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Obesity associated pancreatic ductal adenocarcinoma: Therapeutic challenges

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ABSTRACT

Obesity is a prominent health issue worldwide and directly impacts pancreatic health, with obese individuals exhibiting a significant risk for increasing pancreatic ductal adenocarcinoma (PDAC). Several factors potentially explain the increased risk for the development of PDAC, including obesity-induced chronic inflammation within and outside of the pancreas, development of insulin resistance and metabolic dysfunction, promotion of immune suppression within the pancreas during inflammation, pre- and malignant stages, variations in hormones levels (adiponectin, ghrelin, and leptin) produced from the adipose tissue, and acquisition of somatic mutations in tumor once- and suppressor proteins critical for pancreatic tumorigenesis. In this manuscript, we will explore the broad impact of these obesity-induced risk factors on the development and progression of PDAC, focusing on changes within the tumor microenvironment (TME) as they pertain to prevention, current therapeutic strategies, and future directions for targeting obesity management as they relate to the prevention of pancreatic tumorigenesis.

1. Introduction

The epidemiology of obesity and pancreatic ductal adenocarcinoma (PDAC) is of significant interest due to the strong association between these conditions [1]. Obesity is a global public health concern. In the United States, over 30% of individuals are overweight (BMI>25), with 50% of those individuals being severely overweight (BMI>30). Obese individuals are more likely to develop cardiovascular diseases, type 2 diabetes, hypertension, and certain cancers, including PDAC [2,3]. The occurrence of overweightness (obesity) has steadily increased over recent decades [4]. In contrast, PDAC, while relatively rare compared to other cancer types, ranks among the deadliest [5]. Development of PDAC is associated with several risk factors, including smoking, a family history of PDAC, chronic pancreatitis, specific genetic syndromes, and obesity, which is the focus of this review [6].

Obesity is a pivotal modifiable risk factor associated with the incidence of PDAC [7], mainly exerting its impact on the progression of PDAC through various mechanisms, including the promotion of chronic inflammation [8], the influence of adipose tissue derived soluble mediators on oncogenic Kirsten rat sarcoma viral oncogene homolog (KRAS) signaling [9], the presence of single-nucleotide polymorphisms (SNPs) associated with childhood obesity [10], and the disruption of metabolic pathways [11]. Notably, obesity driven chronic inflammation leads to dysregulation of adipocytokines, insulin resistance, and sex hormones [12]. Furthermore, the inflammation of obesity-associated adipose tissue has garnered significant attention due to its effect on the activity of KRAS, a prominent oncogenic driver in PDAC [13]. An immunosuppressive tumor microenvironment (TME) is also implicated in the correlation between obesity and PDAC [14]. In conclusion, comprehending the intricate connections between obesity and PDAC and recognizing the multifaceted risk factors associated with PDAC enriches our understanding of this complex disease and presents

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potential avenues for its prevention and management.

This review presents PDAC status concerning its incidence, mortality, patient survival, etiology, and risk factors, including genetic and epigenetic alterations that increase the risk of PDAC development. Furthermore, the review discusses preneoplastic lesions associated with PDAC, emphasizing the importance of identifying and understanding their pathophysiology for early detection and intervention strategies. Additionally, we delve into the epidemiology of obesity and its potential association with PDAC, highlighting its significance. Lastly, we describe the underlying mechanisms linking obesity and PDAC and explore potential targeted therapies for PDAC management.

2. Mechanisms of obesity and PDAC

Obesity involves intricate molecular mechanisms that govern energy balance, fat storage, and metabolic homeostasis. While the exact molecular pathways are still an area of active research, several key mechanisms contribute to obesity. Notably, leptin and ghrelin control the neuroendocrine axis-dependent energy homeostasis [15]. Leptin, produced by adipose (fat) tissue, signals to the brain when the body has sufficient fat stores [16]. In obesity, individuals may develop leptin resistance, diminishing the brain's responsiveness to leptin's appetite-suppressing signals, thereby increasing food intake [17].

The dysregulation of adipocytokines leads to increased generation of leptin and reduced production of adiponectin in individuals with obesity [18]. As an oncogenic adipokine, Leptin plays a pivotal role in mediating obesity-associated PDAC by activating various pathways [19]. It promotes tumor growth by enhancing proliferation and glucose uptake via leptin receptor-dependent activation of the AKT pathway [20]. Moreover, leptin mediates PDAC cell growth through multiple pathways involving signal transducer and activator of transcription-3 (STAT3), Phosphoinositide 3-kinases (PI3K), and mitogen-activated protein kinase (MAPK) [21]. Furthermore, it contributes to drug resistance in PDAC by upregulating miR-342–3p and suppressing Krüppel-like factor 6 (KLF6) signaling [22], modulating Notch/retinol binding protein (RBP)- c-Jun N-terminal kinases (JNK) signaling [23], participating in the crosstalk of histone deacetylases (HDAC)-microRNA-leptin signaling [24], and expanding pancreatic cancer (PC) stem cells and their associated transcription factors [25]. The dysregulation of leptin implicated various signaling pathways and drug resistance mechanisms.

