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New insights into pancreatic cancer-induced paraneoplastic diabetes

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Abstract

Up to 85% of patients with pancreatic cancer have diabetes or hyperglycaemia, which frequently manifests as early as 2–3 years before a diagnosis of pancreatic cancer. Conversely, patients with new-onset diabetes have a 5–8-fold increased risk of being diagnosed with pancreatic cancer within 1–3 years of developing diabetes. Emerging evidence now indicates that pancreatic cancer causes diabetes. As in type 2 diabetes, β-cell dysfunction and peripheral insulin resistance are seen in pancreatic cancer-induced diabetes. However, unlike in patients with type 2 diabetes, glucose control worsens in patients with pancreatic cancer in the face of ongoing, often profound, weight loss. Diabetes and weight loss, which precede cachexia onset by several months, are paraneoplastic phenomena induced by pancreatic cancer. Although the pathogenesis of these pancreatic cancer-induced metabolic alterations is only beginning to be understood, these are likely mechanisms to promote the survival and growth of pancreatic cancer in a hostile and highly desmoplastic microenvironment. Interestingly, these metabolic changes could enable early diagnosis of pancreatic cancer, if they can be distinguished from the ones that occur in patients with type 2 diabetes. One such possible biomarker is adrenomedullin, which is a potential mediator of β-cell dysfunction in pancreatic cancer-induced diabetes.

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related deaths in the USA.[1] The incidence and mortality rates of pancreatic cancer are similar (~40,000 people per year in the USA),[1] highlighting its dismal survival and prognosis, principally because the tumour frequently presents at an advanced stage (85% unresectable). [2,3] The relationship between diabetes and pancreatic cancer, a subject investigated for more than a century, has been complicated by the existence of a bidirectional association between the two entities (Figure 1a).[4–6] Indeed, compelling epidemiological, clinical and experimental evidence now supports the concept that diabetes is induced by pancreatic cancer, and precedes the onset of cancer-specific symptoms by several months (Figure 1b). Pancreatic cancer-induced diabetes, which by definition is new-onset diabetes associated with pancreatic cancer, seems to be associated with paradoxical weight loss, which often manifests before the development

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of diabetes (Figure 1b). Understanding the mechanism of diabetes and weight loss in pancreatic cancer not only has broader implications for the field of obesity and diabetes, but also for early diagnosis of pancreatic cancer. In this Review, we summarize the evidence for paraneoplastic diabetes and associated weight loss in pancreatic cancer, and focus on the emerging concepts in the pathogenesis of these metabolic changes.

Pancreatic cancer-induced diabetes

Epidemiological evidence

The association between pancreatic cancer and diabetes was noted as early as 1833,[7] was clearly documented by the 1930s,[8,9] and was described in a large cohort of patients with pancreatic cancer from Mayo Clinic (MN, USA) in 1958.[10] Numerous epidemiological studies have explored the association between diabetes and cancer since the 1980s and three meta-analyses have been published (in 1995,[11] 2005[12] and 2011[13]). The European Prospective Investigation in Cancer and Nutrition (EPIC) cohort correlated increased baseline haemoglobin A_{1C} (HbA_{1C}) levels with subsequent development of pancreatic cancer (OR 2.4 for HbA_{1C} ≥6.5% compared with HbA_{1C} <5.4%).[14] The 1995 meta-analysis reported a twofold increased risk of pancreatic cancer in patients with long-standing (>5 years) diabetes and a greater risk in individuals with diabetes duration <5 years.[11] In the 2005 meta-analysis, patients with diabetes had an overall relative risk of two for pancreatic cancer, but this risk increased to 4–7-fold in those with diabetes duration <3 years.[12] The initial 3-year period after diabetes diagnosis was also found to be important for the development of pancreatic cancer when prospective pancreatographic screening was used.[15] The 2011 meta-analysis confirmed a relative risk of 5.4 (95% CI 3.5–8.3) associated with diabetes duration <1 year with levelling of the risk at ~1.5-fold after 5 years.[13] Thus, long-standing diabetes modestly increases the risk of pancreatic cancer. In fact, long-standing diabetes, insulin resistance and obesity have been shown to modestly increase the risk of several other cancers,[16–21] and the risk might be further modulated by antidiabetic medications.[22–27]

However, the markedly higher risk of pancreatic cancer in patients with new-onset diabetes when compared with long-standing diabetes indicates that pancreatic cancer itself can cause diabetes. Support for this concept was provided by a population-based study by Chari *et al.*[28] of 2,122 patients >50 years of age with new-onset diabetes in which 1 in 125 (0.85%) of the patients was diagnosed with pancreatic cancer within 3 years of diabetes onset (eightfold higher risk than expected for the population). Another population-based study among veterans in the San Francisco area from 2006 reported consistent results, although with a lower relative risk.[29,30]

Diabetes prevalence in pancreatic cancer

Increased prevalence of new-onset diabetes in patients with pancreatic cancer has been consistently seen in most case series, although the reported values have varied depending on the methodology of patient selection and criteria for diabetes diagnosis. Studies that screened for diabetes in patients with pancreatic cancer have reported considerably higher rates of diabetes[31–35] than those relying on chart reviews for physician-diagnosed diabetes.[10,30,36–41] This difference probably reflects the fact that one-third of new-onset diabetes in patients with pancreatic cancer remains unrecognized.[42]

Among studies that have screened for diabetes in pancreatic cancer, an even higher prevalence of diabetes is noted when an oral glucose tolerance test is performed, as opposed to analysis of fasting blood glucose levels.[35] Preoperative oral glucose tolerance testing in 44 patients with resectable pancreatic cancer showed diabetes in 28 (64%) and impaired

glucose tolerance in an additional four (11%) patients.[43] Our group investigated the prevalence of diabetes in a prospectively recruited series of 512 patients with newly diagnosed pancreatic cancer by recording fasting glucose measurements within 30 days of diagnosis.[31] Only 14% (56 patients) of these patients had normal fasting glucose values, whereas diabetes was present in 243 (47%) patients.[31] Among patients with pancreatic cancer and diabetes, the duration of diabetes was <2 years in 74% (177 of 243). Pancreatic cancer-induced diabetes was therefore present in 34% of patients (177 of 512).[31] Additionally, a large proportion of patients with pancreatic cancer (38%) had impaired fasting glucose levels but did not meet the diagnostic criteria for diabetes.[31]

Time course

The majority of diabetes in pancreatic cancer is of new onset.[29,30,36,44,45] In a large retrospective study, fasting glucose measurements up to 5 years prior to the diagnosis of pancreatic cancer (n = 765) and in matched controls (n = 1,865) were reviewed and the prevalence of diabetes compared in the two groups.[45] Although a trend towards a higher prevalence of diabetes was noted in patients as early as 36–48 months prior to diagnosis of pancreatic cancer, a significant increase (when compared with controls) was observed in months 24–36, 12–24 and 0–12.[45] Thus, diabetes caused by pancreatic cancer starts up to 2–3 years before diagnosis of pancreatic cancer.

