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Review

# The intricate relationship between diabetes, obesity and pancreatic cancer

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ABSTRACT

Pancreatic cancer is one of the leading determinants of global cancer mortality, and its incidence is predicted to increase, to become in 2030 the second most common cause of cancer-related death. Obesity and diabetes are recognized risk factors for the development of pancreatic cancer. In the last few decades an epidemic of diabetes and obesity has been spreading worldwide, forewarning an increase in incidence of pancreatic cancer. This review considers the most recent literature, covering the multiple molecular axis linking these three pathologies, aiming to draw a more comprehensive view of pancreatic cancer for a better theragnostic stratification of the population.

## 1. Introduction

Since its initial recognition in the 20th century, Pancreatic Cancer has always been considered a virtually incurable disease; likewise, the prognosis has not changed much in recent years, compounded by a worldwide increase in incidence [1,2]. Pancreatic Ductal Adenocarcinoma (PDAC) is the most common malignancy of the exocrine pancreas, accounting for > 90% of cases, with a very poor prognosis. In this review we will focus exclusively on PDAC.

Increasing evidence indicate the presence of a pathological link between obesity, diabetes and PDAC. This manuscript reviews the most recent findings, discussing and reframing the pathological picture of high-risk populations for potential PDAC-preventive strategies. As summarized, novel blood-based therapeutical and diagnostic markers, such as exosomes, warrant further clinical and interventional investigation in obese and diabetic patients. These blood-based, and tissue specific biomarkers, are essential tools for a better enrichment and stratification of high-risk populations. In this review, we discuss the promises and the pitfalls of personalized screening of individuals on the path to developing PDAC, with the ultimate aim of reducing the foreseeable burden of these chronic diseases.

## 2. PDAC risk stratification

PDAC risk factors can be divided into inherited and non-inherited. The latter can be further divided in modifiable and non-modifiable risk factors. PDAC is known to be associated with several recognized and modifiable risk factors such as obesity, tobacco smoking, heavy consumption of alcohol and different dietary components [3]. Non-modifiable risk factors include age, diabetes, and chronic pancreatitis. These environmental stressors not only increase the likelihood of developing PDAC, but they also underline the development of other chronic metabolic pathologies, such as type 2 diabetes (T2D) and cardiovascular diseases, offering possible insight into this complex pathological relationship known to be enforced via an altered expression of a vast gamut of genes. Smoking is one of the major risk factors for PDAC and smokers can be more than twice as likely to contract PDAC compared to non-smokers (Table 1); nonetheless, compared to other smoking-related cancers, no carcinogen-related mutational signatures have been identified in PDAC [4]. Around 5–10% of PDAC patients have a familial history of the disease characterized by at least two first degree relatives affected by PDAC [5]. Several known hereditary syndromes and genes are associated with an increased risk of PDAC such as *BRCA1, BRCA2, CDKN2A* and DNA mismatch repair genes *MLH1, MSH2,* and *MSH6* (Table 1).

Epidemiological evidence indicates that, for many patients, pancreatic cancer is secondary to metabolic pressures, caused for example by obesity and T2D; conversely, patients-bearing PDAC are at much higher risk of developing diabetes [6]. This strong correlative evidence has been supported by recent studies, offering new avenues for clinical interventions to curb the incidence of PDAC, as well as new insight into the morbidity spectrum associated with metabolic diseases. It is a well-established fact that obese individuals are at higher risk of developing pancreatic precancerous lesions [7]. In particular, the burden of excessive amounts of adipose tissues, especially in early adulthood, raises

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**Table 1**
**PDAC risk factors.** Multiple congenital, and environmental factors are known to increase the risk of PDAC development. A combination of reported confidence intervals is listed for each recognized factor. Data reformatted from [35,36,104,105].

| Risk factor | Overall confidence interval |
|---|---|
| Genetic | |
| STK11/LKB1 | 44–261 |
| BRCA1 BRCA2 PALB2 | 2–3.5 |
| P16INK4A/CDKN2A | 12–47 |
| CFTR | 3.5–6.6 |
| APC | 4.46–6 |
| MLH1, MSH2, MSH6 | 0–8.6 |
| Pathologies | |
| Pancreatitis | 3.5–13 |
| Obesity | 1.3–1.5 |
| T2D overall | 2.0 |
| NOD (< 1 year) | 3.5–8 |
| T2D (> 2 years) | 1.7–2 |
| Long-lasting T2D (> 5 years) | 1.5 |
| Environmental | |
| Smoking | 1.6–2.2 |
| Alcohol | 1.5 |
| Animal fat-rich diet | 1.5 |

the risk for PDAC and overall mortality [8]. Recent evidence expands this tenet, suggesting that the risk is bequeathed to progenies from either obese parent [9]. Similarly, the chronic glucose intolerance seen in maternal diabetes is associated with increased obesity and internal visceral adipose tissue (VAT) in the offspring, which then display an increased risk for PDAC [10]. Taking into consideration that obesity is a risk factor for pancreatic cancer and given its worldwide pandemic status, it is imperative to find new ways to screen this high-risk population for PDAC.

