Inflammation to cancer: The molecular biology in the pancreas (Review)

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Abstract. Inflammatory responses are known to be correlated with cancer initiation and progression, and exploration of the route from inflammation to cancer makes a great contribution in elucidating the mechanisms underlying cancer development. Pancreatic cancer (PC) is a lethal disease with a low radical-resection rate and a poor prognosis. As chronic pancreatitis is considered to be a significant etiological factor for PC development, the current review aims to describe the molecular pathways from inflammation to pancreatic carcinogenesis, in support of the strategies for the prevention, diagnosis and treatment of PC.

Contents

1. Introduction

Pancreatic cancer (PC), for which the overall 5-year survival rate among patients is ~6% (1) , has the fourth highest incidence ratio of cancer-related fatalities, with <10% of patients having the opportunity of radical surgery at diagnostic presentation. Current evidence has indicated that the associated risk factors include smoking, alcoholism, diabetes mellitus, genetic factors and chronic pancreatitis (CP) (2-6). However, the causes and mechanisms of PC remain unclear.

Inflammatory responses play a significant role in cancer development, including the initial malignant conversion. The potential association between inflammation and cancer has been observed in various types of malignancies, including persistent *Helicobacter pylori* infection with gastric carcinoma (7), inflammatory bowel disease with colorectal cancer (8,9) and reflux esophagitis with esophageal adenocarcinoma (10). It is widely believed that tumor initiation is triggered by multiple mutational hits that induce DNA damage and genomic instability. The potential carcinogens produced from inflammatory cells, such as reactive oxygen species (ROS) and reactive nitrogen intermediates, are capable of inducing malignant initiation through accumulation of continuous DNA damage and subsequent abortive repair. Furthermore, the production of growth factors and cytokines during the inflammatory process can enhance the proliferation of initiated cells by eventually converting them to tumor cells (11). Assessing the link between chronic inflammation and tumorigenesis may provide a different approach to understanding the pathological mechanisms of tumor development. Accordingly, the present review discusses the molecular biology of CP to PC, which may contribute to furthering the clinical diagnosis and therapy.

2. Chronic pancreatitis and risk of pancreatic cancer

Several studies have demonstrated a strong link between antecedent CP and PC. The incidence is variable and the standardized incidence ratio (SIR) has been reported to be between 3.8 (12) and 18.5 (13). In 1993, Lowenfels *et al* (14) launched an international cohort study with 2,015 patients, demonstrating that the SIR was 14.4. The risk of malignant transformation 10 and 20 years after diagnosis was 1.8 and 4.0%, respectively. However, certain epidemiological factors, including cigarette smoking and alcohol (15), which are considered as cofactors in the development of pancreatitis, are also responsible for the increased PC incidence (6,16).

Additionally, two recent large-sample case-control studies of PC identified that a short temporal history of pancreatitis

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was highly associated with PC (17), indicating that pancreatitis may be an early manifestation of PC in specific individuals. Patients with PC may be diagnosed with CP in the first diagnosis, while the differential diagnosis between early CP and PC is difficult. The misdiagnosis may elevate the correlation of the two.

However, with adjustments or matching variables, including smoking habit and alcohol consumption, the risk of PC increases in patients with CP (18). In patients with hereditary pancreatitis, the lifetime risk of PC is ~40% (19), and similarly, for those patients with tropical pancreatitis, the risk of PC is also high (20). Furthermore, a study by Talamini *et al* (13) analyzed 715 cases of CP with a median follow-up of 10 years, observing that the risks of PC and non-PC were increased as compared with the general population. Notably, the clearly higher incidence of PC indicated that although cigarette smoking contributed to various tumors, there were certain other factors linked to the chronic inflammation of the pancreas, which may be responsible for the increased risk.

In summary, CP is determinately considered as an independent risk factor for PC. This risk is markedly increased in those patients with hereditary pancreatitis or tropical pancreatitis.

