



Inflammation and development of pancreatic ductal adenocarcinoma

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Abstract: Inflammation plays pivotal roles in the development of pancreatic cancer, from initiation, progression to metastasis. In humans, many known risk factors for pancreatic cancer, including alcohol consumption, cigarette smoking, diabetes and chronic pancreatitis, are often characterized by the induction of chronic inflammation. In mice, while oncogenic Kras itself causes spontaneous infiltration of immune cells, the additional chronic inflammatory damage further accelerates the progression of pancreatic cancer. Infiltrated immune cells in pancreatic cancer are essential for the initiation and development of pancreatic cancer, and produce immune-suppressive signals to dampen antitumor T-cell responses in tumor. Investigation into the mechanisms by which leukocytes contribute to the development of pancreatic cancer will help to find new approaches to improve therapy for this disease.

Keywords: Inflammation; pancreatic cancer; immune cells

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Introduction

Early in the 19th century, according to the observations of the presence of immune cells within malignant tissues, the German pathologist Rudolf Virchow first proposed a possible link between inflammation and cancer (1). However, until the past few decades, Virchow's hypothesis was confirmed by solid supporting evidence. Now, it has been widely believed that the inflammatory microenvironment is a crucial component of most tumors, and plays a key role in the tumorigenesis of various organs. Moreover, epidemiologic studies have established the relationship between chronic inflammation and several cancers, including liver cancer, gastric cancer, colorectal cancer, esophageal cancer, pancreatic cancer, and lung cancer. Infectious agents that cause chronic inflammation would increase the risk of carcinogenesis include hepatitis B and C viruses, *Helicobacter pylori* and *Schistosoma haematobium* (2). Noninfectious inflammatory

stimuli, such as alcohol consumption and tobacco smoking have also been identified (3). In addition, obesity, rapidly increasing in global prevalence, has become a recognized cause of chronic subclinical inflammation and is able to promote tumorigenesis in the liver (4) and pancreas (5). Most solid malignancies occur in older individuals, and aging (6) is postulated to be a tumor promoter, which acts at least partially through inflammatory mechanisms. This review summarized the current knowledge about the role of inflammation and leukocytes in the pathogenesis of pancreatic cancer, and its potential as therapeutic target.

Clinical relevance between inflammation and PDAC

Pancreatitis

Acute pancreatitis (AP), a sterile inflammation, initiates

from acinar cell injury following a series of impairment of pancreatic enzymes activation processes, leading to noticeable pancreatic necrosis and the complication of multiple organ failure (7). Long-term population-based study indicates that fewer than half (approximately 20% to 45%) of the patients could develop recurrent AP, especially for those alcohol-induced AP. Besides, the progression from recurrent AP to chronic pancreatitis (CP) occurred in 4–24% of patients, both alcohol consumption and tobacco smoking at this time are the most common risk factors for the transition from RAP to chronic pancreatitis (8–10). CP is a quite refractory disorder characteristic of progressive inflammatory and fibrosis with irreversible damage to both exocrine and endocrine compartments function of the pancreas. The typical histopathologic features of CP contain acinar cell atrophy, pancreatic fibrosis, leukocytes infiltration and fatty replacement, and distorted and blocked ducts (11).

Recurrent episode of acute pancreatitis would progress to chronic pancreatitis, which is a well-defined risk factor for pancreatic cancer. However, findings about the correlation of pancreatitis and pancreatic cancer from epidemiological studies remain conflicting. Histologically, both chronic pancreatitis (CP) and pancreatic ductal adenocarcinoma (PDAC) share the analogous histologic features, namely massive immune cell infiltration and intensive fibrosis. Patients with CP are more susceptible to develop pancreatic cancer. Individuals with hereditary pancreatitis have a cumulative risk of developing pancreatic cancer of 40–55% rate during their lifetime (3). However, most patients with PDAC actually do not have a history of acute or chronic pancreatitis. It might be due to some less aggressive forms of inflammation, like sporadic or even asymptomatic pancreatitis, which may also induce a fibroinflammatory response and promote development of PDAC.

