Cancer Screening and Prevention **2022** vol. 1(1) | 39–46
DOI: 10.14218/CSP.2022.00012

Review Article

The Positive Feedback Loop Between Inflammation and Mutant KRAS Genes Promotes Malignant Transformation in Chronic Pancreatitis

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Received: June 27, 2022 | **Revised:** October 10, 2022 | **Accepted:** October 19, 2022 | **Published:** November 16, 2022

Abstract

Pancreatic cancer (PC) is one of the most dismal diseases with a five-year survival rate of only 6%. Such poor prognosis is attributed to both a lack of early detection methods and its intrinsic resistance to cytotoxic agents and radiotherapy. Identifying driving events in the initial stage is of great significance for curable pancreatic ductal adenocarcinoma (PDA) detection and effective targeted therapy. Furthermore, Kirsten rat sarcoma viral oncogene (KRAS) plays a critical role in the initiation and maintenance of pancreatic tumors, thus contributing to the conversion of anti-tumor inflammation to pro-tumor inflammation. Both the KRAS mutation and inflammation are concurrent in the initial stage of PDA, and they compose a positive feedback loop to enhance each other's activity. This positive feedback loop generates a harsh environment, which helps pancreatic cells maintain the stemness phenotype, accelerates cell turnover rate, increases genome instability, and hence elevates the incidence of PDA formation.

Introduction

Pancreatic cancer (PC) is one of the most malignant types of tumors and is the seventh leading cause of cancer-related deaths worldwide.[1] Moreover, pancreatic ductal adenocarcinoma (PDA) accounts for more than 90% of all pancreatic cancer cases. In contrast to the steady increase in survival for most cancers, advances have been slow for PC, for which the overall five-year relative survival is currently 6% (2–9%).[2] The low survival rate is partly because more than half of the cases are diagnosed at an advanced stage. Patients with limited lesions of the pancreas have a five-year survival rate of 29.3%, yet the rate for advanced patients is only 2.6%.[2] Hence, an effective screening method for its early detection is still lacking. Furthermore, the modified chemoradiation treatments have a limited impact on the course of disease despite some advances.[3,4]

It has been well established that pancreatic carcinogenesis undergoes an extremely long course during which numerous genetic events accumulate within the pancreatic cells with a stemness phenotype. A list of environmental factors has also been identified to predispose an individual to pancreatic cancer, including smoking, alcohol consumption, chronic inflammation, etc. Compared with the first two factors which only confer a low risk (relative risk ≈2),[5,6] chronic inflammation shows a stronger association with PDA with its increased risk ranging from 3.53 to 16.16.[7] Molecular pathology has shown that most PDA cases begin in the context of inflammation, and are derived from acinar cells.[8] Communication between the acinar cells and the inflammatory milieu converts them into ductal-like cells, then progresses into a pancreatic intraepithelial neoplasia sequence, and finally ends up with PDA.[8] Accredited reports support that inflammation could accelerate accumulations of genetic events within pancreatic cells, and sequentially accelerate the process of pancreatic carcinogenesis. However, though several genes and molecular pathways have been validated to be involved in this process, targeted therapy against these genes have shown little efficacy in the clinic. As a consequence, identification and validation of causative genes and molecular pathways underlying PDA progression are critical for the rational development of effective strategies for diagnosis and intervention.[4,9]

Keywords: Pancreatic cancer; KRAS; Inflammation; Chronic pancreatitis.

Abbreviations: CP, chronic pancreatitis; KRAS, Kirsten rat sarcoma viral oncogene; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; PanIN, pancreatic intraepithelial neoplasia; PDA, pancreatic ductal adenocarcinoma; PI3K, phosphoinositide 3-Kinase; STAT, signal transducer and activator of transcription; TME, tumor microenvironment.

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How to cite this article: Yang F, Li L, Kong XY. The Positive Feedback Loop Between Inflammation and Mutant KRAS Genes Promotes Malignant Transformation in Chronic Pancreatitis. *Cancer Screen Prev* 2022;1(1):39–46. doi: 10.14218/CSP.2022.00012.

