The mutation of *SPINK1* was found to be the most frequent mutation in idiopathic CP (~25 %) [103, 108]. However, the presence of N34S mutation was not associated with early disease onset or disease severity, indicating that this mutation was not sufficient to be responsible for pancreatitis but could induce pancreatitis with other additional environmental factors [108, 109].

Other gene mutations

In CP, mutations of the cystic fibrosis transmembrane conductance regulator gene (*CFTR*) and α1-antitrypsin gene (*SERPINA1*) were often detected [110, 111]. As plugging of the small pancreatic ducts occurs in cystic fibrosis with loss of CFTR function, and the α1-antitrypsin gene acts as physiological trypsin inhibitor in blood, mutations of these genes might be suspected to correlate with CP. In a gene mutation survey for pancreatitis risk, some were detected, but the ratio was not significant, and so genetic screening for these genes is generally not recommended to date [112].

Roles of inflammation in pancreatic carcinogenesis

DNA damage

ROS derived from either inflammatory/immune phagocyte cells or the mitochondria of epithelial cells act as central endogenous carcinogens and induce DNA damage in epithelial cells. Inflammatory cells, especially tumor-associated macrophages, also release cytokines that can promote chronic oxidative stress in the affected tissue. 8-OHdG elevated by oxidative stress induces mutations in replicating cells by preferentially mispairing with adenine during DNA synthesis, resulting in G:C to T:A transversions [113], while tobacco-derived carcinogenic nitrosamines such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) produce O^6-methyl-guanine and induce G:C to A:T transition [114]. Mutations of K-*ras* and other genes, such as *Dpc4*, could have accumulated already in non-malignant, inflammatory pancreatic tissue [115]. K-*ras* mutations in CP were only found after a disease duration of 3 years [116]. These data suggest that CP could induce gene mutations. Of note, some CP patients with K-*ras* mutations were observed prospectively and reported to develop pancreatic cancer [117, 118].

Cell proliferation/anti-apoptosis

Epidermal growth factor receptor

Epidermal growth factor receptor (EGFR) is a transmembrane receptor that binds epidermal growth factor (EGF) and transforming growth factor (TGF)-α then stimulates phospholipase Cγ1 activity, leading to cell proliferation. TNF-α-induced protein 8 (TNFAIP8) expression is positively correlated with EGFR levels in pancreatic cancer [119]. In CP and pancreatic cancer, expressions of EGFR and TGF-α are up-regulated in ductal and acinar cells, and TGF-α is considered to act through autocrine and paracrine mechanisms to excessively activate the overexpressed EGFR [120, 121]. However, EGF is expressed at the late phase of pancreatitis and is involved in pancreatic repair and regeneration [122]. Expression of epiregunin, a member of the EGF family, is also up-regulated in the ductal and acinar cells in CP and pancreatic cancer cells [123].

The regenerating protein family

Regenerating (Reg) protein family members, such as Reg1α, 3β, 3δ, and 4, have anti-inflammatory, anti-apoptic, and mitogenic roles and are associated with various pathologies, including pancreatitis, diabetes, and forms of gastrointestinal cancer.

Reg1, also known as pancreatic stone protein, is expressed in acinar cells despite normal conditions and AP or CP, and cancer. Reg1 may play a role in the transdifferentiation of acinar cells to islets in CP because Reg1 is not observed in healthy islets, but only when the islets are damaged, and it increases as observed in regenerating or hyperplastic islets after damage [124, 125]. Moreover, Reg1α protein is preferentially expressed in carcinoma cells of pancreatic cancer patients with diabetes over that in subjects without diabetes [126].

Reg3β, also known as pancreatitis-associated protein, is secreted as a stress protein through NF-κB activation by TNF-α and inhibits acinar cell apoptosis [124]. Reg3β protein is strongly expressed in acini adjacent to invasive adenocarcinomas, and Reg3β levels in both serum and pancreatic juices are significantly higher in pancreatic cancer patients compared with those of a control group [127].

Islet neogenesis-associated protein (INGAP), a hamster homolog of mouse Reg3δ, is expressed in acinar cells during islet neogenesis, and INGAP protein could initiate duct cell proliferation, a prerequisite for islet neogenesis. INGAP may also act on islet genes involved in β-cell metabolism and insulin secretion [128].

Reg4 is expressed in rat acinar cells and human insulin-producing β cells. Reg4 is up-regulated via the overexpression of glioma-associated oncogene homologue GLI1, a key transcription factor in the Hedgehog signaling pathway, in pancreatic cancer cells [124, 128].

Other growth factors

Fibroblast growth factor (FGF)-1 and 2, insulin-like growth factor (IGF)-1, and hepatocyte growth factor are also markedly increased in pancreatitis tissue [129]. Expression of FGF-2 is strongly associated with the proliferation of tumor cells and

intratumor endothelial cells, suggesting that its increased expression may give tumors a growth advantage [130].

Angiogenesis

The number of blood vessels is significantly higher in PDACs, CP with or without a mutant K-*ras* genome, compared to surrounding normal areas. The fact that microvessel density was significantly elevated in CP patients with mutant K-*ras* in their genome, compared to patients with a normal K-*ras* genome, suggests that oncogenic K-*ras* may modulate tumor angiogenesis [131].

Vascular endothelial growth factor (VEGF) is a key component in pancreatic tumorigenesis, and high expression levels are correlated with poor prognosis. Even if in CP, VEGF is strongly expressed in ductal cells as observed in carcinoma cells [132]. Serum levels of VEGF and another factor, angiopoietin-2, have also been shown to be significantly higher in CP and pancreatic cancer patients than in a control group [133]. In addition, angiotensin II increases the production of VEGF, and VEGF production could be prevented by an angiotensin II type 1 receptor antagonist, losartane, or an angiotensin 1-covering enzyme inhibitor, captopril [134].

Fibrosis

The development of pancreatic fibrosis is a major component of pancreatic diseases including CP, type II diabetes, and pancreatic cancer. In the progression of pancreatic fibrosis, PSCs have been identified as a key mediator. PSCs are normally quiescent cells and characterized by star-like morphology. When activated by tissue injury, oxidative stress, growth factors, or cytokines, they are transformed to a myofibroblast-like phenotype and produce excess extracellular matrices (ECMs), such as collagen and fibronectin. Regarding growth factors and cytokines, TGF-β and platelet-derived growth factor are the strongest mediators of PSC activation. The heparin-binding epidermal growth factor-like growth factor overexpressed in pancreatic islet cells also facilitates fibrosis through secretion of ECMs [135]. Hypoxia also induces migration, type I collagen expression, and VEGF production in PSCs to stimulate fibrosis and angiogenesis [136].

