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Obesity and pancreatic cancer: An update of epidemiological evidence and molecular mechanisms

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ABSTRACT

Despite advances in therapy and achievements in translational research, pancreatic cancer (PC) remains an invariably fatal malignancy. Risk factors that affect the incidence of PC include diabetes, smoking, obesity, chronic pancreatitis, and diet. The growing worldwide obesity epidemic is associated with an increased risk of the most common cancers, including PC. Chronic inflammation, hormonal effects, circulating adipokines, and adipocyte-mediated inflammatory and immunosuppressive microenvironment are involved in the association of obesity with PC. Herein, we systematically review the epidemiology of PC and the biological mechanisms that may account for this association. Included in this review is a discussion of adipokine-mediated inflammation, lipid metabolism, and the interactions of adipocytes with cancer cells. We consider the influence of bariatric surgery on the risk of PC risk as well as potential molecular targets of therapy. Our review leads us to conclude that targeting adipose tissue to achieve weight loss may represent a new therapeutic strategy for preventing and treating PC.

Introduction

Pancreatic cancer (PC) is the most lethal malignancy of the gastrointestinal tract (5-year survival <8%) and the fourth leading cause of cancer death in the United States [1]. Early detection as well as multidisciplinary approaches to develop effective treatment will likely improve survival [2–4]. Despite numerous effort to identify biomarkers for the early detection of PC, such as noncoding RNAs, circulating tumor cells (CTCs), circulating tumor DNAs, and exosomes, large-scale discovery studies and further validation of existing markers are required before their translation to the clinic [2]. Concurrently, extensive studies of the pathogenesis and progression of PC aim to provide novel molecular diagnostics as well as targets for treating PC [3,5].

Obesity is a serious public health problem [6,7] that is associated with common chronic and metabolic diseases such as type 2 diabetes mellitus, hypertension, cardiovascular disease, and metabolic syndrome [7,8]. Moreover, numerous epidemiological studies convincingly show that excess body weight is associated with cancers of the breast, colon, endometrium, liver, and pancreas [9,10] as well as 3.6% of new cancers [11]. Epidemiological and mechanistic studies identify obesity as an independent risk factor of PC that contributes to pathogenesis and metastasis that largely accounts for patients' dismally poor prognoses via complex molecular mechanisms [12,13]. Chronic low-grade inflammation ranks among the most important suggested mechanisms linking obesity and PC [12,14]. Adipocytes in the tumor microenvironment (TME) of PC play a pivotal role in the proinflammation process that contributes to the progression of PC through crosstalk with cancer cells and other stromal cells [14,15]. Here we review recent findings about the association between obesity and PC, the role of adipocytes present in the TME, lipid metabolism, and related hormones and cytokines were systematically studied. The role of bariatric surgery in PC and potential molecular diagnostic and therapeutic targets are discussed as well.

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Obesity and PC

A positive association between the risk of PC with obesity, high body mass index (BMI), or both is demonstrated by the results of cohort studies and meta-analyses. The long-term prognosis of patients with PC with obesity is worse compared with that of patients with normal BMI. However, the results vary according to sex, geographical location, and ethnicity (Tables 1 and 2).

Epidemiological evidence and clinical findings

Obesity, high BMI and PC risk

The first meta-analysis that focused on obesity and PC was published in 2003 includes six case-control and eight cohort studies involving 6391 patients [16]. The results show that the relative risk per unit increase in BMI is 1.02. A subsequent study conducted in the United States confirmed the potential risk of obesity associated with PC [17], which was contradicted by another study [18]. To make matters more complex, a study of 99,670 Japanese subjects found an increased risk of PC associated with men but not women [19]. However, a meta-analysis of prospective studies published in 2008 supports a positive association between BMI and risk of PC in women [20] Further, obesity in persons aged 20–49 years is associated with a greater risk of PC (odds ratio [OR] = 2.58, 95% confidence interval [CI], 1.70–3.90) and a younger age of disease onset [21]. Childhood obesity is an independent risk factor of adult PC, and the higher the BMI, the higher the risk [22].

A meta-analysis conducted in 2012 found that BMI and abdominal fatness are associated with an average relative risk (RR) of 1.10 for a 5-unit increase in the incidence of PC [23]. This positive association is true for African Americans [24] but not people living in Lithuania [25] or the nonsmoker Chinese population of Singapore [26]. Further, a study of Japanese subjects identified a significant positive association between obesity and PC risk among men but not women [27], and there is no significant association between increased BMI and risk of PC (RR 0.94, 0.71–1.24) in the Asian–Pacific population, although there are positive associations in the European–Australian (RR 1.18, 1.09–1.27) and North American (RR 1.07, 1.03–1.11) populations [28]. These results may be explained by different study designs and differences in, for example, the genotypic, socioeconomic, and environmental characteristics of these disparate populations (Table 1).

Prognosis of obese patients with PC

Obesity adversely affects the long-term outcomes of patients with PC. For example, obese patients with PC have a 12-fold higher risk of lymph node metastasis compared with nonobese patients, and the overall survival and disease-free survival rates of the former are significantly shorter compared with those of the latter [29]. However, another study revealed that obese and overweight patients with PC experience longer 5-year survival compared with those with normal weights, even after adjusting for other prognostic factors [30]. Further, other studies found no relationship between obesity and the long-term survival of patients with PC [31,32]. Large prospective studies of cohorts found that BMI ≥35 kg/m^2 is associated with significantly shorter survival of patients with PC [33], which is confirmed by a multicenter cohort study [34] and a meta-analysis [35]. However, BMI was not identified as a risk factor associated with the overall survival of patients with PC in Asian countries [36,37] (Table 2).