## 3. Pre-clinical models

The preclinical study of the complex relationship between obesity, diabetes and PDAC, is complicated by the lack of animal models translating the human pathology. Animals models of obesity, or diabetes, do not normally develop PDAC. Currently, the most common in vivo system used for the study of PDAC is the transgenic KPC mouse, bearing oncogenic K-RAS G12D and p53 R172H in the pancreas. These animals, despite being successfully used for the study of novel therapeutics in PDAC, have been recently shown to be devoid of any sign of para-neoplastic diabetes [11]. KPC mice fed either standard chow or western high-fat high-sugar diets, did not show any worsening of their glucose tolerance; on the opposite, animals with advanced stage PDAC displayed an improved glucose tolerance. Surprisingly, although the obesogenic diet increased the morbidity of PDAC, the animals with more abdominal fat showed the longest overall survival, even on a standard chow diet. This increase in survival was not maintained when the animals were stratified by whole body weight, in disagreement with human data. As the KPC mouse represents a very aggressive and advanced model of PDAC it is likely that environmental stressors might have a limited impact on the disease progression. In this respect, the KC mouse, a transgenic model that only expresses the oncogenic K-RAS G12D allele in the acinar cells of the pancreas, might represent a more useful animal model. In the KC mouse, an obesogenic high-fat diet significantly increases the incidence of neoplastic growths of the pancreas [12], confirming the link between obesity and its potential contribution to PDAC development and progression while, interestingly, the protection from the same obesogenic diet with metformin has antitumoral properties [13]. In the last decade, several studies have demonstrated that obesity potentiates pancreatic cancer growth and dissemination in animal models [14–17]. Incio et al. in particular proved how dietary-mediated obesity aggravated PDAC aggressivity, via PlGF and VEGFR1 activity and modulating the tumoral immune microenvironment [17]. Moreover, in vitro data indicate that soluble factors produced by adipocytes promote epithelial-to-mesenchymal transition (EMT) and aggressiveness in pancreatic cancer cell lines expressing constitutively activated KRAS [18].

An animal model accurately and comprehensively replicating the human pathophysiology of obesity, diabetes and PDAC in one microenvironment is not yet available; this is likely explained by the species-specific biology, and congenital nature of these animals. A recent report tries to overcome these problems with the use of Tamoxifen inducible Cre recombinase; Talbert and colleagues describe the KPP mouse, expressing the same KRAS-G12D dominant protein, while lacking a functional *Pten* gene in pancreatic acinar cells. The KPP mouse represents a useful pre-clinical model for the study of cachexia [72], a condition of muscle wastage and extreme anorexia seen in most PDAC patients. Nevertheless, the glycaemic status of this model is not reported, making the KC mouse model more indicated for studies exploring the diabetes-PDAC interaction. New studies are necessaries for the assessment of the interaction between modifiable risk factors, such as diet-induced obesity, or hyperglycaemia and genetic predisposition.

## 4. Obesity and PDAC

The link between obesity and PDAC provides a way forward to better define and stratify high-risk populations, in particular through the characterization of anatomically different fat deposits, tissues known to be distinct metabolic organs. A first functional distinction that can be drawn is between the intraperitoneal inter, and intra-organ fat, often loosely referred to as VAT, and the sub-cutaneous adipose tissue (SCAT), with the former being associated with worse prognosis in multiple carcinomas including the pancreas [19].

These different physiologies are also explained by their anatomical location, with the VAT being in close proximity with virtually all internal organs. Indeed, in pathologies such as obesity and T2D the inter-organ VAT infiltrates different tissues including the pancreas and the liver, negatively impacting their physiologies.

Accordingly, the pancreatic fat fraction (PFF) has shown to be the common denominator between obesity, T2D, chronic pancreatitis and PDAC [20–22]; moreover, in obese patients, the PFF correlates with PanIN formation and PDAC development, while being inversely correlated with patients survival [23,24].

The ability to distinguish VAT from SCAT, both at the clinical and molecular level, is therefore essential to depict a more holistic view of PDAC, aiding in a better stratification of patients for more tailored interventional strategies. It is now clear that different adipose tissues communicate locally, and distally through the bloodstream, using a complex array of cytokines named adipokines, that can target different tumour microenvironments. Obesity is indeed a known pro-inflammatory insult, with proven capacity to stimulate Tumor Associated Neutrophils (TANs), that activate Pancreatic Stellate Cells (PSCs), which are in turn responsible for the typical desmoplastic fibrotic reaction seen in PDAC, resulting in a poorly perfused and difficult to treat, tumour microenvironment [25]. An additional way of communication from the adipocytes has been recently demonstrated, occurring via an upregulated and distinct type of lipid-filled extracellular vescicles (EVs) that modulate adipose tissue macrophages, or distant organs, establishing a pro-tumoural environment [26] (Fig. 1).

