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What is the origin of pancreatic adenocarcinoma?

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Abstract

The concept of pancreatic cancer origin is controversial. Acinar, ductal or islet cells have been hypothesized as the cell of origin. The pros and cons of each of these hypotheses are discussed. Based on the world literature and recent observations, pancreatic cells seem to have potential for phenotypical transdifferentiation, i.e ductal-islet, ductal-acinar, acinar-ductal, acinar-islet, islet-acinar and islet-ductal cells. Although the possibility is discussed that cancer may arise from either islet, ductal or acinar cells, the circumstances favoring the islet cells as the tumor cell origin include their greater transdifferentiation potency into both pancreatic and extrapancreatic cells, the presence of a variety of carcinogen-metabolizing enzymes, some of which are present exclusively in islet cells and the growth factor-rich environment of islets.

Introduction

The complex cellular structure of the pancreas composed of various exocrine and endocrine cells hampers a clear understanding of the origin of pancreatic ductal-type adenocarcinoma. During the embryonic development of the pancreas all exocrine and endocrine cells are derived from the common precursor cells, the stem cells. It is believed that these stem cells are retained in the adult pancreas and are the foundation for cell renewal and tumors; however, this claim has remained illusive. Recent studies pointing to the enormous plasticity of each type of pancreatic cell in changing their phenotype from one type to another (i.e., transdifferentiation) makes the identification of tumor cell origin more complex. The islet-ductal, acinar-ductal, ductal-islet cell transdifferentiation in purified cell populations [1–6] and *in vivo* [7–10] has been observed. Consequently, all pancreatic cells could be considered as a potential facultative stem cell.

There is accumulating evidence that most pancreatic tumors originate from within islets by islet cell transdifferentiation and that pancreatic islet cells play a significant role in the neoplastic process. There are also observations that favor that the ductal cells are the source of cancer cells. To better understand the neoplastic process in the pancreas, some anatomic-physiological aspects of the tissue should be considered.

Review

Interaction between the exocrine and endocrine cells

It is estimated that the exocrine cells contribute to over 95% (acinar cells 85%, ductal cells 10%) of the volume of the pancreas, whereas the endocrine cells are believed to occupy only 1–2% of the pancreatic volume in adults. Clearly, this estimation is misleading as it does not consider the number of individual cell types. When the size of the cells is disregarded, the figures would be significantly different. The circular three-dimensional shape of the islets composed of relatively small, closely packed cells

causes underestimation of their numbers in histological sections. Considering the diffuse distribution of the islets, accounting for about one islet per 1.1 mm^2 of the tissue [11], and the presence of a large number of a single or small group of islet cells scattered throughout the pancreas and within the ductal epithelium it appears that there are as many islet cells as acinar cells. The same applies to ductal cells, as the calculation does not consider the often-invisible centroacinar cells that are the components of ducts. According to our observation, within an acinus there are as many centroacinar cells as acinar cells. In our view, centroacinar cells are as multipotential as islet cells and can give rise to islet cells, acinar cells and tumor cells [12].

The tight functional and physical interaction between the endocrine and exocrine cells have been well established but not sufficiently investigated. The necessary cooperation between the endocrine and exocrine cells well explains the plasticity of the pancreas to adjust to the internal demands and external stimuli. Hence, each type of pancreatic cells has the ability to provide a function that is dictated by the physiological demand in an organized fashion. Islet cells seem to be the frontrunner of the organization system.

Islet cells, the gatekeeper of the pancreas

The diffuse distribution of islet cells throughout the pancreas either in the form of aggregate (islet) and single or small group of islets indicate their important function. They seem to control the flow of pancreatic exocrine and exocrine function as reflected by their unique ability for transformation to every pancreatic and some extrapancreatic cell type [1–8]. The controlling effect of islet cells on the exocrine tissue is also highlighted by the presence of endocrine cells within the normal, hyperplastic and malignant ductal epithelium, in both humans and animals [13–17]. Another extremely important function of the islet cells, not similarly shared by other pancreatic cells, is the defensive strategy provided by drug-metabolizing enzymes. Among the two major groups of drug-metabolizing enzymes in mammals, cytochrome P450 isozymes (CYP) and glutathione S-transferases (GST) [18–22], which are known to be involved in the metabolism of a variety of toxins and carcinogens, were found to be expressed primarily or exclusively in the islet cells of every species that we have investigated, including humans, monkeys, pigs, dogs, guinea pigs, rabbits, rats, hamsters and mouse [19]. This implies a greater involvement of islet cells in the metabolism of xenobiotics within the pancreas. Strikingly, in humans, four of the CYP isozymes were expressed exclusively in the PP cells, and two isozymes were expressed in a higher concentration in the PP cells than in the other islet cells [22]. Considering the anatomical blood supply of the pancreas, the primary presence of the xenobiotic enzymes in the islets is self explanatory, as in humans and other mammalian species, part of the arterial blood passes through the islets before nourishing the exocrine pancreas [23–27].