The "obesity paradox" of PC

Compared with convincing evidence that obesity increases the risk of diverse solid malignancies, the role of obesity in prognosis of patients with cancer remains controversial [38,39]. Certain studies found that long-term prognosis of obese patients with cancer is

Table 1
Association between obesity and PC risk.

Reference	Study design	Region	No. of studies, cases	Main factors; covariates	Effect estimates
Gonzalez et al. [16]	meta-analysis	Europe, North America	14 studies, 6391 cases	BMI; gender, region, study design, smoking, diabetes, proxy respondent.	RR and 95% CI of PC for 1-unit increment in BMI: 1.02(1.01–1.03)
A.V. Patel et al. [17]	cohort study	USA	145627 cases	BMI; age, smoking, education, history of PC, gallbladder disease, diabetes etc.	RR and 95% CI of PC for BMI > 30: 2.08 (1.48–2.93)
R. Pezzilli et al. [18]	case-control	Italy	800 cases	BMI; smoking	OR and 95% CI of PC for BMI ≥30 vs. 23–29.9 kg/m^2: 0.96 (0.60–1.53); $P = 0.867$
Y. Lin et al. [19]	cohort study	Japan	110792 cases	BMI; age, smoking, diabetes, history of gallbladder diseases	RR and 95% CI of PC for BMI at age 20 years: Man 3.51 (1.26–9.78); Woman 0.43 (0.06–3.15)
A.G. Renehan et al. [20]	meta-analysis	Europe, North America, Asia	16 studies, 4443 cases	BMI	RR and 95% CI of PC for increased BMI: Man1.07 (0.93–1.23) Woman 1.12 (1.03–1.23)
D. Li et al. [21]	case-control	USA	1595 cases	BMI; age, gender, race, smoking, alcohol, history of diabetes, and family history of cancer	OR and 95% CI of PC for BMI ≥30 from the ages of 20–49 years: 2.58 (1.70–3.90)
L. Nogueira et al. [22]	cohort study	Denmark	293208 cases	BMI	HR and 95% CI of PC according to BMI score at age 13: 1.18 (1.09–1.27)
D. Aune et al. [23]	meta-analysis	Europe, USA, Asia	23 studies, 9504 cases	BMI; gender, geographic location, smoking	RR and 95% CI of PC for 5-unit increment in BMI: 1.10(1.07–1.14)
T.N. Bethea et al. [24]	pooled analysis	USA	7 studies, 239597 cases	BMI; age, gender, smoking, education, marital status, alcohol, physical activity	HR and 95% CI of PC for BMI≥35.0 with 5 years of follow-up:1.31 (0.97–1.77)
Kuzmickiene et al. [25]	cohort study	Lithuania	2 studies,7132 cases	BMI; age, smoking status, alcohol consumption, education	HR and 95% CI of PC for BMI≥30.0: 1.66 (0.88–3.15)
S. Untawale et al. [26]	cohort study	Singapore	51251 cases	BMI; age, gender, year of enrollment, dialect, education, diabetes status	HR and 95% CI of PC for non-smoker BMI≥27.5: 1.57 (0.84–2.92)
Y.N. Koyanagi et al. [27]	pooled analysis	Japan	9 studies, 482820 cases	BMI; age, area, smoking	HR and 95% CI of PC for male BMI≥30:1.71 (1.03–2.86); for female BMI≥27: 1.04 (0.80–1.35)
J. Wang et al. [28]	meta-analysis	Europe, Australia, North America, Asia	34 studies, 6115 cases	BMI; gender, study design, follow-up duration	RR and 95% CI of PC for per 5 kg/m^2 increase in BMI: Asia-Pacific 0.94(0.71–1.24); European-Australian 1.18(1.09–1.27); European-Australian 1.07(1.03–1.11)

PC, pancreatic cancer; BMI, body mass index; HR, hazard ratio; OR, odds ratio; RR, risk ratio; CI, confidence interval.

Table 2
Association between obesity and PC prognosis.

Reference	Effect of obesity on prognosis
J.B. Fleming et al. [29]	Obese patients (BMI≥35) had 12-fold risk of lymph node metastasis compared with nonobese patients (BMI < 35). The disease-free and overall survival rates were significantly decreased in the obese patients.
S. Tsai et al. [30]	5-year survival: obese 22%, overweight 22%, normal weight patients 15% (obese & overweight vs. normal $P = 0.02$). Cancer-specific survival: overweight HR 0.68; obese HR0.72 (both $P < 0.05$).
M. Dandona et al. [31]	Median overall survival: obese 22.1 months, overweight 20.0 months, normal weight patients 17.3 months. No statistically significant association between BMI and overall survival ($P = 0.58$).
S. Khan et al. [32]	Overall ($P = 0.49$) and disease-free survival ($P = 0.51$) were not significantly associated with BMI.
C. Yuan et al. [33]	HR for death was 1.53 (95% CI, 1.11 to 2.09) comparing patients with BMI≥35 kg/m^2 with those with BMI < 25 kg/m^2 ($P = 0.001$).
B. Kasenda et al. [34]	Unadjusted 12-month survival rates: 48% (BMI < 18.5), 42% (BMI 18.5–25), 30% (BMI 25–29), and 11% (BMI≥30). Increasing BMI (HR 1.22, 95% CI 1.04–1.41, $P = 0.012$) was significantly associated with worse survival prognosis.
Y.Q. Shi et al. [35]	For every 5 kg/m^2 increment in adult BMI, the summary HR was 1.11 (95% CI: 1.05–1.18) for death risk of PC.
T. Okura et al. [36]	Low BMI was associated with an increased risk of death (normal weight: HR 0.58, $P = 0.038$; overweight/obese: HR 0.54, $P = 0.059$). High BMI was not found to be a postoperative factor for poor prognosis.
Q.L. Jiang et al. [37]	No significant association between BMI and overall survival was found for resectable ($P = 0.99, n = 217$), unresectable locally advanced ($P = 0.90, n = 316$) and metastatic patients ($P = 0.88, n = 1250$), respectively