Examination of possible hypotheses

Unmasking of type 2 diabetes—Many forms of stress, such as pregnancy, weight gain and steroid therapy, can unmask type 2 diabetes. Arguments for this hypothesis as a cause of diabetes in pancreatic cancer include the fact that canonical risk factors for type 2 diabetes (such as older age, obesity and family history of diabetes) are also risk factors for pancreatic cancer-induced diabetes;[31] pancreatic cancer-induced diabetes can also be resolved by successful treatment of the cancer.[31,46] However, the high frequency of new-onset diabetes and hyperglycaemia in patients with pancreatic cancer point to a pancreatic cancer-specific stressor that profoundly, and consistently, decompensates glucose homeostasis.

Consequence of cachexia—A study in 2012 comparing diabetes prevalence among various cancers found diabetes in ~20% of patients with lung, prostate, breast and colon cancer, which was not significantly different from that in the matched control population.[47] By contrast, the prevalence of diabetes was higher in patients with pancreatic cancer than in controls and was noted in ~66% of patients. Although it is well-recognized that cachexia in any cancer is a dysmetabolic state in which diabetes can occur,[48,49] the much higher prevalence in pancreatic cancer compared with other cancers suggests a unique relationship. Moreover, pancreatic cancer has one of the highest incidences of cachexia in any type of cancer.[48,50] However, the onset of diabetes in pancreatic cancer occurs 2–3 years prior to the diagnosis of cancer, whereas cachexia-associated symptoms in pancreatic cancer manifest on average 2 months prior to cancer diagnosis (Figure 1b);[45] therefore, pancreatic cancer-induced diabetes cannot be attributed to cachexia.

Destruction of the pancreas—Although destruction and loss of normal pancreatic tissue owing to pancreatic cancer is possible in advanced stages, three pieces of evidence argue against such a mechanism for pancreatic cancer-induced diabetes. First, diabetes occurs even before the tumour is radiologically detectable.[51,52] Second, insulin levels are relatively high in pancreatic cancer when compared with healthy controls, suggesting insulin resistance.[33,53–56] Third, diabetes improves after resection of the cancerous parts of the pancreas.[31,46]

A paraneoplastic phenomenon—Compelling clinical and laboratory evidence supports the hypothesis that pancreatic cancer-induced diabetes is a paraneoplastic phenomenon caused by the cancer. Evidence for this hypothesis is presented in Box 1.

Box 1

Evidence for pancreatic cancer-induced diabetes

- Diabetes or impaired glucose tolerance occurs in the majority of patients with pancreatic cancer[31] and precedes clinical presentation of cancer by several months to a few years[45]
- Diabetes is prevalent in small pancreatic cancers[142] and diabetes occurs before the tumour is radiologically detectable[52]
- Worsening of diabetes occurs in patients with long-standing diabetes in the months preceding the diagnosis of pancreatic cancer[59,60]
- Diabetes improves after surgical resection of pancreatic cancer[31,46]
- Occurrence of diabetes preceding pancreatic cancer symptoms has been demonstrated in the hamster model of pancreatic cancer,[78,143–145] which is consistent with clinical data
- Insulin resistance and β-cell dysfunction has been reported in patients with pancreatic cancer by homeostasis model assessment[66]
- Supernatants from pancreatic cancer cell lines have been shown to induce insulin resistance in cultured hepatocytes[146,147] and myoblasts,[148] as well as β-cell dysfunction *in vivo*[149] and *in vitro*[70,82–84,150]
- Skeletal muscle tissue obtained from patients with pancreatic cancer demonstrated insulin resistance *in vitro* when compared with tissue from healthy controls[78,79]

Paraneoplastic weight loss

Epidemiology and time course

Weight loss in pancreatic cancer occurring before the onset of cancer-related symptoms was recognized in reports from the 1980s and 1990s[34,57–59] and in previously published cohorts from our centre.[31,44] In the large retrospective cohort described earlier,[45] serial BMI and fasting glucose values were trended up to 5 years prior to the diagnosis of pancreatic cancer.[60] Surprisingly, a reduction in BMI began as early as 3 years before the diagnosis of cancer; despite this reduction, glycaemic control worsened over time in these patients, in contrast to what is observed in individuals with type 2 diabetes (in which glycaemia improves with weight loss).[60] Interestingly, at the onset of diabetes, 59% of patients (17 of 29) with pancreatic cancer-induced diabetes had lost weight whereas weight gain was seen in 56% of patients (24 of 43) with new-onset noncancer-related type 2 diabetes matched for the prediabetes weight.[61] Although most patients with type 2 diabetes continued to gain weight, progressive weight loss was seen in those with pancreatic cancer-induced diabetes, starting as early as 1 year prior to diabetes onset.[61] The mean interval of diabetes onset in pancreatic cancer, and onset of symptoms, respectively, to the diagnosis of pancreatic cancer was 13 months[61] and 2 months.[45] These data suggest that weight loss is associated with occurrence of diabetes, and precedes onset of cancer-specific symptoms and onset of diabetes in pancreatic cancer by several months.

A paraneoplastic phenomenon

Loss of lean muscle mass is the signature feature of cachexia,[48,49] which usually results in >10% weight loss and is seen in the advanced stages of cancer. However, cardinal symptoms, such as fatigue and anorexia, might start before the onset of muscle loss (pre-cachexia).[49] In a report from 2010 examining cachexia in patients with lung and colorectal cancer, weight loss started only ~7 months prior to their death.[62] Unfortunately, pancreatic cancer usually presents in the advanced stage with cachexia symptoms being invariably present at diagnosis (they can be its only clinical manifestation) (Figure 1). Therefore, weight loss in pancreatic cancer after the onset of symptoms is undoubtedly occurring in conjunction with cachexia (Figure 2).

