Summary. Pancreatic cancer is a devastating disease characterized by a dismal prognosis with most patients dying within six months after diagnosis. Surgery is an option in less than one in five of these patients, and even with tumor resection the majority of patients succumb to the disease. Other effective treatment options are not available. Common features of pancreatic cancer are severe cachexia, marked insulin resistance and diabetes mellitus. Several studies have demonstrated connections between pancreatic cancers and the endocrine pancreas and this has raised questions regarding the role of the islets of Langerhans in pancreatic adenocarcinoma. This manuscript reviews the recent literature in this field and addresses several questions regarding the interaction between the islets of Langerhans and pancreatic cancer. This review considers the histological findings in pancreatic cancer, cell culture and animal experiments, the four islet cell types and the hormones they secrete, as well as the influence of the arachidonic acid pathways on islet cell function and pancreatic cancer. While pancreatic adenocarcinomas are ductal in nature, the cell of origin has not been identified and there is even some evidence that the islets may harbor the precursor cell. Considerable evidence suggests that the diabetes is caused by the tumor, while other studies have identified diabetes as a risk factor. Clearly, the islets are important in many aspects of this disease. However, even though progress has been made, some questions regarding the interaction of pancreatic cancer and the endocrine pancreas remain unanswered.

Key words: Pancreatic cancer, Islets, Diabetes, Stem cell, Transdifferentiation, Lipoxygenase

Introduction

Pancreatic cancer is extraordinary in its biology and aggressiveness. This devastating disease is a great challenge for oncologists and researchers throughout the world in their efforts to help patients and improve the most abysmal prognosis in medicine. Pancreatic cancer is the fourth leading cause of cancer death in men and women with a 5-year survival rate of 3% and a median survival time of less than 6 months (Howard, 1966; Parker, 1996; Greenlee et al., 2000). Potential curative surgery is only possible in about one in six patients diagnosed with pancreatic cancer and adjuvant or palliative therapy with gemcitabine is the best available treatment option (Howard, 1996; Yeo and Cameron, 1999). However, the incidence of pancreatic cancer equals its mortality, since 5-year survival is less than 20% after tumor resection. While gemcitabine improves the quality of life of many patients, it prolongs survival by only about 1 month (Greenlee et al., 2001; Heinemann, 2001; Abbruzzese, 2002; Ahrendt and Pitt, 2002). In contrast to several other cancers, the incidence of this disease is not decreasing. Indeed, incidence has increased in Japan and in African Americans in recent years (Ohba et al., 1996; Lin et al., 1998; Oomi and Amano, 1998; Silverman et al., 1998; Greenlee et al., 2001; McCarty, 2001). The key for this trend appears to be changes in lifestyle, with increased smoking and a western world diet rich in ω-6 fats. Because of the extreme resistance of pancreatic cancer to available therapeutics, it is even more important to identify risk factors and to prevent or diagnose this disease at an early stage, before invasive spread. The high fat western diet is obviously a major risk factor for many diseases including cancers of the colon, breast, prostate and pancreas as well as for type 2 diabetes mellitus and heart disease (Rose, 1997; Woutersen et al., 1999). Several studies have shown a high incidence of diabetes in pancreatic cancer and it is generally believed that diabetes is a risk factor for this malignancy (Schwarts et al., 1978; Friedman and van den Eeden, 1993; Fisher et
Histological findings