Few molecular pathways defining the effect of VAT on the tumour microenvironment have been described in different types of cancer, with inflammation being a recognized pathological driver of PDAC [27]. For instance, it has been reported that adipose stromal cells, the progenitors of differentiated adipocytes residing in the VAT surrounding a prostatic tumour, directly committ cancer cells to an EMT transition, possibly via CXCL12, increasing chemoresistance and overall morbidity [28]. A similar interplay is possibly underpinning the

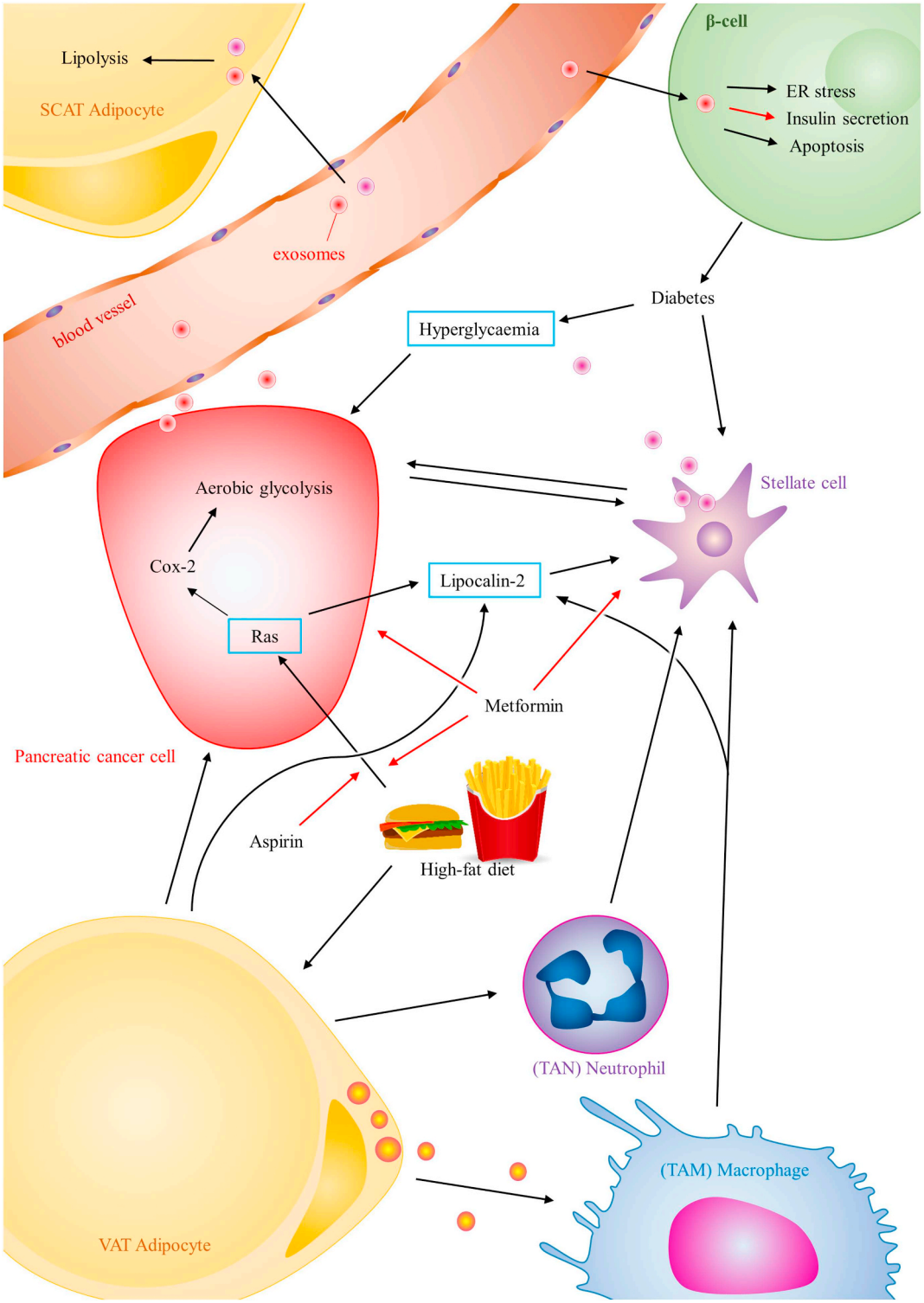


**Fig. 1. The pancreatic cancer microenvironment in obese and diabetic individuals.** Different environmental stressors support the growth of a dysplastic pancreatic cancer cell (shown at the centre-left in red), and its epithelial-to-mesenchymal transition (EMT). Obesogenic diets, rich in fat and ω-6 lipids, have recently been shown to directly sustain a Ras-mediated aerobic glycolysis supporting cellular proliferation reliant on glycolysis [32]. A western-type, high fat diet is a pro-inflammatory and pro-oncogenic stimulus [16,29,30], that can at least partially be blocked with metformin [13]; a drug that has also shown to inhibit the PSCs-mediated oncogenic desmoplastic reaction [101], and directly reduce tumoral metabolic plasticity [102]. Animal data also indicates that aspirin protects from HFD-induced PDAC [95]. Visceral fat directly supports PDAC development with soluble factors such as Lipocalin-2, and indirectly involving TANs, TAMs and PSCs-mediated inflammation [17,23,25,27,32]. The cancerous pancreatic cells, as well as PSCs, have proven to secrete exosomes containing adrenomedullin capable to induce peripheral lipolysis [79–81]. Moreover, the diabetic state, through hyperglycaemia or hyperinsulinaemia, supports the metastatic dissemination and growth of the primary tumour, especially through pancreatic stellate cells (PSCs) [42,43,45,50,63]. Adipocytes have also been proven to bey key players, secreting paracrine Wnt ligands with direct pro-oncogenic properties [18], in addition to pro-inflammatory capacities mediated by recruited TANs, and TAMs in special nanovescicles [25,26]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

development of PDAC, making this axis a valuable target for future therapies aimed at its inhibition.