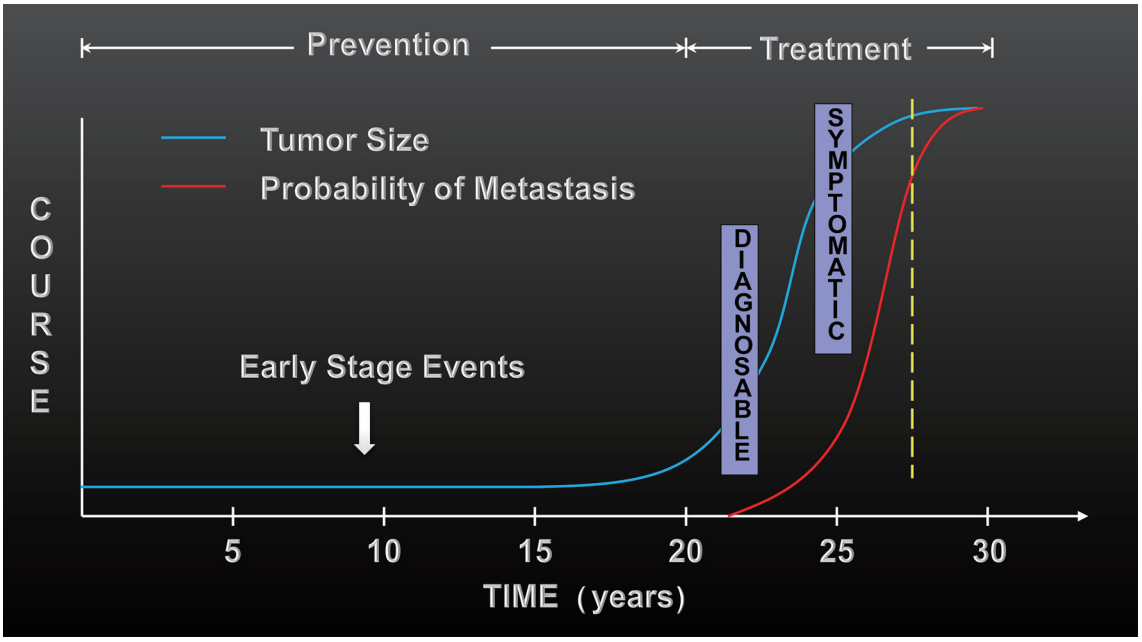

Fig. 1. Natural course for the development of PDA. It takes decades to fully develop into a PDA. However, most PDA cases are diagnosed at an advanced stage (time after the yellow dashed line). The targeted therapy against these patients showed marginal effects. Recent studies stressed the importance of studying the genetic alterations that had occurred in early stages. PDA, pancreatic ductal adenocarcinoma.

Identifying and dissecting driving events in the initial stages of PDA is critically important for PDA research

Based on the clonal relationship between a primary tumor and metastasis, a previous study indicated that this needed an average of 11.7 years to transform the initiating mutation into the parental, non-metastatic founder cell, and an average of 6.8 years was required for the acquisition of the metastatic ability; nevertheless, the patients died on average two years thereafter. These data defined a broad time window of opportunity for early detection to prevent deaths from metastatic disease.[10] However, most PDA cases were diagnosed at an advanced stage (Fig. 1) with a five-year survival rate of less than 3%. In addition, targeted therapy in these patients showed only marginal effects. Furthermore, recent studies have stressed the importance of studying the genetic and immune microenvironmental alterations occurring in the early stages. Therefore, the identification of genes and immune pathways involved in early-stage PDA formation would not only enable us to develop novel early detection strategies, but also help to better understand the primary causal factors for PDA and thus provide potential targets for new therapeutic modalities.