PC, pancreatic cancer; BMI, body mass index; HR, hazard ratio; OR, odds ratio; RR, risk ratio; CI, confidence interval.

much better compared with that of patients with normal weight. This protective association between obesity and cancer is called the "obesity paradox" [38,39]. This discrepancy can be explained as follows: 1) methodological limitations and weaknesses such as confounding factors, selection bias, collider stratification bias, and reverse causality [39,40]; 2) BMI cannot inadequately scale adiposity and body composition [41,42]; and 3) different tumor biology and therapeutic responses [39]. As aforementioned, the role of obesity in the prognosis of PC patients also remains controversial. Tsai S et al. revealed that BMI is not associated with TNM stage, and obese patients undergoing the Whipple procedure had longer cancer-specific survival compared with that of patients with normal weight (hazard ratios [HRs] = 0.68 and 0.72 for overweight and obese patients, respectively) [30]. To be emphasized that BMI cannot distinguish between adipose tissue and muscle, which have a pivotal impact on survival [41].

Sarcopenia is very common in patients with PC, and preoperative sarcopenia, not obesity, is associated with poor prognosis [43,44]. Typically, higher BMI is often associated with higher masses of skeletal muscle and better nutritional status, which may partly explain the better prognosis of obese patients with PC. In addition to adipose tissue, role of sarcopenia and muscle wasting in cancer should also be investigated to determine if there are significant associations among body composition, obesity, and survival [41]. The quantification and scaling tools for evaluating adipose tissue and its distribution, skeletal muscle mass, and body composition may help to advance this emerging area [38,41,42].

Biological mechanisms

Adipose tissue stores energy and regulates endocrine metabolism [45]. Adipose cells around the pancreas or PC tissue of obese persons can produce an obesity-associated inflammatory environment [14]. Cancer-associated adipocytes as well as infiltrating inflammatory and immune cells in the peripancreatic adipose tissue microenvironment can secrete higher than normal levels of adipokines, proinflammatory cytokines, chemokines, and growth factors, which may accelerate pancreatic neoplasia [46] and create a more conducive environment for the growth and metastasis of PC cells [12,47].

Adipokines

Adipocytes secrete adipokines to promote the homing, growth, migration, and invasion of cancer cells [48] through oncogenic signaling or through indirect mechanisms such as angiogenesis and regulation of the immune response [49]. Leptin and adiponectin are the most extensively studied adipokines. In obesity, leptin levels increase and adiponectin levels decrease; and this change in the leptin to adiponectin ratio is associated with a more aggressive malignant phenotype [50]. The effects of leptin on PC are unclear. Several studies show that leptin can inhibit the proliferation and metabolic activity of PC cells [51], although other studies show that leptin can enhance the growth of PC cells [52]. For example, the results of a pooled, nested case-control study supports the conclusion that increasing leptin concentrations are associated with pancreatic cancer [53]. Another case-control study found that high plasma levels of leptin are associated with an elevated risk of PC among men vs women [54]. The mechanism may involve the activity of the leptin-Notch axis, which promotes the invasiveness of PC cells and ensuing metastasis [55].

A prospective study found that low circulating levels of adiponectin are associated with significantly increased risk of PC and that the underlying mechanisms may regulate glucose metabolism and insulin resistance [56]. For example, adiponectin inhibits the proliferation of PC cells by promoting apoptosis [57]. *In vitro* and *in vivo* studies support that the conclusion that adiponectin decreases the risk of PC through activation of the adiponectin receptor, which inhibits leptin-mediated STAT3 activation [58], or through inhibition of the inactivation of GSK-3β [59]. Thus, the adiponectin receptor (AdipoR) agonist AdipoRon may represent a novel agent to treat obesity-related PC [58,60].

The adipokine lipocalin-2 (LCN2) is involved in the regulation of the inflammation of adipose tissue and insulin resistance [61]. A study of mice with pancreatic ductal adenocarcinoma (PDAC) with diet-induced obesity found that LCN2 expression is upregulated in PC tissue, and downregulation of its expression is attributed to reduced inflammation, fibrosis, the incidence of pancreatic intraepithelial neoplasia (PanIN) was well as increased survival [62]. Further, LCN2 can modulate the production of proinflammatory cytokines via regulating the functions of pancreatic cancer stellate cells (PSCs) in the TME [62]. Thus, these studies highlight the pivotal role played by adipokines in linking obesity, inflammation, and PC.

