

Progress in research on pancreatic cancer related signaling pathway

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Abstract: Pancreatic cancer is a very malignant tumor, and its incidence is increasing year by year, which seriously threatens people's health. At present, in addition to surgical treatment, molecular pathway-related targeted therapy is becoming a hot topic for treatment. This article will combine the relevant literatures to review the related molecular pathways of pancreatic cancer, and provide more theoretical basis for targeted therapy.

Keywords: Pancreatic cancer; Signaling pathway; JAK/STAT; GNAS; PIK3CA EGFR; K-ras

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1. Introduction

Pancreatic carcinoma (PC) has been a malignant disease associated with high mortality for decades, and it has been the leading cause of cancer-related deaths worldwide[1,2]. 5-year overall survival rate is less than 5%[3]. Pancreatic cancer mortality will exceed breast and colorectal cancer by 2030, and there is a lack of clinically validated pancreatic cancer screening methods during the treatment phase[4]. Because pancreatic cancer is a retroperitoneal organ, its location is deep. Therefore, its pathogenesis and growth are concealed, and there are no obviously signs. It usually does not cause any symptoms at early stage. At present, the techniques are not good for its early diagnosis. Sensitivity and specificity, most of which are found to be advanced, so only 15% to 20% of pancreatic cancer tumors can be removed[5,6]. The median survival of patients with untreated only 6 months, and the percentage of patients with long-term survival was extremely low. Because pancreatic cancer responds poorly to chemotherapy and radiation therapy[7], surgery is still the only option for cure[8]. The 5-year survival rate for patients undergoing resection is about 23.4%, and the proportion of all patients will fall to 6%. Few other effective treatments can significantly prolong the overall survival of pancreatic cancer[9,10]. Ultimately, most patients death are liver, lung and/or peritoneal metastases[11]. To date, cancer-related research has not had a substantial impact on the natural course of pancreatic cancer. Therefore, it is necessary to understand the molecular pathways that plays a key role in the development of pancreatic cancer, and to discuss potential biomarkers and potential targets for treatment.

2. JAK/STAT signaling pathway

JAK belongs to the cytoplasmic tyrosine kinase family and is composed mainly of four members,

JAK1, JAK2, JAK3 and Tyk2. Activation of the Janus kinase/signal transduction and transcription (JAK/STAT) pathway were found in many human cancers[12]. JAK is activated when ligands bind to receptors on the cell surface, leading to the production of binding sites which interacting with a protein comprising a phosphotyrosine-binding Src homology 2 domain (SH2). STATs belong to a family of downstream transcription factors of JAKs and contain tyrosine residues phosphorylated by JAKs, which promote nuclear translocation[13]. In the nucleus, STATs act as transcription factors that initiate transcription of downstream target genes. Abnormal regulation of the JAK/STAT pathway often leads to cell transformation and promotes cell proliferation, apoptosis and angiogenesis[14]. Targeted inhibition of JAK/STAT3 in combination with the anticancer drug gemcitabine can significantly inhibits tumor growth in a mouse model of pancreatic ductal adenocarcinoma[15].

3. GNAS and PIK3CA signaling pathways

GNAS is a very complex gene that encodes a variety of proteins, such as the G-protein alpha-subunit ($G\alpha$), which utilize seven transmembrane receptors for signal transduction[16]. Activated $G\alpha$ induces an enzyme called adenylate cyclase and produces cyclic AMP (cAMP). cAMP then activated an important signal transducer called protein kinase A (PKA) for cell growth and proliferation[17]. The $G\alpha$ pathway also interacts with and activates other signaling pathways, such as the Wnt and Ras-MAPK pathways, and promotes the growth of malignant cell clones. The presence of GNAS mutations in the development of pancreatic cancer appears to be more pronounced in the early stages of carcinogenesis and is more common in pancreatic cancer precursor lesions known as intraductal papillary mucinous neoplasms (IPMN)[18]. Activated GNAS signaling together with the K-RAS

mutation can induce IPMN, which is a dual interaction between the two oncogenic pathways. Current evidence suggests relatively frequent *GNAS* mutations in pancreatic cancer from IPMN, whereas there is no *GNAS* mutation in neonatal pancreatic cancer. Therefore, the relationship between *GNAS* mutations and pancreatic cancer is limited to premalignant mucinous lesions[18]. These findings suggest that *GNAS* is a key signaling molecule in pancreatic cancer and may be more specifically involved in cancer caused by IPMN.

