Cancer Letters 345 (2014) 203–209

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Mini-review

Chronic pancreatitis: A path to pancreatic cancer

Andreia V. Pinho [a], Lorraine Chantrill [a,b], Ilse Rooman [a,c,d,*]

[a] Cancer Research Program, The Kinghorn Cancer Centre, Garvan Institute of Medical Research, Sydney, Australia
[b] Macarthur Cancer Therapy Centre, Campbelltown Hospital, Campbelltown, Australia
[c] St. Vincent's Clinical School, University of New South Wales, Sydney, Australia
[d] Diabetes Research Center, Vrije Universiteit Brussel, Brussels, Belgium

ARTICLE INFO

Keywords:
Pancreatic cancer
Pancreatitis
Acinar to ductal metaplasia
Oxidative stress
Inflammation
Dedifferentiation

ABSTRACT

Chronic pancreatitis predisposes to pancreatic cancer development and both diseases share a common etiology. A central role has been proposed for the digestive enzyme-secreting acinar cell that can undergo ductal metaplasia in the inflammatory environment of pancreatitis. This metaplastic change is now a recognised precursor of pancreatic cancer. Inflammatory molecules also foster tumour growth through autocrine and paracrine effects in the epithelium and the stroma.

These insights have raised new opportunities such as the manipulation of inflammation as a preventive and/or therapeutic strategy for pancreatic cancer. Finally, we address the need for an in-depth study of the pancreatic acinar cells.

© 2013 Elsevier Ireland Ltd. All rights reserved.

1. Pancreatitis and pancreatic cancer – diseases of the exocrine pancreas

Pancreatitis, in its acute and chronic forms, and pancreatic cancer are the main diseases affecting the exocrine pancreas. The exocrine compartment constitutes the majority of pancreatic tissue, in which the endocrine islets are embedded. The exocrine acinar cells have a secretory function producing hydrolytic digestive enzymes for intestinal digestion, while the exocrine ducts secrete mucins and fluids and form a branched network that guides the pancreatic juice to the intestine [1].

Chronic pancreatitis incidence in industrialised countries ranges from 3.5 to 10 per 100,000 population [2]. It is a progressive inflammatory disorder and is believed to arise from repeated overt or silent episodes of acute pancreatitis, where deregulated secretion and premature activation of acinar enzymes results in increasing residual damage to the pancreas. The damage to both the exocrine and the endocrine compartments of the pancreas eventually results in severe maldigestion and diabetes. The histopathologic features of this disease include acinar atrophy, fibrosis, fatty replacement, chronic inflammation and abnormal ducts [2,3]. In the majority of patients, the disease results from a combination of genetic and environmental factors, with alcohol consumption being the best-defined risk factor [3].

Pancreatic Ductal Adenocarcinoma (PDAC) is the most common neoplasm of the pancreas, accounting for more than 85% of pancreatic tumour cases [4]. Despite the relatively low incidence of about 6–12 per 100,000 per year in western countries [5], PDAC is the fourth cause of cancer related deaths in the United States [6] and the fifth in Europe [7]. The astonishing mortality, a median survival of <6 months and a 5-year survival rate of <5% [4], is attributed to late diagnosis and ineffective therapy. The heterogeneity amongst PDAC may be the cause of failure of most drugs in clinical trials that comprised biologically unselected cases [8].

Pancreatitis has been shown to be a risk factor for pancreatic cancer [9,10]. A recent meta-analysis including 22 studies found an increased relative risk of developing pancreatic cancer of 5.1 in patients with unspecified pancreatitis, 13.3 in patients with chronic pancreatitis and 69 for hereditary pancreatitis [11]. Despite the increased risk, only around 5% of patients diagnosed with chronic pancreatitis will develop carcinoma over a period of 20 years [11]. Hereditary pancreatitis has been associated with mutations in several genes including PRSS1, PRSS2, SPINK1, and CTRC. These individuals have a cumulative risk of developing pancreatic cancer of 40–55% [12].

2. Insights into pancreatitis to rewrite the history of PDAC

Chronic pancreatitis and PDAC were historically regarded as unrelated diseases as they were thought to arise from different cells in the pancreas, acinar and ductal cells, respectively. Based on recent work using mouse models, a common origin in acinar cells has been proposed, as discussed below.

* Corresponding author. Address: Cancer Research Program, The Kinghorn Cancer Centre, The Garvan Institute of Medical Research, 370 Victoria Street, Darlinghurst, Sydney, NSW 2010, Australia. Tel.: +61 2 9355 5806; fax: +61 2 9355 5868.
E-mail address: i.rooman@garvan.org.au (I. Rooman).

0304-3835/$ - see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.canlet.2013.08.015

The progression model where PDAC was thought to develop from cells in the ducts was based on the study of non-invasive lesions named Pancreatic Intraepithelial Neoplasias (PanINs) [13,14]. These are microscopic lesions that can be papillary or flat, and composed of columnar to cuboidal ductal cells with varying amounts of mucin. Depending on the degree of cytological and architectural atypia they are subclassified into PanIN-1, PanIN-2, and PanIN-3 lesions. PanINs are often found in the pancreatic parenchyma adjacent to infiltrating adenocarcinomas, and several case reports have documented patients with PanINs who later developed pancreatic cancer [14]. PanINs harbour many of the genetic alterations that are found in invasive pancreatic cancer, *i.e. KRAS* mutations and loss of *p16/INK4A/CDKN2A*, *TP53* and *SMAD4/DPC4* [13,14]. *KRAS* mutations are thought to be the earliest genetic events, with progressive increase in PanIN-1A, PanIN-1B, and PanIN-2/3 lesions [14] and found in more than 90% of cancer cases [15].

The duct cell of origin in this PanIN-PDAC progression model has been questioned because mouse lineage tracing experiments lacked evidence that oncogenic Kras activation in pancreatic ductal cells could lead to PDAC development [16,17]. The model is however compatible with the concept of acinar to ductal metaplasia preceding the generation of the small ducts.

Acinar to ductal metaplasia has been well documented in experimental rodent models of pancreatitis [18]. The most widely used model involves treatment with the cholecystokinin agonist caerulein, which induces local oxidative stress, inflammation, edema and loss of the acinar parenchyma that is transiently replaced by a duct-like epithelium, reminiscent of human pancreatitis [19,20]. Lineage tracing experiments have shown that the intermediate ductal metaplastic epithelium can arise from acinar cells [19–21]. Our work further documented that upon stress, such as the one present in pancreatitis, acinar cells can dedifferentiate and acquire features of pancreatic progenitor duct-like cells, expressing the transcription factors Pdx1, Ptf1a, Hes1, Hnf1b and Sox9 [22]. The dedifferentiated acinar cells undergo growth arrest through activation of a p53-dependent senescence program [22,23], which constitutes a barrier to malignant transformation.

