptor. EP and FP prostaglandin

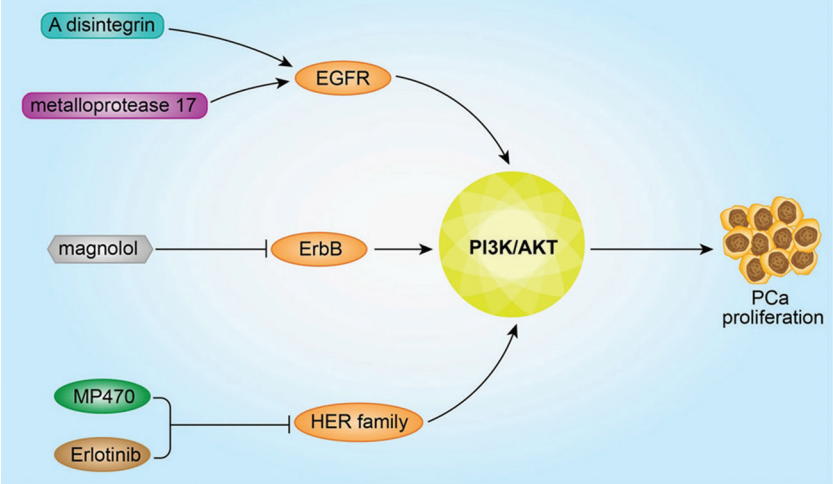

Figure 2. The EGFR/PI3K/AKT, ErbB/PI3K/AKT, and HER family/PI3K/AKT pathways in the proliferation of prostate cancer cells. The EGFR/PI3K/AKT pathway is activated by a disintegrin and metalloprotease 17 and leads to PCa cell proliferation. The ErbB/PI3K/AKT and HER family/PI3K/AKT pathways can be inhibited by magnolol and MP470 (a novel receptor tyrosine kinase inhibitor), respectively, in combination with erlotinib, resulting in tumor growth inhibition.

receptors are expressed in PCa cells (32,33). A study on the PI3K/AKT pathway showed that another member of the PG family, PGD2, promotes the accumulation of proliferative PCa cell signals through the FP and PI3K/AKT signaling pathways (34).

The ErbB, EGFR, and HER family are all upstream factors of PI3K/AKT signaling. The EGFR/PI3K/AKT, ErbB/PI3K/AKT, and HER family/PI3K/AKT pathways all participate in PCa cell proliferation, among which the EGFR/PI3K/AKT pathway is activated by A disintegrin and metalloprotease 17 and lead to PCa cell proliferation (35). The ErbB/PI3K/AKT and HER family/PI3K/AKT pathways are inhibited by magnolol (36) and MP470 (a novel receptor tyrosine kinase inhibitor), respectively, in combination with erlotinib (37), resulting in tumor growth inhibition (Figure 2). These findings suggest new therapeutic targets of PCa in PI3K/AKT signaling.

5. PI3K/AKT IN THE METASTASIS AND INVASION OF PCa CELLS

PCa metastasis mostly occurs in bone. Greater than 70% of PCa patients have bone metastases at autopsy, and the median 5-year survival rate is only 31% for metastatic patients (38). Progressive growth and metastasis of PCa are dependent on angiogenesis. Microvessel density is correlated with PCa progression and the expression of angiogenic factors is altered in PCa and associated with clinical stage, Gleason score, tumor stage, progression, metastasis, and survival (39-42). Angiogenesis is a biological process that involves the division and migration of endothelial cells, resulting in microvasculature formation (43,44). In PCa, through PI3K/AKT signaling, N-cadherin mediates angiogenesis by regulating monocyte chemoattractant protein-1 (45). Furthermore, an increased level of N-cadherin is associated with bone-metastasized prostate tumor cells (45), implying that PI3K/AKT signaling may promote bone metastasis of PCa by regulating N-cadherin. An *in vitro* study showed that PI3K/AKT signaling targeting NF-kappaB can lead to the activation of the bone morphogenetic protein (BMP) signaling cascade, which results in the promotion of PCa bone metastasis (46). This result suggests the upregulation of the PI3K/AKT/NF-kappaB/BMP-2-Smad axis in PCa bone metastasis, which may be a novel therapeutic target. Moreover, TNF-α-mediated migration and invasion of PC3 cells can be inhibited by gambogic acid through the PI3K/AKT and NF-kappaB pathways (47). This effect is associated with downregulation of Snail (47).