Epithelial to mesenchymal transition

Epithelial to mesenchymal transition (EMT) is closely related with tumor growth and metastasis. During EMT, cells lose polarized epithelial phenotypes and acquire highly motile fibroblastoid or mesenchymal phenotypes, invasive properties, and stem cell-like features. TGF-β induces EMT along with overexpression of EMT-relating transcription factors Snail and Slug which repress E-cadherin expression. On the other hand, overexpression of Twist increases N-cadherin expression. It is interesting that these EMT markers are expressed in PDACs [137]. In a mouse model expressing oncogenic K-*ras*, inflammation was shown to enhance EMT in premalignant lesions. In such situations, inflammatory stroma were considered to be necessary for EMT and dissemination [138].

Major molecules and molecular pathways involved in inflammation-related pancreatic cancer

ROS

Oxidative stress is caused by an imbalance between the production of ROS, such as peroxides and free radicals, and the detoxification of reactive intermediates in a biological system. Smoking generates ROS [139]. Obesity also induces systemic oxidative stress. Several observations from human and animal models have suggested that obesity accelerates lipid peroxidation, which is an oxidative stress marker [140]. Oxidative stress could induce DNA damage, inflammation, apoptosis, and insulin resistance, resulting in the development of cancer [141, 142]. ROS can also prolong chronic inflammation by activation of NF-κB and could alter the regulation of adiponectin in adipose tissue [140, 143]. Thus, obesity-induced oxidative stress may contribute to an increased risk of pancreatic cancer.

Oxygen radicals react most readily with polyunsaturated fatty acids, resulting in peroxidation of lipids. Several experimental models of AP demonstrated the development of lipid peroxidation in pancreatic tissue [144–146]. In CP patients, tissue levels of lipid peroxidation products, such as conjugated dienes and malondialdehyde concentrations, were significantly elevated [147, 148]. The activation of oxygen-derived free radicals also occurs in CP tissues [149]. Thus, most studies have shown increased oxidative stress in patients with CP.

Cytokines

In the presence of chronic inflammation, large amounts of pro-inflammatory cytokines, growth factors, and proteases, such as TNF-α, IL-1β, IL-6, TGF-β, and MMPs, are secreted and activate oncogenic pathways in pancreatic cancer cells [150]. Single-nucleotide polymorphisms in TNF-α, IL-1β, and IL-6 have been reported to affect inflammatory response [151].

TNF-α

TNF-α is a pro-inflammatory cytokine and mainly secreted by activated macrophages. Significantly higher levels of TNF-α have been found in serum of CP and pancreatic cancer patients [152]. TNF-α production is also increased in obese adipose tissues and is involved in the development of insulin resistance [153]. TNF-α binds its receptors and activates NF-κB

through IκB kinase activation. TNF-α also activates c-Jun N-terminal kinases (JNKs), which regulate cell growth, differentiation, survival, and apoptosis.

IL-1β

Together with TNF-α, IL-1β also plays central roles in the regulation of immune responses and the inflammatory process. Caspase-1, which has been designated as IL-1β-converting enzyme, is also up-regulated in CP and pancreatic cancer [154]. IL-1β secreted by malignant cells or infiltrating leukocytes contributes to increased tumor adhesiveness and invasion, angiogenesis, and immune suppression [155] through activation of NF-κB [156] and JNK [157].

IL-6

Significantly higher levels of IL-6 have also been found in serum of obese people, type II diabetes, CP, and pancreatic cancer patients [151, 152]. In obese mice, IL-6 seems not to contribute to the increased severity of pancreatitis but delays its recovery from acute inflammation, which is explained by the prolonged activation of Stat3, induction of MMP-7, and sustained production of chemokines [158].

TGF-β

TGF-β is a multifunctional cytokine involved in embryonic development, cell proliferation, differentiation, angiogenesis, and wound healing. TGF-β also plays a role as a tumor suppressor via growth inhibition of premalignant cells, induction of autophagy, senescence and apoptosis, and suppression of inflammation. On the other hand, TGF-β, especially TGF-β1, is overproduced in a variety of human tumors, including pancreatic tumors, and is involved in tumor progression and metastasis via immunosuppression, induction of EMT, and angiogenesis [159]. TGF-β signaling is mediated by Smad-dependent and Smad-independent pathways. In pancreatic tumors, type I and II TGF-β receptors (Tgfbr1, Tgfbr2) or Smad4 are often mutated or deleted. Therefore, Smad-independent pathways could mediate the tumor-promoting effects of TGF-β signaling. In addition, TGF-β enhances motility and stimulates the recruitment of monocytes, macrophages, natural killer cells, neutrophiles, and T cells while directly inhibiting their anti-effector functions [160].

Inducible enzymes

Inducible nitric oxide synthase

Nitric oxide (NO) is an important bioregulatory mediator involved in a variety of processes in the cardiovascular, nervous, and immune systems [161]. Sustained release of NO causes immune cell cytotoxicity. Chronic infection and inflammation are associated with release of many cytokines along with activation of NF-κB, resulting in the expression of inducible nitric oxide synthase (iNOS). iNOS is a calcium-independent enzyme and induced by bacterial endotoxins and cytokines. NO is not only an important mediator in benign diseases but it is also implicated in cancer, considered as an endogenous mutagen, an angiogenesis factor, an enhancer of protooncogene expression, and an inhibitor of apoptosis [162, 163]. These observations suggest that iNOS overexpression with high levels of NO generation provides a plausible link between inflammation and cancer initiation, progression, and promotion.

Increased expression of iNOS has been detected in more than half of human PDACs and in severe AP tissues [164, 165]. In cerulein-induced rat AP, expression of iNOS produces a large amount of NO [166]. We also confirmed that iNOS expression was observed in hamster PDACs and atypical hyperplasia [167]. Our previous study revealed that iNOS expression can be markedly elevated by transfection of K-*ras* mutant cDNA into IEC-6 rat intestinal epithelial cells in the presence of IL-1β or lipopolysaccharides through the activation of promoters at NF-κB, C/EBP, and CRE-like sites. The growth of tumors formed in nude mice by a subcutaneous injection of the K-*ras* mutant-transfected cells can be suppressed by feeding diets containing NOS inhibitors [168]. It is feasible that iNOS expression in PDACs could also be associated with K-*ras* activation since human PDACs frequently harbor K-*ras* mutations [169] and show increased iNOS expression [164]. Chemically induced hamster carcinomas also quite frequently harbor G to A transitions at the second base of codon 12 of the K-*ras* gene [170]. Thus, NO produced by iNOS may be generally involved in tumor development by activated K-*ras*.

