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REVIEW

Inflammation and de-differentiation in pancreatic carcinogenesis

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Abstract

Pancreatic cancer is a malignancy with an extremely poor prognosis. Chronic pancreatitis is a well-known risk factor for pancreatic cancer. Inflammation is thought to influence carcinogenesis through DNA damage and activation of intracellular signaling pathways. Many transcription factors and signaling pathways co-operate to determine and maintain cell identity at each phase of pancreatic organogenesis and cell differentiation. Recent studies have shown that carcinogenesis is promoted through the suppression of transcription factors related to differentiation. Pancreatitis also demonstrates transcriptional changes, suggesting that multifactorial epigenetic changes lead to impaired differentiation. Taken together, these factors may constitute an important framework for pancreatic carcinogenesis. In this review, we discuss the role of inflammation and de-differentiation in the development of pancreatic cancer, as well as the future of novel therapeutic applications.

Key words: Pancreatitis; Inflammation; Organogenesis; Differentiation; Transcription factor; Pancreatic cancer

Core tip: Inflammation is involved in carcinogenesis by causing DNA damage. Recent studies show that

carcinogenesis is promoted by reprogramming factors and by suppressing transcription factors related to acinar cell differentiation. Pancreatitis also shows such transcriptional changes, suggesting that epigenetic changes by several causes leading to the impaired differentiation may constitute an important framework for pancreatic carcinogenesis. New diagnostic, preventive and/or treatment strategies based on the findings described in this review are expected to be clinically applied in the near future.

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INTRODUCTION

The worldwide incidence of pancreatic cancer is approximately 330000 cases in 2012, with trends indicating that rates are higher in men and in developed countries. The number of deaths due to pancreatic cancer are also estimated to be approximately 330000 people a year; it ranks 11th in cancer-related deaths[1,2]. The mean survival time is 19 mo and the 5-year survival rate is 5% or less; these figures indicate that pancreatic cancer has one of the worst prognoses across all forms of malignancy[2,3]. The early stages of pancreatic cancer are almost always asymptomatic. As a result, by the time symptoms become apparent, the disease is already at a very advanced stage. Because the 5-year survival rates of stage Ⅰ and Ⅳ pancreatic cancers are 43% and 7.7% respectively, early diagnosis and treatment are especially crucial to improve the overall prognosis of the disease.

One option, to aid in the earlier diagnosis of pancreatic cancer, is to elucidate more thoroughly the mechanism of carcinogenesis and identify high-risk groups to follow carefully. Well-known risk factors include smoking, obesity, diabetes, and chronic pancreatitis[4]. In particular, the risk of pancreatic cancer in patients with chronic pancreatitis is 13.3 times greater than that of healthy controls, suggesting that inflammation is deeply involved in the pathogenesis of pancreatic cancer[5,6].

It is well known that the *KRAS* mutation and mutational inactivation of the *CDKN2A*, *TP53*, and *SMAD4* tumor suppressors play important roles in the development of pancreatic cancer[4,7-9]. Furthermore, recent studies have shown that carcinogenesis is promoted by reprogramming factors and by suppression of transcription factors related to differentiation[10,11]. Interestingly, pancreatitis also shows the above transcriptional changes, suggesting that multifactorial epigenetic changes that result in impaired differentiation have an important role in pancreatic carcinogenesis.

In this review, we will discuss the mechanisms of pancreatic carcinogenesis from the perspective of pancreatic inflammation and cell differentiation.

INFLAMMATION AND PANCREATIC CARCINOGENESIS

In 1863, Rudolph Virchow first reported inflammatory cells in cancer tissues and hypothesized that inflammation promoted carcinogenesis[12]. In 1915, Yamagiwa induced skin cancer on the ears of rabbits by repeatedly painting them with coal tar, and experimentally revealed a case of carcinogenesis due to inflammation[13]. Furthermore, several cancers are known to be epidemiologically related to inflammatory diseases. For example, *Helicobacter pylori*-related gastritis patients have a 2.6-fold increased risk of gastric cancer[14]. Viral hepatitis and inflammatory bowel disease are risk factors for liver cancer and colon cancer, respectively. Previous epidemiological studies have demonstrated that non-steroidal anti-inflammatory drugs such as aspirin, lowers the overall risk of colon cancer[15,16]. Taken together, these results suggest that inflammation is frequently associated with carcinogenesis.