Evidence for the derivation of tumors from islet cells

Experimental data

The following observations support the unequivocal role of β-cells in transdifferentiation and, thus the carcinogenesis process: 1) Experimentally, the first histological alterations are the appearance of intrainsular ductular structures showing different stages of progression from normal to malignant pattern. These lesions are initially confined within the islet boundary and are sharply demarcated from the surrounding tissue (Fig. 1a,1b,1c). 2) The pretreatment of hamsters with streptozotocin, which selectively destroys β-cells, inhibits the pancreatic tumorigenesis [28]; 3) Genetically diabetic hamsters with depleted β-cells are resistant to the pancreatic carcinogenic effect of N-nitrosobis(2-oxopropyl)amine (BOP), whereas the pancreas of a non-diabetic strain with intact β-cells is not [29]; 4) Stimulation of β-cell neogenesis (nesidioblastosis) enhances pancreatic carcinogenicity of BOP [30]; 5) Transplantation of homologous islets into the submandibular gland (a non-target tissue of BOP) of hamsters and the subsequent BOP treatment of the recipient hamsters results in the development of ductal-type adenocarcinomas in the areas of transplanted islets [31,32]. Histological findings point to the development of malignant glands in the center of islets, the exclusive position of β-cells in hamsters; 6) Malignant transformation of freshly isolated hamster pancreatic islets by BOP *in vitro* [33]. Although the treatment of cultured hamster pancreatic ductal cells also led to the formation of ductal adenocarcinomas [34] these tumors, contrary to those derived from islet cells [33], did not show the mutation of the c-K-*ras* oncogene [35], the most common genetic abnormality in human pancreatic adenocarcinomas [36,37]. Additionally, only the cultured islets cells treated with BOP showed an inactivation of the p16 (INK4a) gene (homozygous deletion) [38], which is found in 90–100% of human pancreatic adenocarcinomas [39]; 7) BOP-treatment of freshly isolated islets containing β-cells, but not those which were depleted of β-cells, resulted in malignant transformation (unpublished); 8) Isolated human islets but not human ductal cells treated with BOP could be grown in serum-free, growth factor-free medium and showed a mutation of c-Ki-*ras* (unpublished). In neither of the *in vivo* and *in vitro* studies could we identify cells which could be regarded as stem cells although more than 50 human and hamster islets were subjected to electron microscopical examination [1–3]. Considering the rarity of stem cells among the mature cells, however, (about 1 in 10,000 in bone marrow [40]), we could have missed the identification of these cells.