The concept of an acinar cell origin for PDAC is not new, in the early nineties, Sandgren et al. showed that transgenic mice in which c-myc is targeted to acinar cells in the embryo, develop mixed acinar and ductal pancreatic adenocarcinomas [24]. In another model from the same group, transgenic expression of TGF-α in acinar cells led to the development of acinar to ductal metaplasia and PDAC [25].

Several more recent mouse models supported the notion that activation of oncogenic Kras specifically in acinar cells during embryonic development induces the formation of PanINs and the development of invasive ductal carcinoma [26–28]. Adult acinar cells are more refractory to Kras-driven neoplastic transformation [26,27,29] but chronic pancreatitis induced by caerulein treatment renders the cells susceptible to transformation by oncogenic Kras and leads to the development of the full spectrum of PanINs and PDAC [26,28]. Even repeated episodes of asymptomatic pancreatitis triggers acinar cell-derived PDAC development [30]. Another group demonstrated that elevated Kras activity is sufficient to cause both chronic pancreatitis and PDAC [31].

In conclusion, pancreatic cancer can originate from acinar cells through acinar to ductal metaplasia and results from the combination of both genetic events (activation of oncogenic Kras and loss of tumour suppressor barriers) and extrinsic factors that produce tissue injury, such as the oxidative stress and the associated inflammatory damage observed during pancreatitis (Fig. 1).

3. A central role for inflammation in pancreatitis and PDAC

Oxidative stress and the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) play a key role in the pathophysiology of acute and chronic pancreatitis and perpetuate acinar cell necrosis and fibrosis, as supported by clinical findings and several experimental models (comprehensively reviewed by Leung and Chan) [32].

ROS/RNS contribute to the pathophysiology of pancreatitis by modification of critical substrates, e.g. nucleic acids, lipid and proteins, that results in DNA fragmentation, membrane disintegration and protein misfolding, as respective examples. This is also a way of activating the immune system. The immune cells and other stromal components, such as endothelial cells and pancreatic stellate cells, produce inflammatory cytokines and chemokines that, together with ROS/RNS, cause epithelial cell damage and increased proliferation. Inflammatory mediators, such as Cyclooxygenase-2 (Cox2), NF-κB and STAT3, play key roles herein. In turn, inflammation can generate sustained and exacerbated secondary oxidative injury and, as such, mediate the further promotion of inflammatory infiltration and acinar cell injury [32,33].

Various studies using genetically engineered mouse models show that genes involved in oxidative stress and inflammatory pathways have a role in pancreatic cancer development, particularly in a Kras mutant context, as summarized in Table 1.

Inactivation of TP53INP1, a protein that controls oxidative status, accelerates pancreatic cancer development in a Kras mutant background [34], whereas KRas and other oncogenes induce enhanced ROS detoxification through Nrf2 activation, which leads to enhanced tumourigenesis [35].

Overexpression of the inflammatory cytokine IL-1β in the pancreas, under the acinar elastase promoter, induces the development of chronic pancreatitis and acinar to ductal metaplasia but no neoplastic lesions or tumours [36]. Cox2 is activated by inflammatory cytokines and its expression is upregulated in pancreatitis and pancreatic cancer [33]. Interestingly, transgenic overexpression of Cox2 in the pancreas induces chronic pancreatitis and the formation of pre-invasive ductal neoplasms [37,38].

In a Kras mutant background, inflammation overcomes barriers that prevent tumour development. One of the well-defined tumour suppressive barriers inhibited by pancreatitis is senescence [22,30,39]. Recent studies from Logsdon's group provided more insights into the inflammatory mechanisms in Kras mutant versus normal backgrounds [31,40]. They have shown that mild inflammatory stimuli in the pancreas can cause an increase in Ras activity, which is only transient in wild type animals. These same inflammatory stimuli in animals bearing a Kras oncogenic mutation trigger an NF-κB mediated positive feedback mechanism, involving Cox2, that amplifies Ras activity to pathological levels [40]. This causes the development of chronic inflammation and preneoplastic lesions. Indeed, oncogenic Kras itself has also been shown to induce the constitutive activation of Ikk2/NF-κB signalling through a feed forward loop of IL-1α and p62, and this is required for the development of PDAC [41]. Another study showed that in a Kras mutant context, TNF-α-induced activation of the NF-κB pathway in pre-malignant epithelial cells enhances Notch signalling, in an Ikk2-dependent manner. The interplay between Ikk2 and Notch creates a feed forward loop that retains the transformed cells in an inflammatory state [42]. Despite this evidence in tumour development, the role of NF-κB in pancreatitis is still controversial with studies showing that activation of the pathway in animal models can lead to both aggravation [43] and amelioration of pancreatitis [44], a paradox that can be explained by the fact that acinar cell NF-κB activation can trigger both pro- and anti-inflammatory pathways [45].

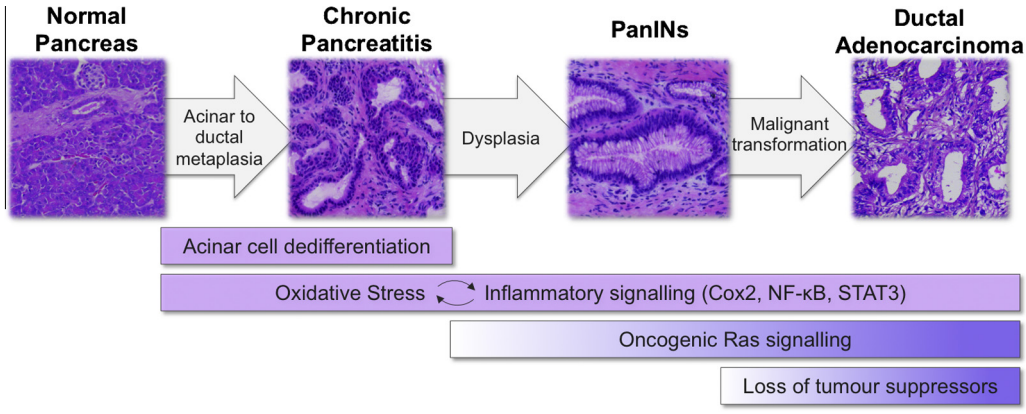

Fig. 1. Acinar to ductal metaplasia in chronic pancreatitis is a recognised precursor of pancreatic ductal adenocarcinoma. Oxidative stress and inflammatory signals contribute to the development of pancreatitis and cooperate with oncogenic Ras signalling and loss of tumour suppressor barriers in the subsequent progression to pancreatic intraepithelial neoplasias (PanINs) and, ultimately, to invasive ductal adenocarcinoma.