Chronic pancreatitis is a risk factor for pancreatic cancer[6]. Patients with hereditary pancreatitis, a rare cause of chronic pancreatitis and a strong risk for pancreatic cancer (49% of the patients develop pancreatic cancer by age 75 years), suffer from recurrent pancreatitis with pancreatic exocrine insufficiency and diabetes mellitus from a young age[17]. Mutations of the cationic trypsinogen (*PRSS1*) and serine protease inhibitor Kazal type 1 (*SPINK1*) genes cause hereditary pancreatitis[18,19]. Because the risk of developing pancreatic cancer does not change with the presence or absence of *PRSS1* or *SPINK1* gene mutations, it is unlikely that the gene itself functions as an oncogene or tumor-suppressor gene[19,20]. The increased carcinogenic risk in hereditary pancreatitis patients is presumed to be carcinogenesis due to prolonged inflammation.

Notably, Bailey *et al*[21] conducted unsupervised clustering of pancreatic cancer RNA sequencing data, and they classified pancreatic cancers into four subtypes: Squamous, pancreatic progenitor, immunogenic, and aberrantly differentiated endocrine exocrine. Each subtype differently expresses unique transcription factors and downstream targets, which are important in lineage specification and differentiation during pancreas development. Among them, the immunogenic subtype is associated with a significant immune infiltrate[21], which may be associated with pancreatitis and carcinogenesis.

The relationship between pancreatic cancer and inflammation has also been explored in experiments using genetically engineered mice. When *Kras* mutations were introduced during the embryonic stage in mice, pancreatic intraepithelial neoplasia (PanIN) formation was promoted while pancreatic cancer developed at a lower frequency[22]. The introduction of *Kras* mutations

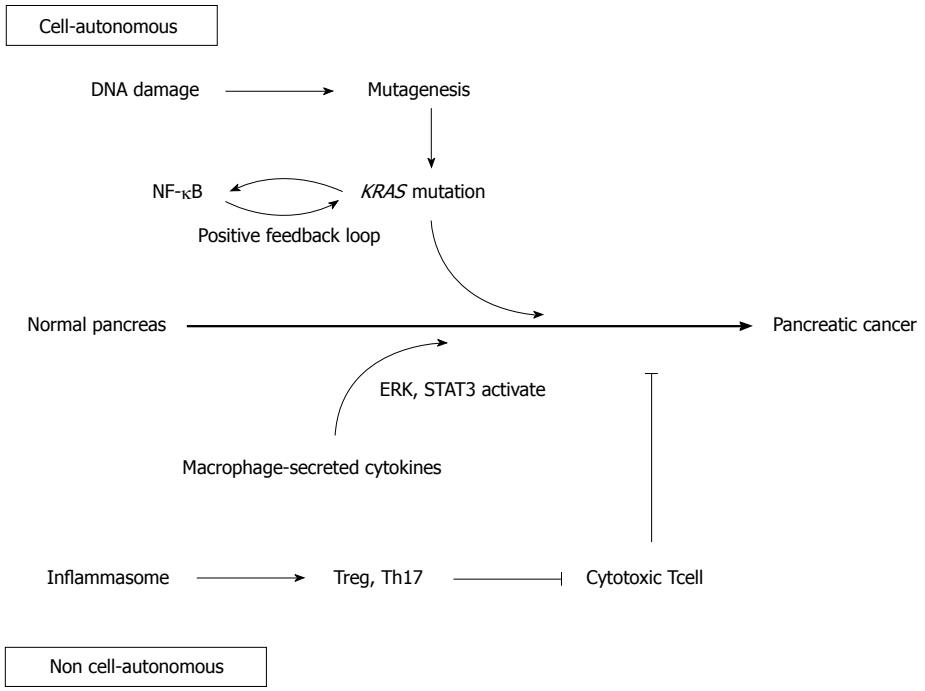

Figure 1 Inflammation induces carcinogenesis both cell-autonomously and non-cell-autonomously. DNA damage caused by inflammation contributes to mutagenesis. Nuclear factor κB and *KRAS* activate each other and sustained *KRAS* activity promotes carcinogenesis. Macrophage-secreted cytokines activate the ERK and STAT3 signaling pathways in epithelial cells. Inflammasomes inactivate cytotoxic T cells *via* the activation of Th17 and regulatory T cells. NF-κB: Nuclear factor κB.

