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Chapter 11

Chronic Pancreatitis as an Inductor of Pancreatic Cancer — Correlations With Inflammatory Pathways

Simona Olimpia Dima, Dana Cucu,
Nicolae Bacalbasa and Irinel Popescu

Additional information is available at the end of the chapter

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1. Introduction

The immune system and inflammation are processes with dual roles in cancer development. Firstly, immunity responds to the presence of a tumour by producing anti-inflammatory agents with the role of restoring the homeostasis and improving adverse health effects. On the other hand, immune cells create a tumoural microenvironment which supports angiogenesis, cell proliferation and migration, being thus correlated with cancer initiation and progression. In the same vein, recent studies show correlations between pancreatic inflammation and pancreatic cancer *(reviewed in [1]*). The most common causative agents of both conditions are generally considered alcoholism, smoking, toxic-metabolic and genetic factors. Because chronic pancreatitis is taken into account as an etiological issue of pancreatic cancer progress, this review aims to explain the molecular pathways from inflammation to pancreatic carcinogenesis, in support of the prevention, diagnosis and therapies of this dreadful disease. Moreover, inflammatory mediators are connected to pain and cachexia, the associated conditions that dramatically affect quality of life in pancreatic cancer. In this context, it is clear that the evaluation of the cellular pathways from inflammation to cancer is an important step in revealing the mechanisms underlying cancer development and opening new avenues for possible therapies. In this chapter, the common features of chronic pancreatitis and pancreatic cancer linked by the inflammatory process will be presented along with some of the anti-inflammatory therapies proposed so far.

2. Incidence of chronic pancreatitis and pancreatic cancer

Over the last years, many studies have reported an increased burden of pancreatic disorders that is expected to amplify even more over time. Acute, chronic pancreatitis and pancreatic cancer are the major disorders described which affect the exocrine pancreas. Acute pancreatitis is the condition with the higher incidence, between five and 80/ 100,000 people annually being reported worldwide [2], and it is considered as one of the most frequent gastrointestinal diseases for admission in hospitals in the US [3]. The annual incidence of chronic pancreatic (CP) is much lower. In Europe and other regions six to seven/ 100,000 persons are affected [4] with a slight increase in China and India [5]. Despite its lower incidence as compared to acute pancreatitis and because of disease exacerbation and secondary endocrine deficiencies, it dramatically impacts quality of life [6]. Although in industrialized countries, CP cases are associated with long alcohol consumption, about 10-30% of them were attributed to unknown causes. In these instances, the term idiopathic CP is used. An important change in the understanding of the disease comes from genetic studies which show that idiopathic CP mainly has a genetic background [7].

3. The role of inflammatory modulators in chronic pancreatitis and the development of pancreatic cancer

Pancreatic cancer is a cancer with a lower incidence, but with one of the worst prognoses. From among the many types of pancreatic tumours, 75% of pancreatic cancers refer to pancreatic ductal adenocarcinoma (PDA). In an attempt to describe and cure these pancreatic diseases (CP and PDA) the insightful question raised is whether there is a continuum of events among them or whether each should be considered as an independent condition. The hypothesis of CP-PDA interplay is based on the connection between chronic inflammation and the increased risk of cancer of the organ affected [8].

Moreover, in the last years, it has become clear that inflammation may be, at least in part, responsible for fibrosis of the pancreatic tissue. Chronic pancreatitis is characterized by progressive, recurrent pancreatic injury leading to fibrosis, ductal and exocrine atrophy and inflammatory response. In the last years, pancreatic stellate cells (PaSCs) have caught the attention of the scientific community, being described as a principal source of fibrosis [9]. During the course of chronic pancreatitis, the fibrotic response depends on the activation of PaSCs, which produce the extracellular matrix (ECM) proteins from the pancreatic tumour stroma [10]. PDA is also characterized by a strong desmoplastic reaction, such that ~90% of the tumour volume is represented by stromal content, a feature specific to PDA. Activated PaSCs were also observed in the vicinity of pancreatic epithelial lesions [11]. Therefore, over the last years many studies have concentrated on the signalling pathways and bidirectional influence between PaSCs, PDA and chronic pancreatitis. Molecular studies showed that ECM synthesis is mediated by the transforming growth factor β1 (TGF-β1) and the fibroblast growth factor (FGF), whereas PaSCs proliferation is supported by ciclooxygenase-2 [11]. In addition

http://dx.doi.org/10.5772/59714

to fibrosis, PaSCs may mediate PDA-associated inflammation via intricate paracrine interactions with inflammatory cells, acinar cells and PDA cells. During the development of chronic pancreatitis or PDA acinar pancreatic cells, immune cells and endothelial cells produce cytokines and growth factors which have the ability to activate PaSCs. Stellate cells also may secrete cytokines and growth factors.