Adiponectin, regarded as a tumor suppressor, exerts its inhibitory effect on PDAC growth by disrupting the cell cycle through the suppression of GSK-3β-dependent nuclear increase of β-catenin, leading to a subsequent reduction in cyclin D1 expression [26]. However, it is worth noting that an SNP in the adiponectin gene has been linked with a more significant risk of PDAC. [27]. In a contrasting study, elevated adiponectin levels correlated with pancreatic cystic lesion prevalence [28]. Interestingly, targeting the adiponectin receptor has been reported to sensitize drug resistance in PDAC, achieved through the modulation of the p44/42 MAPK pathway [29]. Despite its role as a tumor suppressor, adiponectin is linked with a potential risk of growing PDAC due to SNPs in its gene.

Obesity is negatively correlated with insulin sensitivity, a condition in which cells convert less reactive to the consequences of insulin [30]. This metabolic condition is further characterized by chronic low-grade inflammation, where adipose tissue functions as an active endocrine organ, releasing pro-inflammatory cytokines [31]. This inflammatory environment can dysregulate insulin secretion and lead to resistance to insulin. In individuals with obesity, immune cells, particularly macrophages, can infiltrate adipose tissue and release inflammatory mediators that exacerbate inflammation and insulin resistance (Fig. 1) [32]. Both insulin resistance and inflammation, key upstream mediators of KRAS signaling, promote PDAC by triggering the activation of growth-inducing networks through Yes associated protein (YAP)-dependent transcription [33]. Additionally, insulin-like growth factor binding protein (IGF-1), a critical mediator of glucose metabolism, is

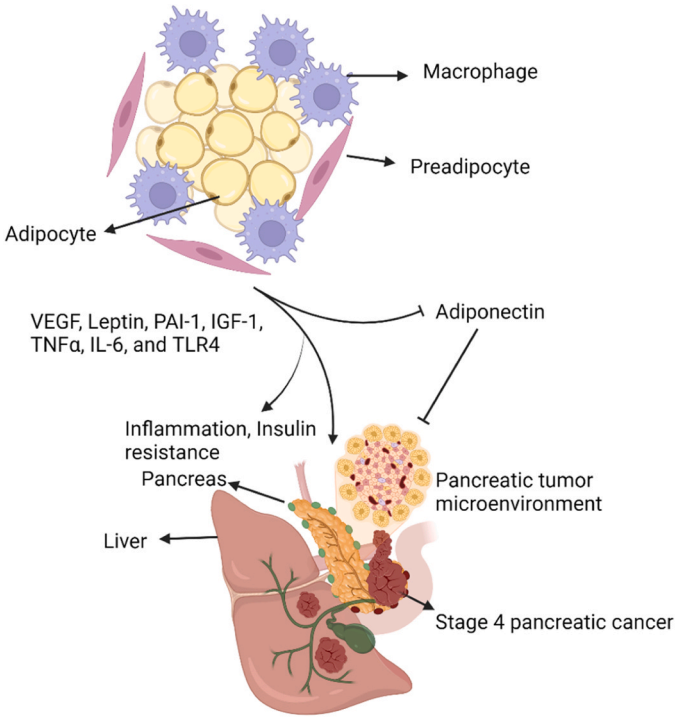

Fig. 1. Active endocrine adipose tissue (chronic low-grade inflammation) produces pro-inflammatory cytokines. This inflammatory environment can impair insulin signaling and contribute to insulin resistance and induces adiponectin inhibition. In individuals with obesity, immune cells, particularly macrophages, can infiltrate adipose tissue and release inflammatory mediators that exacerbate inflammation and insulin resistance. VEGF, vascular endothelial growth factor; PAI-1, plasminogen activator inhibitor-1; IGF-1, insulin-like growth factor 1, TNFα, tumour necrosis factor alpha; IL-6, Interleukin 6; TLR4, Toll-like receptor 4.

pivotal in promoting obesity-associated PDAC by activating PI3K and MAPK signaling pathways [34]. Obesity, inflammation, and insulin-resistance related to PDAC by Toll-like receptor 4 (TLR-4) dependent expression of key inflammatory markers nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), tumour necrosis factor alpha (TNF-α), and interleukin-6 (IL-6) in adipose tissue [35]. Also, plasminogen activator inhibitor-1 (PAI-1) mediates obesity-driven PDAC with inflammation and insulin resistance [36,37]. In conclusion, the intricate interplay between obesity, insulin resistance, inflammation, and molecular signaling pathways (Fig. 1) emphasizes their collective role in promoting PDAC, offering potential targets for intervention and prevention strategies.