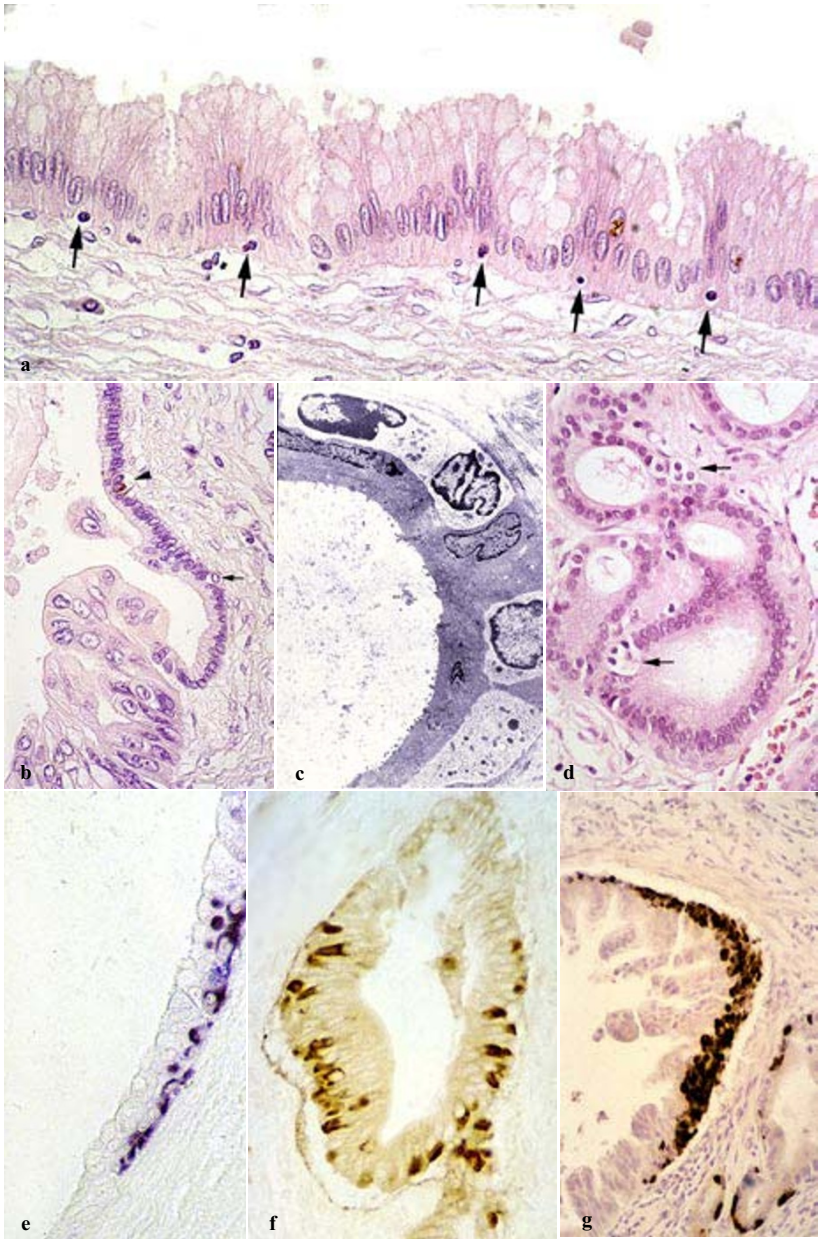

Figure 1
Formation of malignant ductular structures within hamster's islets. **a**) The lesions is confined to the islets and is sharply demarcated from the surrounding tissue by a layer of fibrosis and inflammatory cells invaded by cancer. H&E × 30. **b**) Similar lesions showing irregularly shaped malignant glands replacing the islet. H&E × 30. **c**) In this lesions most part of islet is replaced by malignant gland and sclerosis. Note the sharp delineation of the lesions. Local cancer invasion is seen in the lower portion. H&E × 30. **d**) An atrophic islet in a patients with chronic pancreatitis. A ductular structure (*arrow*) is composed of light eosinophilc and clear cells intermingled with islet cells. H&E × 120. **e**) Another atrophic human islet far remote of a cancer. A dysplastic ductular structure (*arrow*) in the islet without any signs of depression in the surrounding islet cells. H&E × 120. **f**) An islet in the vicinity of a well-differentiated adenocarcinoma containing large atypical cells (*arrows*) intermingled with intact islet cells. H&E × 72. **g**) A human islet cell in a patient with pancreatic adenocarcinoma loaded with material immunoreactive with anti-MUC-1 antibody (fine granules). Although in these islets the immunoreactivity with anti-insulin has diminished, some granules show reactivity with anti-insulin (*arrows*). × 104,000, **h**) Normal human islet. One endocrine cell shows a typical cilia identical to those present in ductal-ductular cells. × 7,200. **i**) Fine structure of a well-differentiated adenocarcinoma, some cells of which show a few regular or rudimentary granules of endocrine type (*arrow*). × 7,200.

Clinical data

Intrainsular ductular formation and their malignant counterparts have also been observed in the human pancreas [17,41–43]. Around 70% of pancreatic cancer patients, who clinically have an altered glucose tolerance, islet cells lose their reactivity to anti-insulin and express ductal cell markers, including carbohydrate antigen CA-19-9, DU-PAN-2 and Tag-72, and develop intrainsular ductular structures (Fig. 1d,1e) that express the same antigens [42,43]. Moreover, the occurrence of the same antigen in islet cells and in intrainsular ductular cells within the same islet [42–44] indicates a causal relationship between the altered islet cells and intrainsular ductular cells. In some islets, single or a group of large atypical cells, suggesting malignant cells (Fig. 1f) can be seen as was also found in our previous studies [17]. Our electron microscopic examinations have shown that the normal-appearing islet cells within the altered islets contain Muc1 (Fig. 1g), the backbone of these carbohydrate antigens. Moreover single cilia, (Fig. 1h), which is a specialized structure of ductal/ductular cells [45], can be found in islet cells. This structure along with other changes observed during transdifferentiation, indicate that islet cells have the inherent ability to make phenotypical changes and that the genes involved in the differentiation of different pancreatic cells are closely related. This process is also highlighted by the presence of endocrine-like granules in some cancer cells (Fig. 1i.), which can express neuroendocrine cell makers, including NSE, neuronal adhesion molecule [46] and β-tubulin (Fig. 2a). The presence of islet cells within the malignant epithelium, sometimes exceeding the number of tumor cells [16] is a clear indication that tumor cells are derived from transdifferentiated islet cells, which seem to present facultative precursor cells.