However, as discussed earlier, weight loss precedes the onset of symptoms in pancreatic cancer by several months. This initial period of weight loss cannot be attributed to cachexia. In fact, in our experience, patients deny feeling tired or eating less during this period, and are pleasantly surprised about having lost weight effortlessly. In our opinion, this weight loss, associated with diabetes and occurring prior to the onset of cachexia, is a paraneoplastic phenomenon induced by pancreatic cancer (Figure 2). In the absence of cachexia (and associated muscle loss), this paraneoplastic weight loss seems to result from loss of adipose tissue. We hypothesize that pancreatic cancer interacts with adipose tissue to induce this paraneoplastic weight loss that paradoxically occurs along with diabetes.

Mechanisms of paraneoplastic phenomena

Mechanisms analogous to type 2 diabetes

In individuals with obesity who are normoglycaemic, peripheral insulin resistance is present but compensated for by increased insulin secretion.[63–65] Insulin resistance progressively worsens in the predisposed individuals along with progressive β-cell dysfunction and reduction of β-cell mass, eventually leading to type 2 diabetes. [63–65] Interestingly, a similar temporal relationship between insulin resistance, β-cell function and development of impaired glucose tolerance and diabetes was demonstrated in patients with pancreatic cancer.[66]

β-cell dysfunction—The existence of a diabetes-causing product of pancreatic cancer has been postulated for over two decades. Initial research led to isolation of amylin[67] and S-100A8 N-terminal peptide,[68,69] which were shown to cause insulin resistance *in vitro*, but their effects on β cells are unknown. A direct tumour-secreted mediator of β-cell dysfunction has been recognized in a collaborative study from Mayo Clinic (MN, USA) and MD Anderson Cancer Center (TX, USA) published in 2012.[70] Gene profiling using microarray analysis of pancreatic cancer cell lines known to inhibit insulin secretion yielded 18 upregulated proteins[70] among which adrenomedullin, a 52 amino acid peptide known to inhibit insulin secretion, [71,72] was identified. Adrenomedullin is a pluripotent hormone; in the pancreas, its receptors are found on β cells[73] and its expression is seen specifically in the F cells of the islets,[74] but the significance of these observations remain unclear.

Adrenomedullin was shown to mediate pancreatic cancer-induced inhibition of insulin secretion in β cells in various *in vitro* and *in vivo* orthotopic and subcutaneous tumour models.[70] Interestingly, plasma adrenomedullin levels were higher in patients with pancreatic cancer than in patients with diabetes or healthy controls; the highest levels were seen in those with pancreatic cancer-induced diabetes.[70] Moreover, overexpression of adrenomedullin was seen in surgically resected specimens of pancreatic cancer.[70] Another group had previously shown that adrenomedullin is upregulated in pancreatic cancer in conditions of hypoxia[75,76] and hypoglycaemia.[76] Thus, adrenomedullin, secreted by the

cancerous pancreas in its hostile microenvironment, is a mediator of β-cell dysfunction. However, it is possible that other (as yet unrecognized) adrenomedullin-independent mediators of β-cell dysfunction might exist.

Insulin resistance in β cells, hyperglycaemia and non-esterified fatty acids (NEFA) are known to indirectly lead to β-cell dysfunction and loss of β-cell mass in type 2 diabetes. [65] As discussed below, these indirect mechanisms also seem to be operational in pancreatic cancer-induced diabetes. The direct and indirect effects of pancreatic cancer on β cells are summarized in Figure 3.

Insulin resistance—Insulin resistance is consistently seen in patients with pancreatic cancer (even in those with normal fasting glucose levels[66]) and resolves after resection of the cancer.[31] At the postreceptor level, insulin signalling is conveyed via insulin receptor substrate proteins through distinct downstream pathways for the control of metabolism and for regulation of cell proliferation in insulin-sensitive cells.[65,77] In type 2 diabetes, selective resistance in the metabolic pathways but continued sensitivity in the proliferation pathways in observed,[77] and the resistance occurs at the postreceptor level.[65,77] Similar to type 2 diabetes, insulin resistance in pancreatic cancer is thought to occur at the postreceptor level. Evidence supporting this assertion was provided in a study[78] that revealed differences in glycogen synthesis and glycogen breakdown in skeletal muscles obtained from patients with pancreatic cancer-induced diabetes compared with those with pancreatic cancer without diabetes and healthy controls. By contrast, insulin receptor binding, tyrosine kinase activity, insulin receptor substrate 1 and glucose transporter type (GLUT) 4 levels were similar.[78] Furthermore, impaired action of phosphoinositide 3-kinase (a downstream effector in the insulin-regulated metabolic pathways) and impaired glucose uptake was observed in the skeletal muscle of patients with pancreatic cancer.[79]

The search for a putative mediator of insulin resistance in pancreatic cancer was boosted in the 1990s with the demonstration that insulin resistance induced by pancreatic cancer-conditioned media could be localized to a <10 kDa fraction.[80] Subsequently, islet amyloid polypeptide (IAPP) was identified; levels of this putative mediator were higher in patients with pancreatic cancer than in patients with other cancers, diabetes or healthy controls[67] and is known to cause insulin resistance in skeletal muscles.[81] IAPP is normally secreted with insulin by β cells and pancreatic cancer was found to cause β cells to selectively secrete IAPP through direct stimulation[82] and by altering responsiveness of β cells to other secretagogues.[83,84] However, it was subsequently shown that IAPP does not have good diagnostic or discriminative potential in patients with pancreatic cancer.[44] No subsubsequent studies have been conducted to explore the pathophysiological role of IAPP in pancreatic cancer. Another potential mediator identified in patients with pancreatic cancer-induced diabetes was S-100A8 N-terminal peptide,[68,69] which induces insulin resistance *in vitro*, but further research is needed to explore its importance in pancreatic cancer. Therefore, at the moment, a biochemical mediator of insulin resistance secreted by pancreatic cancer remains a hypothesis.