Despite these recent data, the exact link between the long-standing process of CP and pancreatic carcinogenesis remains an open question.

As mentioned above, many inflammatory mediators that exist in CP have also been linked to PDA [12]. Inflammatory processes consecutive to ductal or acinary injury represent the activation of the immune system that releases pro-inflammatory factors in order to prevent the harmful effect. These factors include cytokines (tumour necrosis factor (TNF-α), transforming growth factor (TGF) β interleukins (IL-1, IL-6, and IL-8), chemokines (e.g., monocyte chemoattractant protein-1, macrophage inflammatory protein-1, monocyte chemoattractant protein-1, and growth-related oncogenes), adhesion molecules, reactive-oxygen and reactive-nitrogen species. Many of these inflammatory products could also be involved in tumourigenesis. In the digestive system, inflammation has been described in gastric carcinoma subsequent to persistent Helicobacter pylori [13], colorectal cancer associated with inflammatory bowel disease [14, 15] and oesophageal adenocarcinoma following reflux esophagitis [16]. When treated inadequately, chronic inflammation may increase the risk of cancer, both processes sharing the same signalling pathways in increased proliferation rate, apoptosis, angiogenesis.

One mechanism that enhances the risk of cancer and strongly relates to the inflammatory process is the infiltration of immune products into the tumour microenvironment. There is also abundant evidence that pro-inflammatory cytokines and their receptors are expressed in pancreatic cells and infiltrating immune cells within inflamed pancreatic tissues [17, 18]. We review in the next paragraphs the best described pro-inflammatory mediators and their participation in chronic pancreatitis and PDA.

3.1. Tumour Necrosis Factor (TNF-α)

Tumour necrosis factor (TNF-α) is a cytokine produced especially by activated macrophages but also by other cells (e.g., fibroblasts, keratinocytes) as a pro-inflammatory cytokine. and in concequence participates in regulating the cellular homeostasis and the defence of the harmed organisms. In the immune systems, TNF-α contributes to the correct functioning of NK cells, B cells and T cells. Other results suggest that besides these important roles, TNF-α is associated with chronic inflammatory diseases and ultimate tumourigenesis. [19].

TNF-α was first describe by Carswell et al. [20] and many following studies have shown that immune cells produce two types of tumour necrosis factors: TNF-α produced by activated macrophages and TNF-β produced by mitogen stimulated lymphocytes. Pioneering studies by Balkin et al. [21] showed that TNF-α is a tumour promoter of skin cancer. An anti-tumour necrosis factor-alpha antibody inhibits the development of experimental skin tumours [22]. Thereafter, many studies have pointed out that this cytokine has a role

in autoimmune diseases, chronic inflammatory processes and, despite its name, in malignancy. Systemic levels of TNF-α together with various cytokines such as IL-6, Il-8, IL-10 were found to be significantly higher in patients with PDA compared to healthy subjects [23, 24]. PDA cells are exposed to TNF-α secreted by the infiltrated macrophages but also to their own endogenous TNF-α.

The major role of this cytokine is to switch between inflammatory and tumourigenic processes thus stimulating the ability of cancer cells to undergo migration and invasion. The detailed signalling pathways through which TNF-α exerts this role are yet to be revealed. However, the TNF-α receptors are well-described (TNF-R1 and TNF-R2). While TNF-R2 is expressed only in endothelial and immune cells, TNF-R1 was described in many tumoural tissues including PDA. After binding to its ligands, TNF-α receptors suffer a conformational change leading to a stable trimeric form and subsequent activation of various signalling pathways. On the one hand, the NF-κb pathway may be activated and this will trigger the inflammatory response, anti-apoptotic processes and cell survival. On the other hand, TNF-α may induce the activation of the mitogen- activated protein kinase (MAPK) signalling pathway with subsequent effects on proliferation, differentiation, and apoptosis of cells. These rather conflicting signals raised even more questions whether TNF-α may be used as a PDA therapeutic target. Following the anti-apoptotic signalling inhibitors of TNF-α infliximab and etanercept were proposed as possible therapeutic agents in PDA, especially after pancreaticoduodenectomy [25]. Interestingly, both anti-TNF compounds are currently used for the treatment of chronic inflammation. However, this study and others were not able to prove that TNF-α is the missing link between chronic pancreatitis and PDA, but the results obtained so far using inhibitors of this cytokine support this assumption.