Early in 1993, a multicenter historical study with 2015 subjects with chronic pancreatitis (from 6 countries) had reported that the risk of pancreatic cancer is significantly elevated in subjects with chronic pancreatitis and appears to be independent of sex, country and type of pancreatitis (12). A study with a cohort of 1,656 patients in China observed that the risk of pancreatic cancer is significantly elevated in chronic pancreatitis patients compared with the health population, especially in patients with heavy smoking history or with an older age at disease onset (13). Recently, a meta-analysis containing 22 studies reported a statistically significant increased relative risk of developing pancreatic cancer, with summary RRs (relative risks) of 5.1 in patients with unspecified pancreatitis, 13.3 in patients with chronic

pancreatitis and 69 for hereditary pancreatitis. Although the risk is increased, only about 5% of patients with chronic pancreatitis will progress into pancreatic cancer over a period of 20 years (14). Most previous studies investigating the association of acute pancreatitis and pancreatic cancer failed to report risk assessments by follow-up time. Just recent, a nationwide matched-cohort study in Denmark observed an association between diagnosis of acute pancreatitis and long-term risk of pancreatic cancer (15). This study reported that patients hospitalized with acute pancreatitis had a 2-fold increased risk of pancreatic cancer compared with the matched population, even after 10 years of follow-up. However, the authors had limited information on potential co-risk factors, such as alcohol consumption and tobacco smoking, which could have led to overestimation. Overall, whether acute pancreatitis could be considered a risk factor for the pancreatic cancer remain to be further investigated.

Other inflammatory stimuli, such as alcohol consumption and cigarette smoking, have also been investigated in pancreatic cancer (2,3). Recently, Chen group analyzed the survival of 1,037 PDAC patients from two large US prospective cohort studies diagnosed from 1986 to 2013 by smoking history. They found that compared with non-smokers, the multivariable-adjusted HR for death in current smokers was 1.37 (95% CI, 1.11 to 1.69) ($P=0.003$). Similarly, they observed a statistically significant negative trend in survival for increasing pack-years of smoking ($P_{\text{trend}}=0.008$), the HR for death in patients for >60 pack-years of smoking was 1.49 (95% CI, 1.05 to 2.10) comparing with those never smoke (16). In addition, obesity, which is rapidly increasing in global prevalence, becoming a recognized cause of subclinical and chronic inflammation and promotes tumorigenesis in the pancreas (5). In 2011, Jeanine and colleagues conducted a compiled analysis of 14 cohort studies on 846,340 individuals, and 2,135 people among them were diagnosed with pancreatic cancer during follow-up. Surprisingly, they observed a 47% higher risk (95% CI, 23–75%) among obese (body mass index, BMI ≥ 30 kg/m²) individuals compared to individuals whose BMI was at baseline between 21–22.9 kg/m². Meanwhile, waist to hip ratio (WHR) was positively linked to pancreatic cancer risk (17).

Evidence from animal models

Origin cells of PDAC-acinar cells vs. ductal cells

Chronic pancreatitis and PDAC were previously considered

as unrelated diseases because they were thought to arise from acinar and ductal cells respectively. Animal model where PDAC was considered to be derived from ductal cells was based on the study of pancreatic intraepithelial neoplasias (PanINs), the non-invasive lesions composed of columnar to cuboidal ductal cells (18,19). The PanIN-PDAC progression model was based on: (I) several case reports have documented patients with PanINs who later developed pancreatic cancer; (II) PanINs harbor many of the genetic alterations that are found in invasive pancreatic cancer (20). However, the origin of duct cell in this PanIN-PDAC progression model has been challenged as mouse lineage tracing experiments show that oncogenic Kras activation in pancreatic normal ductal cells couldn't trigger the initiation of pancreatic cancer (20,21).