Cyclooxygenase 2

Cyclooxygenase 2 (COX-2) is an inducible immediate early gene involved not only in inflammation and cell proliferation but also in differentiation, anti-apoptosis, metastasis, immunologic surveillance, and angiogenesis [171]. COX-2 expression is regulated via the Wnt and Ras signaling pathways. Mutant β-catenin expression up-regulates COX-2 promoter activity, and induction of mutated K-*ras* increases COX-2 levels through stabilization of COX-2 mRNA [172, 173].

As for pancreatitis, elevated COX-2 activity appears to correlate with chronic inflammation. COX-2 plays an important pro-inflammatory role in experimental pancreatitis models [174, 175]. COX-2 is also strongly increased in pancreatic specimens from patients with CP [176, 177]. These studies revealed that COX-2 was localized to atrophic pancreatic acinar cells, islets, and duct cells, providing a potential target for treatment of patients with CP. The beneficial effects of inhibition of COX-2 or the knock-out of its gene in experimental AP

have been demonstrated [174, 175, 178]. Song et al., using a mouse model of experimental cerulein-induced AP, showed that the severity of pancreatitis was reduced in COX-2-deficient mice compared with the noninhibited strains of COX-2-sufficient mice [174]. Up-regulation of COX-2 has been also observed in PanIN lesions and PDACs in both humans and BOP-treated hamsters [179].

Transcriptional factors

NF-κB

NF-κB is known to be a master inflammatory transcriptional regulator and is highly activated in macrophages. Targets of NF-κB include genes regulating immune response, inflammation, cell proliferation, cell migration, and apoptosis. The nuclear translocation of NF-κB can activate target genes involved in carcinogenesis [180]. NF-κB has the potential to lead the amplification of the inflammatory response in the tumor environment. The expression of both IL-1β and TNF-α is stimulated by NF-κB, suggesting an autoregulatory loop that can amplify the inflammatory response. As mentioned previously, NF-κB also stimulates the expression of iNOS and COX-2 [15].

STAT3

The inflammatory mediator, signal transducer, and activator of transcription 3 (Stat3), a critical component of pancreatitis, has been shown to accelerate PDAC precursor formation. Stat3 is activated by phosphorylation of key tyrosine (Tyr705) and serine (Ser727) residues. The activation is triggered by binding of IL-6 to IL-6 receptors and subsequent activation of receptor-associated tyrosine kinase, Janus kinase. In the nucleus of tumor cells and infiltrating immune cells within the tumor microenvironment, Stat3 and NF-κB co-regulate numerous genes controlling cell proliferation and survival, such as c-Myc, cyclin D1, and Bcl-2, and contribute to metaplasia during inflammation-associated neoplastic development [150].

Stat3 regulates the expression of MMP7, a member of a family of zinc-dependent endopeptidases, during mPanIN development following pancreatitis. Furthermore, MMP7 in carcinoma cells contributes to tumor size and metastasis in mice [181]. In humans, MMP7 is overexpressed in PanINs and PDACs [182, 183] and correlates with decreased survival and possibly tumor size, lymph node metastasis, and distant metastasis [182, 184, 185]. In vitro studies also support the idea that MMP7 is involved in cancer progression by dictating the invasive and metastatic capacity of PDAC cells [182]. Thus, Stat3 and MMP7 are thought to be key mediators of both initiation and progression of pancreatic carcinogenesis. In addition, both Stat3 and MMP7 could be potential novel targets for future therapies since serum MMP7 levels in PDAC patients were correlated with metastatic disease and survival [181].

Evidence of involvement of inflammation in pancreatic carcinogenesis in experimental animals

Animal models for pancreatitis

Ethanol

Excessive alcohol consumption is a major risk factor for developing CP [186]. However, the pathobiology of this disease remains unclear because of a lack of animal models representing alcohol-induced CP. Indeed ethanol feeding by itself does not affect pancreatic injury in animal models. Its metabolites on acinar cells may promote CP changes by its toxic effects [187]. Moreover, oxidant stress [188] and activation of PSCs promote inflammation [186]. Thus, administration of ethanol in combination with caerulein, cyclosporin A, or high-fat diet has been shown to enhance pancreatitis [189, 190].

Caerulein

A caerulein-induced rodent pancreatitis model is widely used and is one of the best-characterized experimental varieties. Caerulein is an analog peptide of cholecystokinin (CCK), and its frequent intraperitoneal (i.p.) injection causes pancreatic hypertrophy, characterized by increased pancreatic weight, increased amylase content, and acinar cell hyperplasia. This model is useful because either AP or CP could be induced by modulating the treatment schedule and its doses [191, 192].

Choline-deficient ethionine-supplemented diet

Choline-deficient ethionine-supplemented (CDE) diet is known to induce AP [193–195]. Ethionine is the analog of the essential amino acid methionine and induces exocrine pancreatic insufficiency by inhibiting the activation of phospholipase C in pancreatic acinar cells [196–198]. Moreover, ethionine diet alone can increase the amount of digestive enzymes by decreasing the digestive enzyme discharge [199]. As a result, AP will develop. Pancreatitis induced by CDE diet is an ideal model because of its natural history, histological features, and biochemical changes that are similar to those of humans [193]. In addition, the method of this model is relatively simple and not expensive. This model could also develop CP by repeating a CDE diet and standard diet by turn [200].

High-fat diet

A long-term high-fat diet can induce rat CP [201]. In mice, a high-fat diet with treatment of IL-12 plus IL-18 can induce

AP [202]. A high-fat diet with caerulein can also increase plasma amylase activity in mice [203]. Moreover, a high-fat diet leads to obesity [204], which enhances the severity of AP [205]. Thus, a high-fat intake may play a pivotal role in the development of CP.

Up-regulation of K-ras activity

Ras signaling pathways are activated by several stimuli, including CCK, known to cause CP [206], or TGF-α [207, 208]. On the other hand, elevation of Ras activity in acinar cells in a genetically engineered mouse (GEM) model has been reported to induce inflammation and fibrosis resembling the histological features of human CP, characterized by loss of acinar cells, acinar-to-ductal metaplasia, leukocyte infiltration, replacement by stroma with collagen, and activated PSCs [209, 210].

Animal models for pancreatic carcinogenesis

Chemically induced PDAC model in hamsters and other rodents

The Syrian golden hamster is in a hyperlipidemic state even under normal diet conditions because the lipoprotein lipase activity in the liver is low compared with mice and rats [211]. The hamster is a unique model animal for the development of PDACs induced by subcutaneous (s.c.) injections of BOP [212]. Histopathologically, the induced lesions possess close similarities to pancreatic cancer in humans. Moreover, point mutations in codon 12 of the K-*ras* gene are frequently observed, and expression of the *fragile histidine triad* (*Fhit*) gene is aberrant in BOP-treated hamsters [213, 214], as was also observed in human PDACs [215, 216]. The *p16* gene is one of the most frequently inactivated tumor suppressor genes in human PDACs [217], and loss of *p16* expression has also been found in hamster PDAC lesions [218].