The pancreas is a complex tissue and is perhaps the least understood organ besides the brain in mammals. Three major components build the structure of the pancreas. Acinar cells represent 85% of the tissue volume and are, therefore, considered as the leaders in organ function and failure (Pour et al., 2002). Ductal cells contribute less than 10% and islets only 1-2% of the volume of the pancreas (Pour et al., 2002). It would be misleading to consider the islets as the least important fraction of the pancreas, however. The Islet cell-specific transcription factor, PDX1 is absolutely essential for the development of the pancreas, while the α-cells which produce glucagon gene products and PYY in the fetus are one of the earliest cell types appearing during pancreatic organogenesis (Herrera et al., 1991; Lukinius et al., 1992; Jönsson et al., 1994; Slack, 1995; Offield et al., 1996). The pancreatic islets were first described by Langerhans in 1869 (Langerhans, 1869). The distribution of islets throughout the exocrine parenchyma, rather than forming a solid gland, is unusual for an endocrine tissue. This provides evidence of a special role for the islets within the pancreas. The pancreas originates from two outgrowths of the primitive foregut, a ventral (head and uncinate process) and a dorsal (pancreas body and tail) anlage. This has an impact on islet cell shape (ventral-diffuse and dorsal-compact spheric) and the cellular composition of the islets (Pour et al., 2002). There are four different islet cell types, the glucagon producing α-cells, the insulin and amylin (also called islet amyloid polypeptide, IAPP) producing β-cells, the somatostatin producing δ-cells and pancreatic polypeptide producing PP-cells. PP-cells are mostly found in the uncinate process, while α-cells are more common in the body and tail of the pancreas (Orci et al., 1978; Stefan et al., 1982). The arrangement of endocrine cells varies between species. In rats and hamsters, there is a clear structure with β-cells in the center and α- and δ-cells in the periphery of the islets (Pour et al., 2002). In rodents, the microcirculation is organized, with much of the blood flowing from the α- and δ-cells to the β-cells and only afterwards reaching the acinar tissue (Pour et al., 2002). Thus, we speak from an islet-acinar portal system, which suggests that the islets are the important metabolizing station in the pancreas, perhaps somewhat akin to the role of the liver in first pass metabolism for the whole body. The cellular arrangement in human islets is not organized like that of rodents, however, and this is reflected in the lack of organized pattern in the microcirculation. PP cells are not only associated with the islets and are found scattered in normal ducts throughout the exocrine tissue (Pour et al., 2002). In contrast, ductal cells can be localized within islets, an observation first made by Bensley in 1911 (Bensley, 1911). Intrainsular ductules were recently described in tissues from patients with pancreatic cancer or chronic pancreatitis (Pour and Schmied, 1999). The islet cells in 70% of pancreatic cancer patients with altered glucose tolerance exhibit reduced insulin content (Kimura et al., 1998) but express ductal cell markers such as CA19-9, DU-PAN-2 and Tag-72 (Kimura et al., 1998; Pour and Schmied, 1999). Furthermore, in the BOP-hamster model, the first morphological changes which occur during pancreatic carcinogenesis are the appearance of ductular structures within or around the islets (Schmied et al., 1999). These ductules proliferate and become microcystic adenomas or hyperplastic, dysplastic, atypical and finally malignant glands, destroying the islets and invading the surrounding tissue (Schmied et al., 1999). This is in accordance with an incidental finding at autopsy, in which a microscopical pancreatic carcinoma was identified in an islet (Schmied et al., 1999). In Figure 1 an islet from adjacent to a pancreatic cancer is shown with the described intra-insular ductules. Immunohistochemical studies have shown the abnormal co-localization of islet hormones and the presence of endocrine cells in invasive regions of pancreatic carcinoma (Pour et al., 1993). The islets within pancreatic cancer tissues contain less β-cells but more α-cells and this is not compensated in the extrainsular tissue (Schmied et al., 2001). These data strongly suggest a relationship between islets and pancreatic cancer. However, doublestaining for chromogranin A and Ki-S5 revealed that the majority of scattered endocrine cells within ductal adenocarcinomas are a non-neoplastic tumor-associated cell population, unless these cells are intimately integrated into the neoplastic glandular epithelium (Ōhike et al., 2003). At present, pancreatic cancers are classified as ductal adenocarcinomas of the pancreas, based on the histological finding that the tumor cells mimic ductal structures. It is, therefore, widely believed that ductal cells are the cells of origin of pancreatic cancer and a progression model from normal ductal epithelium through intraepithelial neoplasia to invasive ductal adenocarcinoma has been developed (Hruban et al., 2000a,b). However, this assumption needs to be questioned in context of above mentioned data and since Sakaki et al. also described non-neoplastic endocrine...
cells between tumor cells which, in turn are in close contact with surrounding islets (Sakaki et al., 2002). It is also remarkable that islets tend to survive in invasive cancers while acinar cells do not (Kodama and Mori, 1983). However, even islets far from the tumor may exhibit changes, suggesting either primary damage by a possible carcinogen or that they are influenced by the cancer cells (Pour et al., 2002). It should be mentioned that endocrine cells are only detected in well-differentiated tumors but not in poorly-differentiated ones, paralleling the loss of islet cell markers in cultured islets during the process of dedifferentiation (Pour et al., 2002). In addition, Regitnig et al. reported a case of a uniform insulinoma in the pancreas where a liver metastasis developed with insular-ductular differentiation (Regitnig et al., 2001). An important paper recently described nestin positive stem cells in the islets and ductal tissues of the mouse pancreas (Hunziker and Stein, 2000). Furthermore nestin-positive progenitor cells have been obtained from adult human and rat pancreatic islets (Zulewski et al., 2001; Lechner et al., 2002). Clearly such stem cells could be the origin of pancreatic cancer. However, once again this area is highly controversial. Other groups have published papers suggesting on the one hand that the nestin positive cells in the pancreas are the endothelial cells in new developing blood vessels and on the other hand that the only nestin positive cells are of mesenchymal origin (Lardon et al., 2002). The observation that islet cells can transform into duct cells suggests that at least some human pancreatic adenocarcinomas may originate within islets via transdifferentiation. Considering all above