3.2. Interleukine-6 (IL-6)

Many other interleukins have increased levels in PDA as well as in CP. Among them, Interleukine-6 was systematically described in many studies as a pro-inflammatory cytokine overexpressed in PDA tumours and in the systemic circulation of patients. Moreover, high levels of IL-6 in the serum of diseased persons directly correlate with increased mortality [26, 27]. IL-6 binds to its specific receptor formed by two subunits; one ligand-specific IL-6Rα and one signal transducer gp130. The intracellular domain of gp130 activates the Junus Kinase (JAK) and MAPK pathways. JAK activates the transcription factor STAT3 involved in invasion and metastasis, and identified in many tumours including PDA [28]. The inhibition of the STAT3 phosphorylation pathway was considered a good therapeutic approach in previous studies [29]. Although IL-6 has shown high levels in chronic pancreatitis, a genetic analysis failed to prove a correlation with the prognosis for this condition [30].

The role of IL-6 and the signalling pathway has yet to be investigated because it is clear that CP is a factor in the development of PDA.

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3.3. Cyclooxygenases

Cyclooxygenases (COX-1 and COX-2), also known as prostaglandin (PG) endoperoxide synthases, are isoenzymes required for in the conversion of arachidonic acid to prostaglandins. COX-1 and-2 share ~65 structural similarities and have almost identical catalytic domains.

COX-1 is a constitutive enzyme and is produced by almost all cells in normal physiological processes, whereas COX-2 is an inducible enzyme with almost undetectable levels in normal cells and with a high expression in many cancer types including PDA [31]. Importantly, COX-2 is induced by inflammatory factors, therefore, it may be one of the mediators between chronic pancreatitis and PDA. The strongest evidence that favours this link comes from a mouse model (BK5.COX-2) in which the over-expression of COX-2 induces pancreatic acinar to ductal metaplasia progression to severe dysplasia [32]. In this model the authors have shown that all transgenic mice develop pancreatic inflammation and metaplasia specific to human CP. Afterward, the initiation of dysplastic lesions featuring PDA was observed. This is one of the most convincing models that favour COX-2 as a key modulator of a tumour microenvironment in response to inflammatory stimuli.

3.4. Transforming Growth Factor (TGF)-β

Transforming growth factor (TGF)-β is a cytokine which inhibits cell proliferation and modulates the immune response. In normal pancreas it blocks the G1/S phase cell cycle progression, whereas in pancreatic cancer it decreases suppressive activity through an impairment of the signalling pathway [33]. It was shown that (TGF)-β is involved in pancreatic fibrosis, because collagen synthesis was augmented secondary to exogenous cytokine treatment. Moreover, in a rat model of caerulein-induced pancreatitis the levels of (TGF)-β were upregulated [34].

The above presented results match the hypothesis that inflammatory products are the hallmarks of pancreatic cancer and that they can bridge the conceptual gap between idiopathic CP and PDA. The inflammatory products operate by shifting this pathway into a tumourigenic one and promote cellular proliferation, invasion and migration. To do so they have to activate oncogenic networks of transcription factors throughout the regulation of specific genes.

4. Oncogenes and tumour suppressor genes common in chronic pancreatitis and pancreatic adenocarcinoma

In the last years, many studies have reported the detection of proto-oncogenes and tumour suppressor gene mutations in the pathogenesis of CP and PDA. Developments in molecular biology and biotechnologies such as ADN microarrays for genome-wide chromosomal localization enable the detection of genetic causes in both conditions. Oncogenes are genes that when mutated have the potential to cause cancer, whereas transcription factors represent a group of proteins that regulate gene transcription by binding to specific DNA sequences and modulate mRNA synthesis.