Chronic inflammation is a hallmark characteristic for PDA

Chronic inflammation is critically important in PDA carcinogenesis

The possible links between inflammation and PDA could be readily deduced from the widespread presence of inflammatory cells in the PDA mass. As such, now clear evidence has been obtained that inflammation plays a critical role in pancreatic tumorigenesis. Moreover, epidemiological studies have shown that chronic inflammation could significantly elevate the incidence of PDA,[7,11] and in hereditary pancreatitis, which begins at a young age (about 10 years old), the cumulative rate of pancreatic cancer diagnosis could reach 22.8% at 70 years.[12] Therefore, genetic mouse models helped us clearly define the critical role that inflammation plays in PDA tumorigenesis. For example, chronic pancreatitis could induce acinar-to-ductal metaplasia (ADM), which has been well established as an important precancerous lesion during PDA formation. Likewise, acinar cells and insulin-expressing endocrine cells in adult mice become refractory to K-RAS^{2V}-induced PanIN and PDA unless they are exposed to chronic pancreatitis.[13,14] The vast majority (90%) of PDA are linked to somatic mutations and environmental factors.[15] Many environmental risk factors, including tobacco smoke,[16] obesity,[17] and even old age,[18] exert an array of pro-tumorigenic signals through inflammatory mechanisms. In certain cases, inflammation could diminish the beneficial effects of the therapy.[19] Additionally, the incidence and mortality of many cancers are reduced when using non-steroidal anti-inflammatory drugs, such as aspirin on nonspecifically suppressed inflammation.[20,21] Regular aspirin use has been associated with a reduced pancreatic cancer risk among participants with diabetes.[22] Thus, all this evidence supports the critical role that inflammation plays in PDA.

Possible mechanisms involved in chronic inflammation to cancer progression

Several lines of evidence support the roles that inflammation plays in carcinogenesis. Firstly, inflammation could induce the production of cellular mutations, directly or indirectly. At the sites of inflammation and infections, activated inflammatory cells like macrophages and neutrophils could generate reactive molecules into the microenvironment, e.g., reactive oxygen species (ROS) and reactive nitrogen intermediates (RNI). All these molecules would be cytotoxic and capable of inducing DNA damage and genomic instability in the pancreatic cells.[23] Chronic inflammation triggering tissue damage could also weaken the barrier function and expose the stem cell compartment to environmental carcinogens or bring stem cells to a close proximity of active inflammatory cells producing genotoxic