**Fig. 1.** 5-LOX and LTB4 receptor expression in human pancreatic tissues. Immunohistochemistry for 5-LOX is shown in panels **A** and **B** and for LTB4 receptor in panels **C** and **D.** **A and C.** Normal human pancreas from a multi organ donor with an unstained islet. **B and D.** Pancreatic adenocarcinoma with islets surrounding the tumor showing strong positive staining in cytoplasm, nucleus and nuclear membrane. **D.** This islet also shows intrainsular ductules. The immunohistochemistry for 5-LOX used mouse-moniconal antibody, 1:250, microwave citrate buffer pretreatment, incubation over night at 4 °C, and DAB and for LTB4 receptor rabbit-polyclonal antiserum, 1:200, incubation over night at 4 °C, and HistoMark Red. Hematoxylin counterstained all sections. x 400
In vitro studies excluded. such as insulin directly provided by them while, a advantage for tumor cells to get important growth factors pancreatic adenocarcinoma could be explained by the advantage for tumor cells to get important growth factors such as insulin directly provided by them while, a possible role in originating these tumors cannot be excluded.

Experimental studies to determine the cell of origin

In vitro studies

Numerous cell culture experiments have been performed to shed light on the cellular origin of pancreatic cancer. However, the isolation, purification and maintenance of human pancreatic cells are difficult and limited. While hamster ductal and islet cells immortalize spontaneously, their human counterparts undergo senescence after approximately 10 months (Ulrich et al., 2002). Human acinar cells could be cultured for only 21 days (Ulrich et al., 2002). Use of a recently described technique allowed the culture of human ductal cells for more than 16 months, without genetic manipulations or by introducing foreign genes as the large T antigen of SV40 which alter regulatory genes such as p53 and pRb (Ulrich et al., 2000, 2002). One group were able to culture immortalized pancreatic ductal cells using large T antigen of SV40 and these cells acquired the ability to form tumors after transfection with mutated K-ras (Jesnowski et al., 1999; Lohr et al., 2001). Hamster islets could successfully be maintained in culture indefinitely and human islets for more than 12 months, however, within 14 days these islet cells lost the ability to produce hormones (Schmied et al., 2000; Ulrich et al., 2002). When purified islets are cultured, acinar cells and ductular structures develop primarily within the center, and these structures express ductal cell markers such as cytokeratin 7, 19, pancytokeratin, carbonic anhydrase II, CA19-9 and DU-PAN-2; markers which are also expressed in most pancreatic adenocarcinomas (Pour et al., 2002). During the process of culture, the islet cells lose their endocrine granules. Cells containing a mixture of insulin and glucagon then appear, imitating the embryonic pancreas. After 60 days, the islet cells are completely replaced by undifferentiated cells expressing cytokeratines, α1-antitrypsin, vimentin and nestin (Pour et al., 2002). Reports have suggested that nestin could be a marker for precursor cells in the pancreas, however, results obtained from western blotting and immunohistochemistry are controversial in localizing these nestin positive cells to either ducts, islets or blood vessels and mesenchymal structures (Lee et al., 2003). Very recently, immortalized Nestin positive cells have been developed by stable expression of hTERT (Lee et al., 2003). This is a major advance that will hopefully help to define the biological role of nestin positive cells and determine the cell of origin for pancreatic cancer. Islet cells are also capable of transdifferentiation into acinar cells, hepatocytes or mucinous and oncocyte-like cells (Yuan et al., 1996; Pour and Schmied, 1999). Indeed, acinar, ductal and islet cells can all act as facultative stem cells, or are able to transdifferentiate in each other under reactivation of PDX1 and finally redifferentiate into cells with a stem cell character (Bardeesy and DePinho, 2002). When cultured hamster islet and ductal cells were treated with the pancreatic carcinogen, BOP invasive ductal adenocarcinomas developed (Pour et al., 1975; Schmied et al., 1999). However, only tumors derived from hamster islet cell cultures showed mutations of K-ras and p16, which are the most frequent genetic mutations in human pancreatic cancer (Ikematsu et al., 1997; Schmied et al., 1999; Muscarella et al., 2001).

Whether the appearance of exocrine cells within islets is caused by transdifferentiation of endocrine cells or activation and proliferation of pancreatic stem cells is still not clear and needs to be determined. It is tempting to speculate that it is a specific genetic alteration rather than a specific target cell that is crucial for the development of pancreatic cancer. However, one cell type could still be more susceptible to genetic mutations than the others.