Pathophysiological consideration

Islet cells are the major pancreatic cells that are equipped with a variety of drug-metabolizing enzymes. Based on the aforementioned insulo-portal blood vessels, xenobiotic first reaches the islets, where it is metabolized to either a non-toxic or a proximate carcinogen. The latter substances generally react in millisecond with the target DNA to form adducts required for the neoplastic process, which triggers the transformation of the affected islet cells to undifferentiated, intrainsular duct-like cells. One can argue that because of the lack of or low concentration of the enzymes, the ductal and acinar cells are exposed to the carcinogen in a much lesser degree and the damaged DNA are repaired quickly. As will be discussed below, the presence of only a few cells containing drug-metabolizing enzymes within the ductal epithelium, from which we believe that ductal cell alteration occurs could explain the reason for the much later appearance of ductal alteration. In the islet cells, however, the extent of DNA damage may exceed the repair capability and the presence of a massive amount of growth factors within the islets could trigger the promotion of the neoplastic process. This may explain the reason for the initial development of the lesions within the islets. In this context, the expression of CYP2E1 by PP cells, which are frequently present in a large number within the ductal epithelium [22], is noteworthy, because this enzyme is involved in the metabolism of carcinogenic nitrosamines, some of which are present in tobacco smoke [47,48], and suggested to present pancreatic carcinogens. Whether or not this peculiar distribution of carcinogen-metabolizing enzymes in PP cells is the reason for the frequent development of pancreatic cancer in the head of the pancreas [20], is a hypothetical question.

Evidence for the derivation of tumors from ductal cells

The ductal cell structure of the majority of pancreatic tumors and the ability of ductal cells to proliferate are the overwhelming reasons to suggest that ductal cells are the origin of pancreatic adenocarcinomas. The expression of ductal markers, in cancer cells goes along with this possibility. Indeed, some types of cancer, the intraductal tumors, seem to arise from ductal cells and remain within the ductal boundary for a while before invasion. The apparent ability of ductal cells to differentiate into other cell types, including squamous, mucinous and pyloric cells further supports the ability of ductal cells to undergo malignant transformation.

One of the landmark studies suggesting histological evidence for ductal cell origin of pancreatic cancer came from a study of Cubilla and Fitzgerald [49], who studied 227 patients and observed that the incidence of ductal hyperplasias in patients with pancreatic cancer was much greater than in those without cancer. The presence of similar spatial distribution of lesions in tumors was consistent with the hypothesis that such lesions might represent incipient pancreatic adenocarcinoma. These findings were later confirmed by other investigators [50,51]. The only problem with these studies was that they were done at one particular stage and hence these findings were arguable in the sense that whether these pancreatic duct lesions represented the intraductal extension of an invasive cancer or they themselves are a true precursor to invasive cancer. In these morphological studies proposing lesions to be the precursor of infiltrating cancer, there was no direct evidence apart from the morphological unusual growth that these lesions actually progressed to invasive ductal cancer.

The suggestion of ductal cells as a precursor of cancer cells is derived mostly from pathomorphological studies. In one study involving two patients who had atypical papillary duct lesions, it was observed that they developed invasive pancreatic adenocarcinoma a couple of years later [52]. In another study, [53] three patients developed infiltrating ductal pancreatic adenocarcinoma one and half to