Table 1
List of genetically engineered mice (GEM) that model the role of inflammatory genes/pathways in the development of pancreatitis, pancreatic intraepithelial neoplasias (PanINs) and pancreatic cancer.

GEM Model	Gene/Pathway affected	Phenotype	Reference
Ela-IL-1β^{Tg}	IL-1β overexpression	Chronic pancreatitis, no neoplastic lesions	Marrache *et al.*, 2008
Krt5-Cox2^{Tg}	Cox2 overexpression	Chronic pancreatitis and ductal neoplastic lesions	Muller-Decker *et al.*, 2006 Colby *et al.*, 2008
Ela-Cre^{ERT}; Cox2^{Tg}	Cox2 overexpression	Chronic inflammation and ductal cysts	Daniluk *et al.*, 2012
Ela-Cre^{ERT}; p65^{Tg}	NFκB pathway activation	Aggravation of chemical-induced pancreatitis	Huang *et al.*, 2013
Ela-Cre^{ERT}; IKK2^{Tg}	NFκB pathway activation	Spontaneous pancreatitis	Huang *et al.*, 2013
Ptf1a-Cre^{ex1}; IκBα$^{Fl/Fl}$	NFκB pathway activation	Amelioration of chemical-induced pancreatitis	Neuhofer *et al.*, 2013
Ptf1a-Cre; Kras^{G12D}; Nrf2$^{-/-}$	Oncogenic Ras + oxidative status deregulation	Decreased PanIN formation and proliferation	DeNicola *et al.*, 2011
Pdx1-Cre; Kras^{G12D}; TP53INP1$^{-/-}$	Oncogenic Ras +oxidative status deregulation	Accelerated PanIN formation, intraductal papillary mucinous neoplasms	Al Saati *et al.*, 2013
Ela-Cre^{ERT}; Kras^{G12D}; Cox2^{Tg}	Oncogenic Ras + Cox2 overexpression	Rapid development of chronic inflammation and PanINs	Daniluk *et al.*, 2012
Pdx1-Cre; Kras^{G12D}; IKK2$^{Fl/Fl}$	Oncogenic Ras + NFκB pathway inhibition	Impaired PanIN progression and decreased PDAC development	Maniati *et al.*, 2011 Ling *et al.*, 2012
Ela-Cre^{ERT}; Kras^{G12D}; IKK2$^{Fl/Fl}$	Oncogenic Ras + NFκB pathway inhibition	Reduction of fibrosis, inflammation and PanINs after caerulein treatment	Daniluk *et al.*, 2012
Ela-Cre^{ERT}; Kras^{G12D}; IKK2^{Tg}	Oncogenic Ras + NFκB pathway activation	Increased fibrosis and rapid development of PanINs	Daniluk *et al.*, 2012
Ptf1a-Cre; Kras^{G12D}; Stat3$^{Fl/Fl}$	Oncogenic Ras +Stat3 inhibition	Decreased PanIN formation, decreased fibrosis and ductal lesions after caerulein treatment	Fukuda *et al.*, 2011
Ptf1a-Cre^{ex1} Kras^{G12D}; Stat3$^{Fl/Fl}$	Oncogenic Ras + Stat3 inhibition	Impaired PanIN progression and decreased PDAC development	Lesina *et al.*, 2011
Ptf1a-Cre^{ex1} Kras^{G12D}; Socs3$^{Fl/Fl}$	Oncogenic Ras + Stat3 activation	Accelerated PanIN progression and increased PDAC development	Lesina *et al.*, 2011
Ptf1a-Cre^{ex1} Kras^{G12D}; sgp130^{Tg}	Oncogenic Ras + IL-6 transsignalling inhibition	Impaired PanIN formation and progression	Lesina *et al.*, 2011
Ptf1a-Cre^{ex1} Kras^{G12D}; IL6$^{-/-}$	Oncogenic Ras + IL-6 loss	Impaired PanIN formation and progression	Lesina *et al.*, 2011

Apart from NF-κB, STAT3 activation has also been shown to be essential for initiation and progression of pancreatic cancer [46,47]. STAT3 contributes to cancer initiation by promoting the dedifferentiation of the acinar cells upon pancreatitis, which consequently become more vulnerable to Kras-mediated transformation [46]. While Lesina et al. [47] suggested that Kras^{G12D}-expressing epithelial cells recruit immune cells, particularly myeloid cells, which produce IL-6 and soluble IL-6R and activate STAT3 in epithelial cells in a paracrine manner, Fukuda et al. [46] suggested that Kras activation drives epithelial cell expression of IL-6 and IL-11, which activate STAT3 in an autocrine fashion. The latter is noteworthy as it indicates that intrinsic factors of

inflammatory nature in the epithelium can contribute to the cellular changes. Accordingly, the loss of acinar differentiation has been neatly described in *in vitro* assays of primary rodent and human acinar cells in the absence of inflammatory cells [22,48–50]. Microarray expression analysis of these cultures revealed intrinsic changes in gene expression of typical inflammatory molecules and pathways, including NF-κB pathway genes [22]. With respect to tumours, more studies suggest that inflammatory cues can also come from the epithelium and exert paracrine effects on stromal components. GM-CSF is one of the inflammatory cues from the tumour cells that modulate the environment [51]. Chemokine production by the tumour epithelium also promotes CTGF secretion from the stromal cells [52]. Moreover, loss of mutant Kras in the tumour epithelium results in involution of the stroma and its inflammatory component with decreases in Cox2, IL-6, STAT3 and MMP7 [53].

In summary, the stroma and its immune cells are essential to overcome senescence barriers and support tumour development. The epithelial cells themselves, in a context of oxidative stress, also initiate the production of inflammatory molecules, both at tumour precursor stages and in established tumours.

4. Anti-inflammatory agents – promising chemoprevention or treatment for pancreatic cancer?

The established link between oxidative stress, inflammatory pathways and cancer development suggests a potential prophylactic and/or therapeutic use of antioxidants and anti-inflammatory agents for pancreatitis and pancreatic cancer.

Despite several studies showing clinical benefit from antioxidant therapy in pancreatitis, this area of research is still largely controversial [32]. Data relating antioxidant intake and pancreatic cancer risk are inconsistent, with most studies reporting null associations [54]. Nevertheless, a recent prospective cohort study showed that participants with high dietary intake of vitamins C and E and selenium had a decreased risk of developing pancreatic cancer [55]. Another study supported that the best chance for reducing the risk for pancreatic cancer comes from dietary selenium intake [54].