Several studies have also investigated the effect of different diets, or selective dietary components on cancer development and progression. For instance, it has been reported that processed meat, or a hyper caloric diet rich in fats, especially omega-6 lipids, directly correlates with more pancreatic intraepithelial lesions (PanINs), resulting in increased invasiveness supported by an inflamed microenvironment [29,30].

Recently, Wang et al. [31] demonstrated that a high-fat diet (HFD), but not a high-carbohydrate diet, upregulates KRAS-G12D and drives a shift toward an aerobic glycolysis in the KC mouse model, resulting in more invasive PanINs and ultimately PDAC. Importantly, the observation that such overactivity of KRAS-G12D depends on the key inflammatory mediator cyclooxygenase-2, further provides a promising novel therapeutical target for the indirect inhibition of KRAS activity.

Lipocalin-2, a protein known to be involved in the development of multiple malignancies, is also a key player in the microenvironment underlying PDAC development. Lipocalin-2 was recently shown to be an important master regulator of the VAT hypertrophy detected in HFD fed animals; its genetic deletion curbs PDAC development in K-RasG12D expressing transgenic mice [32]. Although more studies are required to better understand the clinical importance of these pathways, the available data indicates that the pharmacological modulation of specific types of VAT represents a novel promising approach holding powerful theragnostic potential.

## 5. Diabetes-derived PDAC

The hyperglycaemic status observed in T2D patients is the consequence of excessive hepatic gluconeogenesis, hampered incretin activity and peripheral uptake of glucose, all compounded by an impaired insulin signalling. The pathophysiology of diabetes has many pro-tumoral features, and represents a recognized risk factor for the development of PDAC. Indeed, patients are more likely to develop PDAC within few years from their diagnosis of diabetes, rather than later [6]. To understand the rationale behind this differential risk, and better stratify high-risk populations, it is important to frame it in the context of the metabolic dynamics of type 2 diabetes. Before being diagnosed, patients are often asymptomatic for up to a decade, with a silent glucose intolerance controlled by a growing hyperinsulinemia. Only after a few decades of overt, uncontrolled hyperglycaemia, diabetics become hypoinsulinemic, with ever-present increased levels of glucose in their tissues. Nonetheless, in this timeframe often encompassing at least two decades, the first years appear to be critical, making novel onset diabetes (NOD) patients > 50% more likely to develop PDAC than long-term diabetics [33–37].

Indeed, extensive epidemiological data link hyperglycaemia to PDAC risk [39,40], and recent studies have started to unveil a novel axis that could offer a broader picture of this relationship, offering possible therapeutical targets.

For instance, a study led by Rahn et al. [41] sheds some light on the strong pro-tumoral effects of hyperglycaemia; the authors showed how high blood sugar in mice supports the activation of the transforming growth factor β-1 pathway, causing reduced E-cadherin expression in the ductal epithelial cells, resulting in a more mesenchymal and pro-metastatic morphology.

Mechanistic evidence between high glucose levels and genomic instability has been recently found in pancreatic cancer. High glucose levels increase post-translational O-GlcNAcylation leading to nucleotides imbalance and genomic instability ultimately supporting KRAS mutations [42].

This is corroborated by evidence in patients with resected PDAC, whereby glycated haemoglobin (HbA1c) levels higher than 9.0% are worse prognostic markers than the diabetic status [43].

Beyond hypoglycaemia, recent evidence [44] indicates that lipotoxicity, the accumulation of lipid derivatives in non-adipose tissues, as seen in T2D, activates pancreatic stellate cells (PSCs) residing in the islets, which then impair the viability of pancreatic β-cells, leading to insulin deficiency, while stimulating PDAC cells proliferation and invasion, both in vitro and in vivo in a xenograft mouse model [45,46]. Importantly, such pro-diabetic action could be prevented by the overexpression of sterol regulatory element-binding protein -c1 ex vivo in rat islets [44], possibly suggesting a strategy to counteract diabetes onset in this context. This study however contrasts with older evidence in diet-driven diabetic rats, where the use of the anti-fibrotic agent pirfenidone was shown to impede the migration and activity of PSCs but did not improve the diabetic state [47]. Activated PSCs are also well-known cellular players responsible for the highly desmoplastic microenvironment characterizing PDAC. Although more evidence is needed to pinpoint their pro-fibrotic nature specifically in T2D, studies in orthotopic mouse models of PDAC implicate the HGF/cMET pathway as a viable target in multidrug therapy [48]. PSC are indeed key proxies acting at the interface of multiple cell types, including the immune system, mechanistically linking T2D to pancreatic cancer via their pro-inflammatory nature [34].

Beyond the pathology of T2D itself, PDAC is an iatrogenic condition resulting from diabetes pharmacologic management. Strong correlative evidence indicates that independently from the obesity status, hyperinsulinemia is an unfavourable predictive marker in any type of cancer mortality [49,73]. In diabetics, insulin is either overproduced endogenously to compensate initial peripheral resistance, or is introduced exogenously as a treatment in later stages of the disease. Recent studies have proven that this hormone supports a proliferative niche via the activation of PSCs [50], or directly, in synergism with Insulin-like growth factor 1 (IGF-1), via the activation of the ERK1/2 pathway [51,52], a critical axis in PDAC development as recently demonstrated in human primary, and metastatic tumour tissues [53]. Indeed IGF-1 has proven to be a valid blood marker capable to discriminate diabetic patients bearing PDAC from pancreatitis [54]. The hyperactivity of ERK1/2 is in turn associated with the pathological development of insulin resistance [55], bridging again the pathologies of PDAC and T2D.