alone induced pancreatic cancer development over 1 year; however, when *Trp53* and *Cdkn2a* defects were introduced, it only took 7 and 18 wk, respectively, to develop pancreatic cancer[23]. Furthermore, when pancreatitis was induced by administering caerulein in *Kras* mutant mice, carcinogenesis occurred at 12 wk[24]. These results demonstrated that some secondary abnormalities in *Kras*-mutated mice are necessary for rapid progression to invasive cancer, and that inflammation promotes carcinogenesis in conjunction with *Kras* mutations.

DNA damage caused by inflammation may contribute to carcinogenesis (Figure 1)[25]. Inflammatory cytokines produce reactive oxygen species, which randomly oxidize DNA to cause genetic mutation[26]. NO, induced by inflammation, also inhibits DNA repair enzymes to promote mutations[27]. In fact, the duration of chronic pancreatitis correlates positively with the incidence of *KRAS* mutations, suggesting that DNA damage accumulates due to the persistence of inflammation, promoting further carcinogenesis[28].

Although random genetic mutations caused by inflammation may contribute to carcinogenesis, work done by Guerra *et al*[29] suggests an alternative role of inflammation in the development of carcinogenesis. Guerra *et al*[29] used a Cre Tet-off system to control the expression of mutant *Kras* in mice. When mutant KRas was expressed during the embryonic stage, PanIN was formed at 1-3 mo. However, when mutant KRas was expressed in adult mice 2 mo after birth, PanIN was not formed. Furthermore, even when *Cdkn2a* or *Trp53* gene deficiencies were simultaneously introduced into adult mutant *Kras* mice, PanIN did not develop[29]. These results suggest that the carcinogenic potential through genetic mutation differs between the embryonic and adult stages in mice. Moreover, when pancreatitis was induced by administering caerulein to adult mutant *Kras* mice, PanIN developed and rapidly progressed to pancreatic cancer[30]. However, PanIN did not develop after deletion of *Cdkn2a* or *Trp53* in adult mice accompanied with caerulein pancreatitis. From these results, mutant *Kras* and inflammation are necessary components of pancreatic carcinogenesis in adult mice, with inflammation contributing to carcinogenesis by means other than the introduction of specific gene mutations as a result of DNA damage. Recent studies revealing the association of various signaling pathways and microenvironments with inflammation and pancreatic carcinogenesis may support this concept.

CELL-AUTONOMOUS INTRACELLULAR SIGNALING PATHWAYS IN PANCREATIC INFLAMMATION AND CARCINOGENESIS

Nuclear factor κB (NF-κB) is involved not only in inflammation but also in cell differentiation and proliferation, both of which are activated in pancreatic cancer[31,32]. Mutant KRas is known to activate interleukin-1alpha (IL-1α) *via* AP-1. IL-1α polyubiquitinates tumor necrosis fa-

ctor receptor-associated factor 6 and activates IKK2/β, which activates NF-κB. NF-κB subsequently upregulates *IL-1α* and *p62* transcription, which in turn re-activates NF-κB in a positive feedback loop[33]. Because activated NF-κB activates KRas, another positive feedback loop is generated, resulting in sustained KRas activity which may promote pancreatic cancer development[34].

Additionally, Toll like receptor 4 (TLR4) and TLR7 are upregulated within the pancreatic cancer microenvironment[35,36]. TLRs are receptors that recognize pathogen-associated molecular patterns and diverse byproducts of inflammation and cellular injury. Activated TLRs induce the activation of NF-κB pathway within acinar cells, which may further promote the development of pancreatic cancer.

NON CELL-AUTONOMOUS INTRACELLULAR SIGNALING PATHWAYS IN PANCREATIC INFLAMMATION AND CARCINOGENESIS

The IL-6 / STAT3 pathway is also involved in pancreatic cancer and inflammation[37]. While caerulein-induced pancreatitis transiently activates STAT3, prolonged activity and PanIN development were both observed in *Kras* mutant mice[38]. In these mice, pancreatic *Kras*-mutant epithelial cells recruited macrophages, which secreted IL-6, result in the STAT3 activation in epithelial cells and formation of PanIN. Conversely, inactivation of IL-6 trans-signaling or inhibition of STAT3 resulted in decreased PanIN formation[39].