The role of adipose tissue

Interactions between adipose tissue and pancreatic cancer might explain the occurrence of insulin resistance as well as paraneoplastic weight loss in pancreatic cancer. The role of adipose tissue in the development of the metabolic syndrome and type 2 diabetes is only starting to be elucidated.[65,85,86] Here, insights from the field of type 2 diabetes and the metabolic syndrome are presented, with a discussion of how pancreatic cancer could induce similar pathogenic processes.

Adipose tissue inflammation—A key feature of the metabolic syndrome is inflammation of adipose tissue and alteration of adipokine secretion and sensitivity.[87,88] Insulin resistance precedes and accompanies type 2 diabetes. Adiponectin, leptin, resistin and numerous other adipokines have been identified as possible mediators of insulin resistance within the past decade, although leptin and adiponectin are now believed to be the important ones in diabetes.[65,77,89–91] Accumulation of visceral fat is associated with low-grade chronic inflammation in adipose tissue[65,92] resulting from an interplay between inflammasome activation within adipocytes and sensitization of adipose tissue macrophages.[87,93,94] Macrophages release inflammatory cytokines (which can comprise up to 90% of the hormonal output of adipose tissue) such as tumour necrosis factor (TNF), IL-6 and monocyte chemoattractant protein 1 that contribute to peripheral insulin resistance.[65,77,92,94] Local inflammatory signals alter adipocyte secretion (drop in adiponectin, increase in leptin secretion)[86,95] and responsiveness (resistance to leptin),[65] which ultimately lead to the development of insulin resistance (Figure 4).[77,92,94]

Inflammation of adipose tissue has not been directly studied in pancreatic cancer. One small study reported an increased adiponectin:leptin ratio in patients with newly diagnosed pancreatic cancer, which is comparable to patients with and without diabetes.[32] Prediagnostic inflammatory markers and subsequent development of pancreatic cancer was studied in the EPIC cohort revealing an association with soluble TNF receptor levels (sTNF-R1 in females; sTNF-R2 in individuals with obesity and diabetes of either sex).[96] A review discussing the existence of pancreatic steatosis in the metabolic syndrome and type 2 diabetes argued for the possible relationship of pancreatic adipose tissue and pancreatic cancer,[97] although further research is needed to confirm this relationship.

Lipolysis and NEFA toxicity—Increased lipolysis occurs with excessive fat accumulation in the metabolic syndrome and obesity, leading to the generation of NEFA.[65] The release of NEFA has been regarded as a crucial factor in causing peripheral insulin resistance.[65] Furthermore, direct NEFA toxicity to β cells,[65] as well as insulin resistance in β cells,[98] contribute to β-cell dysfunction and β-cell loss. As discussed earlier, the paraneoplastic phase of weight loss in pancreatic cancer seems to be predominantly mediated by adipose tissue lipolysis, which might be an essential mechanism in the development of insulin resistance, β-cell dysfunction and diabetes in pancreatic cancer (Figure 4). We hypothesize that inflammation of adipose tissue occurs in pancreatic cancer leading to adipokine, cytokine and NEFA-mediated insulin resistance (Figure 4). How pancreatic cancer interacts with adipose tissue remains an intriguing subject. Some possible mechanisms of how pancreatic cancer can cause inflammation of adipose tissue include: direct effects of factors released from a cancerous pancreas on adipose tissue; activation of pancreatic macrophages through inflammasomes, which might seed adipose tissue; and sensitization of naive circulating macrophages that might reach adipocytes. Furthermore, lipolysis of adipose tissue might be induced by pancreatic cancer to supply metabolic substrates for tumour growth and survival. A number of lipid-mobilizing factors, including zinc-α-2 glycoprotein,[99,100] have been suggested in cachexia-related adipolysis (observed in the advanced stages of many cancers). We have proposed the presence of a lipid-mobilizing factor in pancreatic cancer that is secreted by adipose tissue, possibly in response to inflammation of adipose tissue (Figure 4).[61]

Exploring the paradox

Pancreatic cancer-induced diabetes is associated with weight loss, unlike type 2 diabetes, which is associated with weight gain and obesity. How could this paradox be explained?

Topographic differences—The visceral depot of adipose tissue, as compared to the subcutaneous depot, is accepted as being important in the development of insulin resistance and the metabolic syndrome.[86,101–103] In fact, McLaughlin *et al.*[104] showed that each standard deviation increase in subcutaneous adipose tissue reduced the risk of insulin resistance by 48%, whereas a standard deviation increase in visceral adipose tissue mass increased the risk of insulin resistance by 80%. Surgical removal of subcutaneous fat by liposuction did not affect insulin resistance,[105] whereas removal of visceral fat led to improvement[106] or an equivocal response.[107] Multiple structural and functional differences exist between subcutaneous and visceral adipocytes (reviewed elsewhere[108]), which might account for their differential roles in health and disease. Differences in inflammatory gene expression profile between visceral and subcutaneous adipocytes taken from patients with type 2 diabetes (and healthy controls) have also been reported.[109]

Differential responses of adipose fat—Our group has started to focus on the differential responses of adipose tissue compartments in pancreatic cancer. Preliminary data indicate a differential response of visceral and subcutaneous fat compartments, with greater loss of subcutaneous compartment and relative preservation of visceral compartment in patients with pancreatic cancer (S. T. Chari, unpublished work). Progressive worsening of glycaemia and insulin resistance in pancreatic cancer is probably driven by the fairly preserved visceral compartment, whereas selective loss of the subcutaneous compartment might explain the paradoxical weight loss. Although cachexia-associated weight loss is defined by loss of lean muscle mass, marked loss of adipose tissue also occurs and similar loss occurs from both compartments.[62] This paraneoplastic phase of weight loss in pancreatic cancer therefore seems to be unique. Could this feature be related to the difference in diabetes occurrence in pancreatic cancer versus other cancers? This provocative hypothesis needs further investigation.

Enhanced survival and tumour growth

Why do these paraneoplastic metabolic alterations occur in pancreatic cancer? Our understanding of the significance of these alterations is still in its early stages. Pancreatic cancer cells have a hostile microenvironment with poor vasculature, low nutrient supply and hypoxia. Yet these cells show the most aggressive behaviour— resistance to apoptosis, high proliferation rate and invasiveness. In our opinion, pancreatic cancer induces diabetes, lipolysis and weight loss for enhanced survival, proliferation and tumour growth, and possibly carcinogenicity (Figure 5).