Amongst the novel anti-diabetic drugs, glucagon-like peptide-1 (GLP-1) receptor agonists have also similarly been associated with increased risk of PDAC, although the causality is yet unproven [56].

Overall, these studies indicate a complex, inter-cellular network between diabetes and PDAC, unveiling contrasting possible effects of different anti-diabetic drugs on cancer development and progression.

## 6. Diabetes as a clinical manifestation of PDAC

The strong correlation between diabetes and PDAC is indeed a two-way self-reinforcing relationship. As recently reviewed by Singhi et al. [38], patients diagnosed with PDAC are much more likely to have different degrees of glucose intolerance, whereby only less than a tenth displays a normal fasting glycaemia at diagnosis. This strong correlation between diabetes and pancreatic cancer is indeed a two-way self-reinforcing relationship. Most PDAC-bearing patients are chronically hyperglycaemic, and tend to lose both body weight and their pancreatic β-cell activity with the progression of the disease, resulting in overt late-stage diabetes over time.

Indeed, fasting blood glucose is now recognized as an easy-to-measure blood-marker for a better stratification of populations at high-risk for PDAC. Impaired glycaemia has recently been shown to be the clinical manifestation of less differentiated tumours of 1 to 2 $cm^3$ in volume, detectable up to 30 months before PDAC diagnosis [57]. New studies have defined these periods more precisely, showing how patients bearing PDAC experience a loss of body weight averaging 4 kg in the 18 to 6 months prior to diagnosis, and 8 kg in the 6 months preceding diagnosis. Moreover, the same individuals experience reduced levels of their serum lipids, including low-density lipoprotein, high-density lipoprotein, triglycerides and cholesterol [58,59].

Reportedly healthy patients, experiencing unexplained weight loss

and hyperglycaemia, could be further stratified with the use of other blood markers, that albeit yet correlative in nature, could improve the stratification strategy of patients.

## 7. Metabolic abnormalities in PDAC

As described in the previous chapter, patterns of metabolic changes are normally occurring in the prediagnostic phase of PDAC, offering a diagnostic window for the early detection of an ideally localized resectable and curable disease. In a recent comprehensive study, the temporal profile of metabolic parameters has been annotated in a cohort of PDAC patients compared to controls [58]. The authors identified three distinct metabolic phases, starting around 3 years before diagnosis with new onset hyperglycaemia (Phase I, hyperglycaemia). Subsequently, a decrease in circulating lipids coupled with weight loss, occurs 1.5 years before classic diagnosis (Phase II, pre-cachexia). In the last phase (Phase III, cachexia), occurring around 6 months before diagnosis, a further general decrease in lipids, SCAT, VAT and muscle is seen, whereas fasting glucose continues to increase. SCAT loss is accompanied by an increase in body temperature suggesting that this is a consequence of the browning of white SCAT, a known mechanism of SCAT reduction in cancer [66]. Indeed, the vast majority of PDAC patients reports weight loss that meets the criteria of cachexia at diagnosis [67]. Cancer-associated cachexia is hard to treat [68], being a major cause of mortality responsible for at least 20% of cancer deaths has an impact not only on survival but also on quality of life [69]. Cachexia is a recurrent problem in cancer patients, and it is most commonly seen in PDAC patients; characterized by a reduced calorie intake due to loss of appetite, and coupled with increased energy expenditure [70], it results in pronounced muscle wasting and general inflammation induced by a combination of tumour-derived factors and host cytokines secreted by different tissues and cells of the tumour microenvironment [68].

Non-canonical IκB kinases (IKKs) TBK1 and IKKε are another molecular bridge linking this meta-inflammation to cancer, obesity, and diabetes. [74]. Recent studies have shown in blood samples of PDAC patients, reduced expression of pancreatic polypeptide (PP) and glucose-dependent insulinotropic peptide (GIP) in response to a meal [60,61], or increased activity of the GLP-1 degrading serine exopeptidase dipeptidyl-peptidase-IV (DPP-IV) in NOD patients [63]. Further stratification could also be implemented considering increased plasmatic levels of the antigen CA19-9. However, the sensitivity and specificity of this blood marker is still controversial, marred by unacceptably high levels of false negatives, due to 5–10% of patients not producing it for genetic reasons, or false positives indicating benign conditions [65]. Nonetheless, some authors have recently described its use in diabetic patients, defining a cut-off value of 75 U/ml offering a yet unprecedented sensitivity of 69.5%, and specificity of 98.2% [64].

Despite these encouraging results, as discussed recently by Singhi et al. [38], there is currently no recognized marker that can diagnose a silent PDAC as all available studies use cohorts of patients either carrying PDAC or not.