Various studies have revealed that macrophages play an important role in pancreatitis, and are likely to be related to pancreatic carcinogenesis[40]. As mentioned above, macrophages secrete IL-6 and activate the STAT3 signaling pathway to promote pancreatic carcinogenesis. In addition, macrophages are observed around acinar ductal metaplasia (ADM) lesions, which are precancerous lesions formed in response to pancreatitis. They secrete inflammatory cytokines such as TNFα, and the chemokine regulated upon activation of normal T cell expressed and presumably secreted (RANTES). They also promote ADM formation through activation of NF-κB and matrix metalloproteinase-9[41,42]. Macrophages that migrate around ADM and PanIN are polarized dominantly from M1 to M2 by stimulation of IL-13. M2 macrophages secrete CCL2 and IL-1ra, which activate the ERK signaling pathway and promote the growth of PanIN[43].

Th17 is associated with many inflammatory conditions, such as inflammatory bowel diseases. In the pancreas, the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome is also activated in pancreatitis[44]. Macrophages expressing NLRP3 inactivate cytotoxic CD8+ T cells through the activation of Th17 and regulatory T cells, which also contribute to the promotion of pancreatic cancer development[45].

PANCREATIC ORGANOGENESIS AND DIFFERENTIATION

The Guerra *et al*[29] study demonstrated that *KRAS* gene mutations induce PanIN formation in the embryonic, but not the adult stage. From these results, cell differentiation status at the embryonic or adult stage may control organ carcinogenesis. Research on the inflammation and differentiation of pancreatic cells has been increasing in recent years, and elucidation of pancreatic embryology on a cellular level would provide great understanding to pancreatic cancer development.

Pancreatic development begins with the evagination of dorsal mesenchyme of foregut endoderm on embryonic day 26 (E26) in humans and E9.5 in mice[46-48] (Figure 2). The ventral pancreatic bud emerges at 6 d in humans and at 12 h in mice after the appearance of the dorsal pancreatic bud. Branching begins immediately after evagination. Stalk elongation and gut rotation occur on the ventral and dorsal side, while fusion of the ventral and dorsal pancreas occurs during E12 to E13 in mice and E37 to E42 in humans. During E13-14 in mice, there is a dramatic increase in endocrine cells, particularly β-cells, known as "secondary transition". Similarly, acinar cells develop and acinar enzyme gene expression increases. After E15 in mice, the destiny of pancreatic cells is determined.

Pancreatic tissue consists of acinar, duct, and endocrine cells. Lineage tracing using CreERT mice revealed that multipotent progenitor cells differentiate into respective cell populations[49]. Multipotent progenitor cells co-express homeobox protein PDX1, Sry-box protein SOX9, and basic helix-loop-helix (bHLH) protein PTF1A. As differentiation continues, the expression of PDX1, SOX9 and PTF1A are restricted in endocrine, duct, and acinar cells respectively. During early branching morphogenesis, the branch tip is composed of PDX1, PTF1A, and Cpa1 positive multipotent progenitor cells that can differentiate into all three type of cells; however, cells in the tip area lose their multipotency and change into pro-acinar cells after E14[50]. The trunk region is composed of bipotent progenitor cells that can differentiate into either duct or endocrine cells[51]. Some of these cells express neurogenin 3 (NGN3) and will differentiate further into endocrine cells[52].

Various transcription factors and signaling pathways are involved in acinar cell development. NR5A2 is a member of the nuclear hormone receptor family, and is responsible for pancreatic exocrine secretion in the mature pancreas[53]. NR5A2 regulates the various stages of development and is required for OCT4 expression in the epiblast[54]. It is also required for gastrulation and acinar cell maturation during secondary transition[55,56]. Since there is decreased expression of pancreas-related transcription factors during secondary transition, NR5A2 is thought to regulate pancreatic differentiation in cooperation with other transcription factors at this stage[56].