Numerous non-steroidal anti-inflammatory drugs (NSAIDs) have shown an effect in prevention and/or treatment of pancreatic cancer in experimental studies using both cell lines and animal models [56,57]. This includes Cox2 specific inhibitors such as celecoxib [58,59], apricoxib [60] or NS-398 [40], as well as non-specific NSAIDs such as aspirin [61,62], nimesulide [63] or sulindac [30]. Other agents, e.g. curcumin (a naturally occurring anti-inflammatory present in turmeric) have also been shown to have an effect in pancreatic cancer prevention/treatment by supressing inflammatory pathways [56,57].

Epidemiological studies evaluating the association between NSAIDs and pancreatic cancer have been inconsistent, with data supporting aspirin use being associated with both a lower [64] and an increased [65] risk of pancreatic cancer. A more recent study analysed data from several randomised trials of daily aspirin versus no aspirin and found that aspirin significantly reduced deaths due to pancreatic cancer after 5 years of follow up (HR: 0.25) [66]. Accordingly, recent case-control studies suggest a reduction in risk of pancreatic cancer for long-term users of NSAIDs [67,68].

Regarding treatment for pancreatic cancer, there are several reported early phase trials that support the feasibility of Cox2 inhibitors therapeutic use [69]. The first randomised trial to report results from this approach was the Apricot-P study. This was a randomised phase II study of chemotherapy with gemcitabine and erlotinib with or without the Cox2 inhibitor apricoxib. Although it did not reach its endpoint, it showed a trend towards benefit with the anti-inflammatory but at the cost of increased incidence of gastrointestinal haemorrhage [70]. Similarly, phase I/II trials of curcumin combined with gemcitabine have been reported that demonstrate feasibility and tolerance [71] but efficacy has not yet been tested in a randomised fashion.

There are currently 11 ongoing clinical trials registered with clinicaltrials.gov that are testing the addition of anti-inflammatories to chemotherapy for pancreas cancer, most in a palliative setting, but also as an adjunct to surgery and adjuvant chemotherapy [69]. Regarding antioxidant agents, there are 8 actively recruiting trials registered that examine the addition of Vitamin C to treatment for pancreas cancer. Currently, there is no evidence that it improves treatment efficacy but Phase 2 trials are ongoing [69].

Results from these clinical studies will be essential to inform the potential of anti-inflammatory drugs and antioxidants as valuable chemopreventive and/or therapeutic agents for pancreatic cancer.

5. ‘Science never solves a problem without creating ten more’

(*quoted from George Bernard Shaw*)

Only a fraction of PDAC patients have a history of chronic pancreatitis. The question arises as to whether the mouse models that recapitulate pancreatic tumour formation based on pancreatitis are representative of this subpopulation of PDAC cases or, can be used as a generalised model for PDAC, assuming that all patients had a pancreatitis like stress/inflammatory component at disease onset. From the mouse models we have learned that asymptomatic bouts of pancreatitis may be enough to trigger tumour development and that it may merely be to the inflammation and loss of cell differentiation associated with pancreatitis that is the trigger. We would suggest that the population of PDAC patients whose disease is linked with (subtle) pancreatitis/inflammatory insults to the pancreas could be largely underestimated because many are asymptomatic.

There may also be other inflammatory conditions that predispose one to pancreatic tumour development and one such (yet unexplored) example is diabetes. Both type 1 and type 2 diabetes are conditions that have been intimately linked with inflammation (either as the cause or the consequence of destruction or impairment of the insulin secreting cells) [72,73] and with changes in pancreatic cell differentiation [28,74,75]. Evidence has been accumulating for an increased risk for pancreatic cancer in subjects with longstanding (>5 years) diabetes [76,77]. It was even suggested that insulin-producing cells under inflammatory conditions can generate PDAC [28]. Mouse models to study the link between inflammation, diabetes and pancreatic neoplasia would help to understand these associations.

Given that the evidence from lineage tracing models is strongest for acinar cells to be the link between pancreatitis, inflammation and PDAC, this begs a more detailed study of this particular cell population. It is generally assumed the acinar cell population is homogeneous in cellular differentiation and function. However, reports on acinar cell heterogeneity date back to 1975 where distinctions were found between peri-insular and tele-insular acini in terms of content and composition of the secreted digestive enzymes [78]. Over time, researchers have also noted differences in the size of the cells [79], in the ploidy (with about 50% binuclear acinar cells in normal mouse pancreas) [80,81] and in blood group antigens and lectin specific binding [48,82]. Furthermore, in more recent studies, evidence was found that some of the crucial proteins that orchestrate cell fate decisions in the pancreas are heterogeneously expressed among acinar cells: small subpopulations of acinar cells express low levels of Pdx1 [59,83], Sox9 [22,84] and

Bmi1 [85], where the majority are negative. Even the expression of Ptf1a, the master transcriptional regulator of acinar cell differentiation, seems to be heterogeneous in the acinar cell population (own observations, [22,83,86]) and different subpopulations of acinar cells could possibly be discerned if examined carefully. The existence of acinar cell heterogeneity therefore needs attention as it could contribute to the differences observed among, and possibly within, pancreatic tumours, or it could imply that only a subpopulation of acinar cells has the propensity for tumour development. Where inflammation and *KRAS* mutations can be the trigger to changes in cell differentiation, one can imagine that already less differentiated cells may have most plasticity to allow malignant transformation in a permissive signalling context, partly driven by the inflammatory milieu. Comparative expression analyses within the acinar cell population may be of interest and a further characterisation of the 'enigmatic' centro-acinar cell is also warranted.

It is indisputable that the available mouse models in combination with epidemiological and patient-derived evidence have changed a dogma and established a connection between pancreatic cancer and pancreatitis. This knowledge generated more questions for further research and is now being translated into novel preventive and therapeutic approaches to combat pancreatic cancer.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgements

We are thankful to Drs P. Phillips, G. Samimi and R. Laybutt for critically revising our manuscript. We apologise that many important studies have not been mentioned due to space constraints.