3. Molecular pathway between chronic pancreatitis and cancer of the pancreas

With the documented link between CP and PC, the molecular pathway from inflammation to cancer in the pancreas exhibits an increasing significance for deeper analysis. Novel molecular changes have been observed in CP and PC simultaneously, including K-ras mutations (21,22) and serine protease inhibitor Kazal type 1 (SPINK1) gene N34S mutations (23,24). In addition, the cyclooxygenase-2 (COX-2) enzyme and nitric oxide (NO), which are considered to be inflammatory mediators and have been found to be overexpressed in patients with CP (25,26), may act as key factors in the tumorigenesis in CP. Therefore, further discussion in the present review focuses on the roles of novel molecules in pancreatic tumorigenesis.

3.1. K-ras

The Ras family, which consists of three members, known as H-, N- and K-ras, are proto-oncogenes that encode a highly-homologous group of 21-kDa monomeric, membrane-localized guanosine triphosphate (GTP)-ases. The main function of these proteins is to transmit signals between the extracellular and intracellular environment, acting as a 'molecular switch'. As downstream molecules with normal regulation sustaining the homeostasis associated with cell proliferation and apoptosis, the error state-like point mutation, multiple expression, insertion and transposition of the Ras genes are responsible for the carcinogenesis of numerous organs.

The K-ras gene is located on chromosome 12p12, and is ~45,000 bp in length. K-ras is the most cancer-related protein in the p21 Ras proteins, existing in two alternatively spliced forms, K-Ras4A and K-Ras4B, which have differing c-terminal residues resulting in differential post-translational modification. Mutations frequently detected in codon 12, 13 and 61 of the K-ras gene result in the subsequent translational product remaining in the GTP-bound (27), activated state, which may activate the downstream pathways, including Raf/MEK/extracellular signal-regulated kinase (ERK) (28-30) and Ras/phosphatidylinositol-3-kinase (PI3K)/Akt (31,32). The complex intracellular regulations originating from the K-ras mutation finally result in a proliferation and apoptosis-related malignant transformation in certain cells (32,33). Constitutive activation of K-ras has been observed in specific pathological changes in the pancreas, including CP, pancreatic intraepithelial neoplasia (PanIN) and PC (34), among which the simultaneous overexpression of K-ras exhibiting the potential linkage, has attracted widespread attention. Mu *et al* (35) investigated the clinical significance of K-ras gene mutation detection in patients with CP and observed that screening for the K-ras mutation may be useful in identifying patients with pancreatitis that are at a high risk for developing cancer. In 2007, Guerra *et al* (36) established a mouse model with CP induced by caerulein treatment, and observed that the chronic inflammation in the pancreas could facilitate the differentiation of acinar/centroacinar or their precursor cells into ductal-like cells, resulting in PanINs and pancreatic ductal adenocarcinoma (PDA) by the selective expression of an endogenous K-RasG12V oncogene in adult mice. The formation of PanINs followed a defined progression from low- to high-grade lesions that resulted in the appearance of invasive PDA by completely depending on K-RasG12Vgeo expression, as reported similarly in other studies (21,37). Guerra *et al* (36) also assessed the cooperation between K-RasG12V expression and p53 inactivation, observing that the additional mutation of p53 could strongly enhance the metastatic properties of K-RasG12V-induced PDA. As reviewed in these studies, it is now accepted that the K-Ras oncogene forms the linkage between CP and PDA. Recently, Guerra *et al* (38) completed a further study to approach the molecular pathways from CP to PC with expression of a resident K-ras oncogene in adult mice. The study demonstrated that the K-ras mutation could initiate murine PanINs (mPanINs) and murine PDAC (mPDAC) in adult mice with pre-existing pancreatic damage and an inflammatory response. Furthermore, the study also observed that the loss of p16Ink4a/p19Arf and Trp53 in adult acinar cells only contributed to the mPanIN and mPDAC development in the presence of K-Ras oncogenes, which may confirm the key role of K-ras in the carcinogenesis in the pancreas. Finally, oncogene-induced senescence, a natural defense mechanism against tumor development (39), was observed to be repressed by the inflammatory response of pancreatitis, and may be one of the mechanisms by which pancreatitis-induced inflammation contributes to PC, cooperating with simultaneous expression of the K-ras oncogene.