Insulin resistance and insulin-like growth factor (IGF)

Obesity is often associated with hyperinsulinemia and insulin resistance, and the latter is common among patients with cancer [63]. Further, prolonged exposure to proinflammatory cytokines may increase the risk of cancer of obese persons [63]. However, epidemiological studies report different results concerning the relationship between hyperinsulinemia and PC [64,65].

IGF-I is a peptide hormone with structural similarity to insulin.

Binding of insulin or IGF-I to the insulin receptor or to the insulin-like growth factor-I receptor (IGF-IR), stimulates lipogenesis, inhibits lipolysis, increases protein synthesis, and inhibits protein turnover [66]. Further, IGF-I promotes the growth and proliferation of cancer cells [66] by activating the PI3K-mTOR and MAPK signaling pathways [67]. A high-fat diet (HFD), which is an important cause of obesity, can promote insulin resistance and the development and progression of PC through an IGF-I-dependent mechanism [68]. Compared with LSL-Kras^{G12D}/Pdx-1-Cre/Ink4a/Arf$^{lox/+}$ mice fed a HFD, mice fed calorie-restricted diets have reduced serum concentrations of IGF-I, desmoplasia, and develop PC and experience prolonged survival. In liver-specific IGF-I-deficient mice, serum concentrations of IGF-I and the growth of orthotopically transplanted PC cells are reduced, which are rescued by administration of IGF-I [68]. Insulin-like growth factor binding protein (IGFBP) controls the transport of IGF-I from the circulation to the target tissue [69]. Down regulation of IGFBP-2 inhibits metastasis and enhances chemotherapeutic sensitivity in PC [70]. However, prospective studies found that among the six isoforms of IGFBP, the circulating concentrations of IGFBP-3 are not associated with risk of PC [69].

Proinflammatory cytokines and chemokines

Chronic low-grade inflammation is a typical characteristic of obesity, as well as a mediator of cancer development and progression [14,71]. Cytokines and other proinflammatory mediators are implicated in PC. For example, a HFD can significantly influence energy metabolism by promoting pancreatic exocrine insufficiency, metabolic rate, and mitochondrial fatty acid (FA) β oxidation-related gene expression [72]. This study indicated further that the inflammatory response and changes in the synthesis of ATP change may represent potential mechanisms involved in the association between obesity and PC [72]. HFD-induced inflammation can activate oncogenic KRAS and its downstream targets, including COX2 and phospho-ERK, to promote activation of PSCs, infiltration of macrophages, and establishment of a positive feed-forward loop to maintain KRAS activity, which further increases inflammation [73]. These changes result in increased fibrotic stroma, more PanINs and PDACs, and shortened survival in a transgene mouse model [73]. While knockout of COX has no effect on these outcomes, a COX2 inhibitor significantly prevents HFD-induced inflammation and PC pathogenesis and progression [73].

Chemokines contribute to the development of PC associated with an adipose inflammatory environment [10]. A population-based case-control study found that polymorphisms in genes that encode proinflammatory chemokines are significantly associated with pancreatitis in patients with PC [74]. Further, the pancreases of animals fed a HFD show obvious signs of inflammation, increased numbers of infiltrating inflammatory cells (macrophages and T cells), increased levels of cytokines and chemokines, increased interstitial fibrosis, and aggravation of PanIN lesions [75]. Chemokines such as CXCL1 and CXCL8 act through their receptors (C-X-C Chemokine Receptor 1 [CXCR1] and CXCR2, respectively) to mediate the homing of adipose stromal cells (ASCs) to tumors [76]. CXCL1 secreted by malignant epithelial cells in obese patients with prostate cancer binds the ASC receptor CXCR1, mediating the transport of ASCs from adipose tissue to tumors, resulting in poor survival outcomes of patients [76]. Further, evidence indicates that adipose tissue-derived stem cells may promote proliferation and invasion of PC cells via signaling through the SDF-1/CXCR4 axis [77].

Hormones

Adipose tissue is the main site of sex hormones, particularly that of estrogen synthesis, in males and postmenopausal women. Adipocyte-associated hormones can affect lipid metabolism and may promote tumorigenesis and tumor progression [78]. The effects of estrogen on PC are controversial. Women are less likely to develop PC, although this does not fully explain the differences in exposure to risk factors [79]. A population-based matched cohort study found that recipients of menopausal hormone therapy have a 23% reduced risk of PC [80]. An increased incidence of PC mainly occurs in male obese KC mice vs females [81], and plasma leptin concentrations are positively associated with PC risk among men [54], suggesting a role for sex hormones in the pathogenesis of PC. This phenomenon possibly can be implicated that estrogen receptor-β (ER-β) plays an important role in the biological activity of estrogen, and *in vitro* studies have shown that it expresses in PC cells and mediates estrogen signaling to inhibit the growth and proliferation of PC cells [82].

Role of the obese PC TME

In addition to the stimulation and promotion through the systematic circulation of adipokines, adipocytes in the TME play an important role in the proinflammatory and oncogenic processes of PC [15,83]. Fatty infiltration in the pancreas is a risk factor for the development of PanIN and PC [84,85]. Moreover, in a model system of pancreatic cancer, obese mice present with larger tumors, and an significantly greater number of mice develop distant metastasis [84], suggesting that the adipokine milieu and insulin resistance may directly lead to a more robust infiltration of the tumor with adipocytes, accompanied by fibrosis in the TME, which ultimately promotes the proliferation and metastasis of PC cells [86].