4.1. K-Ras proto-oncogene

One of the genes involved in CP may be the K-Ras proto-oncogene. The product of K-Ras gene is a small GTPase protein and a key player in many intracellular signalling processes. As all GTPase molecules, K-Ras has an enzymatic activity that relies on the conversion of GTP to GDP, consistent with the active state of the protein. The switch from the active to the inactivate state is mediated by GTPase-activating proteins (GAP), whereas the activation of K-Ras is promoted by guanine nucleotide exchange proteins (GEFs). In pancreatic cancer one point mutation of the encoding K-Ras gene at codon G12 impairs the inactivation of K-Ras, placing the protein in a permanent active state. All the downstream signalling pathways are subsequently perturbed and thus drive the processes characteristic to cancer [35]. The main process generated by the K-Ras mutation is the activation of the inflammatory microenvironment and subsequent fibrosis. Without any doubt, K-Ras mutation is observed in most PDA. However, a new concept has come out, centred around the mutation level that K-Ras has to reach in order to initiate PDA. This new idea is based on studies showing that healthy people have high levels of K-Ras oncogens at rates exceeding cancer patients. In other words, expression of the oncogenic K-Ras from its endogenous locus is insufficient to activate downstream signaling pathways, so that a pathological threshold is necessary for K-Ras mutation to be reached in order to initiate PDA. When non-endogenous levels are reached, CP and not PDA will develop, at least in one mouse model [36]. These results became extremely important in showing that K-Ras mutation is not important per se in PDA, but rather the level of the subsequent activated signalling pathway. This discrete modulation may be the reason why attempts to inhibit this molecule as a cancer therapy, failed.

Moreover, the same studies suggest the oncogenic K-Ras accelerates tumour development only in an inflammatory milieu in the sense that inflammatory mediators activate the oncogenic K-Ras, which in turn stimulates the desmoplastic reaction. These results are consistent with data obtained from patients showing that 30% of CP persons bear a K-Ras mutation. Therefore, the idea that the K-Ras mutation is a PDA marker should be reconsidered in the context of the inflammatory environment.

4.2. Notch

Notch is another well described oncogene in PDA and experimental CP in mice is connected to the upregulation of Notch and acinar to ductal metaplasia. The Notch gene encodes for transmembrane proteins that regulate the mechanism of lateral inhibition during embryogenesis. Using mice with induced Notch activity, it was shown that only upon coactivation with K-Ras, Notch initiates the promotion of pancreatic lesions [37]. Moreover, using cDNA microarray technology, deregulated Notch pathways were found in CP [38]. This study showed that Notch receptors, Notch1 and Notch2, as well as Notch targets such as HES-related repressor protein, were upregulated in CP. Another study showed how crosstalk between TNF-α and Notch sustains the intrinsic inflammatory profile of pancreatic cancer cells [39]. TNF-α stimulates the transcription factor NF-κB signalling and, together with Notch signals, induced the optimal expression of Notch targets. The enhancement of these target genes

http://dx.doi.org/10.5772/59714

suppresses the anti-inflammatory protein expression and creates a feedback loop that keeps the cells in an inflammatory state.

4.3. Transcription factor Nf-κB

The transcription factor Nf-κB was initially described in activated B lymphocytes and thereafter characterised in almost every cell. It controls the activity of ~ 150 genes and the biological answers to various external stimuli. Nf-κB is a heterodimeric protein sequestered in the cytoplasm by IκB protein. In response to different stimuli (including those of inflammatory origin), IκB is phosphorylated and then degraded. The IκB proteolysis permits the release of Nf-κB and translocation to the nucleus where it binds to specific promoter regions and initiates gene transcription. Several studies indicate that Nf-κB is constitutively expressed in PDA cell lines, in humans and animal models of pancreatic cancer with functions in proliferation, resistance to apoptosis and inflammation-induced cancer development [40, 41]. Importantly, active Nf-κB was determined in experimental models of pancreatitis and was asserted as an early response to inflammation [42]. Other experiments sustain a model in which Nf-κB positively links the oncogenic Ras signalling and the inflammatory process [43]. Augmented values of Nf-κB mRNA favour pro-apoptotic pathways in acinar cells, whereas the islets are not affected. From these results, the authors concluded that in CP only the endocrine cells may be subjected to cell reprogramming by evading immune attack, whereas exocrine cells exibit an altered state resulting from Nf-κB transcriptional activity [44].