In vivo studies

Islets promote pancreatic cancer

Important information has also been gained from different animal models. Syrian golden hamsters treated with the carcinogen BOP develop pancreatic adenocarcinoma that is similar to the human disease both genetically and histologically (Fuji et al., 1990). This is a valuable model for studying tumor development and biology. In this model, destruction of β-cells with streptozotocin inhibits pancreatic tumor development, while stimulation of islet cell proliferation augments pancreatic carcinogenesis after BOP treatment (Pour et al., 1990; Pour and Kazakoff, 1996). This group reported similar results in Chinese hamsters, where genetically diabetic hamsters with atrophic islets did not develop pancreatic cancer following BOP treatment but non-diabetic controls did (Bell and Pour, 1987).

Islets as the origin of pancreatic cancer

Transplantation of hamster islets into the submandibular gland of Syrian golden hamsters followed by BOP treatment led to the development of ductal pancreatic adenocarcinoma in this site (Pour et al., 1997). Cancer was not observed after transplanting ductal or acinar cells into this gland. Moreover, the submandibular gland itself is not a target for BOP.

Ductal cells as the origin of pancreatic cancer

Pancreatic adenocarcinoma can be induced in rats using the carcinogen DMBA (Jimenez et al., 1999).
Islets and pancreatic cancer

cell proliferation from differentiated cells as well as multipotent ductal cells (Sharma et al., 1999). Proliferating duct cells serve as source for both the endocrine and exocrine compartment, recapitulating embryogenesis and showing that differentiated duct cells can become multipotent during this process (Sharma et al., 1999; Bardeesy and DePinho, 2002).

Acinar cells as the origin of pancreatic cancer

In the azaserine rat model, where acinar cells are the cellular target, duct-like cell lines have been derived from an acinar cell carcinoma (Pettengill et al., 1993). Several groups have developed transgenic mouse models of pancreatic cancer. The elastase promoter of acinar cells is usually targeted for transgene expression. Since pancreatic cancers develop in the progeny of transforming growth factor alpha (TGF-α) transgenic mice crossed with p53-null mice, acinar cells can clearly serve as the starting point for trans- or dedifferentiation (Greten et al., 2001; Wagner et al., 2001). In this model, duct-like tubular structures form, proliferate and eventually develop pancreatic ductal adenocarcinoma (Wagner et al., 2001).

Stem cells as the origin of pancreatic cancer

Animal models indicate that there are several possible ways to develop pancreatic cancer, either from a particular stem cell or through transdifferentiation. It appears that, at a certain stage, all three cell types have the plasticity to dedifferentiate and could be the cell of origin of pancreatic adenocarcinoma. This suggests that differentiation is not an irreversible process and that islet, duct and acinar cells are facultative stem cells, able to gain stem cell properties back during the process of trans- and dedifferentiation. In this process of re-entering the cell cycle, PDX1, which is the transcription factor in pluripotent progenitor cells in the embryonic pancreas, becomes reactivated (Bardeesy and DePinho, 2002). Once again, we get the impression that a particular cell state and increased proliferation rate, combined with the effect of a carcinogen is much more important than the cell type for the development of pancreatic adenocarcinoma. However, it should be kept in mind that only the BOP hamster model closely mimics all aspects of the human disease and only islet but not ductal cells transplanted into the submandibular gland were able to develop pancreatic cancer after BOP treatment.

Islet hormones and pancreatic cancer

Diabetes and pancreatic cancer

The observation that diabetes occurs in two thirds of pancreatic cancer patients is one of the most interesting aspects of this disease and has led to the speculation that the endocrine pancreas is in some way connected with this cancer (Schwarts et al., 1978; Permert et al., 1993a,b). The diabetes in pancreatic cancer patients often remains unrecognised or is diagnosed concomitantly with the pancreatic cancer or within a few months before the cancer diagnosis, most probably because of an asymptomatic hyperglycemia in these patients (Chari et al., 2001). This is tragic, because epidemiological and in vivo data suggest that the metabolic defect occurs at a resectable stage of this disease (Liu et al., 1998; Chari et al., 2001; Permert et al., 2001). Logically, there are two possibilities either diabetes is a risk factor for pancreatic cancer or this metabolic disease arises from the tumor. Some data suggest diabetes as a risk factor for pancreatic cancer (Gapstur et al., 2000; Ghadirian et al., 2003). However, several other studies, including epidemiological data, demonstrate that diabetes is a consequence of pancreatic cancer and moreover, that patients with diabetes type I seem to be protected against this dreadful disease (Gullo et al., 1994; Fisher et al., 1996; Gullo, 1999; McCarty, 2001). Based on these latter findings, suggest that diabetes mellitus is not really a risk factor for pancreatic cancer, but rather insulin resistance as a product of obesity predisposes to the development of pancreatic adenocarcinoma as well as type 2 diabetes.