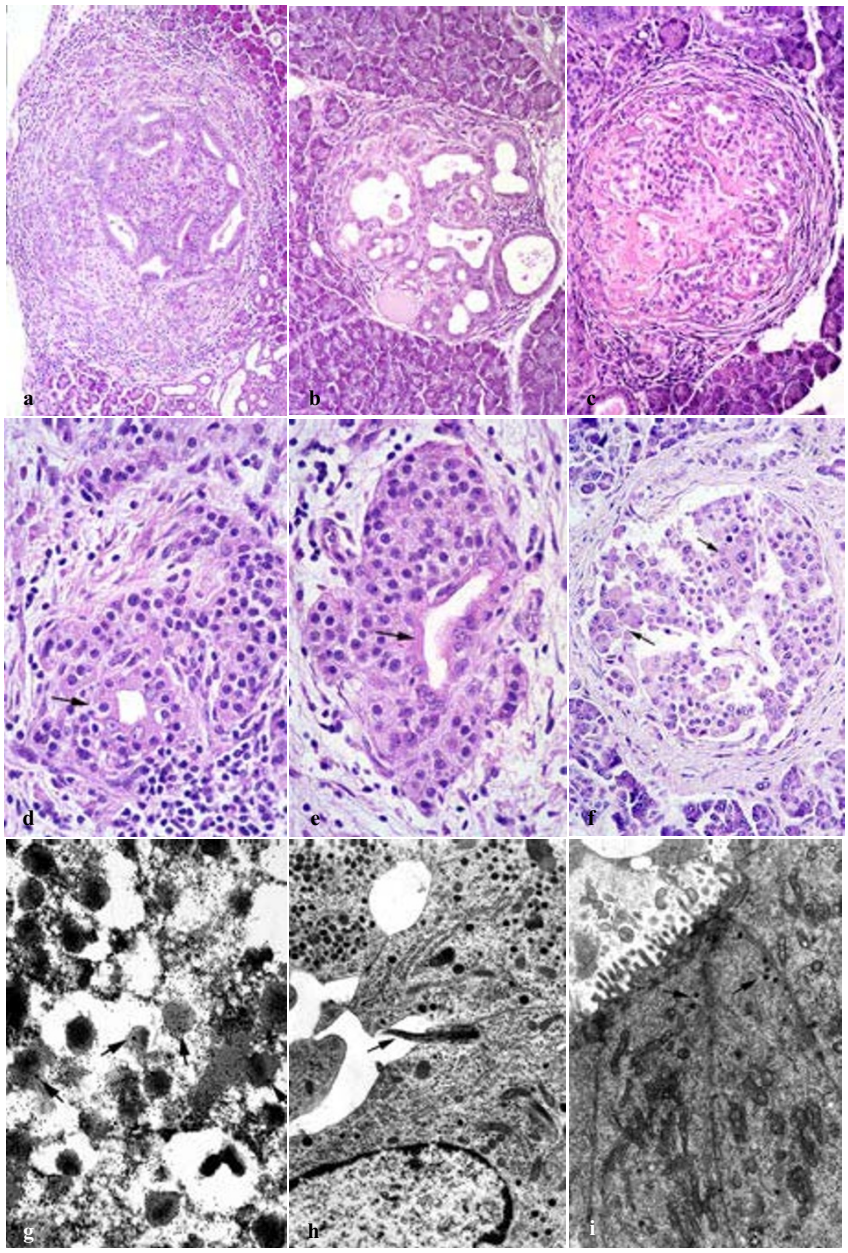

Figure 2
a) Numerous Helle Zelle (light cells) in hyperplastic ductal epithelium corresponding to PanIN2 (*arrows*). The cells are small with light cytoplasm and hyperchromatic round or oval nuclei. Some cells seem to have two nuclei (*the second and third arrows from left*). H&E × 120. **b**) A lesions comparable to PanIN1 to PanIN3 showing clear cells with a small round nuclei surrounded by a halo (*arrow*). One of the clear cells (*arrowhead*) presents two nuclei (post mitotic division?). H&E × 120. **c**) Electron microscopic findings of a similar lesion. Note several clear cells with one or two nuclei. The cells are poor on cell organelles and lay between the basal membran and tumor cells. × 7,200. **d**) Hyperplastic ductules in an elderly man. Several clear cells are seen within the epithelium. A small group of these cells have interrupted the continuity of the epithelium (*bottom arrow*) or extended into the stroma (*top arrow*). H&E × 120. **f**) Many of the clear cells that can form a circular layer all along the duct, are immunoreactive with antibodies against islet hormones, especially to anti-glucagon and -chromogranin A and against drug-metabolizing CYP450 enzymes. ABC method, Anti-glucagon, × 120. *f*) A large number of endocrine cells reactive with anti-chromogranin A antibody in a malignant gland. ABC method, × 120. **g**) A large malignant gland exhibiting papillary infolding of the epithelium. A remarkably large number of overlapping endocrine cells are present in the basal layer of the malignant epithelium. ABC, combination of anti-insulin and anti-glucagon, 120.

ten years later after the histological confirmation of atypical papillary ductal lesions in their pancreata. These findings involving morphological observations suggest that pancreatic ductal hyperplasia is a precursor to pancreatic cancer. Unlike in breast, skin, colon cervix or prostrate, which are accessible for non-invasive biopsies, the recognition of an early form of cancer is difficult. The location of the pancreas, deep in the abdomen and the silent course of pancreatic cancer makes this approach difficult. Due to this reason, the described progression of pancreatic ductal lesions to invasive pancreatic cancer is illusive at best.