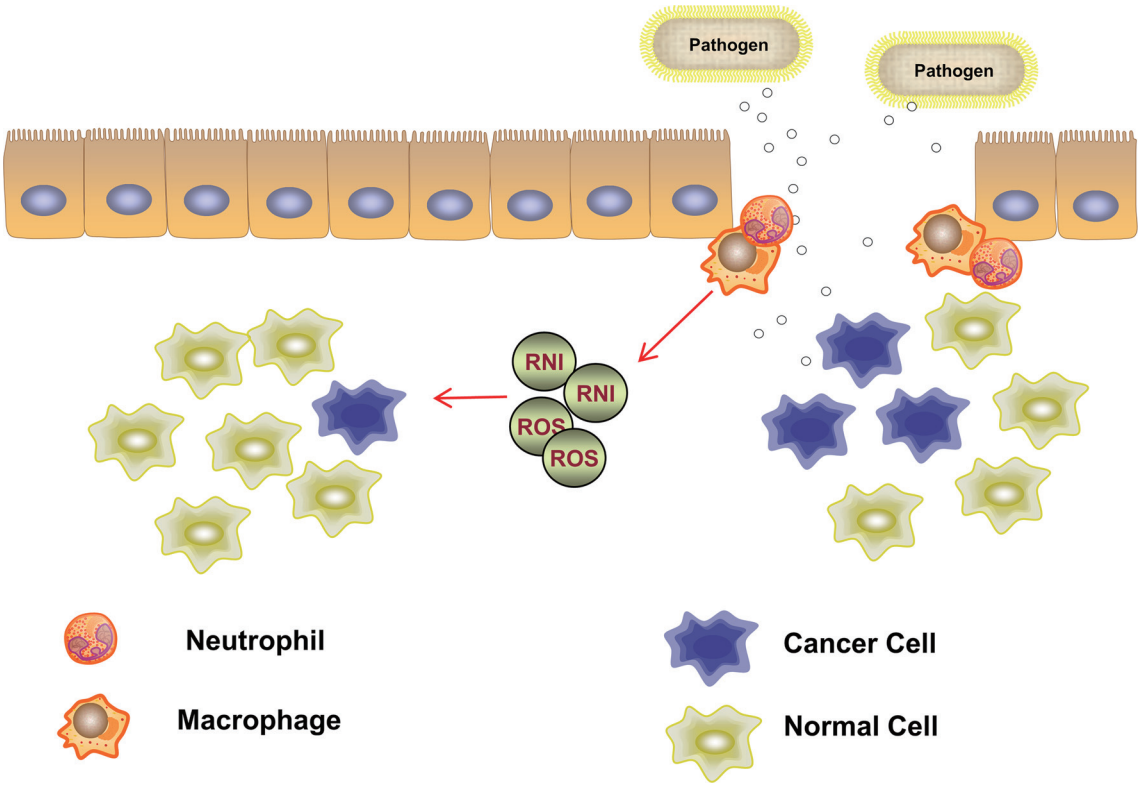

Fig. 2. Inflammation could induce the production of cellular mutations, directly or indirectly. Activated inflammatory cells could generate DNA damage factors, such as reactive oxygen species (ROS) and reactive nitrogen intermediates (RNI) into the microenvironment. Furthermore, chronic inflammation triggering tissue damage could weaken the barrier function and expose the stem cell compartment to environmental carcinogens or bring stem cells to a close proximity of active inflammatory cells producing genotoxic compounds. RNI, reactive nitrogen intermediates; ROS, reactive oxygen species.

compounds (Fig. 2).[19] Secondly, inflammation could accelerate mutation accumulation in the pancreatic cells. Genome instability is the critical characteristic of the cancer cells enabling other hallmarks in cancer development. In normal cells, the genome maintenance systems could detect and resolve the defects in the DNA and ensure the rates of spontaneous mutations would be extremely low during each cell generation.[24] In the setting of chronic inflammation, the cell turnover rate would be greatly accelerated, which would confer increased susceptibility to DNA damage. Thirdly, as PDA is an aged disease and it would take more than one decade to form a PDA, sequentially occurred somatic mutations would accumulate within a subset of long-lived stem cells with a self-renewal property.[25] Many downstream effectors of inflammation, such as nuclear factor-κB (NF-kB)[26,27] and signal transducer and activator of transcription 3 (STAT3),[28] are closely associated with a self-renewal phenotype of the stem cells, which would protect them from being eliminated before the next mutation acts. Last but not least, inflammation could help sustain the malignancy of the transformed cells by supplying bioactive molecules to the microenvironment, including growth factors that would sustain proliferative signaling, survival factors that limit cell death, invasion, and inductive signals that would lead to the activation of epithelial-mesenchymal transition (EMT) and other hallmark-facilitating programs.[29,30] These signaling factors would act on a mutational basis to promote further transformation of precancerous lesions to cancer, metastasis, and the spread of cancer. It has been shown that in order for the early pancreatic intraepithelial neoplasia (PanIN) lesions to develop to PDA in Kirsten rat sarcoma viral oncogene (KRAS) mutated mice, activation of the STAT3 pathway by interleukin 6 (IL6) would be required.[31] A study showed that the ablation of the IkappaB kinase β (IKKβ) led to a reduction in tumor growth in a model of colitis-associated cancer.[32] Preoperative stimulation of the resolution of inflammation or inflammation blockade responses resulted in poor colonization and eradicated the micro-metastases.[33]

Inflammation alone is not sufficient to induce PDA formation

A study of mouse models of chronic inflammation of the pancreas found that mice lacking tumor protein P53 (TP53) developed pancreatic cancer, while TP53 wild-type mice did not, thus suggesting that inflammation alone was not sufficient to cause pancreatic cancer.[34] As previously mentioned, the development of pancreatic cancer would require a long course, in which multiple sequential steps would result in the accumulation of multiple random "hits" to the pancreatic cell DNA from specific types of environmental factors, e.g., inflammation. One strong evidence for this concept comes from hereditary pancreatitis (HP), an autosomal dominant genetic disorder with long-lasting pancreatitis. Although pancreatic inflammation in HP begins at a median age of 10 years, the marked increase in the incidence of PDA does not occur until the sixth decade of life.[12,35] Furthermore, the risk for PDA does not correlate with the severity of the inflammation and fibrosis. As a consequence, all these observations would suggest that the high risk for PDA in the general population would represent a combination of existing pathogenic cancer gene variants plus environmental factors, whereas inflammation itself would only act as a promoter, but not a cell fate determinant in PDA formation.[36]