References

[1] J.M. Slack, Developmental biology of the pancreas, Development 121 (1995) 1569–1580.
[2] H. Witt, M.V. Apte, V. Keim, J.S. Wilson, Chronic pancreatitis: challenges and advances in pathogenesis, genetics, diagnosis, and therapy, Gastroenterology 132 (2007) 1557–1573.
[3] J.M. Braganza, S.H. Lee, R.F. McCloy, M.J. McMahon, Chronic pancreatitis, Lancet 377 (2011) 1184–1197.
[4] A.F. Hezel, A.C. Kimmelman, B.Z. Stanger, N. Bardeesy, R.A. Depinho, Genetics and biology of pancreatic ductal adenocarcinoma, Genes and Development 20 (2006) 1218–1249.
[5] Cancer incidence in five continents. Vol. VIII. IARC Scientific Publications, 2002, pp. 1–781.
[6] A. Jemal, R. Siegel, J. Xu, E. Ward, Cancer statistics, CA, A Cancer Journal for Clinicians 60 (2010) 277–300.
[7] J. Ferlay, D.M. Parkin, E. Steliarova-Foucher, Estimates of cancer incidence and mortality in Europe in 2008, European Journal of Cancer 46 (2010) (2008) 765–781.
[8] A.V. Biankin, T.J. Hudson, Somatic variation and cancer: therapies lost in the mix, Human Genetics 130 (2011) 79–91.
[9] A.B. Lowenfels, P. Maisonneuve, G. Cavallini, R.W. Ammann, P.G. Lankisch, J.R. Andersen, E.P. Dimagno, A. Andren-Sandberg, L. Domellof, Pancreatitis and the risk of pancreatic cancer, International Pancreatitis Study Group. The New England Journal of Medicine 328 (1993) 1433–1437.
[10] D. Malka, P. Hammel, F. Maire, P. Rufat, I. Madeira, F. Pessione, P. Levy, P. Ruszniewski, Risk of pancreatic adenocarcinoma in chronic pancreatitis, Gut 51 (2002) 849–852.
[11] S. Raimondi, A.B. Lowenfels, A.M. Morselli-Labate, P. Maisonneuve, R. Pezzilli, Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection, Best Practice and Research. Clinical Gastroenterology 24 (2010) 349–358.
[12] S. Raimondi, P. Maisonneuve, A.B. Lowenfels, Epidemiology of pancreatic cancer: an overview, Nature Reviews. Gastroenterology and Hepatology 6 (2009) 699–708.
[13] R.H. Hruban, M. Goggins, J. Parsons, S.E. Kern, Progression model for pancreatic cancer, Clinical Cancer Research : An Official Journal of the American Association for Cancer Research 6 (2000) 2969–2972.
[14] A. Maitra, R.H. Hruban, Pancreatic cancer, Annual Review of Pathology 3 (2008) 157–188.
[15] A.V. Biankin, N. Waddell, K.S. Kassahn, M.C. Gingras, L.B. Muthuswamy, A.L. Johns, D.K. Miller, P.J. Wilson, A.M. Patch, J. Wu, D.K. Chang, M.J. Cowley, B.B. Gardiner, S. Song, I. Harliwong, S. Idrisoglu, C. Nourse, E. Nourbakhsh, S. Manning, S. Wani, M. Gongora, M. Pajic, C.J. Scarlett, A.J. Gill, A.V. Pinho, I. Rooman, M. Anderson, O. Holmes, C. Leonard, D. Taylor, S. Wood, Q. Xu, K. Nones, J.L. Fink, A. Christ, T. Bruxner, N. Cloonan, G. Kolle, F. Newell, M. Pinese, R.S. Mead, J.L. Humphris, W. Kaplan, M.D. Jones, E.K. Colvin, A.M. Nagrial, E.S. Humphrey, A. Chou, V.T. Chin, L.A. Chantrill, A. Mawson, J.S. Samra, J.G. Kench, J.A. Lovell, R.J. Daly, N.D. Merrett, C. Toon, K. Epari, N.Q. Nguyen, A. Barbour, N. Zeps, N. Kakkar, F. Zhao, Y.Q. Wu, M. Wang, D.M. Muzny, W.E. Fisher, F.C. Brunicardi, S.E. Hodges, J.G. Reid, J. Drummond, K. Chang, Y. Han, L.R. Lewis, H. Dinh, C.J. Buhay, T. Beck, L. Timms, M. Sam, K. Begley, A. Brown, D. Pai, A. Panchal, N. Buchner, R. De Borja, R.E. Denroche, C.K. Yung, S. Serra, N. Onetto, D. Mukhopadhyay, M.S. Tsao, P.A. Shaw, G.M. Petersen, S. Gallinger, R.H. Hruban, A. Maitra, C.A. Iacobuzio-Donahue, R.D. Schulick, C.L. Wolfgang, R.A. Morgan, R.T. Lawlor, P. Capelli, V. Corbo, M. Scardoni, G. Tortora, M.A. Tempero, K.M. Mann, N.A. Jenkins, P.A. Perez-Mancera, D.J. Adams, D.A. Largaespada, L.F. Wessels, A.G. Rust, L.D. Stein, D.A. Tuveson, N.G. Copeland, E.A. Musgrove, A. Scarpa, J.R. Eshleman, T.J. Hudson, R.L. Sutherland, D.A. Wheeler, J.V. Pearson, J.D. McPherson, R.A. Gibbs, S.M. Grimmond, Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes, Nature 491 (2012) 399–405.
[16] F.H. Brembeck, F.S. Schreiber, T.B. Deramaudt, L. Craig, B. Rhoades, G. Swain, P. Grippo, D.A. Stoffers, D.G. Silberg, A.K. Rustgi, The mutant K-ras oncogene causes pancreatic periductal lymphocytic infiltration and gastric mucous neck cell hyperplasia in transgenic mice, Cancer Research 63 (2003) 2005–2009.
[17] K.C. Ray, K.M. Bell, J. Yan, G. Gu, C.H. Chung, M.K. Washington, A.L. Means, Epithelial tissues have varying degrees of susceptibility to Kras(G12D)-initiated tumorigenesis in a mouse model, PloS one 6 (2011) e16786.
[18] I. Rooman, F.X. Real, Pancreatic ductal adenocarcinoma and acinar cells: a matter of differentiation and development?, Gut 61 (2012) 449–458
[19] V. Fendrich, F. Esni, M.V. Garay, G. Feldmann, N. Habbe, J.N. Jensen, Y. Dor, D. Stoffers, J. Jensen, S.D. Leach, A. Maitra, Hedgehog signaling is required for effective regeneration of exocrine pancreas, Gastroenterology 135 (2008) 621–631.
[20] O. Strobel, Y. Dor, J. Alsina, A. Stirman, G. Lauwers, A. Trainor, C.F. Castillo, A.L. Warshaw, S.P. Thayer, In vivo lineage tracing defines the role of acinar-to-ductal transdifferentiation in inflammatory ductal metaplasia, Gastroenterology 133 (2007) 1999–2009.
[21] B.M. Desai, J. Oliver-Krasinski, D.D. De Leon, C. Farzad, N. Hong, S.D. Leach, D.A. Stoffers, Preexisting pancreatic acinar cells contribute to acinar cell, but not islet beta cell, regeneration, The Journal of Clinical Investigation 117 (2007) 971–977.
[22] A.V. Pinho, I. Rooman, M. Reichert, N. De Medts, L. Bouwens, A.K. Rustgi, F.X. Real, Adult pancreatic acinar cells dedifferentiate to an embryonic progenitor phenotype with concomitant activation of a senescence programme that is present in chronic pancreatitis, Gut 60 (2011) 958–966.
[23] A.V. Pinho, I. Rooman, F.X. Real, P53-dependent regulation of growth, epithelial-mesenchymal transition and stemness in normal pancreatic epithelial cells, Cell Cycle 10 (2011) 1312–1321.
[24] E.P. Sandgren, C.J. Quaife, A.G. Paulovich, R.D. Palmiter, R.L. Brinster, Pancreatic tumor pathogenesis reflects the causative genetic lesion, Proceedings of the National Academy of Sciences of the United States of America 88 (1991) 93–97.
[25] E.P. Sandgren, N.C. Luetteke, T.H. Qiu, R.D. Palmiter, R.L. Brinster, D.C. Lee, Transforming growth factor alpha dramatically enhances oncogene-induced carcinogenesis in transgenic mouse pancreas and liver, Molecular and Cellular Biology 13 (1993) 320–330.
[26] C. Guerra, A.J. Schuhmacher, M. Canamero, P.J. Grippo, L. Verdaguer, L. Perez-Gallego, P. Dubus, E.P. Sandgren, M. Barbacid, Chronic pancreatitis is essential for induction of pancreatic ductal adenocarcinoma by K-Ras oncogenes in adult mice, Cancer Cell 11 (2007) 291–302.
[27] O.J. De La, L.L. Emerson, J.L. Goodman, S.C. Froebe, B.E. Illum, A.B. Curtis, L.C. Murtaugh, Notch and Kras reprogram pancreatic acinar cells to ductal intraepithelial neoplasia, Proceedings of the National Academy of Sciences of the United States of America 105 (2008) 18907–18912.
[28] S.Y. Gidekel Friedlander, G.C. Chu, E.L. Snyder, N. Girnius, G. Dibelius, D. Crowley, E. Vasile, R.A. DePinho, T. Jacks, Context-dependent transformation of adult pancreatic cells by oncogenic K-Ras, Cancer Cell 16 (2009) 379–389.
[29] N. Habbe, G. Shi, R.A. Meguid, V. Fendrich, F. Esni, H. Chen, G. Feldmann, D.A. Stoffers, S.F. Konieczny, S.D. Leach, A. Maitra, Spontaneous induction of murine pancreatic intraepithelial neoplasia (mPanIN) by acinar cell targeting of oncogenic Kras in adult mice, Proceedings of the National Academy of Sciences of the United States of America 105 (2008) 18913–18918.
[30] C. Guerra, M. Collado, C. Navas, A.J. Schuhmacher, I. Hernandez-Porras, M. Canamero, M. Rodriguez-Justo, M. Serrano, M. Barbacid, Pancreatitis-induced inflammation contributes to pancreatic cancer by inhibiting oncogene-induced senescence, Cancer Cell 19 (2011) 728–739.
[31] B. Ji, L. Tsou, H. Wang, S. Gaiser, D.Z. Chang, J. Daniluk, Y. Bi, T. Grote, D.S. Longnecker, C.D. Logsdon, Ras activity levels control the development of pancreatic diseases, Gastroenterology 137 (2009) 1072–1082. 1082 e1071-1076..
[32] P.S. Leung, Y.C. Chan, Role of oxidative stress in pancreatic inflammation, Antioxidants and Redox Signaling 11 (2009) 135–165.