On the basis of morphological, clinical, and genetic observations, a progression model for pancreatic ductal adenocarcinoma has been proposed. According to the new classification of ductal lesions as pancreatic intraductal neoplasia (PanIN), progression of hyperplasia to malignancy through a series of architectural and cytological changes have been described [49]. Based on the degree of cytological and architectural atypia the lesions have been subclassified into PanIN-1A, PanIN-1B, PanIN-2, and PanIN-3 [54,55]. In a global sense, PanIN-1A stage epithelial lesions present tall columnar mucin-containing cells showing slight or no atypia; PanIN-1B designates epithelial lesions that have a papillary, micropapillary, or basally pseudostratified architecture but are otherwise identical to PanIN-1A. PanIN-2 lesions show moderate atypia including loss of polarity, nuclear crowding, nuclear enlargement, pseudo-stratification, and nuclear hyperchromatism. PanIN-3 epithelial lesions are usually papillary or micropapillary with severe atypia.

It is, however, unclear whether these lesions in pancreatic cancer patients were merely the outgrowth of an invasive cancer, as shown experimentally [56] and in humans [57], rather than the precursor themselves. If, as the morphological observations suggest, the duct lesions are *de novo* and indeed the precursors to invasive pancreatic cancer, then the lesions should be clonal and harbor some but not necessarily all of the mutations and genetic alterations found in associated infiltrating carcinomas. Moreover, the incidence of these genetic alterations should increase with severity of cytological and architectural atypia in duct lesions. Studies, however, show evidence that such lesions are polyclonal and show heterogeneity in genetic alterations [58]. The presence of a number of genetic alterations found in pancreatic cancer and in these lesions does not prove a causal relationship, because, as described above, there is no evidence that these ductal lesions are the extention of already existing tumors, which are known to be transferred by pancreatic juice and seed in a location remote from the primary cancer [56,57]. The genes which have been found to be altered include *K-ras*, *p16*, *HER2/Neu*, *MUC4*, *DPC4* and *BRCA2*. Furthermore, the incidence of these genetic changes increases as the degree of cytological and architectural atypia in the duct lesions increases.

Mutations in oncogene *K-ras* and overexpression of HER2 are supposed to be the early events in the progression of ductal carcinoma as they have also been reported in ductal lesions with minimal atypia. *K-ras* has been found to be inactivated in about 95% of pancreatic cancer patients [59]. *HER2/Neu* is reportedly not overexpressed in normal ductal epithelium of the pancreas but is said to be overexpressed in almost all duct lesions having significant cytological and architectural atypia [60]. Our own investigation, however, demonstrated that HER2/Neu is overexpressed in pancreatic ductal cells in chronic pancreatitis and its expression in cancer cells was strikingly heterogenous and weak [61]. Moreover, the antibodies used had a greater reactivity with islet and neuroendocrine cells than with cancer cells [58]. Inactivation of tumor suppressor gene *CDKN2A* (*p16*) cyclin dependent kinase inhibitor occurs later and the loss of expression of the *p16* gene could be correlated with the severity of cytological and architectural atypia [62]. Inactivation of *CDNK2A*, by mutation, deletion or promoter hypermethylation also is a common event in pancreatic cancer and occurs in about 80–95% of invasive pancreatic adenocarcinomas [63]. A number of studies have identified common mutational profiles in simultaneous lesions indicating the relationship between PanINs and the pathogenesis of pancreatic adenocarcinomas. Although common mutation patterns in PanIN and associated adenocarcinoma have been observed for *K-ras* and *p16* [64], as stated earlier, the derivation of ductal cell abnormality from original ductal cells or cancer cells is not clear. It was suggested that alterations of the *p16* gene affect a subset of pancreatic intraductal lesions that contain mutations of the *K-ras* gene and that these mutations might identify high-risk precursors of the invasive malignancy. Loss of other tumor suppressor genes like p53, *BRCA2* and *DPC4* (*Smad4*) occurs later in neoplasia development. The inactivation of K-*ras*, however, is not a marker for malignancy because the mutation can also be found in non-malignant ductal epithelium [65].

The *p53* mutations seem to occur late in PanINs, which have acquired significant features of dysplasia, reflecting the function of *p53* in preventing malignant progression. The loss of *p53* would result in aberrant genetic instability which is very much a characteristic of invasive pancreatic cancer. Mutations in *BRCA2* have been primarily associated with familial breast and ovarian cancers but it has also been observed in approximately 17% of pancreatic cancer patients having a family history [66]. Normally *BRCA2* is responsible for homologous recombination based DNA repair and thereby maintaining the genomic stability.