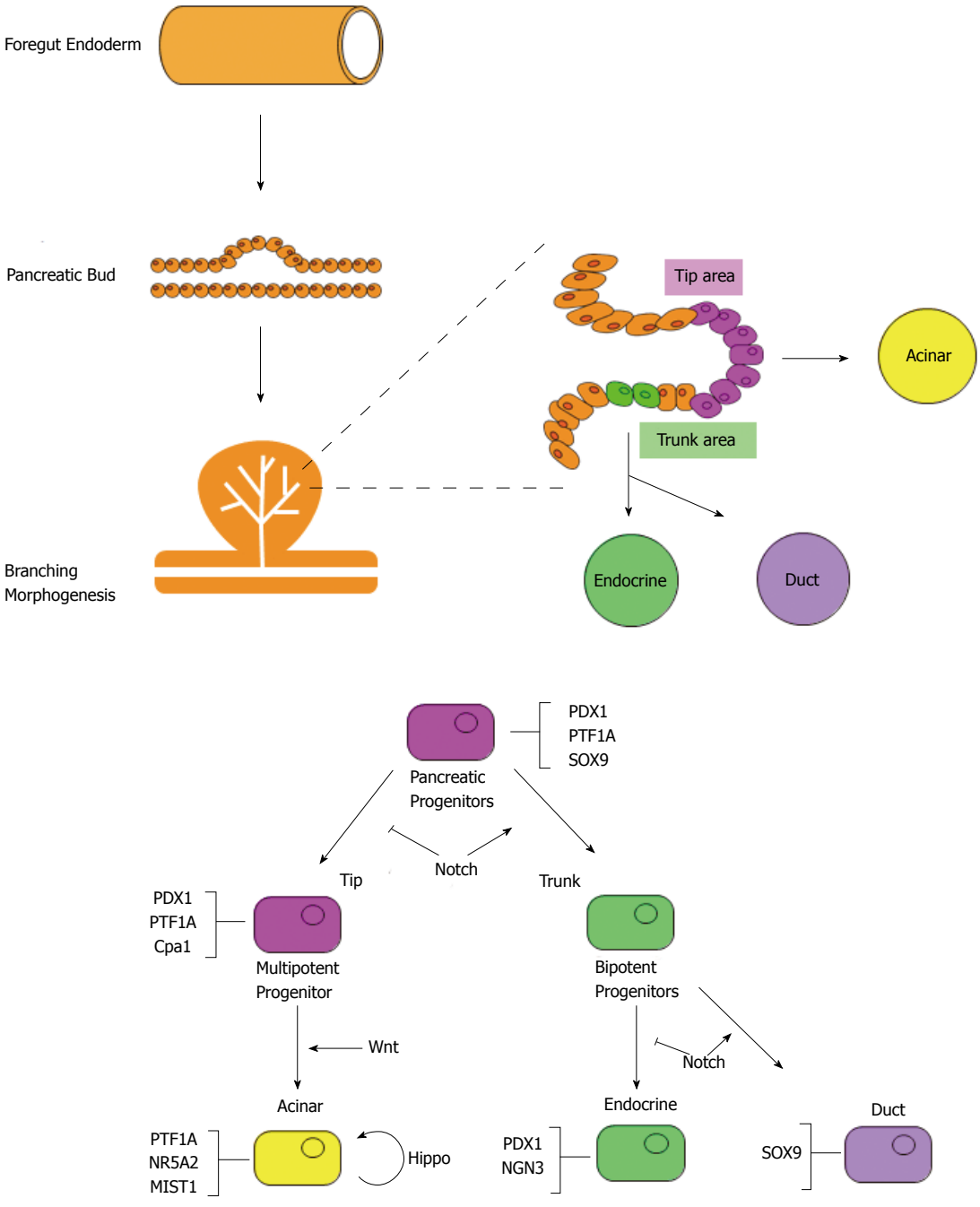

Figure 2 Pancreatic organogenesis and cell differentiation. The pancreatic bud arises from the endoderm foregut. During early branching morphogenesis, the branch tip is composed of multipotent progenitor cells that change into acinar cells. The trunk region is composed of bipotential progenitor cells that can differentiate into either duct or endocrine cells. As differentiation continues, the expression of *PTF1A*, *NR5A2*, and *MIST1* is restricted in acinar cells.

MIST1 is a bHLH transcription factor, highly expressed in acinar cells, as well as the stomach, prostate, and seminal vesicles[57]. Mice with *Mist1* gene knockout developed highly disorganized acinar cells with impaired exocytosis[58]. Furthermore, ADM formation and susceptibility to caerulein pancreatitis were increased in these mice[59]. MIST1 is thought to be required for the maintenance of acinar cell identity.

