Phosphatidylinositol-3-Kinase/Akt Signaling Pathway and Kidney Cancer, and the Therapeutic Potential of Phosphatidylinositol-3-Kinase/Akt Inhibitors

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Purpose: The PI3K/Akt signaling pathway is activated by many cellular stimuli. It regulates fundamental cellular functions, including transcription, translation, proliferation, growth and survival. It also closely interacts with many other key pathways such as mTOR and, thus, is linked to angiogenesis. Disturbed activation of the PI3K/Akt pathway is associated with many human malignancies. We reviewed the available literature on PI3K/Akt and PI3K/Akt targeting drugs for renal cell carcinoma.

Materials and Methods: MEDLINE® and the proceedings of the main oncological meetings were extensively searched to identify the available literature on the role of this pathway in renal cell carcinoma pathogenesis, and on preclinical and clinical activity of compounds specifically targeting this pathway. Clinical data and perspectives on several compounds at different stages of development were also reviewed.

Results: Cumulative evidence links PI3K/Akt alterations with renal cell carcinoma. Thus, renal cell carcinoma is an ideal setting in which to test compounds specifically targeting this pathway. Several PI3K/Akt inhibitors are currently under preclinical and early clinical development as anticancer agents but only perifosine (Keryx Biopharmaceuticals, New York, New York) appears to be at a more advanced stage, having been tested with promising results alone or combined with other molecularly targeted agents.

Conclusions: The PI3K/Akt pathway has a pivotal role in renal cell carcinoma pathogenesis and, thus, represents an ideal target for therapeutic intervention. Of the several compounds in early phases of development only perifosine has already proved to be clinically active. Thus, it should be considered an extremely interesting drug to be used alone or in combination.

Key Words: kidney; carcinoma, renal cell; D 21266; 1-phosphatidylinositol 3-kinase; mTOR protein

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Abbreviations and Acronyms

17-HWT = 17-hydroxy-wortmannin

APC = alkylphosphocholine

ERK = extracellular regulated kinase

GSK3 = glycogen synthase kinase-3

HIF = hypoxia-inducible factor

IC_{50} = half maximum inhibitory concentration

MEK = mitogen-activated and extracellular signal-regulated kinase

MTD = maximum tolerated dose

mTOR = mammalian target of rapamycin

mTORC = mTOR complex

NFκB = nuclear factor κB

PDK = 3′-phosphoinositide-dependent kinase

PI = phosphatidylinositol

PI-3,4,5-P_3 = PI-3,4,5-triphosphate

PI3K = PI-3-kinase

PKB = protein kinase B

PTEN = phosphatase and tensin homolog deleted on chromosome 10

RCC = renal cell carcinoma

VEGF = vascular endothelial growth factor

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THE PI3K/Akt signaling pathway is crucial to many aspects of cell growth and survival for physiological and pathological conditions. In physiology the PI3K/Akt pathway is a key regulator of survival during cellular stress. It is activated by several hormones, growth factors, signals derived from receptors for extracellular matrix molecules such as integrins, several forms of cellular stress such as oxidation and Ras activation.

Since tumors exist in intrinsically stressful environments with limited nutrient and oxygen supply as well as low pH, the role of this pathway in cancer is crucial.[1] Another reason is that it is targeted by genomic aberrations more frequently than any other cancer with the possible exceptions of the p53 and retinoblastoma pathways.[1]

Activation of the PI3K/Akt pathway results in a profound disturbance of control of cell growth and survival, which ultimately leads to a competitive growth advantage, metastatic competence and therapy resistance. Thus, this pathway is more than an attractive target for the development of novel anticancer drugs.

Therapeutic options in patients with advanced RCC used to be limited but this scenario has dramatically changed in the last few years. Indeed, improved understanding of RCC biology has allowed the development of novel targeted therapeutic agents that have changed the natural history of this disease. Particularly HIF/VEGF and mTOR signal transduction pathways have been exploited to develop novel drugs that have improved clinical outcomes in randomized trials by inhibiting these tumorigenic pathways.[2]

Nevertheless, advanced RCC remains an incurable disease and newer treatment options are badly needed. Of the molecular pathways involved in RCC pathogenesis the PI3K/Akt signaling pathway represents an extremely appealing therapeutic target.

PI3K/AKT PATHWAY STRUCTURE AND FUNCTIONS

PI3Ks are a lipid kinase family characterized by the ability to phosphorylate the inositol ring 3′-OH group in inositol phospholipids.[3] Class I PI3Ks are heterodimers composed of a catalytic subunit (ie p110) and an adaptor/regulatory subunit (ie p85). This class is further divided into the subclass IA (PI3Kα, β and δ), which is activated by receptors with protein tyrosine kinase activity, and the subclass IB (PI3Kγ), which is activated by receptors coupled with G proteins.[4]

Activation of growth factor receptor protein tyrosine kinases results in autophosphorylation on tyrosine residues. PI3K is then recruited to the membrane by directly binding to phosphotyrosine consensus residues of growth factor receptors or adaptors through 1 of the 2 SH2 domains in the adaptor subunit, which leads to allosteric activation of the catalytic subunit. In a few seconds PI3K activation leads to the production of the second messenger PI-3,4,5-P_3 from the substrate PI-4,4-bisphosphate. PI-3,4,5-P_3 then recruits a subset of signaling proteins with pleckstrin homology domains to the membrane, including protein serine/threonine kinase PDK1 and Akt/PKB.[4,5]

On its own Akt/PKB regulates several cell processes involved in cell survival and cell cycle progression. For cell survival Akt/PKB can inactivate pro-apoptotic factors such as Bad and Procaspase-9, and the Forkhead family of transcription factors that induce the expression of other pro-apoptotic factors, such as Fas-ligand.[6] Akt/PKB activation is related to increased resistance of prostate cancer cells to apoptosis mediated by TRAIL (tumor necrosis factor-related apoptosis-inducing ligand)/APO-2L.[7] Finally, Akt/PKB also activates IκB kinase, a positive regulator of the survival factor NFκB.[4] For cell cycle progression and cell growth several targets of Akt are involved in protein synthesis, glycogen metabolism and cell cycle regulation,[4] including GSK3, mTOR, insulin receptor substrate-1, the cyclin-dependent kinase inhibitors $p21^{CIP1/WAF1}$ and $p27^{KIP1}$, and possibly also Raf-1, a member of the mitogen-activated protein kinase pathway. These observations link the PI3K/Akt pathway not only to cell cycle regulation, but also through GSK3 and especially mTOR to tumor angiogenesis (see figure).

We briefly address cross-talk of the PI3K/Akt pathway with other pathways relevant to RCC. However, it is clear that all genes involved in this pathway interact with a number of other pathways to create an extremely complex network. Furthermore, with approximately half of the human genome poorly annotated it is likely that additional interactions with this network will be discovered in the near future. This explains why in such a huge network a single block can be easily circumvented by up-regulating some of these interconnections, ultimately leading to its failure as a therapeutic strategy.

PTEN AS PI3K/AKT PATHWAY REGULATOR

PTEN is a key molecule downstream of the PI3K/Akt pathway. This phosphatase, endowed with dual activity on lipids and proteins, acts as a tumor suppressor by inhibiting cell growth and enhancing cellular sensitivity to apoptosis and anoikis, ie an epithelial cell-peculiar type of apoptosis triggered by alterations in integrin-extracellular matrix interactions.[8]

PTEN is often mutated in several advanced human cancers. In addition, PTEN mutations in germ cell lines result in the rare hereditary syndrome known as Cowden disease, which is associated with a higher risk of different cancers, including breast, thyroid and endometrial cancer.[9]