The intrapancreatic implantation of 7,12-dimethyl-1,2-benzanthracene (DMBA) model in rats and mice is known to cause tubular complexes and produce mPanIN lesions and PDACs derived from acinar cells [219, 220]. The tumors developed in this model have also been shown to harbor K-*ras* mutations [221], and activated PSCs surround precancerous duct cells as they do in human pancreatic cancers [222]. Thus, pancreatitis induced by implantation of the chemical carcinogen could develop fibrosis and enhance K-*ras* activation.

GEM pancreatic cancer models

In 2003, Hingorani et al. developed a GEM model that specifically expressed an oncogenenic K-ras^{G12D} mutation from its endogenous gene locus in pancreatic progenitor cells during embryologic development through *Cre*-mediated recombination driven by *Pdx1* regulatory elements [223]. Since then, several GEM models of pancreatic exocrine neoplasia have been developed. An activating mutation of the K-*ras* is the most frequent genetic alteration associated with pancreatic carcinogenesis, having been identified in up to 90 % of all PDACs [224, 225]. K-*ras* mutations are also observed in early lesions, such as atypical ductal hyperplasia and PanIN, in humans [226]. Therefore, the GEM models are commonly based on K-*ras* mutations such as with Pdx-*Cre*/Lox-Stop-Lox (LSL)-*Kras*G12D or $p48^{Cre}$/LSL-$K\text{-}ras^{G12V}$ mice. Unlike in the case of humans, acinar to ductal metaplasia is the predominant precursor lesion for pre-neoplastic and neoplastic lesions in a GEM model. However, pancreatic cancer arising from mPanINs is very similar to human pancreatic carcinogenesis [227]. Furthermore, these mice were modified by conditional deletions or mutations of *p16* [228], *p53* [229], *dpc4* [230], and *TGF−β receptor II* [231]. These combined genotypes cause multiple preinvasive lesions of all grades, invasive adenocarcinomas, and metastasis to other organs, ultimately leading to a significantly reduced median survival. Pancreatic carcinogenesis induced by pancreatitis in K-*ras*-based models is hoped to provide preclinical model systems to analyze the molecular biology of this disease and to evaluate the benefit of new therapies.

Animal models with combination of inflammation and carcinogenesis

Exposure to ethanol

Transplacental treatment with NNK plus ethanol in Syrian golden hamster to induce PDACs is an interesting model to confirm the synergistic effect of cigarette smoking and alcohol drinking on fetuses [232]. Nicotine-derived NNK is one of the most potent tobacco-specific carcinogens and thus is an excellent model compound for studies of the potential carcinogenic effects of cigarette smoke [233]. NNK is also known to be an active transplacental carcinogen in Syrian golden hamsters. Although the main target site for NNK-induced tumor development is the respiratory tract (nasal cavity, lungs, trachea, and larynx) in adult hamsters and offspring, focal ductular hyperplasias and/or small ductal adenocarcinomas of the pancreas were also occasionally found in offspring [234]. The simultaneous treatment of pregnant hamsters with ethanol and NNK significantly elevates the carcinogenic response in their offspring compared to animals exposed in utero to NNK alone. Especially, the simultaneous in utero exposure to ethanol and NNK resulted in the induction of PDACs, while in utero exposure to ethanol alone induces pancreatitis in the offspring [232]. These findings indicate that alcoholic pancreatitis itself does not induce PDACs but markedly enhances smoking-induced PDAC development.

Wendt et al. reported the influence of ethanol on pancreatic carcinogenesis using a DMBA-induced mouse pancreatic carcinogenesis model. The mice received water or 6 % ethanol in their drinking bottle, and 1 mg of DMBA was implanted into the head of the pancreas. The ethanol-drinking group had a significantly greater incidence of invasive adenocarcinomas than the water-drinking group [235]. Thus, association between ethanol and pancreatic carcinoma development was evident.

In a BOP-induced hamster pancreatic carcinogenesis model, administration of 20 % ethanol in their drinking water slightly increased the multiplicity of PDACs, although there were statistically no significant differences regarding lesion incidence [236]. On the other hand, an inhibitory effect of ethanol on BOP-induced pancreatic carcinogenesis in hamsters when given in the initiation phase was reported [237]. The administration period might be important for investigating the modulating effects of ethanol.

Caerulein-induced pancreatitis

Administration of caerulein in hamster pancreatic carcinogenesis model is a beneficial model for inflammation-related pancreatic carcinogenesis. Two groups of hamsters received BOP at a dose of 5 mg/kg once weekly for life by s.c. injection. One group also received exogenous CCK 30 IDU/kgs.c. for 3 days per week for 6 weeks on the day before, the day of, and the day after BOP injection. In the CCK-treated group, a significant excess of panlobular ductular proliferation was found at 10 weeks after the first BOP treatment. At 15 weeks, the incidence of adenocarcinoma in a BOP + CCK group and BOP-alone group was 71 and 20 %, respectively [238]. Thus, CCK treatment enhanced pancreatic carcinogenesis, acting as co-carcinogen or promoter of pancreatic carcinogenesis.

Some pancreatic carcinogenesis experiments in GEM have demonstrated that caerulein-induced pancreatitis can enhance carcinoma development. In LSL-Kras^{G12D}/Pdx1-Cre mice, chronic treatment with caerulein (a single daily i.p. injection of 5 μg/animal at 5 days per week during the duration of the study) induces CP and significantly enhances the development of PDACs [206]. Acute chemical pancreatitis induced by caerulein (seven-hourly i.p. injections at a dose of 50 μg/kg of body weight repeated 48 h later) has also been demonstrated to cause rapid acinar-to-ductal metaplasia and mPanIN progression and accelerate PDAC development in a GEM model in which oncogenic K-*ras* is activated in all pancreatic cell types [239]. Thus, even a brief inflammatory insult to the pancreas, when occurring in the context of oncogenic K-ras^{G12D}, can initiate a cascade of events that dramatically enhances the risk for malignant transformation.

In a K-$Ras^{+/G12V}$;*Elas*-tTA/*tetO*-Cre mouse model, oncogenic K-*ras* expression in acinar cells of adult mice did not cause any pancreatic lesions, even when loss of $p16^{Ink4A}$/$p19^{Arf}$ or *Trp53* tumor suppressors were introduced. The findings indicate that adult acinar cells are extremely resistant to malignant transformation. However, chronic caerulein treatment induced mPanINs and PDACs in mice expressing K-ras^{G12V} in adult acinar cells, suggesting that pancreatitis contributes to tumor progression by abrogating the senescence barrier characteristic of low-grade mPanINs. Even though pancreatitis occurs before the activation of K-*ras* oncogenes, PDACs can also develop in injured acinar cells expressing oncogenic K-*ras* [240]. These findings show that CP could give irreversible or prolonged changes to promote pancreatic carcinogenesis stronger than loss of tumor suppressors.