Obesity and insulin resistance in the context of pancreatic cancer

Several epidemiological studies have shown that obesity is a risk factor for pancreatic cancer and so diabetes should be considered in the context of obesity (Silverman et al., 1998; Ghadirian et al., 2003). Pancreatic cancer patients are mostly lean or cachectic at the time of diagnosis but 75% of these patients were obese or had a significant higher BMI before the onset of symptoms (Chari et al., 2001). Chari et al. found in their patient population, that the prevalence of diabetes associated with pancreatic cancer was higher in obese patients compared to patients with a normal BMI and, therefore, concluded that obesity may predispose these pancreatic cancer patients to diabetes (Chari et al., 2001). However, these data cannot answer the question whether the tumor or diabetes comes first. Therefore, whether obesity or the tumor itself is responsible for pancreatic cancer associated diabetes needs to be further investigated. Nonetheless, obesity is an important risk factor for type 2 diabetes as well as pancreatic cancer.
(Silverman et al., 1998, 1999). It is quite likely that by causing insulin resistance, obesity has a promotional effect on early pancreatic cancer and then later the tumor itself causes insulin resistance and a further promotional effect. A high fat diet has a promotional effect in the BOP-hamster model of pancreatic cancer (Kazakoff et al., 1996). A high fat diet induces peripheral insulin resistance, leading to a compensatory islet cell hyperactivity and proliferation which is an important promoting factor for pancreatic cancer induction (Pour and Kazakoff, 1996). Metformin, a drug used in the therapy of type 2 diabetes can prevent the induction of pancreatic cancer promoted by a high fat diet (Schneider et al., 2001). This drug normalizes insulin levels and the rate of islet cell turnover by improving insulin resistance through an increased glucose uptake, oxidation and glycogenesis in the skeletal muscle and by inhibiting hepatic gluconeogenesis (Schneider et al., 2001). The size of islets in the metformin-treated hamsters was significantly smaller than untreated controls, reflecting suppression of islet cell proliferation and, therefore, a decreased response to the carcinogen BOP (Schneider et al., 2001). Although, this study leads to the impression that diabetes is a risk factor for pancreatic cancer, several epidemiological studies show that diabetes is a consequence of pancreatic cancer but also show that obesity is a risk factor for the disease. Certainly, this could explain the increased incidence of pancreatic adenocarcinoma in Japan and in African Americans and even more efforts needed to be put into this metabolic relationship to pancreatic cancer.

β-cells (insulin and islet amyloid polypeptide producing cells)

Islet β-cells as possible stem cells, activators for carcinogens and the source of growth factor that promote pancreatic cancer

Experiments using the β-cell toxin streptozotocin should be mentioned there, because there are at least four possible explanations for the preventive effect of streptozotocin in the BOP hamster model (Bell et al., 1988, 1989). The destruction of β-cells: 1) abolishes a source of cells able to transdifferentiate and dedifferentiate; 2) prevents the metabolism of the BOP procarcinogen to its active carcinogenic substance; 3) withdraws insulin as an important growth factor; and 4) may destroy putative pancreatic stem cells. These thoughts are consistent with the observations that insulin has a significant impact on pancreatic cancer growth and that patients with type I diabetes mellitus appear to be afforded some protection against this disease. Finally, we again get the impression that islet β-cells play an important role in pancreatic cancer development and growth, because these cells appear to be in a proliferative or regenerative status susceptible to pancreatic cancer causing carcinogens, provide insulin which can promote tumor growth by direct and indirect mechanisms and they release amylin, a peptide which may play a role in peripheral insulin resistance and cachexia.

Insulin promotes pancreatic cancer

The impaired glucose metabolism in pancreatic cancer patients is characterized by hyperinsulinemia and peripheral insulin resistance, caused by a post-insulin receptor defect which reduces skeletal muscle glycogen synthesis and glycogen storage (Liu et al., 2000). Insulin secretion is not impaired, however, with different groups reporting relatively normal to increased insulin secretion (Fogar et al., 1993; Valerio et al., 1999; Liu et al., 2000). Furthermore, the study that revealed relatively normal insulin secretion demonstrated high basal plasma insulin levels (Liu et al., 2000). The resulting hyperinsulinemia appears to be important, because pancreatic cancer patients with diabetes have an even worse prognosis and a shorter survival time than patients without diabetes (Fisher et al., 1996). The anatomical arrangement of the islets scattered throughout the exocrine parenchyma and the estimated 20-fold higher concentrations of insulin in the pancreas than in the systemic circulation, suggest a key role of insulin in pancreatic cancer growth and development (Chandrasekar and Kore, 1991; Ding et al., 2000). Insulin stimulates pancreatic cancer cell proliferation via MAP kinase activation and glucose utilization by PI3 kinase activation and enhancement of expression of GLUT-1, a glucose transporter widely expressed in human tissues that regulates basal glucose transport (Ding et al., 2000). Therefore, insulin promotes pancreatic cancer growth directly as a growth factor and indirectly by increasing substrate uptake and metabolism. Pancreatic cancer cells express insulin as well as insulin-like growth factor 1 (IGF-1) receptors and, regardless of which receptor is more involved, high intrapancreatic insulin concentrations give pancreatic cancer cells a growth advantage (Fisher et al., 1996; Ding et al., 2000). In contrast, one group showed that exogenous insulin had an inhibitory effect on pancreatic cancer induction in the BOP-hamster model (Pour and Lawson, 1984; Pour et al., 1990). However, insulin administered systemically should block endogenous insulin synthesis and secretion. In turn, this should lead to a substantial decrease in intrapancreatic insulin concentrations. This could explain the inhibitory effect of exogenous insulin on pancreatic cancer, since high intrapancreatic insulin concentrations appear to be a very potent stimulus. Interestingly, pancreatectomy in pancreatic cancer patients leads to an improvement in glucose metabolism and peripheral insulin resistance, suggesting that the tumor itself is responsible for this diabetic situation (Permet et al., 1993a,b). This is even more surprising, considering that approximately 85% of the pancreas is removed during surgery, which leads to a marked reduction of total islets (Permet et al., 1993). Therefore, pancreatic cancer associated diabetes could perhaps be considered as an own entity, a type 3 diabetes
The role of amylin in pancreatic cancer