The tumor suppressor phosphatase and tensin homolog deleted on chromosome 10 (PTEN) is recognized as a major inhibitor of PI3K (48) and AKT (49), and is frequently lost in human tumors. PCa is one of the cancers most commonly affected by PTEN abnormalities (50). The biomarker for PI3K/AKT pathway activation and PTEN status was shown to be the insulin growth factor-binding protein 2 (IGFBP-2) in PCa (51). Through the PTEN/PI3K/AKT pathway, overexpressed lamin A/C protein in PCa tissue can promote growth, migration, and invasion, especially in PC cells that have lost PTEN function and harbor a constitutively-activated protein kinase, AKT (52). In the treatment of PCa, PTEN controls the cellular response to cetuximab in PCa cells via regulation of AKT phosphorylation. PTEN significantly restores cetuximab-induced cell growth inhibition and apoptosis induction in part by reducing the

overexpression of phosphorylated-AKT (53). Moreover, PETN can negatively regulate the PI3K/Akt/mTOR pathway (54). *In vitro* and preclinical studies have also shown that inactivation of PTEN leads to constitutively-activated AKT and mTOR, as well as deregulation of cell size and cell growth (55). This suggests a significant role for PI3K/AKT/mTOR signaling in tumorigenesis.

In vitro studies have demonstrated that PI3K/AKT/mTOR signaling is not only involved in proliferation (56) and apoptosis (57) of PCa cells, but also migration and invasion (58). In PCa cell proliferation, PI3K activates the AKT/mTOR/p70(S6K) signaling pathway, leading to G1 cell cycle progression and cyclin expression, then resulting in PCa cell growth (56), which is similar to the effect of 1,25(OH)2D3 (10). The apoptosis of PCa cells can be induced by suppressing PI3K/AKT/mTOR/S6K1 signaling cascades via brassinin (57). Although PI3K/AKT/mTOR signaling downstream in PCa cell proliferation and apoptosis is different, PI3K/AKT/mTOR signaling participates in the migration and invasion of PCa cells. AKT phosphorylation is induced by PGE2 and TGF-β, leading to the activation of the PI3K/AKT/mTOR pathway, resulting in the migration and invasive behavior of PC3 cells (58). Bortezomib has been studied for use in PCa treatment, and the first therapeutic proteasome inhibitor in humans dephosphorylates the phospho-AKT, then leads to the suppression of PI3K/AKT/mTOR, resulting in induction of growth arrest and apoptosis in PCa cells (59). Thus, bortezomib inhibits one of the targets of PI3K/AKT/mTOR signaling (hypoxia-inducible factor-1α (HIF-1α)), which is directly involved in tumor growth (59).

Traditional anti-neoplastic agents, such as camptothecin conjugated with a somatostatin analog (JF-10-81), blocks migration and invasion of highly invasive PCa PC-3 cells via the inactivated phosphorylation PI3K/AKT pathway and downregulates the expression of latent matrix metalloproteinase (MMP)-2 and MMP-9 (60). By targeting PI3K/AKT/MMP-2 and PI3K/AKT/MMP-9, the fisetin (3,3',4',7-tetrahydroxyflavone), a naturally occurring flavonoid, can inhibit PC-3 cell metastasis (61).

6. CONCLUSION

PI3K/AKT signaling plays a significant role in PCa tumorigenesis, including apoptosis and proliferation of PCa cells and tumor metastasis and invasion by regulating several pathways associated with cell growth, apoptosis, or invasion. The mechanisms of PI3K/AKT in PCa tumorigenesis are multiple; inflammation, cell cycling, and angiogenesis are involved in this signaling. These mechanisms are not isolated, and may co-exist during tumorigenesis. Thus, PI3K/AKT may be a key cross-point during PCa tumorigenesis and PCa therapy. Our increasing understanding of the role of PI3K/AKT signaling in PCa biological behavior has led to the hope that novel inhibitors of the pathway will result in therapeutic benefit.

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Abbreviations: PCa: Prostate cancer; PI3K: phosphatidylinositol 3-kinase; RTKs: receptor tyrosine kinases; PDK1: phosphoinositide-dependent kinase 1; TLRs: toll-like receptors; IL-6: interleukin-6; AR: androgen receptor; IGF-I: insulin-like growth factor I; IGF-I: insulin-like growth factor I; SGTA: small glutamine-rich TPR-containing protein alpha; BMP: bone morphogenetic protein; IGFBP-2: insulin growth factor-binding protein 2; MMP-2: matrix metalloproteinase-2

Key Words: Prostate Cancer, PI3K, Toll-Like Receptors, Androgen Receptor, Review

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