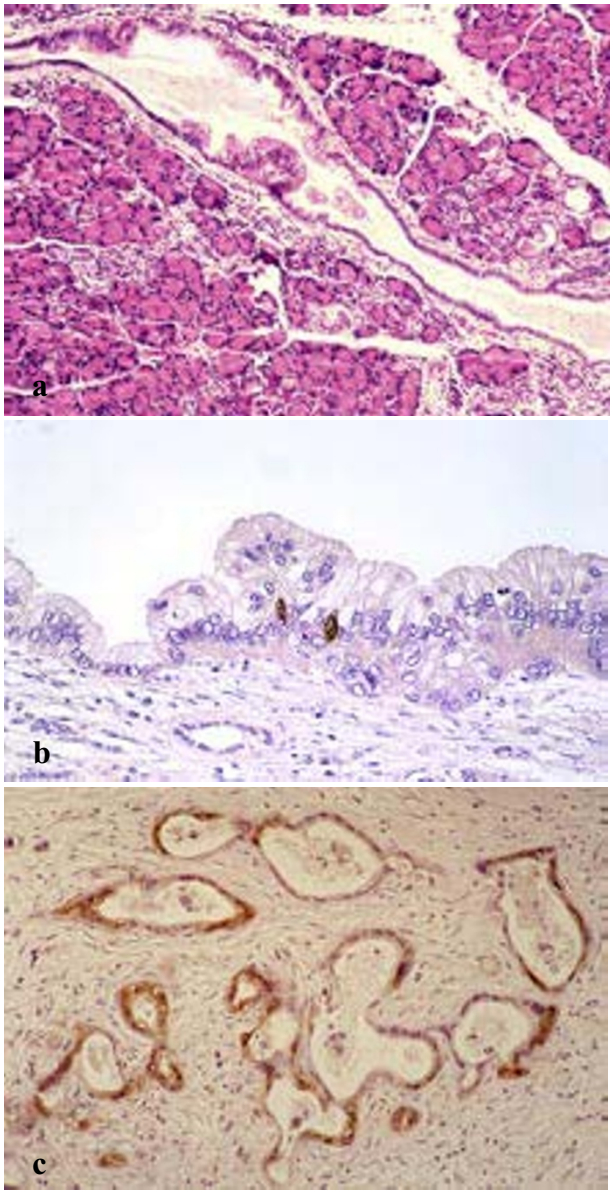

Figure 3
a) focal papillary proliferation of the epithelium of the main pancreatic duct of a hamster. Note the lack of continuity between the hyperplastic foci. In such lesions, generally a few or many endocrine cells are present. H&E × 32. **b**) Part of a malignant epithelium in a male with pancreatic adenocarcinoma. Note the presence of insulin-positive cells (*brown in color*) at the base of papillary configuration of the epithelium. Mulilabeling with several antibodies against the four islet hormones reveals a larger number of immunoreactive cells. ABC method, × 120.

BRCA2 gets mutated later in the progression of dysplasia probably because DNA damaging response pathways might have to be inactivated first (*i.e. p53* mutation so that damages suffered could be tolerated). The *MUC4* mucin has also been shown to be one of the characteristic markers for pancreatic cancer [67]. A recent study on 71 PanIN lesions of different grades and 28 invasive carcinomas shows a steady increase in MUC4 expression along with the increase in severity of pancreatic duct lesion [67,68]. Normal pancreatic ducts do not express *MUC4*. Increasing expression of *MUC4* with an increasing grade of PanIN supports the assumption of PanIN being a precursor for infiltrating pancreatic ductal adenocarcinoma. Our unpublished data, however, shows that MUC4 is expressed in ductal cells of chronic pancreatitis. Whether this finding supports the unspecificity of MUC4 for cancer or chronic pancreatitis-cancer seuqence, remains to be seen.

All this information about the progression of genetic abnormality in pancreatic ductal lesions are illusive until a proof is provided that those lesions are primary alterations. Their association with pancreatic cancer casts doubt on their primary nature. If they were primary alterations and show progression, the incidence of pancreatic cancer multiplicity would be high. The opposite, however, is true.

The argument that the expression of ductal markers in ductal adenocarcinoma notwithstanding indicates the derivation of cancer cells from ductal cells is unsupported. We have shown that during the transdifferentiation process of islet cells, various markers, including markers for stem cells (nestin), ductal cells (cytokeratin 7, 19, pancytokeratin, CA 19-9, TAG-72, DU-PAN-2), mesenchymal cells (vimentin, fibronectin) and others (α-1 antiprotease) are expressed [1–3].

The genetic abnormalities also are not convincing evidence as these alterations can occur in cancer cells derived from transdifferentiated acinar or islet cells. The vital question that has remained is the cell of origin of ductal lesions. Are these lesions the result of proliferation and progression of fully-differentiated ductal cells or by metaplastic conversion of other pancreatic cell types through emigration and transdifferentiaion [69]?