Several experimental studies support the hypothesis that a tumor-associated factor causes peripheral insulin resistance and leads to diabetes. Transplanted MiaPaCa2 cells induce impaired glucose tolerance in SCID mice, a metabolic effect that appeared to be caused by a peptide that was detected in pancreatic cancer cell-conditioned medium (Valerio et al., 1999). A factor that causes changes in \(\beta\)-cell secretion was also demonstrated in conditioned medium from PANC-1 and HPAF pancreatic cancer cells (Ding et al., 1998). This factor does not affect insulin secretion but selectively stimulates amylin (IAPP) secretion (Ding et al., 1998). The peptides described by both groups could be the same factor, however, it has not as yet been fully characterized. Hypersecretion of amylin stimulated by this factor leads to a significant reduction in intracellular amylin content in the cells and this is consistent with immunohistochemical findings, that islets adjacent to tumors show substantially less staining for amylin but have normal insulin content and mRNA for both peptides is readily detected by in situ hybridization (Ding et al., 1998). Amylin is a 37-amino-acid polypeptide co-localized and co-secreted with insulin from \(\beta\)-cells (Westermark et al., 1987). However, the secretion seems to be independently controlled under certain circumstances such as pancreatic cancer (Madsen et al., 1991). Amylin is a physiological inhibitor of insulin secretion and several studies have shown that amylin can have diabetogenic effects in vitro and in vivo, causing peripheral insulin resistance by inhibiting glucose uptake and glycogen synthesis in skeletal muscle as well as opposing insulin effects on the liver (Leighton and Cooper, 1988; Young et al., 1990; Frontoni et al., 1991; Koopmans et al., 1991). However, the physiological significance of this has been questioned in many studies (Wilding et al., 1994; Arnelo et al., 1997). Amylin is also the major constituent of the pancreatic amyloid observed in 90% of patients with type 2 diabetes (Westmark et al., 1987). Plasma amylin levels are significantly increased in pancreatic cancer patients and normalize after surgical tumor extirpation (Permert et al., 1994). Furthermore, cell culture experiments confirmed these data, demonstrating a dissociation of insulin and amylin secretion from islets in pancreatic cancer cell conditioned medium resulting in an increased amylin/insulin molar ratio caused by hypersecretion of amylin (Ding et al., 1998). This supports the hypothesis that pancreatic cancer cells produce an amylin-releasing factor. In addition, amylin also inhibits food intake at physiological concentrations and may contribute to the anorexia associated with the severe cachexia, a major problem in patients with pancreatic adenocarcinoma (Chance et al., 1991; Permert et al., 1994; Arnelo et al., 2000). It was suggested that measurement of plasma amylin levels in patients with recent onset of type 2 diabetes might be valuable for detecting pancreatic cancer at an early stage, when there may be a better chance for cure. However, two subsequent clinical studies have shown that amylin is sensitive enough to detect pancreatic cancer and is inferior to CA 19-9 (Chari et al., 2001; Brand et al., 2002). One problem is the lack of specificity of amylin, because elevated levels are also observed in acute and chronic pancreatitis or periampullary tumors (Chari et al., 2001). The amylin releasing factor could be a more sensitive marker, so efforts to identify this factor would be worthwhile.