Role of lipid metabolism in the obese PC TME

Increased lipid metabolism is a hallmark of cancer invasiveness that increases the use of lipids in the hypoxic TME [87]. Cancer cells can hijack normal stress response mechanisms when the levels of growth-promoting nutrients are limiting [87]. A retrospective meta-analysis of transcriptome data of at least 1200 patients with PC found that the transcriptomes of approximately 23% were enriched in lipid and protein metabolism-related genes [88].

Metabolic changes in peripheral adipose and muscle tissue occur early in PC. Studies of mice show that very small early pancreatic tumors can disrupt the production of critical digestive enzymes [89]. These mice cannot completely digest food, thus they enter a starvation mode in which the body begins to break down other tissues, particularly adipose tissue. Alternative treatment with trypsin can attenuate the consumption of peripheral tissue associated with PC. However, the consumption of these peripheral tissues is not associated with survival [89]. A retrospective study found that metabolic parameters and fatty soft tissues (including subcutaneous adipose tissue [SAT] and visceral adipose tissue [VAT]) dramatically change during the prediagnostic phase of PC. These findings suggest that SAT browning and high levels of UCP1 may serve as biomarkers of early-stage PDAC [90].

FAs and glycerol are the main molecules released by adipocytes and the main precursors of lipids used by tumors as energy sources [91]. Thus, cancer-associated adipocytes act as a source of energy for cancer cells, providing sufficient FAs and lipids that affect the metabolism of adjacent tumor cells and contribute to the growth and progression of malignant tumors [91]. Moreover, adipocytes adjacent to cancer cells contain smaller lipid droplets compared with those farther away [91]. Studies have found that adipocytes with lipid metabolism undergo delipidation, leading to adipocytes/cancer-associated fibroblasts de-differentiation processes [92]. In a hypoxic microenvironment, adipocytes undergo lipolysis to produce more FAs that serve as a source of energy for cancer cells [93,94]. Further, FAs are used to synthesize membranes to produce

signaling molecules that promote the proliferation and invasion of cancer cells [94,95]. Exosomes secreted by PC cells can promote lipolysis in adipocytes through the adrenomedullin (AM)/andromedullin receptor (ADMR)/ERK pathway, inhibit lipolysis, and lower the levels of free FAs, which can inhibit tumor initiation and progression [96]. Targeting FA metabolism may therefore provide a new strategy for treating PC. Industrial trans-fatty acids are positively associated with PC risk [97]. PC cells can use the FAs released by adipocytes to generate energy through an unorthodox reaction, such as β-oxidation, to overcome malnutrition and hypoxic environments. The energy produced by FAs through β-oxidation is approximately twice that derived from glucose [98].

The progression of micro-invasive intraductal papillary mucinous neoplasms to invasive PDAC is associated with the induction of lipid remodeling and fatty acid oxidation [99]. Lipid breakdown and fibrotic changes in the fat microenvironment result in the release of FAs and enhance the invasion and metastasis of PC cells [100]. Lipids in fat cells can sequester cancer drugs, leading to resistance to chemotherapy [101]. FA derivatives include phospholipids, sterols, and sphingolipids, as well as signaling molecules that regulate the proliferation, migration, invasion, and chemoresistance of cancer cells [94]. These studies suggest that changes in lipid metabolism may promote the progression of PC.

Understanding the mechanisms through which changes in obesity and lipid metabolism affect the biology of PC seems to be an intractable, although inevitable, task to prevent and cure PCs. Evidence indicates that FA oxidation (FAO) is the major bioenergetic pathway in nonglycolytic tumors. For example, FAO is mediated by osteopontin secreted under the control of p62 [102]. Deletion of the p62 gene from adipocytes leads to increased secretion of osteopontin, which mediates tumor FAO and promotes tumor invasion and metastasis [103]. Deletion of the p62 gene from pancreatic beta cells may result in mitochondrial dysfunction leading to a decrease in glucose tolerance [104]. Further, studies of a mouse model system show that conditionally activated p62 in adipose tissue leads to increased obesity, independent of food intake or exercise [105].

Cancer cells can increase the uptake and transport of exogenous FAs by FA receptors such as CD36 (also called FA transferase) [106], FA binding protein FABP3/4, and adipophilin (lipid structural proteins) [107]. Elevated levels of CD36 caused by upregulated lipid metabolism can increase the levels of CD36, which promote the endothelial-mesenchymal transition of cancer cells [106] and increases the ability of CD36-positive cancer cells to metastasis and resist chemotherapy [106]. These processes are associated with poor prognosis [108]. These molecular complexes may serve as targets for treating PC.

Role of other metabolic pathways in the obese-PC TME

Adipocytes can promote the proliferation of PanIN and PC cells independent of glutamine [107]. Adipocytes secrete glutamine, and while PC cells regulate glutamine metabolism in adipocytes, glutamine shuttling mediates interactions between adipocytes and PanIN/PC cells [109]. Obesity accelerates the growth of PC through regulating nitrogen metabolism by the induction of arginase (ARG2) that hydrolyzes arginine to ornithine and urea. Silencing or deletion of *ARG2* significantly inhibits PC. Moreover, ARG2 levels in PC cells correlate with the BMI of patients with PC [110].