In a caerulein-induced pancreatitis mouse model NF-κB activation was described [45]. NF-κB activation promotes inflammation and the milieu that favours cancer development [46].

Other transcription factors with oncogenic potential activated by inflammation and described in pancreatic cancer are: i) Nuclear factor of activated T-cells (NFATc1) that belongs to the same family as NF-κB and regulates genes participating in cell growth and differentiation, and ii) the GLI1 family important for tumour microenvironment modulation, cell apoptosis, autophagy and proliferation.

5. Other molecular markers for PDA and/or CP involved in inflammation

5.1. The fibroblast-specific protein 1

A factor that may mediate the cross talk between PDA cells and inflammation is the fibroblast-specific protein 1 or S100A4. S100A4 is an important player in metastatic dissemination, and increased expression of the protein has been associated with poor prognosis in various human cancer types [47]. The metastasis-promoting protein S100A4 belongs to the S100 family of calcium-binding proteins, but its function has not yet been well described. The protein seems to exert dual, intracellular and extracellular functions that may contribute to its pro-metastatic effects [48, 49]. S100A4 is expressed in many cancer cells [50, 51] and in several types of stromal cells, e.g., fibroblasts, lymphocytes, macrophages [52-54]. Previous studies showed that in PDA patients, S100A4 together with S100A2 are associated with more aggressive tumours and

predict worse survival after surgery. These two markers are proposed to stratify resectable pancreatic cancer into different phenotypes of prognosis and response to therapy. S100A4 is also secreted by PDA cell lines in vitro [51, 55] and can be detected in the tumour interstitial fluid [52], suggesting a role for S100A4 in the tumour-stroma interplay.

5.2. Transforming Growth Factor (TGF)-α

Transforming growth factor (TGF)-α is a polypeptide that induces mitogenic and cell differentiation responses. The specific receptor is the tyrosine kinase EGF receptor (EGFR) common for (TGF)-α and epidermal growth factor. The overexpression of both TGF-α and EGFR were upregulated in CP and in pancreatic cancer. Apparently,TGF-α excessively stimulates EGFR contributing in this way to the pathology of these diseases [56].

6. Prophylactic and therapeutic use of the anti-inflammatory agents in CP and PC

Chronic inflammation connected to CP triggers the progression to cancer through the occurrence of the following precancerous lesions: pancreatic intraepithelial neoplasia (PanINs), intraductal papillary mucinous neoplasms (IPMN), and mucinous cystic neoplasms (MCN). The progression of these lesions into pancreatic ductal adenocarcinoma (PDA) involves many diverse molecular pathways.

Many studies published so far have shown increased incidence of pancreatic cancer in CP patients [57]. The cumulative risk of PC in subjects with CP is 1.8% after 10 years and 4% after 20 years, with an incidence ratio of 1.8% [58]. Over the last few years a major breakthrough towards understanding PDA patho-biology was made by deciphering the molecular events responsible for the development of PDA [59, 60].

New chemo-therapeutic drugs are needed in PC. Targeting inflammatory pathways with anti-inflammatory drugs may be of benefit for a combined, multi-target approach to PDA therapy. Anti-inflammatory agents may potentiate the tumoural growth's inhibitory effect of chemo-therapeutic agents, such as Gemcitabine.

6.1. Cyclooxygenase-2 (COX-2) inhibitors (specific and non-specific)

The selective inhibition of the Cox-2 gene expression and of its enzymatic activity may have chemoprotective potential in high-risk patients for PC. Similar to familial adenomatous polyposis (FAP) treated with sulindac, COX-2 inhibitor therapy may delay pancreatic cancer precursor lesion progression and reduce the incidence of pancreatic cancers.

Experimental studies using a genetically modified mouse model of pancreatic cancer development (K-Ras^{G12D}; PDX-1-Cre mice, BOP treated hamster) and cell lines have shown efficacy in reducing the development of high-grade pancreatic intraepithelial neoplasias (PanIN) and ductal adenocarcinoma [61]. Cox-2 inhibitors such as etodolac, sulindac, celocoxib and