Recent studies described a new signaling pathway, the epidermal growth factor receptor (EGFR) signaling pathway, which was indicated to be required for K-ras-driven tumorigenesis and inflammation-associated tumorigenesis in the pancreas (40,41). In the mutant K-ras-driven PDA model, EGFR controls the differentiation of neoplastic precursors and induces tumor initiation, following which, EGFR promotes cancer progression by activating ERK. In addition, certain other signaling pathways are indicated in the participation of K-ras-induced pancreatic tumorigenesis, including the nuclear factor-κB (NF-κB) and Notch signaling pathways (42,43).

The K-ras oncogene is widely believed to be one of the initial components in pancreatic carcinogenesis, as of which several trials have been reported regarding the clinical applications (44,45). However, how the activated K-ras oncogenes are induced by the inflammatory microenvironment remains unclear. More notably, to elucidate the precise timing at which the K-ras mutations become detectable during the chronic inflammatory process will contribute to the early diagnosis of PC. Consequently, much more extensive work on the role of K-ras in pancreatic diseases will be involved in future studies.

3.2. COX-2

COX, also known as prostaglandin-endoperoxide synthetase, is the rate-limiting enzyme responsible for converting arachidonic acid to prostaglandins, leukotrienes and thromboxanes, which are considered to be the proinflammatory cytokines (46). Two isoforms of COX exist. COX-1 is constitutively expressed in numerous tissues and always plays the 'house-keeping' role in tissue homeostasis, whereas COX-2 is an inducible isoform observed to be overexpressed in numerous pathological changes, including inflammation and tumorigenesis (47).

COX-2 expression is elevated in response to a variety of proinflammatory stimuli, including interleukin-1 (IL-1), IL-6, tumor necrosis factor-α (TNF-α) and transforming growth factor-β (TGF-β) (48,49). Several studies have observed the overexpression of COX-2 in CP (25,50), and the COX-2 inhibitors attenuating the severity of acute pancreatitis in a rat model have indicated the correlation between COX-2 and the genesis of pancreatitis (51). Additionally, COX-2 has been found to be upregulated in PanIN (52), intraductal papillary mucinous neoplasm (IPMN) (53) and human PC tissue (53,54). Early suppression of COX-2 may contribute to preventing the progression of inflammatory and pre-malignant lesions to malignance in the pancreas (47-49). COX-2 promotes cell proliferation (58), inhibits apoptosis (59) and facilitates angiogenesis by increasing vascular endothelial growth factor (VEGF) production (60). Previously, a mouse model (61) was generated, in which the overexpression of COX-2 was under the control of a bovine keratin 5 promoter driving pancreatic acinar-to-ductal metaplasia, which revealed that the elevation of COX-2 was significantly correlated with the metaplasia-dysplasia progressing in the exocrine pancreas. However, the precise mechanism by which COX-2 promotes PC growth is unclear.

Thus, COX-2 conducts the definite linkage between inflammation and cancer in the pancreas. However, a number of laboratory and clinical studies, whose conclusions are controversial, have approached the therapeutic significance of targeting COX-2 activity for PC (62-67), and it requires more experimental evidence to confirm whether targeting COX-2 can be applied in clinical treatment.