Adipocytes crosstalk with other cells in the obese PC TME

Adipocytes interact with other cells in the TME through different pathways. Coculture of adipocytes and MiaPaCa2 PC cells *in vitro* increases the expression of WNT5a, which mediates the dedifferentiation of adipocytes to fibroblast-like cells [111]. Such reprogrammed adipocytes produce cytokines and lipids that can promote the uncontrolled growth of PC cells [111]. Moreover, adipocytes can induce the EMT, which promotes the progression of PC via a non-canonical WNT paracrine signaling network [112]. In a transgenic mouse model of PDAC, obesity induces steatosis and a fibroinflammatory TME in which IL-1β is released by adipocytes [14]. These events lead to the recruitment of tumor-associated neutrophils (TANs), activation of PSCs, and a decrease in the number of $CD8^+$ T lymphocytes [14]. Further, there are increased number of regulatory T cells (Tregs), accompanied by interactions between adipocytes, TANs, and PSCs leading to immunosuppression and the aggravation of desmoplasia in the TME [14]. These events eventually promote tumor growth and reduced sensitivity to chemotherapeutic agents [14]. Inhibition or ablation of the expression of the angiotensin II type-1 receptor, which is abundantly expressed in adipose tissue, can reverse obesity-induced PC growth and resistance to chemotherapy [14]. The potential mechanisms that govern the associations of obesity are shown in Figs. 1 and 2.

Controlling obesity and potential targets of therapy

Lifestyle modification and low-carbohydrate diets are the most important measures to prevent obesity that is associated with the development of PC [71]. Regular exercise can reduce body weight by regulating the expenditure of energy, lowering the blood levels of lipids, preventing resistance to insulin as well as inducing DNA damage and chronic inflammation [113]. Further, exercise can regulate the release of cytokines to alter the tumor microenvironment, thereby inhibiting the development of cancer development and progression [113]. A meta-analysis of 10,501 patients with PC

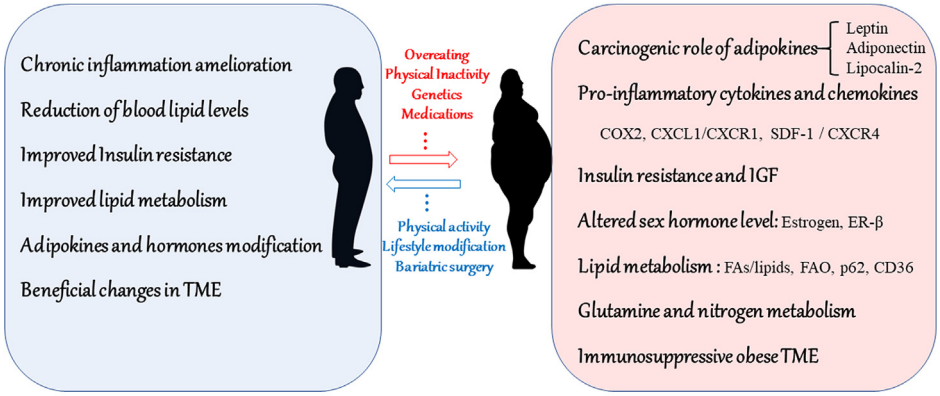

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Fig. 1. Mechanisms involved in obesity-associated pancreatic cancer (PC).