While recently several mouse models supported the notion that activation of oncogenic Kras specifically in acinar cells during embryonic development stage could induce the formation of PanINs and further development of invasive ductal carcinoma (22-24), coming up the concept of an acinar cell origin for PDAC. Thus, upon stress (i.e., Kras activation), acinar cells can dedifferentiate and acquire features of pancreatic progenitor duct-like cells, expressing the transcription factors Pdx1, Ptf1a, Hes1, Hnf1b and Sox9 (25-27). In all, pancreatic cancer cells originate from acinar cells through acinar-to-ductal metaplasia (ADM), however the dedifferentiated acinar cells don't undergo malignant transformation until facing the additional insult (i.e., inflammation or loss of tumor suppressor gene) (24,28).

Pancreatitis is indispensable to PDAC development

Although clinical evidence on the relationship between pancreatitis and pancreatic cancer remains unclear, several groups had proved their causal relationship by a series of mouse models of pancreatic cancer. The most widely used pancreatitis model involves treatment with the cholecystokinin agonist caerulein, which induces necrosis, inflammation, edema and transient acinar to ductal metaplasia (ADM). Pancreatitis induced ADM could be rapidly transdifferentiated into acinar cells for tissue recovery. However, under the oncogenic activation of Kras, instead of regenerating to acinar cell, inflammation-induced ADM would progress to PanIN and PDAC.

Pancreas-specific expression of constitutively active Kras (G12D) using PDX1 or p48 promoter-driven Cre-loxP system resulted in embryonic activation of Kras, which could

develop pre-neoplastic lesions as early as 2-3 months. In 2010, Morris and colleagues confirmed that embryonic activation of Kras cooperating with acute pancreatitis accelerated acinar-to-ductal metaplasia (ADM) and preinvasive lesion formation of pancreatic cancer by blocking acinar regeneration in genetically engineered mice (23).

In view of the fact that the somatic Kras mutation in human PDAC originates from adulthood rather than during embryonic development, several groups with inducible Cre system have surprisingly found that adult acinar cells were more refractory to Kras-induced ADM and PanINs formation, while chronic pancreatitis with caerulein treatment would render the acinar cells susceptible to carcinogenic Kras transformation and leads to the development of the full spectrum of PanINs and PDAC. Early in 2007, Guerra's group generated adult (P90) K-Ras^{G12V}; *Elas-tTA/tetO-Cre* mice (the expression of Cre recombinase under the control of *Elastase* promoter in a tet-off system), and exposed them to different time of caerulein. The results indicated that the inflammatory response was indispensable for induction of PanINs and PDAC in adult mice (24).

In humans, chronic inflammation is one of the highest risk factors for developing PDAC (12), but most PDAC patients do not have a history of acute or chronic pancreatitis. Therefore, it is important to determine whether less aggressive forms of inflammation, including sporadic or even asymptomatic pancreatitis, may also increase the risk of developing PDAC. As reported by Guerra *et al.*, limited bouts of mild pancreatitis lasting as short as 4 weeks were sufficient to initiate mPanIN formation, providing that the injured acinar cells expressed an oncogenic Kras (29). Moreover, PDAC could also develop if pancreatitis occurred before activation of Kras, indicating that the inflammatory response has not subsided. These findings raised the possibility that human PDAC may be also generated from limited episode of pancreatitis, as long as that the inflammatory response co-existed with sporadic KRas mutations.

In addition, Rhim *et al.* showed that EMT (Epithelial-to-Mesenchymal Transition) occurred in PanIN lesion and ADM prior to tumor formation, and this process could be promoted by pancreatitis/inflammation. This result provides an insight that inflammation enhanced cancer progression in part by facilitating EMT and entry into the circulation (30). Taken together, based on engineered mouse model, inflammation enhances initiation and progression of pancreatic cancer, and even facilitates EMT and dissemination at early preinvasive stage of PDAC.

Immune cells in the development of PDAC

Genetically engineered mouse models have facilitated assess the role of immune cells in the development of PDAC. PDAC are characterized by abundant immune cells infiltration, including T cells, B cells, neutrophils monocytes/macrophages and mast cells. However, these cells produce an insufficient antitumor immune response and even promote tumor growth. In recent decade, accumulating evidence has shown that immune cells existed in the tumor microenvironment contributed to PDAC initiation and progression, immuno-suppressive microenvironment formation and even chemotherapy resistance. In general, immune cells interact with cancer cells and/or their surrounding stroma cells by means of direct contact in autocrine and paracrine manners.