Another important reason for the inflammation's insufficiency in inducing PDA would come from the theory that the ever-alert immune system could constantly monitor the cells and tissues. In normal cells, the anti-tumorigenic function of immunity would exert immunosurveillance and immunological sculpting of tumor heterogeneity. Such immune surveillance could recognize and eliminate the vast majority of incipient cancer cells and thus nascent tumors. Studies have also shown that people with a personal history of allergies have been known to have a protective effect against pancreatic cancer. Individuals with allergies have a decreased risk of cancer and an increased survival rate compared to those without allergies.[37] This could explain why striking increases of certain cancers occur in immunocompromised individuals.[38,39] However, with the accumulation of the mutation in the tumor microenvironment (TME), cell death and microbial signals would altogether feed into a feed-forward loop of inflammation-induced signaling and inflammatory cell recruitment. Hence, the sterilizing immunity would not remove the mutation, thus resulting in cancer-promoting inflammation.[19] Such immune escape is a hallmark of all cancer types, and cancer cells must well evade immune destruction by disabling the components of the immune system that have been dispatched to eliminate them, so to grow successfully into a solid tumor mass.[24,40] These two immune models existing in different microenvironments would also confirm that inflammation alone would not be sufficient to induce PDA formation.

KRAS mutation is critically important for PDA initiation

KRAS mutation is the initial and ubiquitous event in pancreatic carcinogenesis

Genome instability and associated genetic diversity are the key characteristics of tumors underlying those so-called "hallmarks of cancer".[24] Substantial efforts have been devoted to determine the genetic mutations of PDA, and hundreds of changes of gene expression have been identified compared with normal pancreatic cells.[41] Though a small group (2–10%) of PDAs seem to be associated with hereditary factors, most are associated with high-frequency somatic mutations in a subset of genes, including KRAS, cyclin-dependent kinase inhibitor 2A (CDKN2A), TP53, and SMA- and MAD-related protein 4 (SMAD4).[42] Of note, KRAS mutation is nearly universal (>95%) in human PDA. Furthermore, PDA is associated with non-invasive, preneoplastic lesions that are thought to be precursors to the disease. PanIN is the most common and most widely studied putative precursor. A sequential transformation model, from PanIN-1, PanIN-2, PanIN-3, until PDA, has been well established for PDA, and numerous genetic alterations have also been documented in different stages. In PanIN-1, mutated KRAS was frequently detected (estimated to be over 36%[43,44]), whereas the other PDA associated mutations, e.g., TP53 or SMAD4, remained intact. Owing to its near universal frequency in PDA, the mutation of KRAS was proposed as the initiating genetic lesion in PDA. Genetic models holding constitutively active KRAS helped us dissect the key role that mutant KRAS plays in PDA progression.

Genetic models developed in the context of oncogenic KRAS provide important tools in PDA studies

Hingorani *et al*. first developed the conditional KRAS-driven PDA mouse model that recapitulated the progression observed in humans.[45] From then on, almost all PDA genetic models were generated on the basis of cre-mediated KRAS mutation, e.g., KC (Pdx1-Cre; LSL-KRAS^{G12D} or Ptf1a-Cre; LSL-KRAS^{G12D}) and KPC (most commonly Pdx1-Cre; LSLKRAS^{G12D}; LSL-Trp53^{R172H} or Ptf1a-Cre; LSL-KRAS^{G12D}; LSLTrp53^{R172H}) mouse models. Employing these models, researchers explored the origination of PDA by cell lineage tracing, dissected unraveled mechanisms by cross-breeding with other genetic mutation models, and evaluated the therapeutic efficacy of certain anti-cancer agents to PDAs. Neither the presence of inflammation, nor the loss of tumor suppressor genes would be sufficient to initiate PDA in the absence of oncogenic KRAS, which would highlight the unique role that KRAS would play in the onset of PDA.[46]