Supply of metabolic substrates

In addition to metabolic changes in the patient, the intracellular metabolic machinery of pancreatic cancer is reprogrammed towards a metabolism more suitable for proliferation in the midst of hostile conditions. Preferential aerobic glycolysis (Warburg effect[110]) is one such intracellular reprogramming of glucose metabolism in pancreatic cancer cells, which is accompanied by aberrant expression and activity of metabolic enzymes and of cellular receptors for glucose uptake.[111–113] Despite high uptake of glucose in pancreatic cancer cells, it is metabolized inefficiently by aerobic glycolysis.[111] Biosynthetic intermediates are generated in exchange for this inefficient energy production, which sustains proliferation and confers a survival advantage.[111] Hyperglycaemia and lipolysis might therefore provide a supply of glucose and substrates for the metabolic and growth demands of the reprogrammed ‘hungry’ pancreatic cancer cells (Figure 5).

The mechanisms of such metabolic reprogramming is only starting to be unravelled.[111] Oncogenic K-ras protein mutations strongly associated with pancreatic cancer seem to be important in reprogramming cells to anabolic glucose metabolism and maintaining

tumorigenicity in a harsh environment.[114] Other important pathways recognized to link cellular metabolism to proliferation and carcinogenicity are: p53;[111] c-Myc;[111] liver kinase B1 (LKB1, encoded by *STK11*)–AMPK;[111] mammalian target of rapamycin (mTOR; activated by insulin signalling); and hypoxia-inducible factor 1-α (HIF1-α). An involvement of microRNAs in fine regulation of these pathways has also been suggested to occur in pancreatic cancer.[115]

Proliferation and tumorigenesis

Emerging evidence indicates that glucose[116] and advanced glycation end products (AGE)[117,118] are mitogenic. In fact, hyperglycaemia has been shown to enhance proliferation,[119,120] local invasiveness and metastatic potential in pancreatic cancer.[121,122] The expression of receptor for AGE (RAGE) was shown to promote pancreatic cancer tumorigenesis.[123,124] However, a case–control study failed to show any association between AGE and pancreatic cancer risk, but found an inverse association with RAGE levels at onset, in patients diagnosed with pancreatic cancer within 2 years of follow up.[125] Another study from Finland reported a similar inverse association.[126]

Hyperinsulinaemia also stimulates proliferation of pancreatic cancer,[24,122] which is known to overexpress insulin-like growth factor receptor and G-protein coupled receptors.[127] These proliferative effects of hyperglycaemia and hyperinsulinaemia might also explain the increased risk of pancreatic cancer in long-standing diabetes, which is even higher among insulin users.[122] Insulin and insulin-like growth factors are implicated in proliferation and neoplastic transformations in other cancers.[128] Interestingly, metformin has been shown to reduce the risk of pancreatic cancer,[26,129] as well as several other cancers. This phenomenon has provided interesting insights into the links between energy supply, metabolism and proliferation.[129] Metformin is known to activate the LKB1–AMPK pathway, a cellular energy stress-sensing mechanism, and blocks proliferation through inhibition of mTOR (which drives the proliferation effects of the insulin signalling pathway).[129] In fact, *STK11* is a tumour suppressor gene and its germline mutations are associated with Peutz–Jeghers syndrome (patients with this syndrome have an increased risk of pancreatic cancer);[130] mutations in this gene have also been reported in sporadic pancreatic cancers.[131]

Furthermore, pathway analysis of genome-wide association study data in patients with pancreatic cancer suggested an association between susceptibility for pancreatic cancer and the pancreatic development genes *HNF1A, HNF1B* and *PDX1* and also another development gene *NR5A2* that is involved in lipid and glucose metabolism.[132] *HNF1A, HNF1B* and *PDX1* are known to be associated with maturity-onset diabetes of the young type 3, type 5 and type 4 respectively; *HNF1A* and *HNF1B* are also associated with type 2 diabetes.[132] These data highlight the complex relationship between diabetes and pancreatic cancer, and provide another mechanism of increased risk of pancreatic cancer with long-term diabetes and conversely, might partly explain the metabolic alterations in pancreatic cancer.

Desmoplasia and hypoxia

Pancreatic cancer is a highly desmoplastic tumour with a stressful microenvironment. In response to hypoxia and other cellular stressors, HIFs are induced that modulate a range of cellular responses conferring survival advantage in the hostile microenvironment. HIF1-α is thought to be particularly important in pancreatic cancer.[133–135] Constitutive expression of HIF1-α was seen in the majority of pancreatic cancer cell lines, but not in most cell lines of other cancers.[134]

HIF1-α conferred resistance to apoptosis, upregulated glycolytic proteins and selectively upregulated GLUT subtypes that favour glycolysis.[134] Dominant negative HIF1-α

expression was shown to inhibit tumorigenicity of pancreatic cancer and led to suppression of glycolytic metabolism.[135] A hypoxia-independent mechanism might also regulate HIF1-α in pancreatic cancer.[133] Mucin-1, which is known to be overexpressed in pancreatic cancer, activates and stabilizes HIF1-α, and its expression enhances glycolytic activity both *in vitro* and *in vivo*.[133] Thus, HIF1-α might be important in metabolic reprogramming of pancreatic cells suitable for its hostile microenvironment, as well as providing resistance to apoptosis (Figure 5). In addition, HIF1-α is also a transcription factor for adrenomedullin[76] and might mediate the overexpression of adrenomedullin in pancreatic cancer. Adrenomedullin, shown to be induced in hypoxic conditions,[75,76] mediates β-cell dysfunction[70] and enhances cancer invasion,[75] and therefore might be a survival mechanism (Figure 5).