There are circumstances that argue against the involvement of mature ductal cells in malignancy. It is totally unclear, whether it is ductal cells *per se* or other cells within the ductal epithelium with the ability for transdifferentiation and malignancy. It has been suggested that some cells with stem cell characters reside within ductal epithelium [70,71]. In histological sections stained with hematoxyllin and eosin we have identified cells, smaller than ductal

cells with "clear" cytoplasm and round oval hyperchromatic nuclei, which seems to correspond with the "Helle Zelle" (light cells) described by Feyrter [70] and Bonner-Weir [71] in the normal epithelium. A large number if hyperplastic, dysplastic and malignant epithelium, corresponding to PanIN 1–3 (Fig. 2a,2b). Some of these cells are double nucleated and perhaps represent cell division (Fig. 2c). Single clear cells can be observed within the epithelium at the level of other ductal cells or as a single cell or in a small group outside of the ductal basal membrane and in connection with the basal clear cells (Fig. 2d). These observations suggest that the clear cells have the potential to form either ductal cells (to produce hyperplastic epithelium) or endocrine cells. Many, but not all of these clear cells express endocrine cell markers and the same drug-metabolizing enzymes as islet cells. (Fig 2e). In some cases, the number of the endocrine cells nearly exceeds the number of tumor cells (Figs. 2f and 2g).

Considering the event that ductal cell hyperplasia or dysplasia initially occurs locally and expands gradually (Fig. 3a), and because within the altered epithelium various number of endocrine cells can be identified (Fig. 3b), it is reasonable to assume that ductal alterations arise from clear cells, possibly derived from transdifferentiated endocrine cells. Equally, it is possible that the clear cells are the precursor of both ductal and endocrine cells. The original source of these clear cells is also unclear. They are few in the normal duct, but plenty in hyperplastic ducts. In the latter case, their random distribution within the epithelium makes their origin from a few preexisting cells unlikely. Their derivation from mature ductal cells by transdifferentiation is equally hard to accept as mature ductal cells have a tendency to divide directly without going through an intermediate stage. Whether or not these clear cells originate from extrapancreatic cells, as described in other tissues [69] is a hypothetical possibility. Nevertheless, the ability of these cells for the proliferation and metabolism of various xenobiotics make them the primary origin of tumors.

Hence, the data on the origin of pancreatic cancer cells leaves much room for speculation. There is as yet, no definite proof for islet cells or ductal cells as cancer precursor cells, although the possibility of the involvement of islet cells is overwhelming. Future molecular biological studies during cell differentiation in the embryonic and adult tissue could help to understand this presently controversial issue.

Evidence for the derivation of tumors from acinar cells

Based on the suggested transformation of acinar cells to duct-like cells, a school of thought considers acinar cells as the tumor progenitor cells. Evidence, however, is missing. Although, in the rat model, as well as in humans, transdifferentiation of acinar cells to duct-like structures (pseudoductules) have been reported [70]. The question whether peudoductules develop from centroacinar cells or from acinar cells, however, has not been settled. Our studies have shown that during carcinogenesis centroacinar cells enlarge, form long cytoplasmic extensions that cover the entire surface of acinar cells, separate acinar cells from each other and from the basal membrane, hence, by necrotizing the acinar cells that replaces them [10]. We have made the same observation in human chronic pancreatitis tissue (unpublished). During this degenerative, reparative process, some centroacinar cells seem to form islet cells as endocrine cells are identified within the affected acini [12]. The suggested transdifferentiation of acinar cells to ductular cells *in vitro* [72,73] does in no way exclude the role of centroacinar cells in pseudoductular formation, as generally, centroacinar cells are tightly attached to acinar cells. Presently, however, a transformation of acinar cells to ductular cells can not be entirely ruled out with certainty. Detailed morphological and molecular biological studies are needed to settle the controversy. Nevertheless, considering the plasticity of pancreatic cells, tumor cells can derive from any pancreatic cells.

Conclusion

The overwhelming evidence points to the derivation of pancreatic cancer from transdifferentiated islet cells within islets and within the ductal epithelium. The remarkable transdifferentiation tendency of islet cells to a variety of pancreatic and extrapancreatic cells, found also in both induced and human cancers, the presence of various drug-metabolizing enzymes in all tested species make this cell the most possible primary tumor origin. The striking transdifferentiation capability of islet cells into other cell types also indicates a close functional relationship between the genes that are responsible for the differentiation toward acinar, ductal and islet cell phenotypes. The circumstances favoring the origin of cancer cells from islet cells could well be the environment rich on growth factors.

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