PIK3CA is another downstream signaling molecule of the tyrosine kinase receptor that activates the Akt-mTOR pathway. PIK3CA-activated Akt-mTOR promotes cancer cells growth and proliferation[19]. The mutant PIK3CA stimulates downstream signaling, which initiates transcriptional activity and produces cancer cells that survive in the nutrient-deficient microenvironment and invade the matrix[20]. PIK3CA-activated Akt-mTOR pathway also inhibits apoptosis by increasing the expression of anti-apoptotic Bcl-2 family proteins[21]. In addition, overactive PIK3CA signaling resists K-Ras-induced senescence in the early stages of carcinogenesis[22]. The PIK3CA-mTOR cascade enhances Ras-MAPK-mediated cell growth by inhibiting tumor suppressor gene activation. Research works have shown that activation of PIK3CA occurs in the early stages of pancreatic cancer and also detectable in IPMN lesions[22]. Due to the potential anti-apoptotic effects and growth stimulating potential, PIK3CA may have a more pronounced effecting on pancreatic cancer[20]. For example, in vitro studies have shown that apoptosis can be successfully induced after inhibition of upstream and downstream signaling pathways of PIK3CA. Xenograft models of human pancreatic cancer have also shown inhibition of tumor growth by mTOR inhibitors[23].

4. EGFR signaling pathways

The most studied epidermal growth factor receptor (EGFR) is HER-1 (c-erbB-1) and HER-2 (c-erbB-2), which is closely related to the occurrence and development of many malignant tumors. EGFR is a trans-membrane Glycoprotein, when a ligand binds to the extracellular domain of a receptor, causes autophosphorylation of the receptor's intracellular domain and activates intracellular tyrosine kinases, triggering a series of downstream signaling pathways that regulate various aspects of cellular function, including cells proliferation, apoptosis, angiogenesis, etc. In many tumors, these conduction pathways regulate abnormalities which resulting in excessive cell proliferation, migration, infiltration, etc[24]. The EGFR family is a subset of receptor tyrosine kinases that have been shown to be active in many epithelial cancers such as colorectal cancer, breast cancer and lung cancer[25]. EGFR is known to be an activator of

K-RAS, PIK3CA, signaling and transcriptional activator (STAT), and phospholipase C (PLC)[26]. They promote cell growth, proliferation and invasion by modifying gene expression profiles and creating unique pathways for each cancer cell.

Related studies have confirmed that EGFR is highly expression in pancreatic cancer tissues[27]. Clinical data suggest that up-regulation of EGFR may be closely associated with more aggressive behavioral tumors[25]. Higher EGFR activity is also associated with a higher recurrence rate after pancreatic cancer surgery[28]. Therefore, an in-depth study of the role of EGFR signaling inhibitors in pancreatic cancer has a very important role.

5. K-RAS signaling pathways

Genomic studies have confirmed that the proto-oncogene K-RAS mutation is a hallmark of PDAC, and it has been reported that more than 90% of patients with pancreatic cancer have mutations[29]. K-Ras is a small GTPase that is regulated by downstream signaling pathways such as EGFR, which plays a role in the body tyrosine kinase. Mutations in the K-Ras oncogene lead to increasing function of the extracellular signal-regulated kinase pathway (MAPK, ERKs) and constitute an activation of the extracellular signal-regulated kinase pathway[30]. Once ERK is activated, it transfers to the nucleus and promotes the transcriptional activity of target genes involved in cell survival, growth and proliferation[31]. The RAS oncogene also interacts with other important signaling molecules and plays an important role as a survival pathway. Phosphatidylinositol-3-OH kinase (PIK3CA) is an important signal transduction molecule for G1 phase protein synthesis in the cell cycle[32]. Other growth-stimulated receptors such as K-RAS and EGFR activate PIK3CA, which promotes tumor cell growth and prepares for the next phase of the cell cycle[33]. K-Ras oncogenes are also associated with other stress responses and cell growth. Signaling molecule interactions, such as c-jun N-terminal kinase (JNK) and protein kinase C (PKC)[34], which suggest that the signaling network of pancreatic cancer cells is very complex. Once the pathways associated with growth stimuli are activated, others Cellular responses are also activated to respond to cellular stress and microenvironmental changes such as hypoxia and free radical production. KRAS is a member of the rats gene family and is one of the earliest discovered mutant genes in pancreatic cancer. It is an important and common mutant oncogene observed in pancreatic tumors[35]. Many reports have confirmed that KRAS mutation plays an important role in tumorigenesis in PDA and IPMN[36,37].

Studies in a genetic mouse models have shown that acute pancreatitis significantly leads to rapid development of pancreatic intraepithelial neoplasia and accelerates the progression of pancreatic cancer in

mice expressing Kras[38]. Some research works have also shown that Kras can regulate glucose metabolism by pentose phosphate ways to maintain persistent growth of pancreatic tumors[39].

6. Summary and outlook

The current research on the pancreatic cancer signaling pathway in the development and progression of pancreatic cancer is still a research hotspots in the field of targeted therapy of malignant tumors. We briefly reviewed the mechanism of action of pancreatic cancer signal transduction pathways. With the development of related pathways, it is believed that the researches of various pathways will be a clinically effective treatment for pancreatic cancer. The puzzle provides a brighter future.

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