Tumor-associated macrophages (TAMs)

Monocytes/macrophages are the main component of the immune infiltration during the onset of pancreatic carcinogenesis, their infiltration is also noted early on around neoplastic ducts in PanIN lesion and persists around neoplastic epithelium in invasive carcinomas (31). Generally, circulating monocytes are recruited into tumor microenvironment in response to tumor cells-induced chemokines/cytokines. Both pancreatitis (32,33) and Kras oncogenic activation (34) could trigger the infiltration of monocytes/macrophages, which would further enlarge the local inflammation. As is known to all, the CCL2/CCR2 chemokine axis is critical to the mobilization of monocytes from the bone marrow to sites of inflammation where they differentiate into macrophages. It has been reported that human pancreatic cancers express CCL2, triggering CCR2⁺ immunosuppressive monocytes/macrophages infiltration into the tumor site (35). Targeting CCL2/CCR2 axis is proved to be an effective immunotherapeutic strategy in pancreatic cancer (36,37).

Storz group had shown that Kras oncogenic activation induced the expression of ICAM-1, served as a chemoattractant for monocytes /macrophages, and expedited the formation of PanINs (34). Macrophages are a heterogeneous population with strong plasticity, thus in the context of a large variety of microenvironment signals, recruited monocytes/ macrophages could be differentiated into distinct functional phenotypes. Classically activated macrophages (M1) are activated mainly by Th1 cytokines such as interferon- γ (IFN- γ), interleukin-1 β (IL-1 β) and

lipopolysaccharide, which are characterized by production of high levels of IL-12, IL-23 and TNF α . While alternatively activated macrophages (M2) are activated largely by Th2 cytokines such as IL-4 and IL-13, which are defined by production of transforming growth factor TGF β and IL-10 (38-40). Recently, compelling evidence has emerged that macrophage polarization state and spatial localization with tumor microenvironment influenced the initiation, progression and invasion of PDAC. Macrophage secreted factors like TNF α and CCL5 had been shown to induce ADM through activation of NF κ B, and macrophage depletion blocked pancreatic ADM (41). Zhang *et al.* showed that epithelial-myeloid cell crosstalk regulated ADM in mice, at least in part, on activation of EGFR/MAPK signaling (42). Recent research showed that recruitment of metastasis-associated macrophages (MAMs) was crucial for liver metastasis in PDAC. And granulin secretion by MAMs could transdifferentiate resident HSCs into myofibroblasts, resulting in a fibrotic microenvironment to sustain metastatic tumor growth (43). PI3K γ , a key macrophage-lipid kinase, regulated macrophage polarization programming, leading to suppression of CD8 T cells and liver metastasis in pancreas adenocarcinoma (44). Just recently, a study from Lyssiotis group identified that TAM released a spectrum of pyrimidine nucleosides that were consumed by pancreatic cancer cells. Among these, deoxycytidine could directly compete with gemcitabine, hindering its efficiency as a chemotherapy (45). Moreover, TAMs have been shown to promote an immunosuppressive environment via inhibiting T cell immunity (46), to regulate angiogenesis and lymphangiogenesis (47).

Myeloid-derived suppressor cells (MDSCs)

MDSCs represent a heterogeneous population of myeloid-derived cells with suppressive activity that comprised of myeloid progenitor cells and immature myeloid cells (48,49). Growing evidence has been shown that MDSCs negatively regulated both CD4⁺ and CD8⁺ T cell functions and were responsible for significant immune dysfunction during cancer and other diseases (50-52). Increased number of MDSCs with immunosuppressive potential had been found in PanINs and PDACs tissues compared with normal pancreatic tissues (31). Moreover, patients with PDACs had elevated number of MDSCs in the bone marrow and peripheral blood (53). Recently, GM-CSF was shown to promote MDSCs maturation and recruitment to the tumor microenvironment of PDAC (54). Recently, the study

demonstrated that targeted depletion of MDSC subset unmasked PDAC to adaptive immunity (55).