3. Etiology, risk factors and progression of PDAC

PDAC is a globally significant disease known for its grim prognosis. With 496,000 diagnosed cases and 466,000 deaths reported in GLOBACON 2020, PDAC is the seventh leading cause of cancer-related mortality. The worldwide incidence rate is 2.6, notably higher in males (5.7) than in females (4.1), highlighting gender-specific factors [38]. Regional disparities are prominent, with Europe and Northern America recording the highest incidence rates (9.9 in males, 5.6 in females), often associated with higher Human Development Index (HDI) scores [39]. According to a population-based time-trend assessment in the US, there is a rising rate of PDAC among younger females [40]. Incidence and mortality rates exhibit relative stability or slight increases, influenced by risk factors like obesity, diabetes, and alcohol consumption, alongside improved diagnostics [41]. Projections indicate that PDAC may exceed breast malignancy as the third leading cause of malignance death by 2025 in certain regions, underscoring the critical

need for continued research into the risk factors, early detection methods, and therapeutic strategies for PDAC. Another projection anticipated that PDACs would reach 18.6 cases per 100,000 people by 2050, reflecting an average annual growth rate of 1.1% globally [42]. This projection shows up the substantial impending public health challenge posed by PDAC.

PDAC presents a formidable challenge with a mortality/incidence ratio of 98% and a 5-year overall survival (OS) rate ranging from 2% to 9% [43]. Interestingly, OS rates exhibit minor variations between developed and developing countries. In the US, approximately 9.4% of PDAC cases are diagnosed locally, with a notably higher 5-year OS of 33.3%, while over half (52%) are diagnosed at a distant stage, resulting in a stark 2.1% 5-year OS [6]. Across Europe, 5-year PDAC-OS rates for PDACs vary, with England, Wales, Denmark, and Sweden below 3% and Italy at 1.2% [44,45]. Germany reported a slightly higher rate of 9.0% [46], while the EUROCARE study highlighted disparities, ranging from 0.0% in Malta to 7.5% for Czech Republic women and 7.0% for Estonian men [47]. Overall, OS in Germany for PDAC patients in the early 21st century was marginally higher at 9.0% [48]. Factors like cancer type, diagnosis stage, serum albumin levels, tumor size, treatment options, healthcare accessibility, and individual characteristics such as age, sex, health, and lifestyle influence these OS rates.

PDAC is one of the fatal malignancies with an unknown etiology. However, known modifiable and non-modifiable risk issues are associated with the disease. The modifiable risk issues include obesity, diabetes [49], chronic pancreatitis [50], tobacco smoking [51], a diet rich in red and processed meat [52], alcohol consumption [53], and viral infections [54]. However, the non-modifiable risk issues of PC include age [55], familial history [56], mutations in tumor suppressor genes BRCA1 and 2 [57], TP53, CDKN2A, and SMAD4), and oncogenes (For example, KRAS) [58]. Obesity is one of the major changeable risk factors, while genetic mutations are one of the non-changeable risk factors, significantly contributing to PDAC development.

4. Genetic and epigenetic alterations

Many genetic and epigenetic alterations contribute to PDAC progression [59]. Kirsten Rat Sarcoma (KRAS) gene mutations are a prominent PC driver, facilitating tumor growth through distinct mechanisms [60,61]. In conjunction with the gain-of-function mutations in the KRAS gene, the loss-of-function mutations affecting TP53, CDKN2A, and SMAD4 are associated with PDAC [62]. Mainly, TP53 mutations are linked to aggressive tumor behavior and therapy resistance in PDAC [63]. Notably, KRAS effectors stimulate FOXA1-dependent transcriptional networks associated with metastasis by triggering a physical interaction between CREB1 and mutant p53 through the induction of WNT/β-catenin signaling [64].

Recent research has showed that p53 mutants enhance KRAS activity by compelling RNA splicing, facilitated by increased heterogeneous nuclear ribonucleoprotein K (hnRNPK) levels. HnRNPK, a positive splicing regulator, promotes the insertion of cytosine-rich exons within guanosine triphosphate guanosine triphosphate hydrolases (GTPase)-dependent proteins and negative regulators [65]. CDKN2A gene mutations, frequently observed in PC, disrupt the function of the p16 protein, leading to uncontrolled cell division [66,67]. Similarly, SMAD4, a tumor suppressor gene often mutated or inactivated in PC, promotes tumor invasion and metastasis when its function is lost [68]. The transforming growth factor beta (TGF-β)-SMAD4 signaling axis further contributes to tumorigenesis by regulating the TME through interactions between PDAC cell and stroma [69]. Recognizing their clinical significance, a recent meta-analysis stresses the utility of mutant KRAS, P53, and SMAD4 genes as prognostic markers in PDAC [70].