In response to caerulein-induced AP, acini dedifferentiate to develop duct-like structures with transient expression of embryonic factors, a characteristic of pancreatic embryonic progenitors. In the absence of mutant K-*ras*, re-differentiation into functional acinar cells occurs rapidly within a week [241–245]. In contrast, mutant K-*ras* locks damaged acinar cells in a persistently dedifferentiated ductal state that can rapidly give rise to PanINs [244, 245]. Thus, pancreatitis provides a permissive environment for K-*ras*-driven neoplasia. Moreover, Stat3 activation in pancreatic epithelial cells may play a significant role in the process [181]. Pancreatitis induction in K-*ras*-driven mouse pancreatic carcinogenesis models has revealed that inflammatory damage can promote and/or accelerate mPanIN and carcinoma formation.

Augmentation of cancer development by CDE diet

Long-term administration of a CDE diet can induce CP. The set of 7 days was defined as one cycle and the cycles were repeated to develop CP in mice. In this set of 7 days, mice were starved for 24 h (day 0) and then fed a CDE diet for 72 h (days 1 to 4) and after that fed regular laboratory chow for 72 h (days 5 to 7). After 24 weeks, CP-like features characterized by acinar atrophy, fibrosis, and well-developed tubular complexes were established. Key events in the process of pancreatic carcinogenesis, such as EGFR overexpression, FGF receptor phosphorylation, and K-*ras* gene mutation, were also detected in the mice fed the long-term CDE diet [200]. However, CP in this model is not sufficient for the development of PDACs. A further combination of the CDE diet with the administration of other promoting insults or genetic alterations may result in PDAC development.

A rapid production model, called "augmentation pressure," was established for PDAC development in Syrian hamsters [246, 247]. In this method, Syrian hamsters received s.c. injection of BOP (70 mg/kg) as the initiation dose. At 11 days after BOP initiation, the animals received four daily i.p. injections of DL-ethionine (500 mg/kg) combined with a choline-deficient diet. The hamsters were then returned to basal diet and given a single i.p. injection of L-methionine (800 mg/kg)

followed by a single s.c. injection of BOP (20 mg/kg) at day 5 after the beginning of the augmentation pressure cycle. In hamsters receiving BOP initiation followed by three cycles of augmentation pressure, atypical hyperplasia of the ductal epithelium and intraductal carcinomas were evident on day 46 after the beginning of the experiment, and development of intraductal carcinomas and invasive PDACs was observed on day 70. K-*ras* mutations were observed to occur in atypical hyperplasia (56 %) and in intraductal carcinomas (57 %) [247]. The augmentation pressure model is useful for investigating potential modulating factors of pancreatic carcinogenesis because large numbers of lesions can be developed within only 10 weeks.

Increases in ectopic fat and inflammatory factors by high-fat diet

Feeding high-fat diets has been demonstrated to increase PDAC development in several animal models. However, the promoting mechanisms of obesity on pancreatic carcinogenesis have yet to be completely elucidated.

We examined whether aggravated hyperlipidemia with a high-fat diet affects pancreatic carcinogenesis using BOP-treated hamsters. A high-fat diet is shown to increase serum lipid levels and enhance fatty infiltration in the pancreas along with abnormal adipokines production. Acinar cell damage caused by BOP treatment and hyperlipidemia may contribute to fatty infiltration [248]. Pancreatic fatty infiltration has been shown to be associated with a high body mass index, elevated visceral fat weight and serum lipids, and diabetes mellitus in humans [249, 250]. Thus, fatty infiltration may also accelerate and enhance pancreatic cancer through elevation of adipokines and inflammatory factors. Indeed the expression of inflammatory-related genes, including MCP-1, IL-1β, and COX-2, was found to be increased or tended to be increased in the pancreas of hamsters treated with BOP + high-fat diet [248]. The levels of mRNAs encoding growth-related genes such as insulin, IGF-I, and cyclin D1 were also elevated in the pancreas in the BOP + high-fat diet group, indicating enhanced proliferation by the high-fat diet. The enhanced pancreatic fatty infiltration and the elevation of inflammatory- and proliferation-associated genes in the hamster pancreas by the high-fat diet were suggested to be involved in the promotion of PDAC development.

In addition, a high-fat/high-protein diet containing 30 % protein and 30 % fat was shown to increase the prevalence of PDACs in rats implanted with DMBA compared to those in rats fed a normal diet containing 23.4 % protein and 4.5 % fat, the prevalence being 29 vs 17 % at 9 months. [221].

Inflammation-related pancreatic carcinogenesis with a high-fat diet was also investigated in mice with pancreas-specific (p48-Kras) and acinar-specific (Ela-Kras) expression of oncogenic K-*ras* [251]. In 30-week-old p48-Kras mice, the incidences of mPanIN1b, mPanIN2, and mPanIN3 lesions were higher in the high-fat diet group compared to the regular chow diet group, being 75, 50, and 12.5 vs 44, 22, and 0 %, respectively. Feeding with a high-calorie diet accelerated mPanIN development in p48-Kras mice. Along with increased infiltration of inflammatory cells in the pancreas, inflammatory cytokines such as TNF-α, IL-1β, and IL-6 mRNA and circulating levels of TNF-α and IL-6 were significantly elevated in p48-Kras mice. To investigate the role of TNF-α on increased mPanIN development, p48-Kras mice were further crossed with TNF receptor (TNFR) 1-deficient mice. TNFR1 deletion significantly attenuated high-fat-diet-induced PanIN development in p48-Kras mice. TNFR1$^{-/-}$-p48-Kras mice revealed lesions mostly residing at the head of the pancreas. The pancreas contained mostly intact acini and reduced fibrosis. Thus, increases in inflammation and TNF-α played an important role in developing tumor promotion by feeding a high-fat diet in p48-Kras mice.

Inflammation induced by elevated levels of Ras activity

Ras activity is greatly up-regulated in all PDAC cells in mice and humans. In GEM models, transformation of acinar cells by endogenous levels of mutant K-*ras* needs another genetic ablation of the tumor suppressor genes. On the other hand, overexpression of mutant K-*ras* in acinar cells has been shown to develop abundant mPanINs, cystic papillary carcinomas, and PDACs, accompanied with widespread senescence of acinar cells, profound inflammation, and fibrosis. Expression of tumor suppressor genes *p15* and *p16* were found to be elevated in K-*ras*-driven inflammatory tissue but lost in cancer cells [209]. Loss of tumor suppressors is permissive for cells to evade oncogenic K-*ras*-induced senescence, and spontaneous loss of those is accelerated by Ras activity due to the increase in genetic instability. It has also been reported that Twist expression elevated by oncogenic K-*ras* suppresses p16 expression [252].