The Wnt/β catenin signaling pathway is necessary for differentiation of acinar cells. Pancreatic hypoplasia was observed in *β-catenin* knockout mice[60]. Furthermore, acinar cell proliferation was promoted by deficiencies in the *Apc* gene, which has endogenous β-catenin inhibitory activity. Because this abnormal proliferation stops when *c-myc* is deleted, *c-myc* is considered to be an important downstream component of the Wnt/β catenin pathway[61].

The Hippo signaling pathway has been associated with pancreatic development. Deletion of the core Hippo kinase genes *Mst1* and *Mst2* induced pancreatic hypoplasia *via* YAP, the downstream mediator. Interestingly, in *Mst1* and *Mst2* double knockout mice,

expression levels of MIST1, PTF1A, and NR5A2 were equivalent to those seen in wild type mice, with normal pancreatic sizes at birth. However, after 1 mo, the acinar cells changed to duct-like cells while the overall size of the pancreas was approximately half that of wild type mice. This suggests that the Hippo signaling pathway is necessary to maintain acinar cell identity and pancreas size after birth in mice[62].

The Notch signaling pathway is also indirectly related to acinar cell differentiation *via* lateral inhibition. NGN3 is a transcription factor that promotes differentiation to endocrine cells. Cells expressing NGN3 upregulate the expression of DLL1, which is a Notch ligand. DLL1 binds to the Notch receptor of surrounding cells and activates the Notch signaling pathway, thereby upregulating HES1 expression. HES1 inhibits NGN3 and suppresses endocrine cell proliferation. HES1 also maintains the expression level of PTF1A in multipotent progenitor cells and is thought to contribute to multipotent progenitor cell proliferation[63].

PANCREATIC CELL DE-DIFFERENTIATION, INFLAMMATION, AND CARCINOGENESIS

As described above, pancreatic cell differentiation and their identities are maintained by the cooperation of various transcription factors and signaling pathways. However, recent research has revealed that differentiated pancreatic cells show plasticity under specific circumstances. Acinar cells transdifferentiate or de-differentiate into duct cells and endocrine cells after pancreatic duct ligation. During this change, cells express SOX9 and HNF1β multipotency factors[64,65]. The conversion from an acinar cell to embryonic progenitor phenotype that exhibits ductal markers, is called ADM. ADM is thought to be a reversible process and is frequently observed in pancreatic inflammation and injury. However, it becomes irreversible when combined with a *Kras* mutation. This alteration results in a lesion that is considered a precancerous stage of pancreatic cancer[66,67].

Epigenetic factors play crucial roles in differentiation and carcinogenesis. A recent study showed that Brg1, a catalytic ATPase subunit of the SWI/SNF chromatin remodeling complex, is inactivated in approximately 10% of pancreatic cancer[68]. Brg-1 binds to the SOX9 promoter and regulates the expression of SOX9. Acinar cell-specific deletion of Brg-1 attenuates ADM/PanIN formation in *Kras* mutant mice[69].

NR5A2 suppression and forced expression of SOX9 or PDX1 can induce ADM[11,70-72]. These results suggest that transcriptional changes that cause the loss of acinar cell identity promote ADM formation. Interestingly, although the pancreatic tissues of *Nr5a2*$^{+/-}$ mice are histologically normal, transcriptome analyses of *Nr5a2*$^{+/-}$ mice show inflammasome upregulation. In humans, similar transcriptomic changes occur in the pancreas with low levels of NR5A2 expression. Furthermore, NR5A2 is relocated from the promoters of differentiation-specific genes to the promoters of inflammation-related genes. AP-1 is upregulated in these mice and the deletion of *Jun* results in the downregulation of AP-1 and NR5A2 binding to AP-1 and inflammatory gene promoters[73].

In another study, temporal activation of reprogramming factors (*Oct3/4*, *Sox2*, *Klf4*, *c-Myc*) in the pancreas of *Kras* mutant mice promoted ADM formation and pancreatic cancer[10] (Figure 3). In previous transcriptome analyses, when the reprogramming factors are activated, acinar cell-related genes *Ptf1a* and *Mist1* were downregulated. In addition, when pancreatitis was induced *via* caerulein administration in *Kras* mutant mice, similar transcriptional patterns were observed. Conversely, forced expression of *Ptf1a* or *Mist1* in *Kras* mutant mice with caerulein-induced pancreatitis suppressed PanIN formation. These results demonstrate the crucial role of epigenetic regulation in the initiation of pancreatic carcinogenesis.