KRAS plays a central role in the initiation and maintenance of PDA by activating downstream effector pathways

Activated KRAS mutants initiate numerous signaling pathways. All of these pathways contribute to the oncogenic and proliferative power of KRAS, including the mitogen-activated protein kinase (MAPK) pathway, phosphoinositide 3-Kinase (PI3K) pathway, Ras-like (RAL)A–RALB pathway, the p38 mitogen-activated protein kinases (p38-MAPKs) pathway, Jun N-terminal kinase (JNK) pathway, and NF-κB pathway. MAPK signaling promotes the formation of PanINs by enabling the dedifferentiation of acinar cells into duct-like cells that are susceptible to transformation.[47] Activation of the PI3K family would lead to the activation of phosphatidyl inositol triphosphate and to the downstream activation of the Ak strain transforming (AKT) and mammalian target of rapamycin (mTOR) molecules. This pathway has been shown to be upregulated in PDA.[48] In pancreatic cancer, RALA promotes tumor initiation, whereas RALB is essential for invasion and metastasis.[49] The p38-MAPKs pathway promotes invasive abilities of pancreatic tumors,[50] while the JNK pathway promotes pancreatic tumor formation and cancer stem cell maintenance.[51] The NF-κB pathway modulates pancreatic cancer cell malignancy and tumor growth through cell cycle signaling.[52] In addition to these classic pathways, many other proteins containing putative KRAS- association or KRAS-binding domains have been described, including the SARC, STAT3, cyclooxygenase-2 (COX2), and early growth response 1 (EGR1) pathways.[53]

Oncogenic KRAS alone might not be sufficient to transform a cell

Though KRAS is indispensable for PDA formation, numerous studies have reported that healthy humans carry oncogenic KRAS in different organs, including the pancreas,[54] colon,[55] and lungs,[56] at rates far exceeding the rates of cancer development.[46] Furthermore, mice that express oncogenic KRAS, either in the whole body or in specific organs, develop cancers from only a small fraction of the cells that contain the oncogenic KRAS.[57,58] Mouse models showed that the oncogenic KRAS remained locked in an "Off" state but could be readily activated by upstream stimulants to lead to prolonged strong Ras activity.[59] Consequently, a threshold level of KRAS activity might be essential to initiate the carcinogenesis process.[60,61] Therefore, these results indicated that oncogenic KRAS alone was not sufficient to transform a cell, and other genetic/epigenetic factors would be required to elevate the activity level of mutant KRAS to initiate carcinogenesis.

KRAS-inflammation feed-forward loop plays important roles in PDA initiation

Oncogenic KRAS could regulate the inflammatory environment of PDA

A list of inflammatory signals has been validated to be down-

stream effectors of KRAS,[62] e.g., COX-2, STAT3, and NF-κB, which have indicated that oncogenic KRAS itself is closely associated with inflammatory pathways. During the earliest stage of the PanIN formation, the lesions would accumulate proliferating cells of mesenchymal origin that might comprise fibroblasts and pancreatic stellate cells (PSCs). In a mouse model of pancreatic disease harboring elevated KRAS activity in the acinar cells, the number of activated PSCs greatly increased following the induction of pancreatitis,[63] which showed that even low levels of KRAS activity could generate signals that would influence the microenvironment. In addition KRAS would maintain the stroma activated by regulating the production of factors, such as sonic hedgehog,[64] IL6,[31] and prostaglandin E.[65] When KRAS was inactivated in low-grade PanINs, the activated fibroblasts that populated the stroma stopped expressing markers of activation, exited the cell cycle, and were eliminated from the pancreas via an unknown mechanism.[46] Inactivation of KRAS also led to resolution of the chronic inflammation associated with PDA. The immune cells that infiltrated the pancreas could also be regulated by KRAS. In mouse models of PDA, tumor cells carrying mutant KRAS could secrete cytokines, such as the granulocyte-macrophage colony-stimulating factor (GM-CSF) into the microenvironment, which would promote the infiltration of myeloid-derived suppressor cells that would inhibit anti-tumor immune responses.[66] As such, oncogenic KRAS could sustain the "smoldering inflammation" mostly in a paracrine manner.