Anti-inflammatory agents as a good candidate for chemopreventive agents

Importance of prevention against pancreatic cancer

Similar to other solid tumors, the curative potential for pancreatic cancer is dependent on the stage of disease at diagnosis. As the progress of pancreatic cancer is very silent, symptoms do not develop until it is either unresectable or metastatic, and the majority of patients with pancreatic cancer are diagnosed incurable. Moreover, even when patients are diagnosed at an early stage, the likelihood of cure remains very low with currently available therapies. As

a result, the survival rate of patients with pancreatic cancer has not substantially improved over the last few decades. Therefore, it is very important to develop effective chemotherapeutic and chemopreventive agents and to elucidate causative factors and mechanisms underlying pancreatic carcinogenesis. Epidemiological studies have suggested that several agents may have a chemopreventive potential against pancreatic cancer [253]. Here, we focus on the inflammatory factors in pancreatic carcinomas and the chemotherapeutic and chemopreventive agents having anti-inflammatory activity.

Agents that inhibit COX-2

COX-2 selective inhibitors

As described, COX-2 expression is elevated both in CP and PDACs. Selective COX-2 inhibitors prevent the growth of cancer cells [254]. In addition, preclinical and clinical data suggest that selective COX-2 inhibitors have the potential to prevent pancreatic cancer prolongation [255, 256]. It is thus likely that increased expression of COX-2 is an important contributor to pancreatic tumor formation, and compounds that inhibit the activity and/or expression level of this enzyme are potentially of great interest as candidate chemopreventive agents against pancreatic carcinogenesis. On the other hand, although major efforts have been made to develop selective inhibitors of COX-2 as chemopreventive agents against pancreatic cancer, efforts to identify agents that can selectively suppress the expression of COX-2 at the gene level appear to be equally important. It is also likely that the combination of suppression of COX-2 gene expression and selective inhibition of its enzyme activity may provide a most effective approach to pancreatic cancer prevention. Therefore, developing a simple screening system, which could detect the suppression of COX-2 gene expression, might be useful in searching for novel chemopreventive agents.

Nimesulide (4-nitro-2phenoxymethanesulfonanilide), a preferential COX-2 inhibitor of non-steroidal anti-inflammatory drugs (NSAIDs) [257], is used clinically as an anti-inflammatory drug in several European countries. This compound is a potent anti-inflammatory agent with fewer ulcerogenic effects than other NSAIDs, and severe side effects have not been reported [257].

Nimesulide has been demonstrated to suppress the development of precancerous lesions (atypical hyperplasia) and PDACs in BOP-treated hamsters. Proliferating cell nuclear antigen labeling indices of pancreatic ducts were also significantly reduced by nimesulide [258]. Therefore, the mechanism underlying the chemopreventive effect of nimesulide was suggested to be the inhibition of cell growth.

Funahashi et al. also evaluated the efficacy of nimesulide in preventing the progression of mPanINs using a *LSL-KRAS^{G12D};PDX-1-Cre* mouse model. Treatment with nimesulide inhibited COX-2, significantly decreased PGE_2 levels in the pancreas, and led to reduced mPanINs, particularly later-stage lesions (mPanIN2 and mPanIN3) [259]. These data clearly suggest that COX-2 and COX-2-derived prostanoids are critical mediators in pancreatic carcinogenesis. Inhibition of COX-2 may represent an intriguing strategy to prevent pancreatic cancer in high-risk patients.

NSAIDs

NSAIDs are some of the most commonly used pharmaceuticals worldwide. They are used for the prevention and treatment of inflammatory diseases. Aspirin is the most frequently used NSAID and has been reported to reduce cancer risk in several organs such as the colon [260]. However, in the pancreas, epidemiological data on aspirin use are controversial. A cohort study of post-menopausal women has shown that current use of aspirin is associated with reduced risk of pancreatic cancer (the multivariate-adjusted RR=0.57) [261], whereas another cohort study of nurses demonstrated that more than 20 years of regular aspirin use is associated with increased risk (RR=1.58) [262]. It is difficult to understand these epidemiological data because regular users of aspirin possibly include CP patients.

In GEM models, aspirin treatment has been shown to delay the progression of PanINs in *LsL-KrasG12D;Pdx1-Cre* mice and to partially inhibit the development of invasive carcinomas in *LSL-KrasG12D;LsL-Trp53R172H;Pdx1-Cre* mice [263]. Meanwhile, the NF-κB pathway has been implicated in pancreatic cancer biology [264]. Aspirin is a surrogate pharmacological inhibitor of the NF-κB pathway, and aspirin treatment inhibited tumor formation in mice [265, 266].

Laboratory studies indicate that aspirin may inhibit pancreatic carcinogenesis, but epidemiologic data to support this finding are limited. To identify aspirin as an effective chemotherapeutic and chemopreventive agent against pancreatic cancer, further detailed studies of its role might be warranted.

Takahashi et al. investigated the effects of prostanoid synthesis inhibitors, such as indomethacin, phenylbutazone, and aspirin, on the development of BOP-initiated hamster pancreatic tumors [267]. The incidence of pancreatic carcinoma was significantly lower in hamsters receiving phenylbutazone than in the controls and the numbers of carcinomas per hamster were significantly reduced by indomethacin and phenylbutazone treatment compared with the control group value. Aspirin also showed a tendency to decrease pancreatic tumor incidence, although not significantly. Thus, inhibition of prostanoid synthesis might help reduce the development of pancreatic cancer.

Other (COX-2 specific and non-specific) NSAIDs, including etodolac, sulindac, ibuprofen, celecoxib, and NS-398,

have also shown efficacy in cellular and animal models [268–272], but they have not been fully evaluated for the prevention and/or treatment of pancreatic cancer.

For instance, some case report studies have also shown that NSAIDs such as aspirin, sulindac, indomethacin, ketoprofen diclofenac, and naproxen could induce acute pancreatitis [273–278]. To resolve the discrepancy, further investigation is needed to better elucidate how COX-2 inhibition might affect pancreatitis.

The effect of dual COX-1/2 inhibitor sulindac on mPanIN and PDAC development was studied using caerulein-treated K-*Ras*$^{+/G12V}$;*Elas-tTA/tetO-Cre* mice. Sulindac treatment for 3 months after caerulein exposure for 3 months significantly reduced the numbers of high-grade PanIN lesions and PDACs [240]. These results suggest that inflammation is a key contributor to the effect of pancreatitis not only in promoting mPanIN formation but also in inducing progression to PDAC.