Predicting pancreatic cancer

Prognosis of pancreatic cancer is extremely poor despite surgical resection and chemotherapy. Early diagnosis might be the best hope of increasing survival in pancreatic cancer.[3] Individuals with new-onset diabetes are at high risk of developing pancreatic cancer with ~1% of patients developing pancreatic cancer within 3 years.[28] However, type 2 diabetes is at least 100 times more common than pancreatic cancer-induced diabetes. To utilize its potential in screening for pancreatic cancer, one has to be able to distinguish between pancreatic cancer-induced diabetes and type 2 diabetes.[136]

New-onset type 2 diabetes is classically associated with the metabolic syndrome, weight gain and family history of diabetes. By contrast, pancreatic cancer-induced diabetes is seen even in individuals without associated family history and other manifestations of the metabolic syndrome.[31,45] However, these epidemiological features alone are insufficient to distinguish between these two types of diabetes. Presence of weight loss in the preceding months prior to onset of diabetes might be an important predictor of the development of pancreatic cancer-induced diabetes,[61] although this feature will probably have limited diagnostic utility in clinical practice. Adrenomedullin levels are higher in pancreatic cancer-induced diabetes than in new-onset type 2 diabetes,[70] but its diagnostic utility remains to be explored in a large cohort. A second biochemical marker for pancreatic cancer-induced diabetes is essential to distinguish those at high risk of pancreatic cancer from all patients with new-onset diabetes.[3] The search for a good biomarker remains in progress (discussed extensively elsewhere[3,136]).

Type 3 diabetes (or pancreatogenous diabetes) is defined as diabetes resulting from diseases of the exocrine pancreas[137–139] and is probably an underdiagnosed entity.[137,138] By this anatomical definition, pancreatic cancer-induced diabetes has been classified as type 3c diabetes.[4,137,139] Type 3 diabetes is characterized by low insulin and pancreatic polypeptide levels, increased peripheral insulin sensitivity, but reduced hepatic insulin sensitivity,[4,137,138] which is in contrast to type 2 diabetes.[140,141] However, as discussed previously, patients with pancreatic cancer-induced diabetes have high insulin levels and peripheral insulin resistance similar to type 2 diabetes rather than type 3 diabetes.[33,53–56] Rightfully, the American Diabetes Association[139] acknowledges that pancreatic cancer-induced diabetes differs from the other diseases listed in the type 3 category (such as diabetes related to chronic pancreatitis), although further studies are needed to better characterize these differences.

Conclusions

Pancreatic cancer is associated with paraneoplastic diabetes. Furthermore, paradoxical weight loss occurs in the face of worsening diabetes in pancreatic cancer. The mechanism

and significance of these metabolic alterations is only starting to be uncovered but such understanding might yield biomarkers for the early diagnosis of pancreatic cancer.

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Key points

- Compelling evidence now indicates that pancreatic cancer causes paraneoplastic diabetes
- As in type 2 diabetes, β-cell dysfunction and peripheral insulin resistance occur in pancreatic cancer-induced diabetes; however, unlike type 2 diabetes, weight loss occurs alongside worsening diabetes in pancreatic cancer
- Paraneoplastic diabetes and weight loss manifest many months prior to the onset of cachexia or clinical presentation of pancreatic cancer
- Differential responses of visceral and subcutaneous adipose tissue compartments in pancreatic cancer might underlie the development of insulin resistance and paradoxical weight loss
- These metabolic alterations might be induced by pancreatic cancer for enhanced survival and tumour growth in an otherwise hostile microenvironment

Review criteria

We searched PubMed and Ovid databases using the following key words alone or in various combinations: “pancreatic cancer”, “diabetes”, “diabetes mellitus”, “pancreatic cancer associated diabetes” and “weight loss”, and retrieved articles from 1985 to 2012. We reviewed original studies and reviews for relevance and included all pertinent studies in the preparation of the manuscript. We also reviewed the bibliographies of the selected articles for other relevant articles.

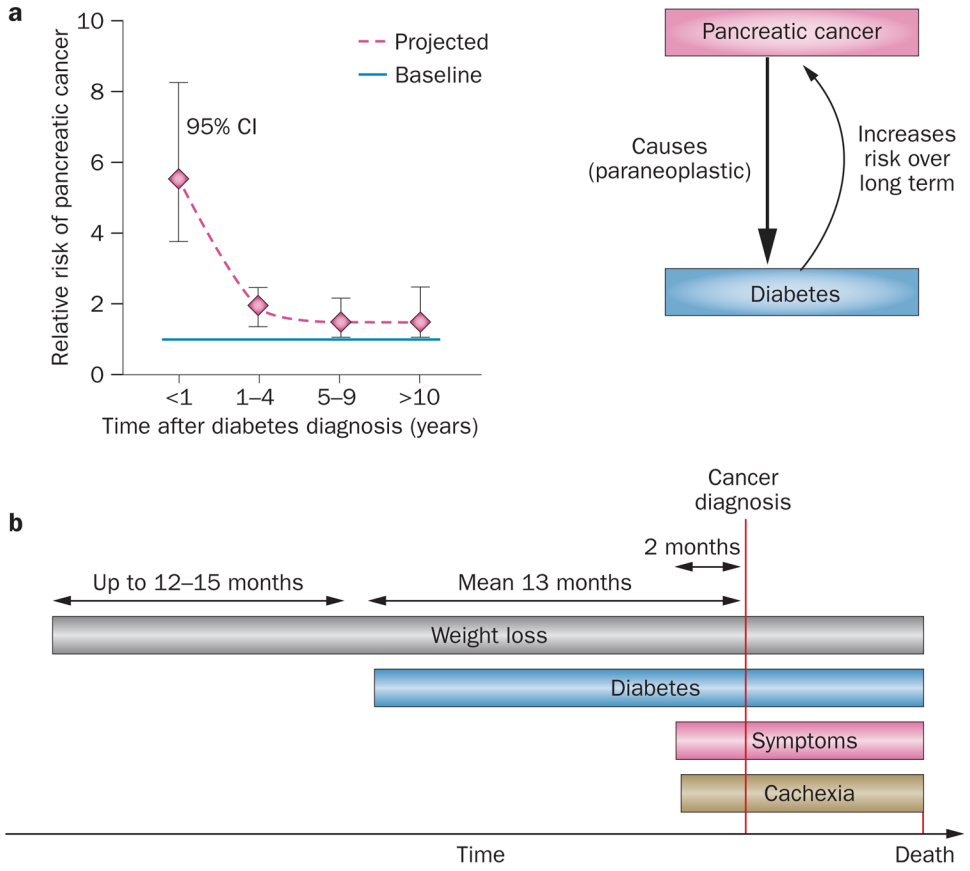

Figure 1.