[33] B. Farrow, B.M. Evers, Inflammation and the development of pancreatic cancer, Surgical Oncology 10 (2002) 153–169.
[34] T. Al Saati, P. Clerc, N. Hanoun, S. Peuget, H. Lulka, V. Gigoux, F. Capilla, B. Beluchon, A. Couvelard, J. Selves, L. Buscail, A. Carrier, N. Dusetti, M. Dufresne, Oxidative stress induced by inactivation of TP53INP1 cooperates with KrasG12D to initiate and promote pancreatic carcinogenesis in the murine pancreas, The American Journal of Pathology 182 (2013) 1996–2004.
[35] G.M. DeNicola, F.A. Karreth, T.J. Humpton, A. Gopinathan, C. Wei, K. Frese, D. Mangal, K.H. Yu, C.J. Yeo, E.S. Calhoun, F. Scrimieri, J.M. Winter, R.H. Hruban, C. Iacobuzio-Donahue, S.E. Kern, I.A. Blair, D.A. Tuveson, Oncogene-induced Nrf2 transcription promotes ROS detoxification and tumorigenesis, Nature 475 (2011) 106–109.
[36] F. Marrache, S.P. Tu, G. Bhagat, S. Pendyala, C.H. Osterreicher, S. Gordon, V. Ramanathan, M. Penz-Osterreicher, K.S. Betz, Z. Song, T.C. Wang, Overexpression of interleukin-1beta in the murine pancreas results in chronic pancreatitis, Gastroenterology 135 (2008) 1277–1287.
[37] J.K. Colby, R.D. Klein, M.J. McArthur, C.J. Conti, K. Kiguchi, T. Kawamoto, P.K. Riggs, A.I. Pavone, J. Sawicki, S.M. Fischer, Progressive metaplastic and dysplastic changes in mouse pancreas induced by cyclooxygenase-2 overexpression, Neoplasia 10 (2008) 782–796.
[38] K. Muller-Decker, G. Furstenberger, N. Annan, D. Kucher, A. Pohl-Arnold, B. Steinbauer, I. Esposito, S. Chiblak, H. Friess, P. Schirmacher, I. Berger, Preinvasive duct-derived neoplasms in pancreas of keratin 5-promoter cyclooxygenase-2 transgenic mice, Gastroenterology 130 (2006) 2165–2178.
[39] M. Collado, J. Gil, A. Efeyan, C. Guerra, A.J. Schuhmacher, M. Barradas, A. Benguria, A. Zaballos, J.M. Flores, M. Barbacid, D. Beach, M. Serrano, Tumour biology: senescence in premalignant tumours, Nature 436 (2005) 642.
[40] J. Daniluk, Y. Liu, D. Deng, J. Chu, H. Huang, S. Gaiser, Z. Cruz-Monserrate, H. Wang, B. Ji, C.D. Logsdon, An NF-kappaB pathway-mediated positive feedback loop amplifies Ras activity to pathological levels in mice, The Journal of Clinical Investigation 122 (2012) 1519–1528.
[41] J. Ling, Y. Kang, R. Zhao, Q. Xia, D.F. Lee, Z. Chang, J. Li, B. Peng, J.B. Fleming, H. Wang, J. Liu, I.R. Lemischka, M.C. Hung, P.J. Chiao, KrasG12D-induced IKK2/beta/NF-kappaB activation by IL-1alpha and p62 feedforward loops is required for development of pancreatic ductal adenocarcinoma, Cancer Cell 21 (2012) 105–120.
[42] E. Maniati, M. Bossard, N. Cook, J.B. Candido, N. Emami-Shahri, S.A. Nedospasov, F.R. Balkwill, D.A. Tuveson, T. Hagemann, Crosstalk between the canonical NF-kappaB and Notch signaling pathways inhibits Ppargamma expression and promotes pancreatic cancer progression in mice, The Journal of Clinical Investigation 121 (2011) 4685–4699.
[43] H. Huang, Y. Liu, J. Daniluk, S. Gaiser, J. Chu, H. Wang, Z.S. Li, C.D. Logsdon, B. Ji, Activation of nuclear factor-kappaB in acinar cells increases the severity of pancreatitis in mice, Gastroenterology 144 (2013) 202–210.
[44] P. Neuhofer, S. Liang, H. Einwachter, C. Schwerdtfeger, T. Wartmann, M. Treiber, H. Zhang, H.U. Schulz, K. Dlubatz, M. Lesina, K.N. Diakopoulos, S. Wormann, W. Halangk, H. Witt, R.M. Schmid, H. Algul, Deletion of IkappaBalpha activates RelA to reduce acute pancreatitis in mice through up-regulation of Spi2A, Gastroenterology 144 (2013) 192–201.
[45] I. Gukovsky, A. Gukovskaya, Nuclear factor-kappaB in pancreatitis: Jack-of-all-trades, but which one is more important?, Gastroenterology 144 (2013) 26–29
[46] A. Fukuda, S.C. Wang, J.P.T. Morris, A.E. Folias, A. Liou, G.E. Kim, S. Akira, K.M. Boucher, M.A. Firpo, S.J. Mulvihill, M. Hebrok, Stat3 and MMP7 contribute to pancreatic ductal adenocarcinoma initiation and progression, Cancer cell 19 (2011) 441–455.
[47] M. Lesina, M.U. Kurkowski, K. Ludes, S. Rose-John, M. Treiber, G. Kloppel, A. Yoshimura, W. Reindl, B. Sipos, S. Akira, R.M. Schmid, H. Algul, Stat3/Socs3 activation by IL-6 transsignaling promotes progression of pancreatic intraepithelial neoplasia and development of pancreatic cancer, Cancer cell 19 (2011) 456–469.
[48] I. Houbracken, E. de Waele, J. Lardon, Z. Ling, H. Heimberg, I. Rooman, L. Bouwens, Lineage tracing evidence for transdifferentiation of acinar to duct cells and plasticity of human pancreas, Gastroenterology 141 (2011) 731–741. 741 e731-734.
[49] A.L. Means, I.M. Meszoely, K. Suzuki, Y. Miyamoto, A.K. Rustgi, R.J. Coffey Jr., C.V. Wright, D.A. Stoffers, S.D. Leach, Pancreatic epithelial plasticity mediated by acinar cell transdifferentiation and generation of nestin-positive intermediates, Development 132 (2005) 3767–3776.
[50] I. Rooman, Y. Heremans, H. Heimberg, L. Bouwens, Modulation of rat pancreatic acinoductal transdifferentiation and expression of PDX-1 in vitro, Diabetologia 43 (2000) 907–914.
[51] Y. Pylayeva-Gupta, K.E. Lee, C.H. Hajdu, G. Miller, D. Bar-Sagi, Oncogenic Kras-induced GM-CSF production promotes the development of pancreatic neoplasia, Cancer Cell 21 (2012) 836–847.
[52] H. Ijichi, A. Chytil, A.E. Gorska, M.E. Aakre, B. Bierie, M. Tada, D. Mohri, K. Miyabayashi, Y. Asaoka, S. Maeda, T. Ikenoue, K. Tateishi, C.V. Wright, K. Koike, M. Omata, H.L. Moses, Inhibiting Cxcr2 disrupts tumor-stromal interactions and improves survival in a mouse model of pancreatic ductal adenocarcinoma, The Journal of Clinical Investigation 121 (2011) 4106–4117.
[53] M.A. Collins, F. Bednar, Y. Zhang, J.C. Brisset, S. Galban, C.J. Galban, S. Rakshit, K.S. Flannagan, N.V. Adsay, M. Pasca di Magliano, Oncogenic Kras is required for both the initiation and maintenance of pancreatic cancer in mice, The Journal of Clinical Investigation 122 (2012) 639–653.
[54] X. Han, J. Li, T.M. Brasky, P. Xun, J. Stevens, E. White, M.D. Gammon, K. He, Antioxidant intake and pancreatic cancer risk: the Vitamins and Lifestyle (VITAL) Study, Cancer 119 (2013) 1314–1320.