Agents that inhibit iNOS

As mentioned, increased expression of iNOS has been frequently detected in pancreatic cancers and severe AP patients [164, 165]. We have demonstrated that an iNOS inhibitor, ONO-1714, can effectively suppress the development of atypical hyperplasia and carcinomas, especially invasive adenocarcinomas, in hamster pancreas after treatment with BOP [167]. The results indicated that iNOS plays important roles in the development of pre-neoplastic lesions at an early stage of pancreatic carcinogenesis and also in carcinoma invasion and expansion in later stages. ONO-1714 also attenuated rat diaphragmatic dysfunction associated with cerulein-induced AP through the reduction of iNOS activity and lipid peroxidation [166]. These results could serve as basis of clinical research to assess whether the use of iNOS-selective inhibitors is a promising approach to the management of patients with pancreatitis and pancreatic cancer.

Agents that inhibit oxidative stress

There is increased oxidative stress in experimental animals as well as in patients with CP, and suppression of oxidative stress by antioxidative agents has been demonstrated to reduce the severity of pancreatitis in animals and humans. Moreover, suppressive effects of antioxidative agents on pancreatic cancer development have also been demonstrated in animals.

Treatment with the flavonoid quercetin markedly reduced the severity of cerulein-induced pancreatitis, malondialdehyde, and the serum levels of TNF-α, IL-1β, and IL-6 in mice [279]. Quercetin ameliorates the severity of cerulein-induced AP by acting as an anti-inflammatory and antioxidant agent. Treatment of mice with green tea polyphenol attenuates the degree of cerulein-induced mouse pancreatitis by reducing the activation of NF-κB, the production of pro-inflammatory cytokines, and the formation of lipid peroxidation [280]. Patients with topical pancreatitis received oral curcumin, which reduced erythrocyte malondialdehyde levels and increased the glutathione levels compared with a placebo [281]. When methionine was supplemented along with selenium, β-carotene, vitamin C, and vitamin E, CP symptoms were improved [282, 283].

Furthermore, treatment with the combined antioxidant supplement decreased the serum levels of the free radical marker 9-*cis*,11-trans linoleic acid, which was initially significantly higher in CP patients [282, 283]. A randomized clinical trial for combined antioxidant supplementation has been reported. One hundred twenty-seven CP patients were randomly assigned to receive either an antioxidant supplement, which contained selenium, ascorbic acid, β-carotene, α-tocopherol, and methionine, or a placebo. After 6 months, reduction in the levels of thiobarbituric acid-reactive substances and superoxide dismutase, which are markers of oxidative stress, was observed in the antioxidant group compared with the placebo group. Pain was also diminished in patients receiving the supplement. Significantly fewer painful days per month compared with the placebo group were reported by questionnaire [284]. Combined antioxidant supplementation might appear to be more promising for CP treatment than single antioxidant supplementation.

Protochatechuic acid, green tea extracts, and butylated hydroxyanisole are antioxidative agents which have demonstrated inhibitory effects on pancreatic cancer development during the post-initiation stage of the BOP-initiated hamster model [285–287]. Sarcophytol A, which is known to be an anti-tumor promoter, and methionine, which is an essential amino acid and associated with antioxidation, have also been shown to suppress pancreatic carcinogenesis in the BOP-treated hamster model [288, 289]. Woutersen et al. [290] reported that antioxidant products, such as β-carotene, selenium, and vitamin C, inhibit pancreatic carcinogenesis in azaserine-treated rat model. Therefore, it is considered that treatment with antioxidants may have practical application in chemoprevention of pancreatitis and pancreatic cancer.

Anti-hyperlipidemic/anti-type II diabetic agents

A high-calorie diet and low physical activity are associated with an increased risk of pancreatic cancer. Moreover, they are also closely associated with hyperlipidemia [291]. High serum TG levels are known to cause pancreatitis. It is also known that hypertriglyceridemia often precedes hyperglycemia in type II diabetes. Interestingly, Syrian golden hamsters are in a hyperlipidemic state even under normal diet conditions [211]. Thus, hyperlipidemia in hamsters may also be an enhancing factor for PDAC development.

Peroxisome proliferator-activated receptor γ (PPARγ) is a member of nuclear receptor superfamily of ligand-activated nuclear transcription factors, which prominently express in adipose tissue and in the immune system [292, 293]. Moreover, PPARγ is involved in the regulation of lipid and glucose homeostasis and also controls inflammation [294].

Thiazolidinediones (TZDs) are ligands for PPARγ, and one of the TZD derivatives, pioglitazone, has been clinically accepted as an anti-diabetic drug. Our previous study showed that dietary intake of pioglitazone improves hyperlipidemia and suppresses the incidence and multiplicity of pancreatic tumors in BOP-treated hamsters; the PDAC incidences in the BOP + 800 ppm pioglitazone group and the BOP-alone group were 38 vs 80 % ($P<0.01$) and the multiplicities were 0.55±0.15 vs 1.37±0.22 ($P<0.01$), respectively [211]. It is well established that administration of TZDs improves hyperlipidemia and hyperglycemia in animal models [295, 296]. Thus, anti-hyperlipidemic drugs may deserve more consideration as candidate chemopreventive agents against pancreatic cancer.

Metformin (1,1-dimethylbiguanide hydrochloride) is a biguanide class of oral hypoglycemic agents and it is the world's most widely used anti-diabetic drug for the treatment of type II diabetes mellitus. In a study using a hamster model, hamsters fed a high-fat diet and metformin had lower numbers of pancreatic carcinoma, proliferative lesions, and pre-neoplastic lesions than hamsters fed a high-fat diet alone [297]. In addition, administration of metformin significantly decreased the growth of pancreatic carcinoma cells xenografted into the flank of nude mice [298]. A large case–control clinical trial regarding the use of metformin for pancreatic cancer risk was conducted from 2004 to 2008 involving 973 pancreatic cancer patients (including 259 diabetes mellitus patients) and 863 controls (including 109 diabetes mellitus patients) [299]. Diabetes mellitus patients who were administrated metformin had a significantly lower risk of pancreatic cancer compared to those who did not receive metformin (OR, 0.38; 95 % confidence interval (CI), 0.22–0.69, $P=0.001$). These recent studies clearly suggest that the administration of metformin is positively associated with a decreased risk of pancreatic cancer in diabetes mellitus patients. Based on these positive associations between hyperinsulinemia, diabetes, and pancreatic cancer, therapeutic targets aimed at treating diabetes should decrease the risk of pancreatic malignancy. Metformin has been found to inhibit the production of inflammatory cytokines such as TNF-α and IL-6 as well as VEGF, probably via inactivation of NF-κB and HIF-1α [300–302]. Additionally, antioxidant and tumor growth inhibition activities have been shown for the potential function of metformin [303, 304]. These data imply that metformin may appear to exert a protective role