http://dx.doi.org/10.5772/59714

nimesulide inhibited the proliferation of pancreatic cancer cells [62, 63]. The antitumoural activity of aspirin, a nonsteroidal anti-inflammatory drug (NSAID), involves numerous molecular targets, including Cox-2. Sclabas et al. showed that aspirin inhibits the activation of the NF-kB pathway in cultured cells and decreased the expression of the COX-2 gene [42, 64]. Moreover, aspirin may activate adenosine monophosphate-activated protein kinase (AMPK), and may affect Notch, Wnt/β-catenin, and other signalling pathways [65]. Nimesulide (4-nitro-2 phenoxymethanesulfonanilide), another NSAID, significantly decreases PDA in mice treated during the postinitiation phase of pancreatic carcinogenesis [66]. Moreover, the progression of later stage PanIN was lowered by this drug [62]. While experimental data are highly available, only a few clinical trials of pancreatic cancer using COX-2 inhibitors as chemopreventive agents have shown a possible clinical benefit. A randomized phase II study (Apricot-P) evaluated Apricoxib in combination with Gemcitabine and Erlotinib (Modiano M. et al., personal communication). Similarly, celocoxib was also evaluated in combination with Gemcitabine and Cisplatin in patients with metastatic PC or combined with Gemcitabin [67]. In both studies, the primary endpoint was a survival rate at six months, although no improvement in Gemcitabine activity has been observed.

6.2. TGF-β inhibitors

Traberdersen, a specific inhibitor of TGF-b2, was used as a 2nd line treatment in a phase I/II study of 37 patients with PDA. The median survival was 13.4 months and one patient showed a complete response [68]. Although the study is in an incipient phase, TGF-β shows to be a promising clinical target.

6.3. Aspirin

In vitro findings suggest that aspirin might inhibit pancreatic carcinogenesis, but epidemiological data are inconsistent. There are studies indicating that nonsteroidal anti-inflammatory drugs (NSAIDs) reduce the risk of gastrointestinal (GI) cancers and pancreatic cancer, but other results indicate that there is no significant association between aspirin use and pancreatic cancer risk. A limited number of populational-based studies are available. According to Streicher SA et al., significant relationships between aspirin use and decreased pancreas-cancer incidence and mortality have been shown in four out of 13 studies [69]. In some studies the benefit was positively correlated with the frequency of aspirin intake [70]. In a systematic review and meta-analysis, Cui X et al. analysed the association between aspirin intake and its effect for the chemoprevention of pancreatic cancer. They carried out a total of 10 studies (four case-control studies, five prospective cohort studies, and one randomized controlled trial) published between 2002 to 2011 with 7,252 cases of pancreatic cancer and more than 120,0000 healthy control subjects enrolled in the studies. The conclusion of the study was that high-dose, rather than low-dose, aspirin intake was associated with an 0.88-fold decreased risk for pancreatic cancer compared with non-use [71]. Table 1 overviews the information from studies that analysed the association of the aspirin or NSAID intake with pancreatic cancer.

Study design	No of patients	Period	Drug type	Dose and duration of NSAID use	Conclusions
Prospective cohort study [72]	28,283 postmenopausal women- 80 incident cases of pancreatic cancer	1992 to 1999	Aspirin and other NSAIDs	Not collected	Aspirin might be chemopreventive for pancreatic cancer
Case-control Surveillance Study [73]	149 patients with pancreatic cancer (n = 504), stomach (n = 254), oesophagus (n = 215), gallbladder (n = 125), or liver (n = 51) and Controls were 5,952 (non tumoral diseases)	1977 to 1998	Salicylates (e.g., aspirin), indoles (e.g., indomethacin), propionic acids (e.g., ibuprofen), fenamates (e.g., mefenamic acid), and/or oxicams (e.g., piroxicam).	At least four days/week for at least three months, initiated at least one year before admission.	No effect of NSAID use
Case-control study [74]	12,174 incident cancer cases (396 pancreatic cancer) and 34,934 controls	1993 to 1995	13–36 months before cancer diagnosis	13-36 months before cancer diagnosis	The increased risks of pancreatic cancer could be due to chance or to undetected biases
Clinic-based case-control study [75]	904 cases and 1,224 controls	April 2004 to September 2010	Aspirin, NSAID and acetaminophen	Aspirin use ≥ 1 day/month	Aspirin use, but not non-aspirin NSAID use, is associated with a lowered risk of developing pancreatic cancer
Hospital-based case-control study (Roswell Park Cancer Institute) [76]	194 patients with pancreatic cancer were compared to 582 age and sex-matched patients with non-neoplastic condition	1982 to 1998	Aspirin	At least one tablet per week for at least six months was classified as regular aspirin use.	Regular aspirin use may not be associated with a lower risk of pancreatic cancer
Multicentric hospital-based case-control study in Italy [77]	308 patients with incident pancreatic cancer and controls were 477 with acute conditions	1991 and 2008	22 cases (7%) and 37 controls (8%) - regular aspirin	Nonregular use	No association between regular aspirin use and pancreatic cancer risk, although our results suggested a possible protective effect for long-term current users