In addition to well-established driver mutations, several other mutant genes, including mutant BRCA1 and BRCA2 genes, DNA mismatch repair genes, and mutant GATA6, have been associated in the development of PDAC in specific patient populations. Specifically, a subset of PC cases is linked to hereditary mutations in the BRCA1 and BRCA2 genes, primarily recognized for their roles in breast and ovarian cancer [71]. These mutations elevate the risk of PDAC development and may hold significant implications for treatment strategies.

In a limited fraction of PDAC cases, deficiencies in the DNA mismatch repair system result in microsatellite instability, increasing the likelihood of a positive response to immunotherapy [72,73]. GATA6, a transcription factor gene, undergoes occasional mutations in PDAC, which can influence cell differentiation and contribute to tumor development [74,75]. These additional mutant genes broaden our understanding of the genetic landscape of PDAC and underscore the need for personalized treatment approaches based on the specific genetic alterations present in individual patients.

Beyond genetic modifications, epigenetic alterations, including histone modifications, DNA methylation, and nucleosome remodeling, profoundly influence PDAC metastasis [76]. Notably, gene alterations (NSD1 and SETD2) encoding histone H3K36 methyltransferases were metastasis promoters in PDAC and its pathological precursors [77]. In PDAC, hypermethylation primarily accounts for alterations in TP53, CDKN2A, and SMAD4, while hypomethylation affects multiple oncogenes, including KRAS [78]. Furthermore, research has highlighted the role of N6-methyladenosine (m6A) methylation in mRNA, which promotes metastasis in PDAC through alterations in its "writer," "eraser," and "reader" regulators [79]. Consequently, comprehending genetic and epigenetic alterations is paramount for various reasons. These include the development of targeted therapeutic strategies tailored to specific molecular profiles and the identification of possible biomarkers for early prognosis in PDAC.

5. Pathological precursors

PDAC often originates from preneoplastic lesions, making identifying and understanding their pathophysiology essential for early detection and intervention strategies [80]. These lesions encompass various types, including Intraductal Mucinous Cystic Neoplasms (MCN), Mucinous Neoplasms (IPMN), and Papillary Pancreatic Intraepithelial Neoplasia (PanIN) [81], Serous Cystadenomas (SCAs), Ampullary Adenomas (AAs) and Cystic Pancreatic Neuroendocrine Tumors (PanNETs) [82]. Therefore, a comprehensive understanding of these preneoplastic lesions is crucial for early intervention and improved PC management.

PanIN lesions emerge as the most prevalent precursors to PDAC [83]. PanIN is a typical precancerous lesion of PDAC patients, accounting for 80% of PDAC precursor lesions [84]. It is often harboring mutant KRAS mutations. However, these lesions rarely progress to the invasive form of PDAC. Higher-grade PanIN lesions pose an increased risk of progressing to invasive cancer [85]. Recent investigations have shed light on the potential acceleration of PanINs to PC when KRAS mutations are present. This acceleration is facilitated by the upregulation of a peroxisome proliferator-activated receptor-delta (PPARδ), lipid nuclear receptor, and a high-fat diet's heightened activation of PPARδ. Consequently, this leads to the secretion of CCL2 and the subsequent activation of CCL2/CCR2 signaling, which orchestrates the infiltration of myeloid-derived suppressor cells (MDSCs) and macrophages, creating an immunosuppressive environment [86]. The F-actin bundling proteins, Fascin1 and α-actinin-4, which exhibit distinct structural organizations, are abnormally expressed in PanIN and are associated with its progression to PC [87]. Additionally, the expression of collapsin response mediator protein 4 (CRMP4) is linked to the advancement of PanIN to PDAC [88]. Understanding these molecular mechanisms in the context of PanIN progression to PC is essential for developing targeted interventions.

In PDAC development, IPMN represents another potential precursor account for 15–20% [89]. It typically manifests as cystic lesions originating from mucin-secreting cells within the pancreatic ducts [90]. Grading, dependent on the degree of cellular atypia and architectural alterations, characterizes this condition [91]. Recent research has

highlighted the indispensable role of MNX1-HNF1B signaling in regulating MYC, SOX9, and OLFM4 in the lineage of IPMN [92]. Notably, IPMN is the only precursor lesion of PC detectable through imaging, often presenting as low-grade dysplasia and harboring abundant effector T cells [93]. Significantly, it rarely progresses to an invasive phenotype, primarily due to the infiltration of immunosuppressive cells. The prediction of IPMN's progression to an invasive phenotype hinge on factors such as intra-cystic glucose levels, carcino embryonic antigen (CEA), cystic fluid cytology, and CA 19–9 levels [94]. Understanding the intricate biology of IPMN and its progression factors is pivotal for enhancing PC's early detection and management.