Diagnosing a clinically silent PDAC requires the validation of a panel of markers in prospective longitudinal studies, whereby different high-risk populations are followed for multiple years. Nevertheless, current evidence already warrants the clinicians' attention in NOD patients reporting weight loss [57,58]. It is in this growing high-risk population that all the potential PDAC specific biomarkers must be investigated to improve the likelihood of early detection while maximizing both sensitivity and specificity. Given this complex picture, it is important to further segment cohorts based on the underlying pathology, distinguishing obesity from T2D or NOD, and considering the overall internal anatomy of PFF, VAT, and SCAT.

## 8. Extracellular vesicles as proxies of the tumour microenvironment

EVs are emerging as key players in multiple neoplastic microenvironments [75]. EVs are divided functionally and morphologically into microvesicles, apoptotic bodies, both derived from the plasma membrane, and exosomes, formed from late stage endosomes with a unique cell-specific cargo.

Recently, PDAC cells have been shown to secrete exosomes capable to suppress the gut-derived insulin-secretagogues GIP and GLP-1 via micro RNAs (miRNAs) in vitro, which compounded by the increase in DPP-IV activity mentioned in the previous section, results in lower levels of GIP reported in PDAC patients.

These miRNA-containing exosomes (*exo*-miRNA), are delivered to the gut via pancreatic juices, and exacerbate the diabetic state often seen after PDAC diagnosis [76]. Some of the glucose lowering properties of metformin can also ascribed to its GLP-1 secreting capabilities [77]. Nonetheless this loss of GLP-1 activity seen in PDAC appears benign given the retrospective evidence also mentioned in section 5; iatrogenic GLP-1 receptor over-activation is associated with PDAC development, especially in the short term [57], although the timing also needs to be considered to discern either causality.

Overall exosomes are valuable blood-markers and, as recently reported, they are capable to distinguish patients with non-malignant pancreatitis from PDAC. Nakamura et al. isolated exosomes from pancreatic juices of patients with either pancreatitis or PDAC, and showed elevated levels of the *exo*-onco-miR-21 and exo-miR-155 while, interestingly, their levels in the whole pancreatic juice were non-discriminatory [78]. Overall, cytology of the pancreatic juice, combined with exo-miR-21 and exo-miR-155, are reported to offer an accuracy of 91% for the diagnosis of PDAC.

Furthermore, both PDAC cells and PSCs are known to secrete exosomes containing adrenomedullin and CA19-9, with the ability to induce peripheral lipolysis [79,80] (Fig. 1), as well as endoplasmic reticulum-stress, to β-cells, resulting in impaired insulin secretion and ultimately leading to cellular death and overt diabetes [81]. This molecular axis explains the weight loss that precedes the diagnosis of NOD and underpins the diagnostic potential of CA19-9 in the plasma as described in the previous section 7.

## 9. Microbiota, immune system and pancreatic cancer

Recent evidence indicates that the human intestinal microbiota can migrate into the pancreatic ducts, establishing an intra-pancreatic microbiome that has been reported to support the development of PDAC and other malignancies in multiple mouse models [82]. The majority of PDAC patients possess an intra-pancreatic microbiota [83], primarily Gram negatives of the phyla *Proteobacteria*, with a marked decrease in their gut levels compared to healthy controls [84].

The PDAC-associated pancreatic and intestinal microbiomes were proven to be pro-tumoral in animal models, while their ablation by oral antibiotics was sufficient to slow down PDAC progression in KC mice [85].

The pro-oncogenic microenvironment supported by this microbiome is shown to involve immune tolerance through the hyperactivation of multiple pattern recognition receptors in monocytic cells [85].

Surprisingly, in addition to a dysbiotic intestinal and pancreatic microbiota, a recent study indicates that the oral microbiota of PDAC patients is also disease-specific, holding a promising non-invasive theragnostic potential [85].

Data also indicate that PDAC treatments can affect the gut microbiome and affect the progression of the disease. For instance, Panebianco et al. [86] have recently shown that treatment with Gemcitabine increases the presence of *Akkermansia muciniphila*, *Escherichia coli*, and *Aeromonas hydrophila* in a mouse xenograft model, while