http://dx.doi.org/10.5772/59714

Study design	No of patients	Period	Drug type	Dose and duration of NSAID use	Conclusions
Prospective cohort study [78]	161 cases with pancreatic cancer (88,378 women without cancer at the baseline)	1980 to 1998	Aspirin	Two or more standard tablets per week	Extended periods of regular aspirin use appear to be associated with a statistically significantly increased risk of pancreatic cancer among women
Population-based cohort study [79]	11,683 patients with rheumathoid arthritis, 840 patients with cancer, 32 with pancreatic cancer	1965 to 1983	NSAID	No information regarding doses	Slightly reduced risk for pancreatic cancer
Population-based Connecticut study [69]	362 pancreas-cancer cases frequency matched to 690 randomly sampled controls.	2005 to 2009	Aspirin (low dose, regular dose)	Daily	Daily aspirin regimen may reduce risk of developing pancreatic cancer
Prospective cohort study [80]	Cancer Prevention Study II (CPS-II) cohort- 98,7590 4,577 deaths from pancreatic cancer	1982 to 2000	Aspirin	Frequent aspirin use (> or =30 times per month)	Aspirin use was not associated with pancreatic cancer mortality

7. The "therapeutic" role of surgical treatment in the progression of chronic pancreatitis to PDA

Pancreas resection is indicated in CP patients who have small-duct disease or those in whom endoscopic drainage fails.

There are experimental and clinical studies that take into consideration the fact that the surgical treatment of chronic pancreatitis may reduce the risk of the development of PDA. Even though the mechanism of the protective role of surgery remains unknown, possible explanations could be linked to the fact that through the endoscopic drainage procedures or resection procedures of the CP, pancreatic tissue and the inflamed tissue are removed or diminished. Ueda J et al. have found that patients who underwent surgical treatment for chronic pancreatitis had a significantly lower incidence of pancreatic cancer. According to this study, 5.1% of patients who had not received surgical treatment for CP developed pancreatic cancer, whereas PDA was observed in 0.7% of patients who had undergone surgery for chronic pancreatitis [81]. G.H. Sakorafas et al. reviewed the experience of 484 consecutive patients who underwent surgery for chronic pancreatitis; pancreatic cancer was diagnosed after a mean of 3.4 years after the initial operation for chronic pancreatitis in 2.9% of the 484 patients [82]. Even though

the percentage of patients who underwent pancreatic resection for CP and subsequently developed PDA is higher than in the study by Ueda J et al., it is smaller than in the studies that analyse patients with CP without surgical treatment.

8. Conclusions

The tumour microenvironment is a critical determinant of PDA progression and treatment outcome. From the above presented studies, it is clear that CP may be considered as a prerequisite of the PDA condition. The major evidence supporting this assumption is based on studies revealing that the tumour microenvironment of the ductal epithelium increases the risk of neoplastic transformation. In the onset of CP, the pathways and molecules described so far are activated and promote the transformation from normal epithelium to metaplasmic, early neoplasmic lesions (PanIN) and finally pancreatic cancer. Despite the fact that many studies determined that inflammatory components and downstream effectors are present in both CP and pancreatic cancers, there is not a clear common pathway for pancreatic cancer development which includes chronic inflammatory processes and finally stroma formation. When revealed, these findings may guide us to novel strategies for pancreatic cancer therapy.

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Author details

Simona Olimpia Dima[1*], Dana Cucu[2], Nicolae Bacalbasa[3] and Irinel Popescu[1]

*Address all correspondence to: dima.simona@gmail.com

1 Center of General Surgery and Liver Transplantation “Dan Setlacec”, Fundeni Clinical Institute, Bucharest, Romania

2 Department of Anatomy, Physiology and Biophysics, Faculty of Biology, University of Bucharest, Bucharest, Romania

3 Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

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