MCNs represent a rare type of precursor lesion for PDAC, characterized by the development of cysts, typically located in the body or tail of the pancreas [95]. MCNs are frequently observed in women and feature ovarian-type stroma with characteristic histology. Significantly, they can potentially progress into invasive cancer [96]. The transformation of MCNs into a malignant phenotype is often associated with independent risk factors, including patient age, the presence of mural nodules, pancreatic duct dilatation, and tumor size [97]. These factors highlight the importance of identifying and monitoring MCNs, offering insights into their potential progression to invasive PDAC.

SCAs are benign pancreatic cysts that have been implicated rarely as precursors to PDAC [98]. Approximately half of all SCAs have been associated with Von Hippel–Lindau disease (VHL) somatic and germline mutations [99]. AAs serve as precursors to ampullary carcinoma, a distinct type of PDAC originating in the ampulla of Vater, where the common bile duct and pancreatic duct converge [100]. On the other hand, PanNETs represent atypical pancreatic cysts associated with von Hippel-Lindau and multiple endocrine neoplasia type 1 syndrome [101]. Recognizing the precursor role of AAs in ampullary carcinoma, the benign nature of SCAs alongside their association with VHL mutations and the association of PanNETs with specific syndromes provides valuable insights into their potential role as precursors to PC.

6. Tumor microenvironment

Inadequate blood amount and hypoxia are mutually connected in PDAC-TME and are involved in the invasion and progression of PDAC cells [102]. As PDACs grow, the requirement for nutrients and oxygen tends to increase, and there is a more substantial increase of hypoxia inducible factor (HIF-1α) in PDACs [102]. Hypoxia induces PDAC migration through epithelial mesenchymal transition (EMT) by activating heat shock factor 1 (HSF1), inhibiting mammalian target of rapamycin (mTOR), pyruvate kinase M2, and hexokinase 2 (Fig. 2A). Adenosine monophosphate-activated protein kinase (AMPK) is an energy sensor. It plays a critical function in cell homeostasis. AMPK is reduced during PDAC growth, EMT, and migration [103]. Further, AMPK loss led to decreased lactic acid and ATP levels and rate of glucose intake in PDAC (Fig. 2A). HIF-1α activates vascular endothelial growth factor (VEGF), TGF-β, and immunosuppression (Fig. 2B) [102]. In TME, HIF-1α activates immunosuppressive proteins and contributes to immune escape. Immunosuppressive cells include tumor-associated macrophage (TAMs), MDSCs, Tregs, and molecules such as VEGF, TGF-β, and programmed death-ligand 1 (PD-L1), which stimulate PDAC progression (Fig. 2B) [104]. HIF-1α recruits Tregs by stimulating the elevated expression of CCL28, FOXP3, epidermal growth factor receptor (EGFR), and TGF-β [104].

TGF-β is essential for the elevated PD-L1 expression on $CD8^+$ T cells, generating the conversion of active T-cells into Tregs [105]. In PDAC cells, HIF-1α raises the PD-L1expression by binding with the promotor