Inflammation could enhance KRAS activity

Though KRAS mutation would be indispensable in pancreatic carcinogenesis, oncogenic KRAS would not be constitutively active, and the activity of KRAS would surmount a threshold to ensure its transformation ability toward the pancreatic cells. Hence, the PDA associated microenvironment would be infiltrated with different inflammatory cells, which could generate various chemokines, cytokines, and growth factors, such as IL6, IL8, IL17, tumor necrosis factor-alpha (TNF-α), microphage inhibitory factor (MIF), IL1β, transforming growth factor-beta (TGF-β), and IL10.[67] All these inflammatory mediators would act on their downstream effectors in the pancreatic cells and activate those dominant oncogenes, e.g., KRAS through a paracrine manner. There would also be two core effectors, NF-κB and STAT3, connecting the inflammation and PDA. NF-kB is a nuclear transcription factor that regulates the expression of a large number of genes in response to various stimuli. NF-kB is known to be constitutively activated in most PDA patients.[68] Once stressed by inflammatory stimuli, NF-kB in pancreatic cells would translocate into the nucleus, and mechanistically induce the expression of a set of downstream genes and amplify the KRAS activity.[69] Like NF-kB, STAT3 would also be ubiquitously activated in most PDA cases. Activation of STAT3 could transduce upstream signals, e.g., IL6 and IL17, into the pancreatic cells and complexes with other transcription factors to sustain the KRAS activity.[70] In KRAS-driven mouse models, STAT3 was a critical component of spontaneous and pancreatitis-accelerated PDA precursor formation and supported cell proliferation and metaplasia-associated inflammation (Fig. 3).

The Model of "KRAS-inflammation positive feed-back loop" in PDA initiation

As KRAS mutation and inflammation are concurrent in the initial stage of PDA, it would be quite logical to assume that a "KRAS-inflammation positive feed-back loop" exists. The "KRAS-inflammation positive feedback loop" would be extremely important in sustaining the KRAS activity at a relatively high level and enhancing its transformation ability. Oncogenic KRAS in transformed PDA cells would drive the secretion of inflammatory cytokines/chemokine, thus causing the production of more cytokines and chemokines in the TME.[46] These secreted factors would engage with the inflammatory receptors on the PDA cells, consequently driving a network of signaling pathways that would synergize with the oncogenic KRAS signaling in propelling the various malignant feats of PDA. Some classical inflammatory signaling pathways would include NF-kB, Janus kinase/signal transducers and activators of transcription (JAK-STAT), toll-like receptor (TLR) pathways, cyclic GMP-AMP synthase (cGAS)/stimulator of interferon genes (STING), and MAPK. Tumor progression locus 2 (TPL2, also known as MAP3K8 or COT) is a serine-threonine protein kinase that mediates the IL1 receptor (IL1R), TLR, and TNF-dependent MAPK and NF-κB activation.[71] In PDA cells, TPL2 is activated via a KRAS-MAPK driven IL1β autocrine signaling loop that engages IL1R, IRAK4, and IKKβ. In this setting, the inhibition of TPL2 would suppress MEK-ERK, p-105, and p65 NF-kB activation, hence leading to enhanced survival and chemoresistance.[72]