[55] P.J. Banim, R. Luben, A. McTaggart, A. Welch, N. Wareham, K.T. Khaw, A.R. Hart, Dietary antioxidants and the aetiology of pancreatic cancer: a cohort study using data from food diaries and biomarkers, Gut (2012).
[56] S.D. Stan, S.V. Singh, R.E. Brand, Chemoprevention strategies for pancreatic cancer, Nature Reviews. Gastroenterology and Hepatology 7 (2010) 347–356.
[57] M. Takahashi, M. Mutoh, R. Ishigamori, G. Fujii, T. Imai, Involvement of inflammatory factors in pancreatic carcinogenesis and preventive effects of anti-inflammatory agents, Seminars in Immunopathology 35 (2013) 203–227.
[58] D. Wei, L. Wang, Y. He, H.Q. Xiong, J.L. Abbruzzese, K. Xie, Celecoxib inhibits vascular endothelial growth factor expression in and reduces angiogenesis and metastasis of human pancreatic cancer via suppression of Sp1 transcription factor activity, Cancer Research 64 (2004) 2030–2038.
[59] K.L. Wu, M. Gannon, M. Peshavaria, M.F. Offield, E. Henderson, M. Ray, A. Marks, L.W. Gamer, C.V. Wright, R. Stein, Hepatocyte nuclear factor 3beta is involved in pancreatic beta-cell-specific transcription of the pdx-1 gene, Molecular and Cellular Biology 17 (1997) 6002–6013.
[60] A. Kirane, J.E. Toombs, K. Ostapoff, J.G. Carbon, S. Zaknoen, J. Braunfeld, R.E. Schwarz, F.J. Burrows, R.A. Brekken, Apricoxib, a novel inhibitor of COX-2, markedly improves standard therapy response in molecularly defined models of pancreatic cancer, Clinical Cancer Research : An Official Journal of the American Association for Cancer Research 18 (2012) 5031–5042.
[61] G.M. Sclabas, T. Uwagawa, C. Schmidt, K.R. Hess, D.B. Evans, J.L. Abbruzzese, P.J. Chiao, Nuclear factor kappa B activation is a potential target for preventing pancreatic carcinoma by aspirin, Cancer 103 (2005) 2485–2490.
[62] V. Fendrich, N.M. Chen, M. Neef, J. Waldmann, M. Buchholz, G. Feldmann, E.P. Slater, A. Maitra, D.K. Bartsch, The angiotensin-I-converting enzyme inhibitor enalapril and aspirin delay progression of pancreatic intraepithelial neoplasia and cancer formation in a genetically engineered mouse model of pancreatic cancer, Gut 59 (2010) 630–637.
[63] H. Funahashi, M. Satake, D. Dawson, N.A. Huynh, H.A. Reber, O.J. Hines, G. Eibl, Delayed progression of pancreatic intraepithelial neoplasia in a conditional Kras(G12D) mouse model by a selective cyclooxygenase-2 inhibitor, Cancer Research 67 (2007) 7068–7071.
[64] K.E. Anderson, T.W. Johnson, D. Lazovich, A.R. Folsom, Association between nonsteroidal anti-inflammatory drug use and the incidence of pancreatic cancer, Journal of the National Cancer Institute 94 (2002) 1168–1171.
[65] E.S. Schernhammer, J.H. Kang, A.T. Chan, D.S. Michaud, H.G. Skinner, E. Giovannucci, G.A. Colditz, C.S. Fuchs, A prospective study of aspirin use and the risk of pancreatic cancer in women, Journal of the National Cancer Institute 96 (2004) 22–28.
[66] P.M. Rothwell, F.G. Fowkes, J.F. Belch, H. Ogawa, C.P. Warlow, T.W. Meade, Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials, Lancet 377 (2011) 31–41.
[67] M. Bonifazi, S. Gallus, C. Bosetti, J. Polesel, D. Serraino, R. Talamini, E. Negri, C. La Vecchia, Aspirin use and pancreatic cancer risk, Europian Journal of Cancer Prevention 19 (2010) 352–354.
[68] M.C. Bradley, C.M. Hughes, M.M. Cantwell, G. Napolitano, L.J. Murray, Non-steroidal anti-inflammatory drugs and pancreatic cancer risk: a nested case-control study, British Journal of Cancer 102 (2010) 1415–1421.
[69] http://www.clinicaltrials.gov/.
[70] M. Modiano, G.P. Keogh, R. Manges, P.J. Stella, G. Milne, E. Looper, S.L. Zaknoen, Apricot-P: A randomized placebo-controlled phase II study of COX-2 inhibitor apricoxib or placebo in combination with gemcitabine and erlotinib in advanced or metastatic adenocarcinoma of the pancreas, ASCO Meeting Abstracts 30 (2012) 253.
[71] N. Dhillon, B.B. Aggarwal, R.A. Newman, R.A. Wolff, A.B. Kunnumakkara, J.L. Abbruzzese, D.S. Hong, L.H. Camacho, C.N.A.R. Kurzrock, Curcumin and pancreatic cancer: Phase II clinical trial experience. ASCO Annual Meeting Proceedings vol. 25, 2007, pp. 4599.
[72] M.Y. Donath, S.E. Shoelson, Type 2 diabetes as an inflammatory disease, Nature Reviews. Immunology 11 (2011) 98–107.
[73] D.L. Eizirik, M.L. Colli, F. Ortis, The role of inflammation in insulitis and beta-cell loss in type 1 diabetes, Nature Reviews. Endocrinology 5 (2009) 219–226.
[74] Y. Dor, B. Glaser, Beta-cell dedifferentiation and type 2 diabetes, The New England Journal of Medicine 368 (2013) 572–573.
[75] G.C. Weir, S. Bonner-Weir, Five stages of evolving beta-cell dysfunction during progression to diabetes, Diabetes 53 (Suppl 3) (2004) S16–21.
[76] Y. Cui, D.K. Andersen, Diabetes and pancreatic cancer, Endocrine-Related Cancer 19 (2012) F9–F26.
[77] P. Maisonneuve, A.B. Lowenfels, Epidemiology of pancreatic cancer: an update, Digestive Diseases 28 (2010) 645–656.
[78] F. Malaisse-Lagae, M. Ravazzola, P. Robberecht, A. Vandermeers, W.J. Malaisse, L. Orci, Exocrine pancreas: evidence for topographic partition of secretory function, Science 190 (1975) 795–797.
[79] M. Bendayan, J. Roth, A. Perrelet, L. Orci, Quantitative immunocytochemical localization of pancreatic secretory proteins in subcellular compartments of the rat acinar cell, The Journal of Histochemistry and Cytochemistry : Official Journal of the Histochemistry Society 28 (1980) 149–160.
[80] R.G. Morgan, B.K. Schaeffer, D.S. Longnecker, Size and number of nuclei differ in normal and neoplastic acinar cells from rat pancreas, Pancreas 1 (1986) 37–43.
[81] N. Sphyris, D.J. Harrison, P53 deficiency exacerbates pleiotropic mitotic defects, changes in nuclearity and polyploidy in transdifferentiating pancreatic acinar cells, Oncogene 24 (2005) 2184–2194.
[82] T.L. Jeraldo, J.A. Coutu, P.A. Verdier, P.N. McMillan, J.W. Adelson, Fundamental cellular heterogeneity of the exocrine pancreas, The Journal of Histochemistry