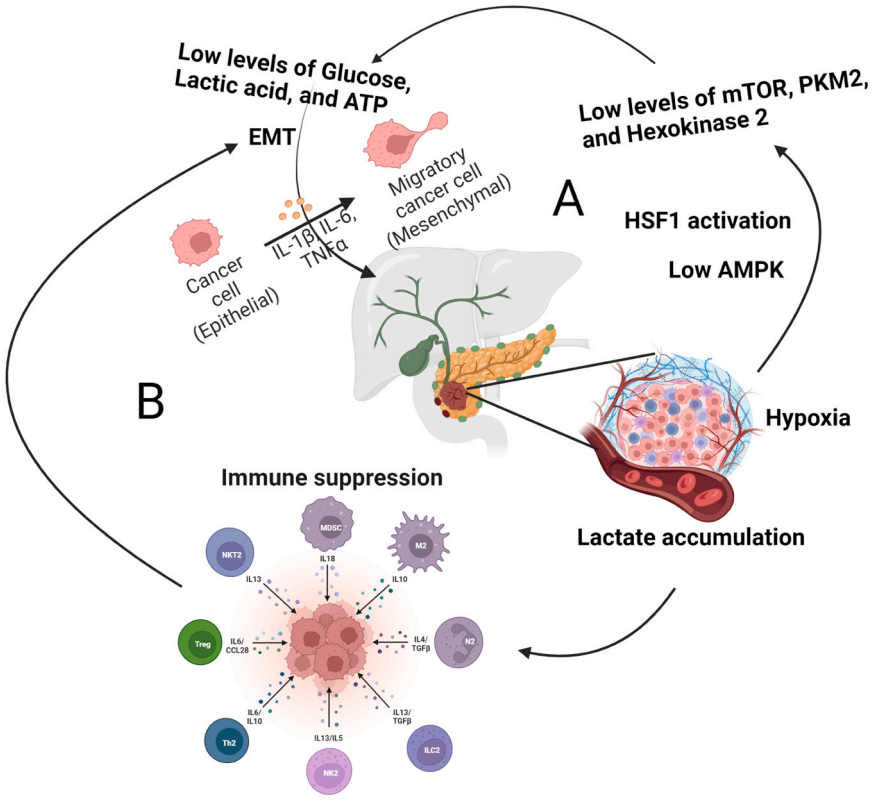

Fig. 2. Tumor microenvironment (TME) on immunosuppression, epithelial and mesenchymal transition (EMT), and migration of pancreatic ductal adenocarcinoma (PDAC). (A) Inhibition of adenosine monophosphate-activated protein kinase (AMPK) reduces various metabolic enzymes, causing decreased adenosine triphosphate (ATP) and glucose levels in PDAC, which causes PDAC cells to be involved in EMT. (B) Metabolic altering and lactate buildup stimulate the infiltration of immune suppressive cells and help EMT and migration in PDAC. HSF1, heat shock factor 1; mTOR, mammalian target of rapamycin; PKM2, pyruvate kinase muscle isozyme M2; IL-1β, interleukin-1 beta; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha.

hexa nucleotide repeated expansion (HRE) of PD-L1 or PI-3 K/PTEN pathway [105]. EMT is essential in tissue remodeling and organ fibrosis during PDAC progression [106]. EMT-associated transcription factors (ZEB1 and Snail) regulate CCL2 expression, which induces MDSCs, TAMs, and Tregs in PDAC-TME [107]. After EMT happens, PD-L1 is triggered, and mesenchymal PDAC cells are low susceptible to NK cells attack and cytotoxic T lymphocyte (CTL) lysis [107]. IL-8 decreases the CD8 T cell's function by elevating the PD-L1 expression on the macrophages.

The TME plays a significant function in the development, and advancement of PDAC. Comprising various cells, including adipocytes, CAFs, stellate cells, T lymphocytes, and myeloid cells, each serves a unique function [108]. PDAC often arises adjacent to adipose tissue, with adipocytes acting as a source of lipids, and fatty acids contributing to disease progression, and participating in the remodeling of the TME. PDAC cells are surrounded by a dense desmoplastic stroma, causing in hypoxia and poor nutrients within the tumor. Satellite cells and cancer-associated fibroblasts become activated within this TME and can promote PDAC growth by secreting growth factors and extracellular matrix (ECM) proteins [109]. These cells are significant contributors to collagen formation in the tumor stroma. Among the critical myeloid cells show in the TME are MDSCs and TAMs [110]. MDSCs play a role in suppressing immune responses, while TAMs can actively promote tumor growth. T cells in PDAC tumors remain debatable; although $CD4^+$ and $CD8^+$ T cells are found in some tumors; their functional activity may not always be assured. Dendritic cells (DCs), another immune system component, regulate immune responses but can be compromised within the PDAC-TME [110]. Additionally, B cells and specific subsets, such as IL-35-producing B cells, can potentially promote pancreatic neoplasia. Understanding the functions of various cell types in the TME is crucial, as it can aid researchers in identifying potential therapeutic targets [108].

Obesity plays a significant role in influencing the PDAC-TME, influencing various aspects of PDAC cell progression. One critical aspect is the chronic inflammation associated with obesity. In obese individuals, adipose tissue changes such as hypertrophy and hyperplasia, leading to the release of pro-inflammatory cytokines and chemokines [3]. This pro-inflammatory environment creates a favorable milieu for the initiation and growth of PDAC, potentially influencing tumor initiation in early adulthood. Immature fat cells, Preadipocytes produce inflammatory molecules that attract and activate immune cells like macrophages and endothelial precursors [111]. This perpetual inflammation hampers preadipocyte differentiation and perpetuates a chronic inflammatory state within adipose tissue [112]. This inflammation fuels tumor growth and triggers a cascade of events, including the proliferation of preadipocytes and the formation of new blood vessels, further promoting tumor progression.

Leptin, a hormone adipose tissue produces, is critical in this context [113]. It possesses mitogenic and inflammatory functions and is linked to the expression of Notch receptors, cancer stem cell markers, and various signaling pathways that enhance the aggressiveness of PDAC cells [113]. Leptin's effects are mediated through pathways like JAK2/STAT3, promoting PDAC cell migration, invasion, and metastasis [111]. The interaction between obesity, inflammation, and signaling pathways is complicated and interconnected. Notch signaling, for instance, is associated with multiple aspects of tumor progression, including proliferation, EMT, and resistance to chemotherapy [114]. Inflammatory mediators, particularly IL-1, facilitate crosstalk between Notch and leptin signaling, amplifying the pro-carcinogenic effects [114]. Furthermore, the chronic inflammation in the TME activates the NF-κB pathway, contributing to inflammatory operated EMT, increased PDAC resistance, and proliferation to therapies. Additionally, adipose tissue's high angiotensin II type 1 receptor expression in an inflammatory setting is linked to pro-fibrotic pathways, further enhancing the desmoplastic reaction in PDAC [115]. Obesity's role in the PDAC-TME is multifaceted and interconnected. It involves chronic inflammation, signaling pathways like Notch and NF-κB, and the influence of adipokines like leptin [14]. Understanding these complex interactions is crucial for developing strategies to prevent and treat PDAC in obese individuals. It highlights the need for early prevention campaigns promoting healthy lifestyles and weight control.