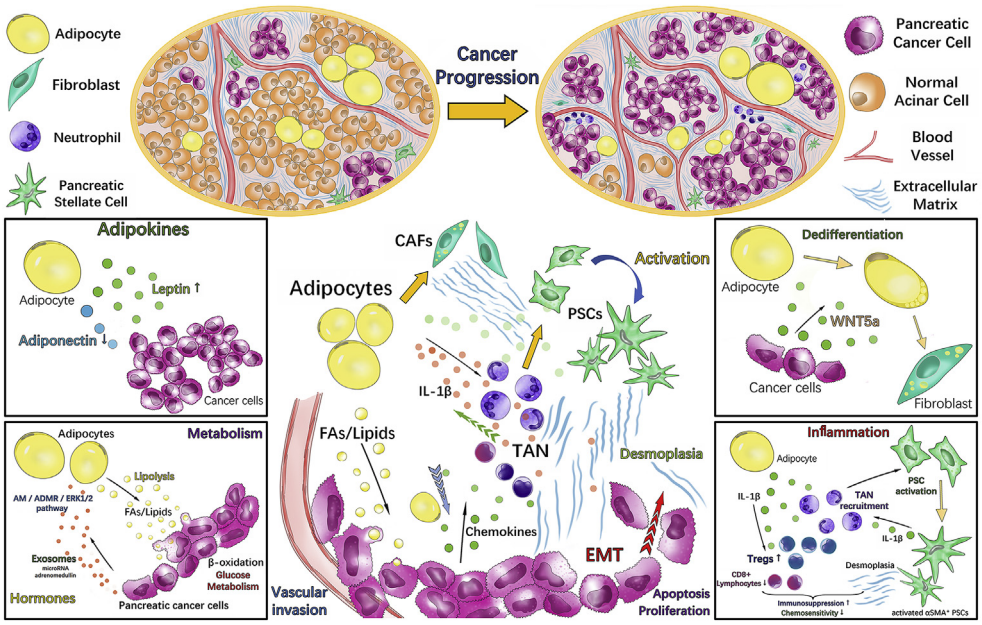

Fig. 2. Role of adipocytes in the tumor microenvironment (TME) of PC.
Adipocytes in the TME of PC play a key role in the proinflammatory process. Adipocytes interact with cancer cells and other stromal cells through direct or indirect mechanisms to recruit inflammatory cells into the TME, leading to immunosuppression, connective tissue formation, and angiogenesis, which promote the development of PC. Factors such as lipid metabolism and its associated hormones and cytokines are involved in this process.Adipocytes secrete adipokines to promote homing, growth, migration and invasion of PC cells. Leptin levels increase in obesity while adiponectin levels decrease. Exosomes transmit andromedullin (AM
) from PC cells promote lipolysis in adipose tissue via the (AM)/AM receptor (ADMR)/ERK pathway. Metabolites generated from lipolysis in adipocytes, such as FAs or lipids, affect the metabolism of lipids and glucose in PC through β-oxidation, which promotes the initiation and progression of PC. Adipocytes can increase lipid metabolism through dedifferentiation of adipocytes/cancer-associated fibroblasts via the WNT5a pathway. Adipocytes enhance the recruitment of tumor-associated neutrophils (TANs) to activate pancreatic stellate cells (PSCs), which increase desmoplasia of the TME in obese patients with PC. Adipocytes can increase production of IL-1β, recruiting more Treg cell that reduce the number of $CD8^+$
lymphocytes, resulting in immunosuppression and chemoresistance of PC.

found that although exercise is not closely associated with the risk of PC, the potential risk of PC decreases with the accumulated time that individuals engage in exercise [114]. Moreover, diets rich in vegetables and fruit are associated with reduced risk of PC [115], and diets enriched in omega-3 fatty acids prevent the development of PC in a preclinical model [116].

Bariatric surgery and PC

Evidence indicates that intentional weight loss reduces the risk of obesity-related cancer and thus improves the survival of obese patients with cancer [117]. Lifestyle modification and pharmacological approaches can help to reduce weight, although the effect is modest and limited. Clinical trials report weight loss ranging from 5.1% to 10.9% (average 5.8 ± 0.2 kg), although the maintenance of weight loss was poorly sustained over 2 years [118,119]. Unfortunately, no evidence is available that supports the conclusion that weight loss achieved by lifestyle modification or pharmacological intervention reduces cardiovascular mortality [120].

Compared with the above two approaches to reduce the weight of obese patients, bariatric surgery offers the most effective treatment strategy for weight loss, long-term weight maintenance, and higher remission rates of patients with type 2 diabetes [121]. Moreover, bariatric surgery can reduce the incidence of cancers of the pancreas, endometrium, postmenopausal breast, and colon. In contrast, this approach does not reduce the incidence of cancers of the thyroid, kidney, and rectum [122]. However, few published studies specifically focus on the relationship between bariatric surgery and PC. Only 1/1035 patients (0.1%) was diagnosed with PC after bariatric surgery, while 19 patients in the control group had PC (19/5746, 0.33%) (estimated RR = 0.29 (95%CI = 0.39–2.175; $P = 0.166$) [123]. Another study did not find a significant difference in the incidence of PC between patients who underwent gastric bypass surgery and those who did not (9/6596 vs 8/9442, (hazard ratio = 1.75; 95%CI = 0.66–4.63, $P = 0.26$) [124]. A more recent study of 8794 patients revealed that bariatric surgery is associated with a decreased risk of hormone-related cancers, including those of the breast, endometrium, and prostate; whereas gastric bypass surgery was associated with an increased risk of colorectal cancer. However, the incidence of PC was not mentioned in this study [125]. Thus, the role of bariatric surgery in the prevention of PC requires studies of large numbers of patients with long follow-up.

The beneficial effects of bariatric surgery on cancer prevention may be explained by different molecular mechanisms. First, chronic inflammation is a common feature of obesity and cancer. Thus, proinflammatory cytokines released by adipocytes in the TME or adipose tissue can promote the proliferation of cancer cells, which can be mitigated by bariatric surgery to reduce chronic inflammation [9,117,126]. Second, bariatric surgery can regulate the levels of sex hormones, which accounts for the decrease in the incidence of hormonally responsive tumors such as those of the breast and endometrium [9,126]. Evidence indicates that diabetes and insulin resistance are ameliorated after bariatric surgery; which confers a protective effect on cancer risk, particularly for PC [117,126]. Finally, the nature of the gut microbiota is associated with inflammation as well as with metabolic disorders and cancer [127,128]. Bariatric surgery may positively modify key pathways involving the composition and activity of the gut microbiota such that the modified gut microbiota may regulate complex interactions between the immune system and signaling pathways involved in the regulation of inflammation, which may prevent tumorigenesis [127,128].

Targeting PC with fatty acid synthesis (FASN) inhibitors

The association of lipid metabolism with the development and progression of PC strongly suggests that targeting lipid metabolism in cancer cells and adipocytes, combined with standard treatment, represents a potentially effective strategy [129]. Specifically, adipocyte-derived metabolites such as free FAs, cholesterol, and regulators of the adipose TME may be important targets of therapy.

Further, inhibition of lipolysis and the reduction of free FA levels can inhibit and therefore control the proliferation of cancer cells [93]. For example, the acetyl-CoA carboxylase (ACC) inhibitor BAY ACC022 inhibits the growth of pancreatic tumors [130], epigallocatechin-3 gallate inhibits the growth of PC in orthotopically transplanted mice [131], and the anti-obesity drug orlistat inhibits the growth of human PC cells [132].