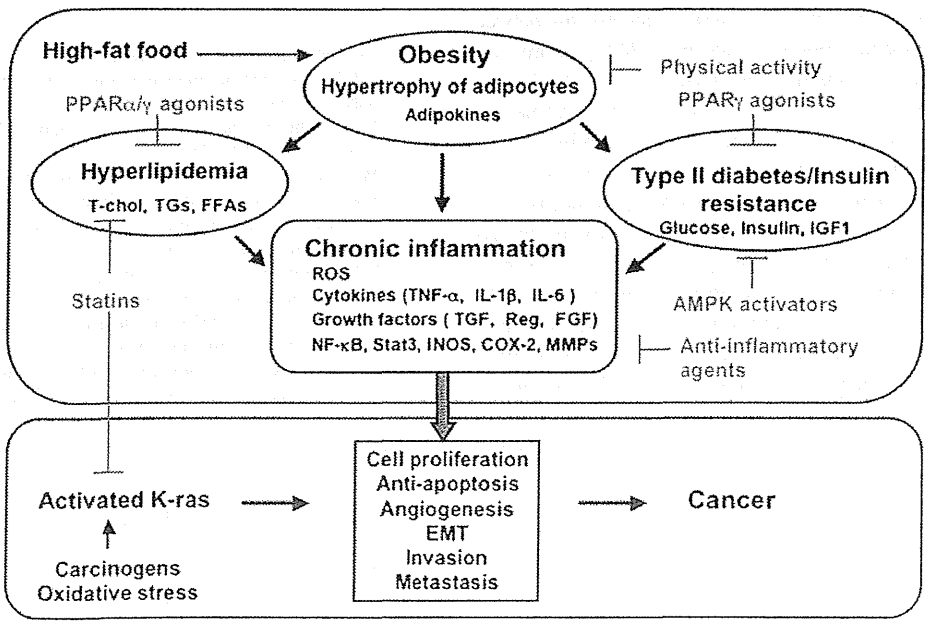

Fig. 2 Cancer promotion by chronic inflammation and its prevention by anti-inflammatory agents. K-*ras* mutations plus inflammatory status including CP, hyperlipidemia, type II diabetes/insulin resistance, and obesity effectively cause PDAC development. Chemopreventive agents targeting these inflammatory factors may prevent PDAC development. *TG* triglyceride, *FFA* free fatty acid, *ROS* reactive oxidative species, *TNF* tumor necrosis factor, *IL* interleukin, *TGF* transforming growth factor, *FGF* fibroblast growth factor, *NF-κB* nuclear factor-κB, *Stat3* signal transducer and activator of transcription 3, *iNOS* inducible nitric oxide synthase, *COX-2* cyclooxygenase-2, *MMP* matrix metalloproteinase, *EMT* epithelial to mesenchymal transition

against the development and progression of pancreatic cancer through improvement of inflammation.

Statins, inhibitors of 3-hydroxy-3-methylglutaryl coenzyme-A reductase, are widely used for the treatment of lipid disorders, especially hypercholesterolemia [305]. Furthermore, several preclinical studies revealed their pleiotropic actions, such as apoptosis induction, anti-angiogenesis, tumor growth suppression, metastasis suppression, anti-inflammation, and K-ras prenylation inhibition properties [306–308]. Thus, the use of statins as pancreatic cancer chemopreventive agents is expected.

Treatment with pravastatin started after the induction of CP attenuates progression of pancreatic inflammation in a rat experimental model. Pravastatin also downregulated the expression level of pro-inflammatory cytokines such as TNF-α and markedly increased the production of anti-inflammatory cytokines such as IL-10 [309]. In experimental data, statins were associated with a decreased risk of pancreatic cancer [310, 311]. Furthermore, one case–control study demonstrated 67 % risk reduction in incidence of pancreatic cancer among statin users (adjusted OR, 0.33; 95 % CI, 0.26–0.41; $P<0.01$) [312]. However, other observational studies suggested that there is no association between statin use and pancreatic cancer risk [313]. Thus, the use of statins as a chemopreventive agent remains a matter of debate.

Still some studies have declared the availability of statins for adjuvant chemotherapy. A dramatic synergism between lovastatin and troglitazone (a TZD-type PPARγ agonist and used for improving insulin sensitivity in type II diabetes mellitus patients) in anti-cancer at clinically achievable concentrations has been indicated [314]. The combination of fluvastatin with the anti-cancer agent gemcitabine (the cytosine arabinoside analog 2′,2′-difluorodeoxycytidine) is an effective cytotoxic, proapoptotic treatment in vitro and in vivo against MIAPaCa-2 cells harboring a mutated K-*ras* by a mechanism of action mediated, at least in part, by the inhibition of prenylation of K-ras and rhoA proteins [315]. These results support the probability of statins for the adjuvant chemotherapy treatment of pancreatic cancer. Further investigations may be needed to ensure the combination chemotherapy of anti-diabetic drugs or anti-cancer agents and statins for pancreatic cancer.

Conclusions

Epidemiological studies and animal model studies have shown an increase of pancreatic cancer risk by inflammatory status, such as CP, hyperlipidemia, type II diabetes, and obesity (Fig. 2). Acinar/ductal cell damages caused by exposure to alcohol, carcinogens derived from tobacco, lipids, high amounts of glucose, pancreatic enzyme/bile reflux by ductal obstruction, and following cellular proliferation stimulated by further exposure to pro-inflammatory cytokines, chemokines, adipokines, and growth factors are considered to favor the development of pro-tumorigenic environments. In addition, K-*ras* activating mutations, which can be induced by tobacco carcinogens or ROS, are essential for pancreatic cancer development. Indeed animal model studies have demonstrated that chemical or genetic induction of K-*ras* mutations plus inflammation effectively causes PDAC development.

In humans, a number of epidemiological studies have suggested reduced pancreatic cancer risk with the use of anti-inflammatory agents. However, this is difficult to prove in randomized control studies because of the relatively low incidence of pancreatic cancer in humans and the absence of early biomarkers to predict pancreatic cancer. Thus, in vivo carcinogenesis studies using animal models are important to support the epidemiological findings and provide direct evidence. Some anti-inflammatory agents that target COX-2, iNOS, oxidative stresses, insulin resistance, and hyperlipidemia have indeed been shown to exert suppressive effects on pancreatic carcinogenesis in animal models, indicating that factors related to inflammation are candidate targets for pancreatic cancer prevention.

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