3.3. NF-κB

NF-κB is a family of transcription factors, including NF-κB1, NF-κB2, Rel A, c-Rel and Rel B. These proteins are constitutively expressed in the cytoplasm of eukaryotic cells in an unactivated state as a result of combining with an inhibitory protein, inhibitor κB (IκB). The exact mechanism of NF-κB activation is complex and not completely clear. The impact of various pathogenic stimuli, including the proinflammatory factors TNF-α, IL-1 and bacterial lipopolysaccharide, enabling phosphorylation of IκBα subsequently results in the degradation of IκBα and exposures the sequence for DNA binding and nuclear translocation in NF-κB. Activated and nuclear translocated NF-κB, as a transcription factor, plays a significant role in the transcriptional control of certain inflammatory and cancer-related genes, including COX-2 (68), IL-8 (69), inducible NO synthase, cyclin D1 (68), c-Myc and VEGF. These molecules, by which NF-κB promotes PC growth, are upregulated and responsible for cell cycle control, angiogenesis and the inhibition of apoptosis in PC progression. Genetic mutations in NF-κB, IκB kinase (IKK) or upstream components of its signaling system have rarely been observed. Otherwise, exposure to the proinflammatory microenvironment resulting in activation of NF-κB in cancer has been widely hypothesized and demonstrated (70,71). The molecules for the activation of the IKK/NF-κB signaling pathway include growth factors, cytokines, lymphokines and microRNA (72), most of which may bridge the gap between inflammation and cancer.

Constitutive activation of NF-κB has been observed in several PC cell lines (73) and human PC tissue (74-76). The proinflammatory cytokine-paracrine loops established by inflammatory, immune and cancer cells potently activate NF-κB in PC (11,77). The autocrine secretion of IL-1α, induced by activator protein-1 activity, has been demonstrated to play a key role in the activation of NF-κB in metastatic PC cell lines (78). In turn, the activation of NF-κB can enhance expression of IL-1α, which results in a positive feedback loop for the constitutive NF-κB activation in PC. Additionally, IL-1α can enhance the expression of several NF-κB-regulated genes, including IL-8 and VEGF, which are responsible for the metastatic processes and angiogenesis of cancer, in PC cells (79). In conclusion, the IL-1α-NF-κB positive feedback loop makes great contributions to support the malignant phenotype in PC.

By contrast, previous studies have shown the essential role of the NF-κB pathway in K-ras-mutant PCs (43,80). As there have been less therapeutic strategies of PC-targeting on the K-ras signaling pathway, the inhibition of NF-κB is an attractive strategy for the treatment of K-ras-dependent PC.

3.4. SPINK1

SPINK1 has been identified as a trypsin inhibitor and is also known as a pancreatic secretory trypsin inhibitor (81). SPINK1 is secreted by the acinar cells of the exocrine pancreas into the pancreatic juice and is able to bind to trypsin to inhibit its activity. SPINK1 protects the pancreas from the impact of prematurely activated trypsinogen, and SPINK1 mutations, particularly the N34S mutation (82), have also been reported to lower the threshold for pancreatitis from other genetic or environmental factors (83) instead of initiating the development of CP.

SPINK1 mutations in patients with pancreatitis are firmly demonstrated in numerous studies (82,84-86). Notably, the intronic mutations, including N34S, IVS1-37T>C and

IVS3-69insTTTT, do not affect the mRNA expression of the SPINK1 gene, and these mutations have not been observed to be capable of affecting the binding affinity and inhibitory activity of SPINK1 to trypsin. Ohmuraya *et al* (87) created a mouse model with deficient SPINK3 (a mouse homologue gene of human SPINK1) and showed that excessive autophagy in pancreatic acinar cells could be induced by the loss of the regulation of SPINK3, indicating that SPINK3 may act as a suppressor of autophagy. Therefore, the pathogenesis of pancreatitis may be more complex, and further studies will be required to elucidate the role of SPINK1 in the onset of pancreatitis.