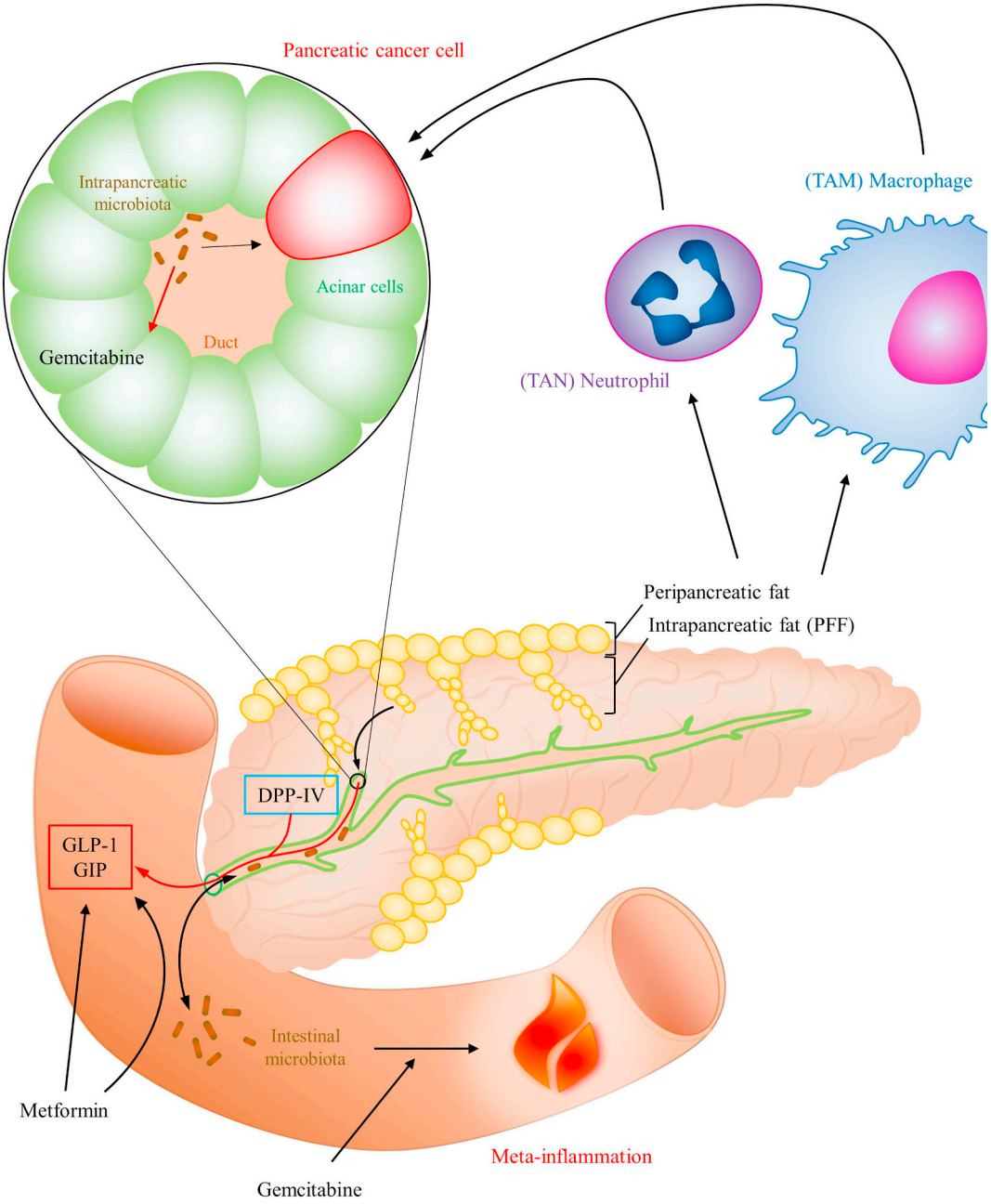


**Fig. 2. The role of microbiota in PDAC associated with diabetes and obesity.** A key molecular player bridging the environment, with obesity, diabetes and the PDAC is the microbiota. A section of the duodenum and the pancreas is shown, highlighting the main pathological axis seen in obese, diabetic patients with PDAC. Tumour bearing patients display high levels of *Proteobacteria* in their pancreatic ducts, capable to exert both pro-tumoral, and chemoresistant properties to PDAC cells [83,90]. Gemcitabine has also shown to support a pro-inflammatory intestinal microbiota [87]. An obesogenic environment supports the growth of visceral, inter-organ and intra-organ fat, which elicits pro-inflammatory and pro-tumoral effects mediated by TAMs, and TANs [14,15,17,23–26]. PDAC derived exosomes containing different miRNAs, have shown to lower the levels of the incretins GLP-1 and GIP [76], a finding compounded by the elevated DPP-IV activity seen both in plasma and in PDAC tissues [63]. Conversely, the anti-diabetic drug Metformin has shown GLP-1 secreting capabilities directly from gut L-cells [77], or indirectly through the microbiota [87]. The clinical monitoring of this pathological microenvironment holds strong potential for a better screening of patients bearing a silent pancreatic cancer. Black and red arrows indicate proven positive and negative modulations respectively. Molecular players found to be upregulated, or down-regulated are squared in blue or red respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

decreasing the two phyla of *Firmicutes* and *Bacteroidetes*, supporting a pro-inflammatory microbiome. Reduced levels of Akkermansia muciniphila have also been described in T2D independently from PDAC status [87]. Furthermore, some Gamma *Proteobacteria*, detected in the majority of pancreata of PDAC patients, are able to metabolize Gemcitabine, therefore mediating chemoresistance [84]. These studies not only underline the importance of the microbiota during PDAC development and progression, but they also suggest its central role during drug resistance development [88]. The role of the immune system, specifically the neoantigen number and quality of CD8 positive T-cell infiltrates, represents a critical parameter that long-term PDAC survivors display. [89]. Indeed, a new study provides experimental evidence that the PDAC associated microbiome is not only protumoral [90], but its composition holds prognostic potential, in long-term

survivors was shown to be more diverse, and less immune-tolerant in mouse models.