and Cytochemistry : Official Journal of the Histochemistry Society 44 (1996) 215–220.
[83] X. Molero, E.C. Vaquero, M. Flandez, A.M. Gonzalez, M.A. Ortiz, E. Cibrian-Uhalte, J.M. Servitja, A. Merlos, N. Juanpere, M. Massumi, A. Skoudy, R. Macdonald, J. Ferrer, F.X. Real, Gene expression dynamics after murine pancreatitis unveils novel roles for Hnf1alpha in acinar cell homeostasis, Gut 61 (2012) 1187–1196.
[84] S. Xuan, M.J. Borok, K.J. Decker, M.A. Battle, S.A. Duncan, M.A. Hale, R.J. Macdonald, L. Sussel, Pancreas-specific deletion of mouse Gata4 and Gata6 causes pancreatic agenesis, The Journal of Clinical Investigation 122 (2012) 3516–3528.
[85] A. Fukuda, J.P.T. Morris, M. Hebrok, Bmi1 is required for regeneration of the exocrine pancreas in mice, Gastroenterology 143 (2012) 821–831. e821-822.
[86] E. Wauters, V.J. Sanchez-Arevalo Lobo, A.V. Pinho, A. Mawson, D. Herranz, J. Wu, M.J. Cowley, E.K. Colvin, E.N. Njicop, R.L. Sutherland, T. Liu, M. Serrano, L. Bouwens, F.X. Real, A.V. Biankin, I. Rooman, Sirtuin-1 regulates acinar-to-ductal metaplasia and supports cancer cell viability in pancreatic cancer, Cancer Research 73 (2013) 2357–2367.