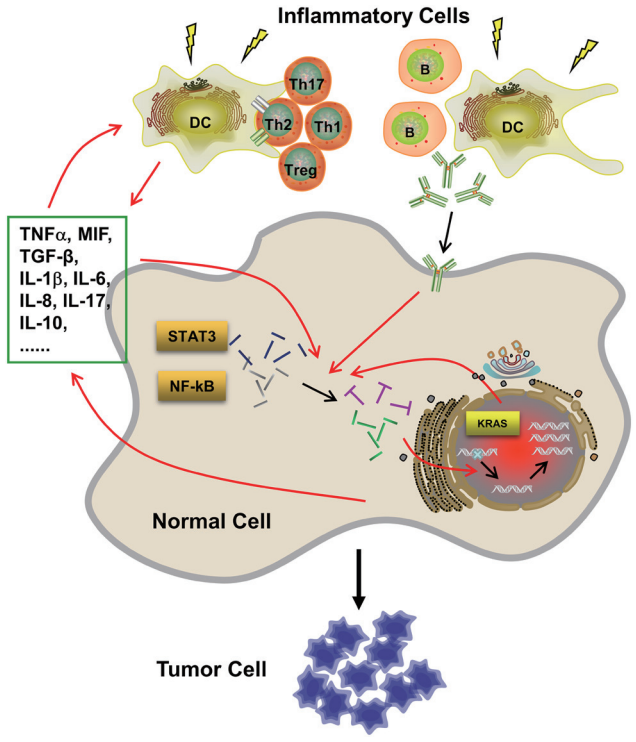

Fig. 3. The model of the "KRAS-inflammation positive feedback loop" in the PDA initiation. Inflammatory mediators would act on their downstream effectors in the pancreatic cells and activate those dominant oncogenes, e.g., KRAS, through a paracrine manner. NF-κB and STAT3 would be two core effectors connecting the inflammation and PDA. Once stressed by the inflammatory stimuli, they would mechanistically induce the expression of a set of downstream genes and amplify the KRAS activity. Then, they could also be induced as the downstream effectors of KRAS. DC, dendritic cells; IL, interleukin; KRAS, Kirsten rat sarcoma viral oncogene; MIF, microphage inhibitory factor; NF-κB, nuclear factor-κB; PDA, pancreatic ductal adenocarcinoma; STAT, signal transducer and activators of transcription; TGF-β, transforming growth factor-beta; Th, helper T cell; TNF-α, tumor necrosis factor-alpha; Treg, regulatory T cells.

Furthermore, oncogenic KRAS has slower kinetics of return to its guanosine diphosphate-bound status than non-oncogenic forms, which would provide extra time for activated KRAS to receive enough signals from the inflammation stimuli, and to finally generate a feedback loop that would sustain its activity. Reagents which inhibit inflammation, such as the COX2 inhibitor celecoxib, could block the feed-forward loop and prevent the induction of PDA in models with endogenous oncogenic KRAS.[73-75] This model would also be supported by epidemiological reports that certain anti-inflammatory agents would be associated with a lower risk in the general population's PDA development.

Conclusions

The "KRAS-inflammation feed-forward loop" model plays an important role in maintaining the activity of KRAS and initiation of PDA. However, pancreatic cells harboring this feed-forward loop would not be destined to become cancer cells. Thus, chronic pancreatitis (CP) would be the best model to evaluate the magnitude that the role of our proposed model would play in PDA initiation. It has also been confirmed that the incident of PDA in CP patients was obviously higher than in the general population.[11] Moreover, molecular research has indicated that more than one third of the CP cases harbor KRAS mutations, whereas the incidence of PDA in CP was less than 4% in 20 years, which means as least 20% of CP cases. Though they held oncogenic KRAS cells in a harsh inflammatory milieu, this would not progress into PDA throughout their lifespan. Just as mentioned before, the loop could be blocked by immune surveillance in a normal situation. This would need the accumulation of time and other genetic promotors for the loop to maintain and eventually show a cascade amplification effect. Other important mechanisms would need to be involved in the CP to PDA progression. This would need more research about the other driver factors, as well as those noncoding RNAs that could play causal roles accompanying the "KRAS-inflammation feed-forward loop" model.

Acknowledgments

None.

Funding

Supported in part by grant 81872043 (LL) from the National Natural Science Foundation of China; grant 82072760 (XYK) from the National Natural Science Foundation of China; National Key R&D Program of China No. 2019YFC1315900 and 2019YFC1315802.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Contribution to the study concept and design (XYK), design of the outline and supervision of the whole process (LL), and drafting of the manuscript (YF).

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