7. Preventative strategies

7.1. Calorie restriction and bariatric surgery

Calorie restriction (CR) plays a vital role in PDAC prevention. CR in preclinical studies has shown that it decreases PDAC progression. For instance, in a PDAC xenograft model, CR C57BL/6 mice have low weight and regressed tumors compared to mice fed with a regular diet [116]. Likewise, CR affects nude mice bearing Mia PaCa-2 tumor growth by activating NF-κB and insulin-like growth factor-1 (IGF-1) in a dependent manner [116]. CT delays the progression and PanIN-3 lesions in the loxP-flanked stop codon (LSL)-KrasG12D-Pdx-1/Cre mouse model of PDAC compared with the ad libitum group [117].

Obese patients usually have chronic disorders such as hyperlipidemia, type 2 diabetes, heart disease, and hypertension. Bariatric surgery (BS) helps to increase life span and reduce weight and chronic conditions [118]. Many approaches are used for BS, including laparoscopic sleeve gastrectomy (LSG), Roux-en-Y gastric surgery (RYGS), and gastric band (GB). RYSG, enhanced 25% weight loss compared to initial body weight, which has been reviewed (20-year follow-up) [119]. This approach helps sustain long-period weight loss. Randomized and prospective cohorts showed that the excess weight loss for GB was 45% vs. 65.7% for RYGS (3–5 year follow-up; 29 studies; 7971 patients) [120]. The use of GB has low weight loss, and the chances of future complications are very high [121]. LSG is the most popular bariatric surgical approach in the United States for the reason of its technical ease, low complications, and tremendous weight loss [121,122]. Even though several studies have steadily shown reduced PDAC risks and deaths after BS, the mechanism for weight loss and reduction of PDAC is still uncertain. In the Canadian investigation, PDAC was observed in 1/1035 (0.1%) BS patient and 19/5746 (0.33%) control patients [123]. The Utah investigation observed PDAC in 9/6596 BS patients and 8/9442 control group [124]. Multi-institutional investigations with long follow-ups are required to examine the BS effects on the incidence of PDAC.

BS may lower the PDAC risk. In obese patients, BS can decrease the secretion of cytokines (interleukin-6, IL-6) and inflammatory factors (C-reactive protein, CRP). BS decreased tissue inflammation in obese patients. BS significantly decreased insulin resistance. Patients with type 2 diabetic, who undertook the GBS/CR diet, the liver fat content declined rapidly, corresponding with decreased liver insulin resistance and stabilization of fasting glucos (7 days) [125]. BS also increases intestinal microbiota and plays a key function in obesity. Intestinal microbes promote the fat storage and homeostasis PDAC cells [126,127]. High-fat, food-fed (HFFF), obese PDAC-bearing mice are resistant to paclitaxel and gemcitabine compared to control food-fed mice [128]. Fecal stuff transplant from lean mice (control) to obese mice sensitized PDAC to paclitaxel and gemcitabine due to supplementation of obese with S-adenosyl methionine (SAM) [128]. These results demonstrate that relative levels of queuosine and SAM in the fecal stuff of PDAC patients will be a possible biomarker and beneficial target in chemotherapy-resistant PDAC. Dietary fibers product butyrate increased gemcitabine efficacy against BXPC-3 and PANC-1, inducing viability and apoptosis [129]. Combination treatments are not significantly different from the individual (butyrate or gemcitabine) treatment. However, butyrate decreases the cancer-associated new stroma formation, preserves gut mucosa integrity and pro-inflammatory microbes, and elevates helpful bacteria (produces short-chain fatty acids [129]. This observation suggests that butyrate supplementation can change PDAC biology and improve some gemcitabine-related damages. A low dose of

simvastatin, metformin, or both administered orally to HFFF KC mice expressing KrasG12D reduced fibro-inflammation, weight gain, and development of PDAC in KC mice (male) when managed individually [130]. Combination treatment also inhibited transcriptional levels of TAZ and YAP, which are essential for PDAC growth and decreased proliferation and colony formation of PDAC cells [130]. These observations suggest that simvastatin and metformin are potential agents for preventing PDAC progression in the clinic.