Tumor-associated neutrophils (TANs)

Neutrophils, the most abundant myeloid population derived from bone marrow, is believed as the first effector cells infiltrated to the sites of infection (56). Emerging evidence supports that neutrophils assist immune escape and tumor progression in various cancers. Tumor-associated neutrophils (TANs) have been classified as two distinct functionally population: the anti-tumor N1 and the pro-tumor N2 neutrophils. Neutrophils were prone to be N2 in the presence of TGF β , and were able to convert into N1 subtype with TGF β blockade (57). A systematic analysis of neutrophils in clinical specimens indicated that neutrophils infiltration was typically presented in the micropapillary and undifferentiated types of PDAC with poor prognosis (58). A recent study reported that CXCR2⁺ TANs were elevated in human PDAC and related to poor prognosis (37). Consistently, Steele *et al.* showed that CXCR2 signaling in the myeloid compartment could promote pancreatic tumorigenesis and was required for pancreatic cancer metastasis (59).

Mast cells

Mast cells as another type of leukocyte in the innate immune response, have begun to receive attention for its role in human cancers. Mast cells regulate adaptive immune responses via the release of cytokines and other immunomodulatory factors, and these factors can promote immune suppression and may contribute to PDAC progression. Recently, several studies had proved that mast cells in tumor microenvironment were indicative of poor prognosis in human PDAC, and were essential for PDAC tumorigenesis (60,61). Mast cell promoted PDAC growth and progression via communicating with pancreatic cancer cells and stromal cell respectively (62-64).

CD4⁺ T cells and subtypes

Encountering antigenic stimulation, Th cells respond to differentiate into several mature-state subsets including Th1, Th2, Th17 and Th22 respectively under different induction. Several groups had shown that PDAC stroma was predominantly infiltrated by Th2 (GATA-3⁺) over Th1 (T-bet⁺) cells (65,66), and the ratio of GATA-3⁺/T-bet⁺

tumor infiltrating lymphoid cells was an independent predictive marker of patient survival (65).

IL-17A derives from both Th17 cells and $\gamma\delta$ T cells and can exert pro-tumorigenic effects by virtue of a variety of mechanisms (67,68). With respect to pancreatic cancer, McAllister and his colleagues demonstrated that IL-17A, produced from Th17 cells and $\gamma\delta$ T cells, served as a potent and requisite driver of PanINs through hematopoietic to epithelial IL-17 signaling axis. Oncogenic Kras induced functional IL-17 receptors expression on the PanIN epithelial cells, meanwhile also stimulated the infiltration of IL-17-producing immune cells, both effects could augment upon chronic inflammation (69). Furthermore, they revealed that immune cell-derived IL-17A could induce stemness features of PanINs via induction of DCLK1, POU2F3 and ALDH1A1 (70).

$\gamma\delta$ T cells are a non-major histocompatibility complex (MHC)-restricted lymphocyte subset closely aligned with innate immunity, which constitute about 40% of tumor-infiltrating T cells in human PDAC. Recent study from Miller group showed that deletion, depletion, or blockade of $\gamma\delta$ T cell recruitment was protective against PDAC and resulted in increased infiltration, activation of Th1 cells, suggesting $\gamma\delta$ T cells were key regulators of effector T cell activation in pancreatic cancer (71).

IL-22 producing CD4⁺ T cells (Th22) are a new subset of Th cells discovered in recent years, which mainly play a critical role in anti-inflammatory response and in tumorigenesis (72-74). Our previous study revealed that IL-22 secreted from CD4⁺ T cells could enhance the stemness and tumorigenicity of PDAC cells through activation of STAT3 signaling (75). Moreover, we found that chronic pancreatitis (CP) patients with a smoking history had elevated serum IL-22 compared to those without smoking history. With CP animal models, we revealed that cigarette smoking promoted Th22 both in the pancreas and PBMC via activation of aryl hydrocarbon receptor (76).