Bidirectional association between pancreatic cancer and diabetes. **a** | Risk of diabetes after diabetes diagnosis. The risk of pancreatic cancer is high with new-onset diabetes (5–8-fold) whereas the risk levels out at about 1.5-fold 4 years after diabetes diagnosis.[13] **b** | Timecourse of paraneoplastic diabetes and weight loss in relation to pancreatic cancer diagnosis, onset of symptoms and cachexia.[45,61]

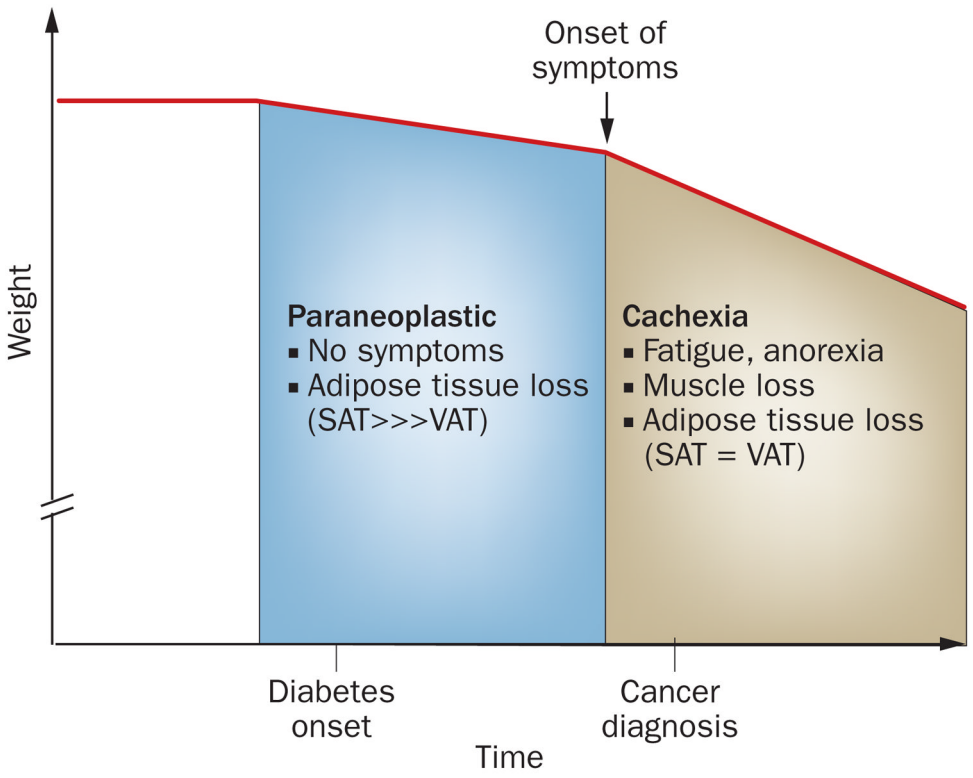

Figure 2.

A model depicting the phases of weight loss in pancreatic cancer. Weight loss precedes any symptoms related to cancer or cachexia by several months. We propose that the weight loss, associated with diabetes and occurring prior to the onset of symptoms, is a paraneoplastic phenomenon induced by pancreatic cancer. Abbreviations: SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

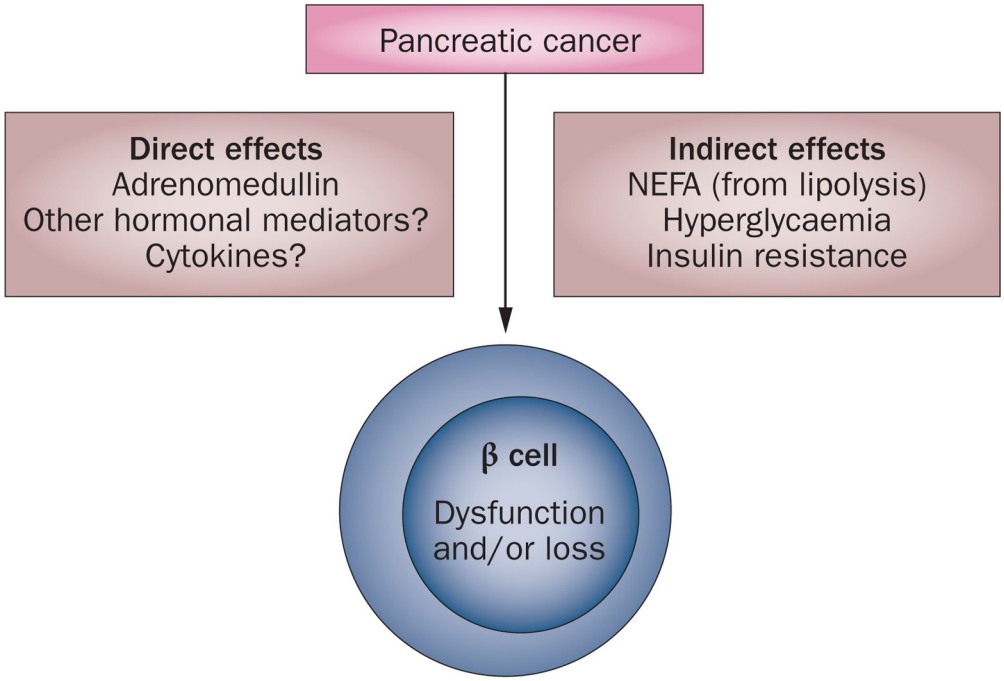

Figure 3.
A model demonstrating pancreatic cancer and β-cell interactions resulting in the pathogenesis of paraneoplastic diabetes. Pancreatic cancer-derived products might directly affect β cells. Indirect effects resulting from the consequences of insulin resistance and adipose tissue interactions on β cells might also be important. Abbreviation: NEFA, non-esterified fatty acids.