Increased inflammation factors, cytokine secretion, insulin resistance, and altered microbiome have been connected to the progression of obesity-associated PDAC (Fig. 3) [131]. Bench and bedside results showed that BS could indicate reduced tissue inflammation, adipokine secretion, and improved microbiome insulin sensitivity [132–134]. However, no epidemiology investigations have shown a conclusive decrease in PDAC incidence after BS due to a low sample size. Extensive, multi-institutional trials/investigations with extended follow-up periods may solve this problem. Well-designed in vivo models may be helpful to investigate the function and mechanisms of BS in PDAC prevention.

7.2. Metformin

Metformin is a first-line anti-diabetes drug and a potent activator of AMPK. Emerging evidence suggests that metformin enhances energy utilization by browning white adipose tissue and reduces body weight [135]. In addition to its anti-diabetic activity, metformin has inhibited obesity in extensive cohort studies [136]. The underlying mechanism involves the reduction of hepatic gluconeogenesis and insulin production. Furthermore, metformin-induced weight loss mediated the modulation of the hypothalamus by controlling its regulatory center and altering the gut microbiome via AMPK and mTOR signaling [136]. The anti-obesity function of metformin includes reducing body weight, reducing insulin resistance, and improving glucose metabolism through the regulation of brown adipose tissue (BAT) thermogenic action in obese animal models. Mechanistically, it affects thermogenic transcriptional factors (UCP1, NRF1, and PGC1-α) to enhance the mitochondrial function of BAT and raise energy expenses. Metformin treatment activated AMPK and fibroblast growth factor 21 (FGF21) in preclinical obese models, vital mediators of glucose metabolism and energy regulation [137].

Metformin inhibits the mTOR complex function and modulates aging and its associated diseases [138]. In the preclinical model, metformin activates AMPK expression and disease free from aging [139]. However, in human beings, it remains uncertain how metformin reduces aging. Clinical trials are on track to explore the role of metformin on weight loss and aging-associated diseases. Until now, no agent precisely targets weight loss and sarcopenic obesity. Recent evidence revealed from preclinical (mouse and *C. elegans*) and epidemiological investigations that metformin has promising effects on obesity and glycemia [140]. Metformin has been known to decrease body weight, decrease the prevalence of and death from PDAC, and extend lifespan due to the contribution of multiple pathways [140]. These properties show that metformin is an attractive drug to explore the opportunity for PDAC associated with obesity.

8. Conclusion and future directions

Obesity is a worldwide issue linked to increased PDAC prevalence, death, and cost. The increase in PDAC risk is due to obesity (via multiple mechanisms, including insulin resistance, inflammation, and altered microbiota). Several approaches managed these mechanisms. BS is reported to be a stable weight loss (obesity patients) in the long period and lowers the risks of PDAC and other cancers. More findings are needed to confirm that BS and or/weight loss can ease the risk of PDAC progression. Develop the mice BS models to test if BS can reverse PDAC progression. CR and BS in mice PDAC models help to explain the PDAC prevention mechanisms in obese mice. Finally, prospective multi-institutional investigations with more BS patients and long-period follow-up will establish the association between PDAC prevention and weight loss in obese patients.

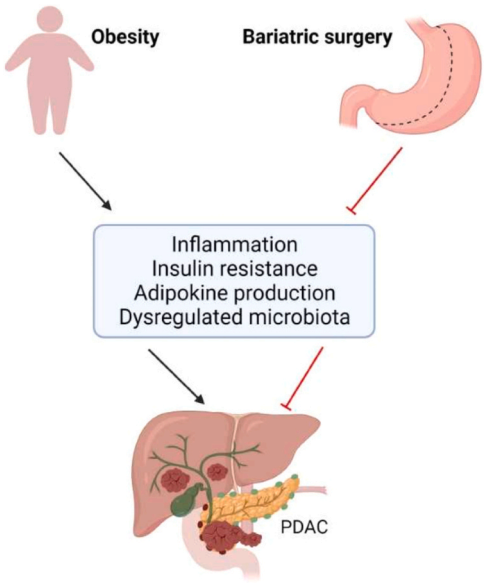

Fig. 3. Progression of obesity-associated pancreatic ductal adenocarcinoma (PDAC). Increased inflammation, adipokine production, insulin resistance, and altered microbiome have been connected to obesity-associated PDAC. Bariatric surgery reduces the chance of obesity-associated PDAC by inhibiting inflammation, insulin resistance, adipokine production, and microbiota alteration.

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CRediT authorship contribution statement

Mundla Srilatha: Literature collection, Writing – original draft, Conceptualization. **Ramarao Malla:** Literature collection, Writing – original draft. **Megha Priya Adem:** Writing – original draft. **Jeremy B. Foote:** Literature collection, Writing – original draft, Writing – review & editing. **Ganji Purnachandra Nagaraju:** Conceptualization, Visualization, Investigation, Supervision, Writing – review & editing, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

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