CD8⁺ cytotoxic T cells

Cytotoxic CD8⁺ T lymphocytes are important effector cells in adaptive immunity, which can specifically recognize tumor targets and clear the tumor cells. However, the presence of CD8⁺ cytotoxic T-cell is usually rare in the stromal microenvironment of PanINs and PDAC (31). Unlike other immune cells, increasing number of CD8⁺ cytotoxic T-cell was associated with significantly

prolonged survival in human pancreatic cancer (77,78). Recent studies have been suggested that MDSCs were equipped to effectively drive the exhaustion of CD8⁺ T-cell infiltration in PDAC (31). It is worth mentioning that a recent study demonstrated that activated PSC in PDAC sequestered anti-tumor CD8⁺ T-cell migratory and adhesive function in a CXCL12-dependent manner in the pan-stromal compartment (79). It is widely accepted that the interaction between PD-1 and PD-L1 checkpoint would lead to T cell dysfunction, exhaustion, and tolerance. In PDAC, Zhang group demonstrated that CD11b⁺ myeloid cells blocked anti-tumor CD8⁺ T cells immune responses via activating the PD-1/PD-L1 checkpoint. Depletion of CD11b⁺ myeloid cells reversed immune suppression and enabled CD8⁺ T-cell effector function, which resulted in the prohibition of tumor growth (80).

Immune-based therapeutic strategies

Inflammation plays a key role in cancer progression. PDAC is a highly malignant disease that is one of the worst 5-year survival rates among all cancers. Local recurrence and metastasis are common for patients with PDAC, even in patients undergoing gross total surgical resection. Because standard therapies have only modest effect on survival, novel therapeutic and diagnostic strategies are urgently needed for PDAC.

Based on the current understating of inflammation and PDAC, anti-inflammatory treatment has been tested in multiple mouse models (35,81).

Sulindac, a non-steroidal anti-inflammatory drug targeting on COX-1 and COX-2 enzymes, was able to delay progression of pancreatitis-induced mPanIN lesions (29). As we describe above, myeloid lineage cells, including macrophages, neutrophils, mast cells, and myeloid-derived suppressor cells, play important roles in the initiation of pancreatic carcinoma and in establishing an immune-suppressive microenvironment. Therefore, suppression in PDAC by inhibiting myeloid cell trafficking or activation (35,36), or by reactivating adaptive immune responses (82,83), or by the application of checkpoint inhibitors (80) has shown that targeting of the immune system may become novel and effective strategies for pancreatic cancer treatment. Furthermore, targeting immune cells combined with conventional chemotherapy is likely to yield promising outcome.

Due to lack of CD8⁺ T cells in the tumor microenvironment of PDAC, the strategies to inhibit the immune checkpoint

PD1/PD-L1 and CTLA-4 fail to demonstrate efficacy in advanced PDAC patients. Many studies have been performed to identify a possible role of modulators of innate immunity in PDAC therapy. CD40 is a costimulatory protein that is necessary for the activation of T lymphocytes. The efficacy of CD40 agonist was assessed in a Phase I clinical trial in metastatic PDAC patients, with partial responses reported in almost 20% of patients (84). Steele *et al.* showed that loss or inhibition of CXCR2 in the myeloid compartment improved T cell entry, and combined inhibition of CXCR2 and PD1 in mice with established PDAC significantly extended survival (59). Consistently, dual targeting of CCR2⁺ TAM and CXCR2⁺ TAN improved anti-tumor immunity and chemotherapeutic response in PDAC compared with either strategy alone (37). Besides blocking the trafficking of immune cells, taking advantage of plasticity of TAMs, pharmacologic inhibition of PI3K γ with TG100-115 could reprogram TAMs and suppress PDAC growth and metastasis (44).

Conclusions

The gathered data clarify the relationship between inflammation and cancer, and provide new insights into development and treatment of pancreatic cancer. Inflammation impacts every single step of tumorigenesis, from initiation through tumor promotion, all the way to metastatic progression, as well as the response to chemotherapy. A better understanding of mechanisms by which leukocytes promote PDAC progression will help us find a way to improve therapy for this disease.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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