Targeting cholesterol synthesis by PC cells

Inhibitors of acyl-CoA cholesterol acyltransferase-1 inhibit the growth and metastasis in mice of orthotopically transplanted pancreatic tumors [133]. Statins reduce the risk of PC and improve survival of patients with PC. Statins reduce the risk of PC, particularly of patients who have taken statins for at least 4 years [134]. Preclinical studies conducted *in vitro* and *in vivo* show that statins inhibit the proliferation of PC cells, delaying the progression of PanIN to PC, and inhibiting the formation of pancreatic tumors [135]. A phase 3 study of the effects of metformin, atorvastatin, doxycycline, and mebendazole on patients with PC (NCT02201381), as well as a phase 2 study of the effects of gemcitabine alone or combined with simvastatin on patients with advanced PC (NCT00944463), are underway.

Metformin

Obesity, which is associated with chronic, excess dietary caloric intake [8]. Moreover, obesity is associated with insulin resistance and chronic hyperinsulinemia increases the risk of cancers of the colon and endometrium as well as those of the pancreas and kidney [136]. There are many overlapping and distinct mechanisms of diabetes and obesity that promote the development of PC. Metformin is a commonly used antidiabetic drug that inhibits the formation of connective tissue in PC by reducing remodeling of the ECM [14] and inhibiting angiogenesis by significantly reducing obesity-related progression of cancers [137]. A double-blind, randomized, placebo-controlled phase 2 trial found that the addition of the standard antidiabetic dose of metformin did not improve the prognosis of patients with advanced PC treated with gemcitabine and erlotinib [138].

In vitro and *in vivo* studies show that metformin combined with aspirin significantly inhibits the growth of PC cells by regulating the expression of proapoptotic and antiapoptotic Bcl-2 family members, supporting the continued use of the combination of these two drugs to prevent or treat PC [139]. In certain PC cell lines, metformin partially inhibits the activity of mTORC1 by stimulating AMP-kinase. Therefore, metformin can enhance the anti-proliferative effects of mTORC1 and PI3K/mTOR inhibitors [140]. In genetic mouse models of PC, metformin decreases pancreatic acinar-to-ductal metaplasia (ADM) and mouse pancreatic intraepithelial neoplasia (mPanIN) and reduces chronic pancreatitis-mediated ADM and the induction of mPanIN [141].

Other inhibitors

Obesity is increasingly recognized as chronic, systemic, low-grade inflammation. Aspirin, as a classical COX inhibitor, inhibit cyclooxygenase activity. It has been confirmed to be chemopreventive in PC according to the epidemiological study [142,143]. However, the results still remain controversial. Among participants in several large prospective cohort studies, regular taking aspirin or not was not associated with future risk of PC. The risk of PC in diabetic patients who regularly use aspirin may be reduced and should be further investigated in preclinical and human studies [144].

Although IGF-1 is associated with higher tumor grade and lower survival of patients with PC, IGF-1R inhibitors such as cixutumumab [145] and ganitumab [146] are not effective for treating metastatic PC. A recent preclinical study suggests that istiratumab (MM-141), a novel bispecific antibody that blocks IGF-1R and ErbB3, enhances sensitivity to chemotherapy and increases the activities of gemcitabine and nab-paclitaxel [147]. After the ablation of oncogenic KRAS or c-MYC in mice, combined targeting of IGF-1R signaling and downregulation of tumorigenic drivers can reduce minimal residual disease and cancer recurrence, which may represent a key step in developing a more effective strategy for treating PC [148].

When treated with an antiangiogenic drug, tumor cells convert from glycolysis to FAO metabolism, which induces hypoxia, limits the supply of glucose, and induces lipolysis [149]. Thus, dual inhibition of angiogenesis and FAO enhances the anti-tumor efficacy of antiantiogenic drugs [149]. The lack of a blood supply impedes the delivery of drugs to hypoxic tumor tissues. The chemokine SDF-1α and its receptor CXCR4 are required for the homing of stem cells to ischemic tissues and were therefore evaluated for potential use in drug-delivery vehicles [150]. Polymeric nanoparticle-induced CXCR4-overexpressing human adipose-derived stem cells exhibit long-range migration toward intracranial xenografts of glioblastoma multiforme in mice and preferentially penetrate the hypoxic tumor core [150]. This system may therefore serve as an effective cellular vector for targeting hypoxic PC tissues. Therefore, developing appropriate treatment options for obese patients promises to improve their survival [151].

Conclusion

Obesity underlies chronic systemic inflammation and metabolic syndrome, and epidemiological evidence confirms the positive association between the risk of PC and obesity. Systemic circulation of adipokines and the adipocyte-mediated inflammatory and immunosuppressive microenvironment creates fertile soil for the development and progression of PC. Interactions between adipocytes and cancer cells and other stromal cells in the TME regulate the morphology and function of adipocytes to cause fibrosis and aggravated desmoplastic stroma. Moreover, modification of the metabolism of inflammatory cytokines and lipids induces the malignant transformation of pancreatic cells and contributes to the progression of PC and its resistance to chemotherapy. However, the molecular mechanisms involved in the regulation of these processes by adipose tissue and adipocytes should be further investigated. In particular, a better understanding of the interactions between adipocytes and cancer cells in the TME of PC is necessary for developing novel treatment strategies. Moreover, the differences in tumor biology between obese and lean patients with PC should be investigated. Therapeutics targeting adipocytes, lipid metabolism, or adipocyte-related cytokines may provide novel interventions for PC. This may be a long journey of exploration, and the best preventive approaches in the meantime are lifestyle modifications that include a healthy diet and physical activity.

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