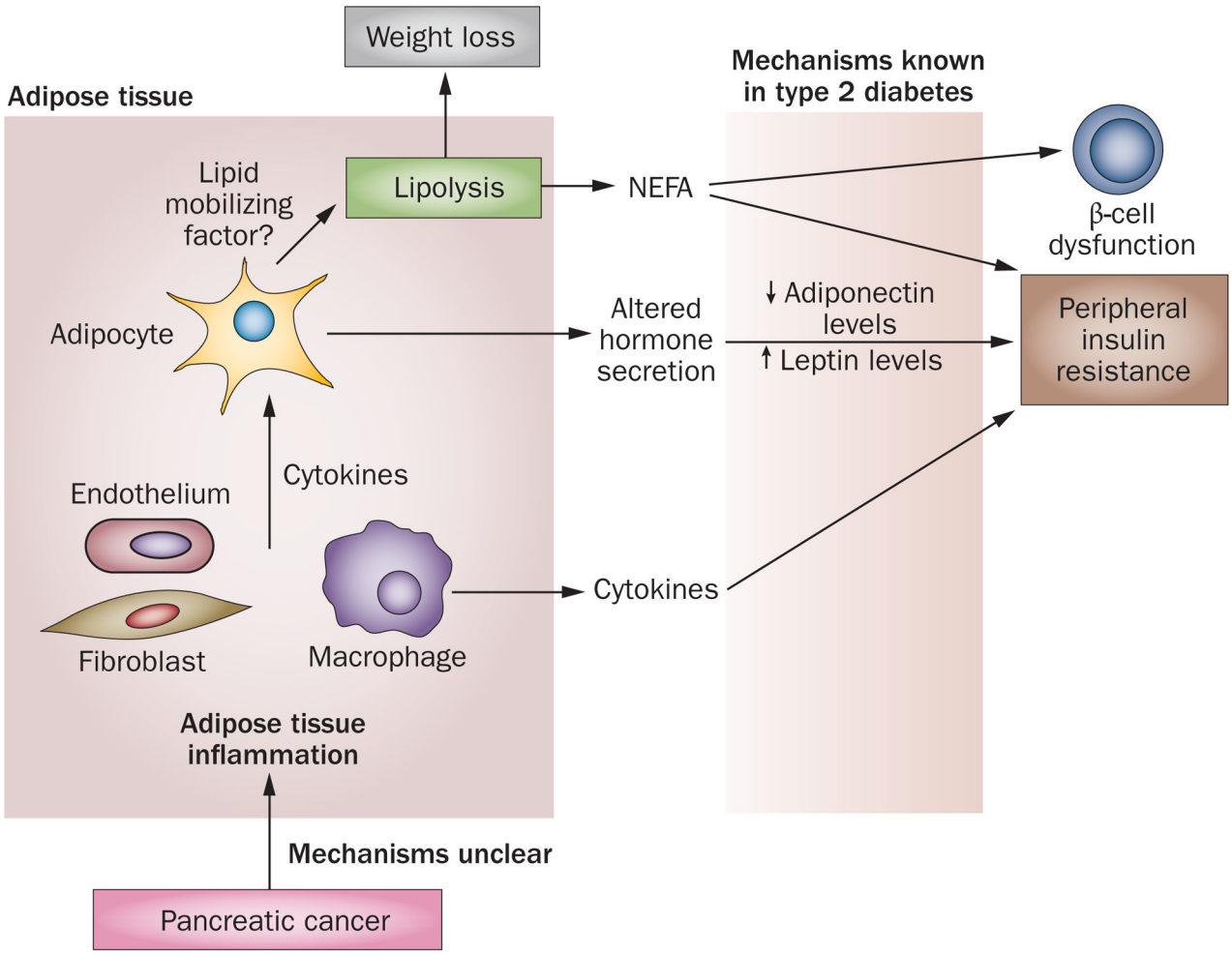

Figure 4.

A model demonstrating pancreatic cancer and adipose tissue interactions resulting in the pathogenesis of paraneoplastic diabetes and associated weight loss. Interactions between pancreatic cancer and adipose tissue might lead to adipose tissue inflammation resulting in a systemic cytokine response, altered adipokine secretion and lipolysis. Eventually, these factors cause peripheral insulin resistance and β-cell dysfunction. Abbreviation: NEFA, non-esterified fatty acids.

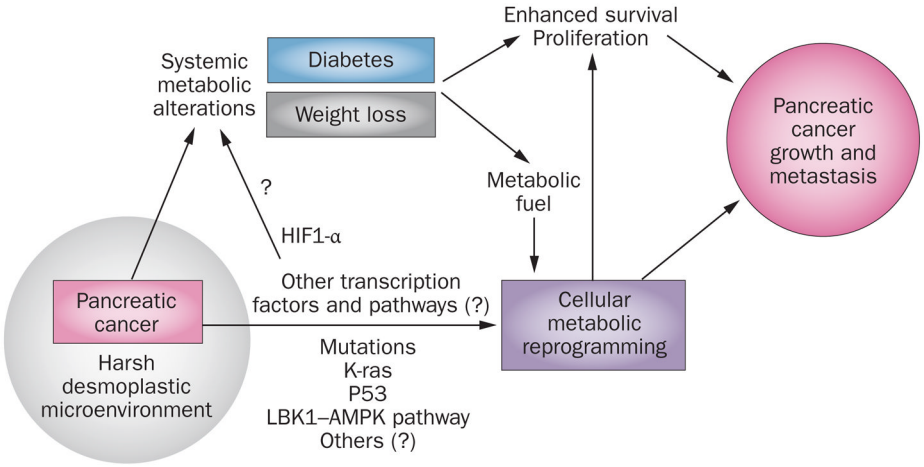

Figure 5.

Significance of metabolic alterations in pancreatic cancer. Paraneoplastic diabetes and weight loss are induced by pancreatic cancer possibly to enhance survival, proliferation, tumour growth and carcinogenesis. Pancreatic cancer is highly desmoplastic with an extremely hostile microenvironment. The pancreatic cancer cell is metabolically reprogrammed for survival and proliferation in harsh conditions. Multiple cellular pathways have been identified that contribute to aerobic glycolysis and might lead to the release of tumour factors, which mediate systemic metabolic alterations. Diabetes and lipolysis might supply substrates for reprogrammed metabolic machinery resulting in enhanced survival of cancer cells and tumour growth whereas hyperglycaemia and hyperinsulinaemia might directly enhance proliferation and carcinogenicity.