Glucagon-producing \(\alpha\)-cells

Glucagon has no proliferative effect on pancreatic cancer cells, which is not really surprising because glucagon receptors are not expressed in cells from the exocrine pancreas or in pancreatic cancer cells (Ding et al., 2000). However, glucagon levels are elevated in pancreatic cancer, suggesting that \(\alpha\)-cells are stimulated in this disease (Permert et al., 1997). Like those of amylin, glucagon levels normalize after subtotal pancreatectomy, suggesting that the hypersecretion is a response to stimulation by the tumor (Permert et al., 1997). Pancreatic cancer cell-conditioned media has been shown to increase glucagon secretion from an islet cell line. While elevated glucagon levels seem to be unimportant for tumor growth, this catabolic hormone may contribute to the cachectic state.

Somatostatin producing \(\delta\)-cells

Effect of somatostatin on tumor cell growth

Pancreatic cancer cell growth may be regulated by somatostatin and elevated plasma levels of this hormone have been reported in patients with pancreatic cancer associated diabetes (Takeda and Escribano, 1991; Permert et al., 1997; Wang et al., 1998; Ding et al., 2000). In contrast to amylin and glucagon, plasma levels of somatostatin do not normalize after subtotal pancreatectomy (Permert et al., 1997). It is tempting to speculate that hypersecretion of somatostatin may be a defence mechanism and the sustained elevation of this islet hormone could indicate failure of cure of the cancer. It could be interesting to investigate plasma somatostatin concentrations in patients with small tumors (<1cm) before and after surgery. While some recent studies have demonstrated that somatostatin can induce significant inhibition of tumor cell growth and increase apoptosis, the literature is highly controversial on this point. For example, the growth response of MiaPaCa2 cells to somatostatin and its analogues have been variously reported as inhibition, stimulation and lack of any effect because of absence of receptors (Gillespie et al., 1992; Fisher et al., 1996; Douziech et al., 1999). Concentration-dependent growth inhibition of PANC-1 cells was seen after somatostatin treatment together with
stimulation of activity of membrane phosphotyrosine phosphatase SHP-1 (Douziech et al., 1999). In contrast, MiaPaCa2 cell growth was stimulated, regardless of the expression level of somatostatin receptors (Douziech et al., 1999). SHP-1 was absent in MiaPaCa2 cells, suggesting that the growth inhibitory effect in PANC-1 cells is mediated through SHP-1 activation (Douziech et al., 1999). SHP-1 was absent in MiaPaCa2 cells, and therefore, found also a failure of response to somatostatin (Gillespie et al., 1992). These different results could be caused by different technical approaches or just differences due to passage of this cell line. The expression of somatostatin receptors in pancreatic cancer tissue is also controversial, with one group reporting up-regulation compared to normal pancreas and another reporting loss of receptors (Tang et al., 1998; Rochaix et al., 1999). In one study, in which somatostatin receptors were detected in pancreatic cancer cells, chemotherapeutics, such as gemcitabine caused down-regulation of the high affinity receptors (Fueger et al., 2001). A novel therapeutic approach could be the reintroduction of somatostatin receptors via gene transfer, however, it is difficult to see how this could be accomplished effectively in cancers (Rochaix et al., 1999; Vernejoul et al., 2002).

**Clinical studies**

A phase III clinical trial showed that the somatostatin analog, octreotide was inferior to 5-fluorouracil in terms of delay of tumor progression and survival and as a consequence the octreotide arm of the study was abandoned (Burch et al., 2000). Clearly, somatostatin analogues cannot generally be recommended for treating pancreatic cancer. Screening the tumor for somatostatin receptors as well as SHP-1 and testing the response of each individual tumor to somatostatin e.g. in a xenograft model would have to be seriously considered before embarking on such an approach.

**Pancreatic polypeptide (PP) producing cells**

PP cells are very interesting because of their relative localization in the head of the pancreas where most pancreatic adenocarcinomas arise (Pour et al., 2002). Cytochrome P450 isoenzymes (CYP) are expressed primarily or exclusively in islet cells (Pour et al., 2002). These enzymes are involved in the metabolism of carcinogens such as nitrosamines which are present in cigarette smoke, a risk factor for pancreatic cancer (Pour et al., 2002). Four of the CYP isoenzymes are exclusively expressed in PP cells, which are frequently scattered within the ductal epithelium (Pour et al., 2002). The islet cell hormone, PP secreted by these cells inhibits pancreatic adenocarcinoma growth (Fisher et al., 1998). Certainly, PP-cells warrant further attention and future investigation as the data to date are very limited.