FUTURE PERSPECTIVES

A growing body of research in pancreatic carcinogenesis demonstrates that the loss of acinar cell identity caused by the suppression of transcriptional networks by reprogramming factors plays a crucial role in ADM formation. In addition, *Kras* mutation and epigenetic regulation play important roles in pancreatic carcinogenesis. Furthermore, inflammation induces an intracellular transcriptional state similar to the de-differentiated state of pancreatic cells, implying that inflammation, cell differentiation, and carcinogenesis are very closely related.

Some questions remain to be resolved. Inflammation may induce not only de-differentiation but also stem cell damage and impaired differentiation, and subsequently cause carcinogenesis. Further research is needed to determine the origin of pancreatic cancer. There is a strong association between chronic pancreatitis and pancreatic cancer. However, only 1.34% of pancreatic cancers are thought to be caused by chronic pancreatitis[74]. Furthermore, pancreatic cancer concomitant with intraductal papillary mucinous neoplasm, a premalignant lesion of pancreatic cancer, is not associated with pancreatitis or pancreatic atrophy[75]. However, these epidemiological and pathological data do not completely deny the connection between carcinogenesis and inflammation. One possible explanation is that pro-inflammatory states may exist in the absence of histologically observed pancreatitis[73]. Further studies are required to clarify the inflammation-like changes in "inflammation-absent" pre-neoplastic pancreatic lesions. This may subsequently allow the identification of high-risk patients.

Many novel therapeutic strategies for pancreatic cancer are aimed at reprogramming pancreatic cancer cells to behave like normal pancreatic cells[76]. For example, PD 325901 inhibits MEK1/2 and induces PanIN

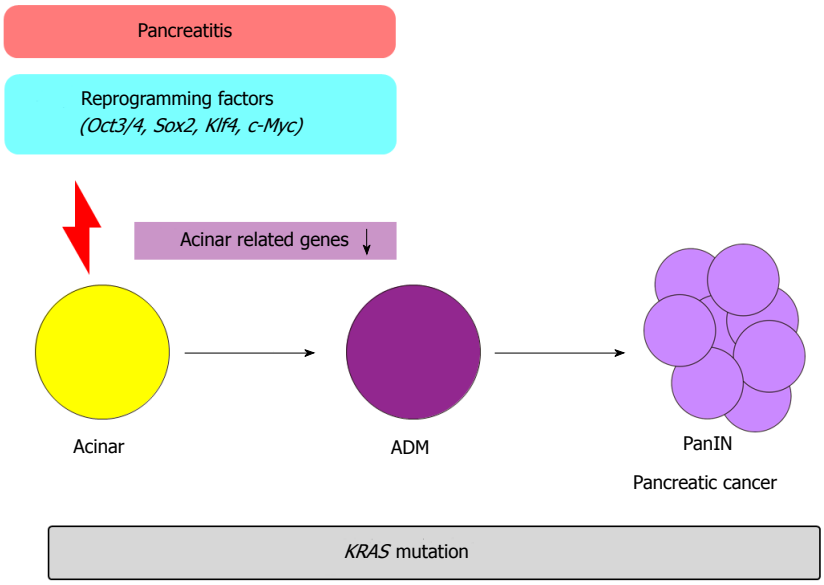

Figure 3 Pancreatic cell de-differentiation, inflammation, and carcinogenesis. Carcinogenesis is promoted by reprogramming factors (*Oct3/4*, *Sox2*, *Klf4*, and *c-Myc*). When the reprogramming factors are activated, acinar cell-related genes are suppressed. Pancreatitis also shows such transcriptional changes.

re-differentiation into acinar cells[77]. Another study has shown that the overexpression of bHLH transcription factors E47 and PTF1A resulted in increased acinar cell gene expression, suppressing cancer proliferation[78,79]. It is highly expected that in the near future, new diagnostic and/or treatment strategies based on the findings described in this review will be clinically applied, improving the prognosis of patients with pancreatic cancer.

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