Another recent study reports that the faecal microbiota of KPC mouse models in the early stages of the disease is enriched in *Proteobacteria* and *Firmicutes*, representing another easy to access tumour marker [91]. As the gut microbiota represents a dynamic ecosystem that shifts under metabolic insults as seen in obesity [92], both the intestinal and intrapancreatic microbiota are key proxies bridging environmental insults, such as diet, to obesity, diabetes and PDAC [93], playing a significant role in their reciprocal triple-causality (Fig. 2). The benefits of metformin can also be ascribed to its interaction with the gut microbiota, increase in Short chain fatty acids (SCFAs) secreting bacteria, conjugated bile acids, and levels of *Akkermansia muciniphila*, which have shown to play in concert resulting in improved incretin secretion, blood lipidomic, gut barrier integrity and consequent reduction of inflammation [88]. This interplay offers an important therapeutical opportunity adding a new layer of complexity to segment high-risk population screenings, while also providing the grounds for its therapeutical manipulation in future pre-clinical and clinical studies of diabetic individuals at high risk of PDAC. The understanding of the interactions of the immune system with different microbial populations throughout the tumoral evolution is of paramount importance for the development of improved future immunotherapies.

## 10. Pancreatic cancer chemoprevention

Chemopreventive strategies could be useful in individuals that are at high risk of developing pancreatic cancer, or presents premalignant lesions [3]. Different natural and synthetic compounds have been suggested as pancreatic cancer chemopreventive agents both in cellular in vitro and in vivo animal models.

As discussed in section 4, high-fat diet is pro-tumoral in mouse models, with proven capacity to generate metabolic shift via hyper activation of mutagenic KRAS [31]. Another study indeed builds upon this concept, demonstrating that simple anti-inflammatory treatment with aspirin is sufficient to protect from this risk in HFD mice [94].

This study implies that other environmental factors, such as smoking, infection and aging, could influence the phenomenon of cell competition which is physiologically present, and sees normal epithelial cells extruding, and eliminating transformed ones. Nonetheless, results on the utility of aspirin to prevent PDAC risk in humans are debated. Indeed, cholesterol lowering statins, but not aspirin, was found by Archibugi et al. to be associated with a reduced PDAC risk [95].

In particular, the use of statins in combination with aspirin did not reduce further the risk compared with statin alone; moreover, the protective effect of statins was dose-dependent and more evident in smokers, elderly and obese patients. More recently, a more comprehensive meta-analysis study compounds on this evidence indicating that statins use, especially with atorvastatin, is associated with a 30% reduction of PDAC risk [96]. However, the use of statins as chemopreventive agents should take into account the confirmed adverse events caused by their use including the effect on incidence of NOD [106].

Another drug actively investigated in cancer clinical trials, in combination with other treatments and for chemoprevention, is the biguanide drug metformin, commonly used for the treatment of T2D patients. Recent meta-analysis studies, as well experimental evidence in animal models, have indicated that metformin, protects from and improves the prognosis of different types of cancer including PDAC [13,71,97], supporting this first line of treatment for any newly diagnosed T2D. Metformin in particular, appears to exert its tumour suppressing properties by phosphorylating 5′ AMP-activated protein kinase (AMPK), and inhibiting the desmoplastic pro-tumoral reaction of activated PSCs [102]. Further compelling evidence supporting metformin comes from another recent study indicating that it is possible to impair the tumour plasticity by using metformin coupled with intermitted-fasting induced hypoglycaemia. This time-dependent treatments simultaneously blocks oxidative phosphorylation and glycolysis, impairing tumour growth in vitro, and in vivo in mice xenografted with patients-derived melanoma cells [103]. However, other studies dispel the benefits of metformin on PDAC survival [98], with others reporting some benefits specifically in post-pancreatitis diabetes mellitus (PPDM) patients with PDAC [99], a particular subtype of diabetes, different from T2D, often referred to in literature as Type-3c diabetes [100].

## 11. Conclusions

Considering the current worldwide epidemic of obesity and T2D, an increase in the incidence of pancreatic cancer can be foreseen. In this manuscript, we have highlighted the most recent studies that link these three pathologies, defining a complex inter-organ microenvironment summarized in Figs. 1 and 2.

With our current understanding of PDAC, we can better stratify patients with NOD, mainly considering a reported body weight loss and multiple blood-based biomarkers that need to be further evaluated to justify the invasiveness of imaging techniques such as endoscopic ultrasounds (EUS). The latter, is indeed the only available tool for the detection of a localized, early-stage malignant neoplasm with volumes inferior to 2–3 mm, invisible to any other high-content technique such as CT or MRI [38].

Major clinical evidence is necessary to evaluate the druggability of this complex inter-organ pathological interplay, in order to formulate the next generation of therapies for improved prevention, detection and cure of PDAC.

To achieve this goal, longer multi-centred prospective studies are required for a more detailed monitoring of obese and diabetic patients, aiming to better stratify their cohorts, including the important variable of dietary intake. As recently reported, fasting-mimicking diets (FMD) have a profound impact on the body [103], offering an important tool worth exploring as part of preventive, and possibly curative, regimens to disrupt the pathological array of pathways described in this manuscript.

An extended blood chemistry analysis should consider circulating adipokines, which are essential to dissect the role of visceral mesenteric fat, peri-pancreatic fat, and even liver steatosis, given their recognized and distinct role in the pathophysiology of T2D and PDAC. The secretome of the microbiota and other tumoral players such as PSCs are also offering valuable opportunities.

This comprehensive approach could result in more personalized and targeted diagnostic and therapeutic strategies, ultimately providing much needed improvement to the current abysmal survival rates for PDAC patients.

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## Author contributions

S.P. collected analysed and interpreted data from available PUBMED literature, conceptualized and wrote the manuscript. M.F. conceived, revised, supervised and wrote the study; both authors approved the final version of the article.

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