**Inflammatory pathway**

This final section highlights the involvement of the inflammatory arachidonic acid pathways in islet cell physiology and recent findings demonstrating overexpression of these enzymes in pancreatic adenocarcinomas. Up-regulation of cyclooxygenase-2 (COX-2) expression has been described in islets, pancreatic cancer cells and pancreatic intraepithelial neoplastic lesions (PanINs) (Koshiba et al., 1999; Molina et al., 1999; Okami et al., 1999; Tucker et al., 1999; Kokawa et al., 2001; Maitra et al., 2002). However, the COX inhibitors, aspirin and indomethacin do not influence insulin secretion, so the role of COX-2 expression in islets is uncertain (Yamamoto et al., 1983; Pek and Nathan, 1994). In contrast, lipoxygenase inhibitors like NDGA inhibit insulin and glucagon secretion (Yamamoto et al., 1983; Pek and Nathan, 1994). A negative feedback mechanism has been suggested, where formed eicosanoids inhibit glucose-induced arachidonic acid and insulin release (Nathan and Pek, 1990). Whether lipoxygenase metabolites such as 5-, 12- and 15-HETE or leukotriene B4 (LTB4) inhibit or stimulate insulin secretion is controversial, perhaps reflecting the use of different study models (Yamamoto et al., 1983; Metz et al., 1984; Pek and Walsh, 1984, 1985; Walsh and Pek, 1984a,b; Nathan and Pek, 1990; Pek and Nathan, 1994). Using immunocytochemistry, we recently found marked overexpression of 5-lipoxygenase (5-LOX) as well as the receptor for its downstream ligand, leukotriene B4 (LTB4) in human pancreatic cancer cells as well as islets surrounding the tumors, while few cells in islets from normal pancreatic tissues stained positive (Hennig et al., 2002) (Fig. 1). Interestingly, a clinical study revealed that patients with either type 1 or type 2 diabetes mellitus have higher LTB4 levels than healthy controls and this was also positively correlated with glycated haemoglobin levels; (Parlapiano et al., 1999). Trogilazone inhibits LTB4 production by direct inhibition of 5-LOX activity (Yamashita et al., 2000). This drug is a well-known peroxisome proliferator activated receptor γ (PPARγ) agonist, improving insulin resistance and glucose homeostasis in type 2 diabetics and also inhibits pancreatic cancer cell proliferation (Motomura et al., 2000). It should be kept in mind, that insulin is an important growth factor and LTB4 a possible regulatory element. Therefore, the 5-LOX pathway may play an important role in pancreatic adenocarcinoma and its associated diabetes mellitus. However, further studies
will be necessary to identify the underlying mechanisms. Nuclear localization of 5-LOX has been described. Finding this enzyme in the region of active gene transcription (euchromatin), raises the intriguing possibility that 5-LOX might regulate transcriptional events in the nucleus (Peters-Golden and Brock, 2001). Since the nuclear envelope is the place of leukotriene biosynthesis, it is reasonable to speculate that these metabolites might act as transcriptional regulators as well as through G-protein coupled receptors (Funk, 2001). The leukocyte type of 12-LOX is expressed in islet α- and β-cells and this pathway participates in cytokine-mediated β-cell dysfunction and cytotoxicity (Shannon et al., 1992; Bleich et al., 1995, 1998; Kawajiri et al., 2000). There is sufficient evidence for an interaction between lipoxygenase products and PPARγ, which is involved in cell differentiation and glucose homeostasis (Shi et al., 2002). Activation of PPARγ with ligands such as troglitazone induces differentiation in colon cancer cells or liposarcoma cells, reversing the malignant phenotype (Hsi et al., 2001). PPARγ ligands consistently induce marked growth inhibition and apoptosis in pancreatic cancer cells (Motomura et al., 2000; Eibl et al., 2001). Furthermore, PPARγ has been reported to be overexpressed in human pancreatic adenocarcinomas. While we could not confirm these results, we saw up-regulation of PPARγ in the islets adjacent to tumors in our own immunohistochemical study (unpublished data) (Motomura et al., 2000). The complex interrelationship between lipoxygenase metabolism, PPARs, islets, pancreatic cancer and the associated diabetes is far from clear, but considering the influence of this inflammatory pathway on glucose metabolism as well as pancreatic cancer growth and development, it is likely to be important. Future studies in this field are anticipated with interest.

Conclusion

We are still not able to say whether or not islet cells may be the origin of pancreatic adenocarcinoma. However, some questions can be answered. The diabetes associated with pancreatic cancer appears to be a consequence rather than a risk factor. Islet cell hormones play very different roles in pancreatic cancer growth. Insulin is growth promoting, while somatostatin and pancreatic polypeptide generally appear to be growth inhibiting. The current data suggest that at a certain stage, all pancreatic cell types are capable of trans-differentiation or dedifferentiation and can ultimately develop into pancreatic adenocarcinomas. However, the presence of a multipotent pancreatic stem cell remains as the possible cell of origin for pancreatic cancer, but pancreatic stem cell research is still in its infancy. Certainly, the topic of “islets and pancreatic cancer” remains an exciting one. The remaining questions will hopefully be answered in the near future. Considering the abysmal prognosis of this disease, the need for significant progress for these patients is even more acute.

References

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