Previously, Rebours *et al* (88) described the case of a CP-diagnosed patient with an N34S mutation of SPINK1. Cystic fibrosis transmembrane conductance regulator minor mutations were found in the multifocal moderate-dysplastic lesions of PanIN-2 in the duct epithelium following a left pancreatectomy. Shimosegawa *et al* (89) examined whether the SPINK1 gene N34S mutation could be a risk factor for PC in patients with CP. The study investigated the development of PC in three out of 16 CP patients with the N34S mutation (18.8%), while only three of 216 CP patients without the SPINK1 mutation (1.4%) developed PC, indicating that the N34S mutation of the SPINK1 gene may be a significant risk factor for the development of PC in patients with CP. By contrast, SPINK1 itself has been shown to have growth factor activity in various cell lines, including certain cancer cells (90,91). SPINK1 is described as a ligand for the EGFR. Ozaki *et al* (91) observed the increase in the cell numbers of PC cell lines following treatment with SPINK1. The results of their subsequent study demonstrate that SPINK1 stimulates the proliferation of PC cells through EGFR and its downstream signal molecules. The immunohistochemical study showed that SPINK1 and EGFR are co-expressed not only in pancreatic tubular adenocarcinoma, but also in PanINs (92). As EGFR is confirmed to be overexpressed in the tissues of CP and PC (93,94), and SPINK1 is produced by the acinar cells and is then secreted into the pancreatic duct, the interaction between SPINK1 and EGFR may be involved in the malignant transformation of normal pancreatic cells during the inflammatory process. A high level of SPINK1 expression has been reported to be associated with cancer progression, tumor recurrence and patient survival rates in certain other cancers, indicating that SPINK1 has additional functions in extrapancreatic cancers (95,96).

In summary, SPINK1 is described as an inhibitor of the onset of pancreatitis, and the mutation of SPINK1 is able to lower the threshold for pancreatitis from other genetic or environmental factors. In addition, SPINK1 itself can promote PC development through the EGFR pathway, while the other roles of SPINK1 in inflammatory incidence and tumorigenesis remain unknown. More laboratorial and clinical studies are required to support the role of SPINK1 between pancreatitis and PC.

3.5. ROS

ROS are highly reactive oxygen metabolites such as the superoxide radical (O_2^-) the hydroxyl radical (OH^-) hydrogen peroxide (H_2O_2) and trioxygen (O_3). ROS are produced in mitochondria as by-products of oxidative phosphorylation, and are part of the normal cellular metabolism. In inflammatory processes ROS are produced by phagocytes. Additionally, inflammatory cells may use cytokines, including TNF-α and TGF-β (97), to stimulate ROS accumulation in surrounding epithelial cells. In cancer cells, comparatively high levels of ROS can also result from increased metabolic activity, mitochondrial dysfunction, oncogene activity and the increased activity of oxidases, COXs and lipoxygenases (99,99).

ROS can oxidize lipids in the cell membrane, oxidatively modify protein, depolarize the mitochondrial membrane and induce DNA fragmentation to directly damage DNA and induce genomic instability (100). In addition to ROS-induced direct DNA damage, certain by-products produced from ROS-generated lipid peroxidation, including malondialdehyde (MDA) and 8-oxodeoxyguanosine, also known as oxidized DNA adducts, can be potent carcinogenic molecules (101). Varying levels of ROS always result in different effects on cell proliferation. ROS at acute high levels may act as potent cytotoxic molecules inducing cell apoptosis (102). Chronic low levels of ROS can affect genome stability and cause tumorigenesis (103,104), emphasizing the role of ROS in the initiation of malignancy in CP tissues.

Higher levels of oxidative DNA adducts and MDA have been found in patients with CP (105) and also in human pancreatic tumor tissue (106). Identically, the primary intracellular antioxidant enzymes, superoxide dismutase (SOD), catalase and glutathione peroxidase, are detected in the pancreas, and a gradually decreased expression of the three antioxidant enzymes has been shown in pancreatic cells from the normal pancreas to CP to PC (107). The upregulation of SODs can effectively suppress PC growth *in vitro* and *in vivo* (108). It has been indicated that chronic low levels of ROS promote malignant initiation and cancer cell proliferation in the pancreas. By contrast, ROS can active several signaling pathways, including the mitogen-activated protein kinase, PI3K/Akt NF-κB signaling, protein kinase C and p53 signaling pathways (109-111), which may tend to activate cell survival or cell death. ROS can participate in the apoptotic or anti-apoptotic mechanisms in oxidative stress-targeting therapeutics or oncogene-induced malignant transformation (112-115). Therefore, the actual role of ROS in pancreatitis-derived PC was really determined by the extent of accumulation and the regulation of activity. The balanced regulation of ROS in pancreatitis and PC should be further investigated, which may also be regarded as the potential therapy target for PC.

