Review

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The Role of Phosphatidylinositol 3-Kinase Signaling Pathways in Pancreatic Cancer

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Key Words
Pancreatic cancer · PI3K · Signaling pathway

Abstract
Background: Pancreatic cancer is a highly malignant cancer and the fourth leading cause of cancer-related death. It is characterized by a rapid disease progression, a highly invasive tumor phenotype, and frequently resistance to chemotherapy. Despite significant advances in diagnosis, staging, and surgical management of the disease during the past decade, prognosis of pancreatic cancer is still dismal. ***Methods and Results:*** The phosphatidylinositol 3-kinase (PI3K) signaling pathways regulate cellular growth, metabolism, survival, and motility in pancreatic cancer. Pancreatic cancer is associated with a high degree of genetic alterations that can result in aberrant activation of the PI3K signaling pathway. Elucidating the role of the PI3K signaling pathway in pancreatic cancer may thus be both meaningful and necessary. ***Conclusion:*** Improved knowledge of the PI3K signaling pathway in pancreatic cancer would furthermore be helpful in understanding mechanisms of tumor initiation and progression, and in identifying appropriate targeted anticancer treatment in pancreatic cancer.

Introduction

Pancreatic cancer is a highly malignant cancer and the fourth cause of cancer-related death. It is characterized by a rapid disease progression, a highly invasive tumor phenotype, and resistance to chemotherapy [1–4]. In the USA, the incidence of pancreatic cancer almost equals mortality, with 43,140 estimated new cases and 36,800 deaths in 2010. Worldwide, the incidence is approximately 230,000 new cases every year [5–6]. Despite significant advances in diagnosis, staging, and surgical management of the disease during the past decade, the overall 2-year survival in the USA, Europe, and Australia is around 20%, while the 5-year survival rate is <5% [7–9].

The transformation of a normal cell to a tumorigenic phenotype can be initiated via genetic alterations or epigenetic events, including loss of function of tumor suppressor genes, such as p53 and phosphatase and tensin homolog (PTEN; deleted on chromosome 10), or activation of oncogenes, such as c-Myc or K-Ras. Pancreatic cancer is one of the human solid tumors with the highest degree of genetic alterations.

Most of the genetic mutations in pancreatic cancer are associated with changes in biological signaling pathways, such as phosphatidylinositol 3-kinase (PI3K), hedgehog, and Src. Extracellular and cellular stimuli may regulate

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gene activation or inactivation via the signaling pathways with certain effects on the tumor cells. Somatic mutations of *PIK3CA* or other signaling components are uncommon or rare in pancreatic ductal adenocarcinoma (PDAC) [10]. However, somatic mutations of *PIK3CA* have been reported in a minority of intraductal papillary mucinous neoplasms, which are cystic non-invasive precursor lesions of pancreatic adenocarcinoma. This pathway might therefore serve as a diagnostic biomarker in clinical samples like cyst fluid, a therapeutic target as well as a target for chemoprevention [11]. In addition, somatic mutations of *PIK3CA* have been reported in a minor fraction of pancreatic neuroendocrine tumors, and overall, ~15% of them show activation of PI3K/mTOR signaling [12]. Thus, this pathway is a potential therapeutic target in this rarer variant of pancreatic cancer.

Increased knowledge of the PI3K signaling pathways would be helpful in understanding mechanisms involved in pancreatic tumorigenesis and for the identification of novel targeted anticancer treatments in pancreatic cancer. Numerous cancer studies provide evidence for multiple links between PI3K and a diverse array of cellular functions. In this review, we discuss the role of PI3K in pancreatic cancer with a focus on its effects on cancer cell generation, proliferation, metabolism, invasion, metastasis, apoptosis, and sensitivity to therapy.

PI3K Biological Properties

The PI3K signaling transduction and downstream effector function is closely related to its biochemical structure. There are three subtypes (class I–III) in the PI3K family in mammalians. Among the three subtypes, class I is most frequently documented and most widely implicated in cancer, and it is also the class mainly discussed in this review. All class I PI3Ks are heterodimers comprised of a p85 regulatory subunit and a p110 catalytic subunit. The regulatory subunit has three subtypes (α, β, γ), all containing several modular protein-protein interaction domains: (1) a Src-homology 3 (SH3) domain; (2) a breakpoint clustered homology (BH) domain; (3) two Src-homology 2 (SH2) domains, and (4) an inter-SH2 (iSH2) domain. The iSH2 domain is the primary p110-binding domain. Regulatory subunits of p85 link p110 to upstream signals, stabilize p110, and suppress its catalytic activities in absence of upstream signals. The catalytic subunit also occurs in four subtypes, i.e. p110α, p110β, p110γ, and p110δ. All p110 subtypes have the same domains: (1) an amino-terminal adaptor-binding domain that provides the principal interaction surface with the regulatory subunit; (2) a Ras-binding domain that mediates the interaction between p110 and Ras-GTP, and contributes to the stimulation of PI3K and to the Ras-driven signaling pathway; (3) a protein-kinase-C homology-2 domain with affinity for lipid membranes; (4) a helical domain acting as a scaffold for other domains of p110, and (5) a carboxyl-terminal kinase domain [13]. In addition, class I PI3Ks are further subdivided according to their regulatory subunits. Class IA is encompassing p110α, p110β, and p110δ, which are predominantly activated by growth factor receptor tyrosine kinases (RTKs). In contrast, class IB consists only of p110γ, which are activated by G-protein-coupled receptors (GPCRs) [14].

Activation of PI3K at the plasma membrane can occur by binding of its p85 subunit to phosphorylated tyrosine residues, e.g. on activated RTKs and GPCRs, or by binding of its p110 subunit to constitutively active membrane-bound Ras [15]. Activation of PI3K leads to the conversion of PIP_2 (phosphatidylinositol 3,4-biphosphate) to PIP_3 (phosphatidylinositol 3,4,5-triphosphate) and phosphorylation of Akt (protein kinase B) by phosphoinositide-dependent kinase (PDK1) [16, 17]. Only class I PI3Ks are capable of converting PIP_2 to PIP_3, while class II PI3Ks generate 3,4-bisphosphate and 3-monophosphate of inositol lipids, and class III PI3Ks generate 3-monophosphate. Class I PI3Ks can thus initiate signaling transduction via phosphorylation of Akt (pAkt) [13, 16, 18]. Downstream targets of pAkt are involved in cell cycle regulation (p70S6 kinase), protein synthesis through mammalian target of rapamycin (mTOR), and cell survival by inactivation of pro-apoptotic Bad.

PI3K Signaling in Pancreatic Cancer

PI3K and Cell Cycle Regulation

The PI3K pathway controls G_1-phase progression of PDAC cells by regulating a complex genetic program, involving several key G_1-phase-controlling genes like S-phase kinase-associated protein 2 (SKP2) and cyclin D1. The PI3K pathway is linked to the SKP2 gene promoter via E2F transcription factor 1 (E2F1) [19]. Recently, it was demonstrated that PI3K/Akt/glycogen synthase kinase 3 (GSK3)-dependent control of c-Myc protein expression was connected to E2F1 gene transcription in PDAC cells, leading to S-phase progression of the cell cycle [20]. A positive feedback loop between PI3K and E2F1 may exist, potentially involving the adaptor protein Grb-associated binder 2 (Gab2) pathway, as found in the liver [21, 22].