3.6. Proinflammatory cytokines

Proinflammatory cytokines that are secreted by immune and inflammatory cells are significant components in the inflammation and tumor microenvironment. Several cytokines, including IL-1, TNF, IL-6 and IL-23, are critical for inflammation and tumor growth. Varying cytokines affect certain downstream effectors, including NF-κB, activator protein-1, signal transducers and activators of transcription and SMAD transcription factors, to exhibit either promotion or inhibition effects in tumor progression (11,116). By contrast, oncoproteins, such as Ras and Myc, can also promote the secretion

of proinflammatory cytokines, which have direct effects on cancer cell growth and survival (117). Altogether, proinflammatory cytokines significantly mediate the mechanisms of inflammation-related tumor initiation and promotion.

Significantly higher levels of TNF-α, IL-1, IL-6 and IL-8 have been observed in patients with CP and PC compared with healthy controls (118-121). IL-1 acting through the IL-1 receptor type I can promote the invasion and angiogenesis of PC cells (123). The cyst fluid IL-1 levels predict the risk of carcinoma in IPMN, indicating that IL-1 may facilitate malignant transformation in the pancreas (123). TNF-α is classically considered to be an inhibitor of the apoptosis of cancer cells by activating the expression of NF-κB (124-126). Additionally, the inflammatory-derived TNFα is able to stimulate migration and induce the epithelial-mesenchymal transition of human pancreatic carcinoma cells (127). IL-6 has been identified as a growth factor that enhances PC cell proliferation (118,128,129). An elevated IL-6 level is correlated with advanced PC, which is represented by cachexia and a poor-life status (130). IL-8, also known as chemokine (C-X-C motif) ligand 8 (CXCL-8), is a CXC chemokine that is produced by numerous types of cells in response to inflammatory stimuli. IL-8 plays a significant role in neutrophil chemotaxis and activation. In addition to its inflammatory role, IL-8 has been found to be an autocrine growth factor in PC (131,132). The expression of IL-8 is driven by NF-κB activation (133), and numerous cytokines, including TNF-α and leukemia inhibitory factor, can enhance the expression of IL-8 (131). IL-8 acts as a significant effector molecule bridging the gap between inflammation and cancer in the pancreas.

Recently, more cytokines have been identified that are correlated with the clinical stage and prognosis in patients with PC (134-136). Cytokines, as molecules derived from inflammatory cells and immune cells, should be highlighted as prospects for the future exploration of the molecular mechanism from inflammation to cancer in the pancreas.

4. Conclusion

Despite advances in oncology and surgery, patients with PC frequently have a poor performance and clinical prognosis. Clinical evidence has confirmed the correlation between inflammation and pancreatic tumorigenesis. Inflammatory responses play a significant role in PC initiation and progression. In turn, cancer-induced inflammatory microenvironment or secreted inflammatory molecules can enhance the proliferation of cancer cells and promote the inflammatory responses. Exploring the variation in molecular expression and function from inflammation to cancer may aid in the development of a route to reveal the causes and mechanisms of PC. Inflammation-targeted treatments and examinations exhibit an appealing perspective in the therapy and diagnosis (121) of inflammation-related cancer in the pancreas (135,137-139). In addition, great importance should be attached to the inflammatory responses in the process of assigning chemotherapies and surgeries for PC treatment. The treatment of inflammatory changes may be necessary for the preventive and therapeutic schedules of PC.

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