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The complexities of obesity, diabetes, and the development and progression of pancreatic cancer

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Abstract

Pancreatic cancer (PC) is one of the most lethal malignant diseases with the worst prognosis. It is ranked as the fourth leading cause of cancer-related deaths in the United States. Many risk factors have been associated with PC. Interestingly, large numbers of epidemiological studies suggest that obesity and diabetes, especially type-2 diabetes, are positively associated with increased risk of PC. Similarly, these chronic diseases (obesity, diabetes and cancer) are also a major public health concern. In the U.S. population, 50 percent are overweight, 30 percent are medically obese and 10 percent have diabetes mellitus (DM). Therefore, obesity and DM have been considered as potential risk factors for cancers; however, the focus of this article is restricted to PC. Although the mechanisms responsible for the development of these chronic diseases leading to the development of PC are not fully understood, the biological importance of the activation of insulin, insulin like growth factor-1 (IGF-1) and its receptor (IGF-1R) signaling pathways in insulin resistance mechanism and subsequent induction of compensatory hyperinsulinemia has been proposed. Therefore, targeting insulin/IGF-1 signaling with anti-diabetic drugs for lowering blood insulin levels and reversal of insulin-resistance could be useful strategy for the prevention and/or treatment of PC. A large number of studies have demonstrated that the administration of anti-diabetic drugs such as metformin and thiazolidinediones (TZD) class of PPAR- γ agonists decreases the risk of cancers, suggesting that these agents might be useful anti-tumor agents for the treatment of PC. In this review article, we will discuss the potential roles of metformin and TZD anti-diabetic drugs as anti-tumor agents in the context of PC, and will further discuss the complexities and the possible roles of microRNAs (miRNAs) in the pathogenesis of obesity, diabetes and PC.

Keywords

obesity; diabetes mellitus; pancreatic cancer; metformin; and TZD

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Introduction

Pancreatic cancer (PC) is one of the most lethal malignant diseases with the worst prognosis. The incidence of PC is higher in American men compared with women and its occurrence is seen more frequently in African Americans compared to Caucasian Americans [1]. It has been estimated that 37,000 patients are newly diagnosed with PC, and 34,000 patients die of PC each year in the United States [2]. High cancer mortality confers this malignancy as the fourth leading cause of cancer-related deaths in the U.S. [2]. PC is also responsible for about 227,000 deaths each year in the world [3]. Due to the absence of specific symptoms and the lack of early detection tests, PC is usually diagnosed at an advanced incurable stage [1,4]. Thus, the median overall survival is 5–6 months after conventional therapy for locally advanced and metastatic disease. Consequently, the 5-year overall survival rate is less than five percent [1]. Therefore, identification of risk factors, especially those that are modifiable for PC is a very important task for preventing the development and progression of PC. Tobacco smoking, alcohol consumptions, chronic pancreatitis, and genetic risk factors, have been recognized as potential risk factors for the development and progression of PC [5–7]. However, the etiology of PC is poorly understood. A large number of epidemiological studies have suggested that obesity and diabetes are associated with increased risk of PC, and thus the focus of our article is restricted to the role of obesity, diabetes and PC.

1. Obesity and the risk of the development and progression of PC

Obesity and overweight conditions are prevalent in the world. A World Health Organization (WHO) report demonstrates that more than 400 million people are obese in the world, with a predicted increase to 700 million by 2015 [8,9]. In the United States, the current prevalence of obesity for adults is 30–35 percent [10,11], and thus the general population combining obesity and overweight is a major public health concern. According to WHO/Food and Agriculture Organization (FAO), obesity and overweight conditions can be diagnosed by measuring the body mass index (BMI) of the individual. The BMI is calculated by dividing body weight in kilograms by height squared in meters (kg/m^2). The current standard categories of BMI are as follows: underweight, <18.5 ; normal weight, $18.5\text{--}24.9$; overweight, $25.0\text{--}29.9$; obese, $30.0\text{--}34.9$; and severely obese, ≥ 35.0) [11–13].

It has long been recognized that being obese or overweight increases the risks of cardiovascular disease, hypertension, and type-2 DM. Similarly, numerous epidemiological studies have demonstrated that high BMI is positively associated with increased risk of many common cancers, such as liver, endometrium, breast, pancreas, and colorectal cancers [14–23]. Recently, high BMI has also been considered as an additional risk factor for PC [4,15,17,18]. Although early epidemiological studies showed inconsistent or inconclusive results concerning the association between BMI and the risk of PC, the majority of prospective epidemiological studies have shown that high BMI is indeed associated with an increased risk in the incidence or mortality of PC, independent of prior history of DM [24–33]. The inconsistencies in early findings are believed to be in part due to small sample size, study design bias, retrospective approach, residual or uncontrolled confounders such as smoking history and gender, as well as inadequate statistical power [4,33–36].

In 2003, a meta-analysis of six case-control and eight prospective studies including 6,391 PC cases were conducted to examine the association of high BMI with the risk of PC [37]. The results demonstrated a weak positive association between them (2% increase in risk per 1 kg/m^2 increase in BMI). In 2007, a meta-analysis of 21 prospective studies was conducted including 3,495,981 individuals and 8,062 PC cases [38]. Of the 21 prospective studies, 10 were from the United States, 9 were from Europe, and 2 were from Asia. With the exception of one nested case-control prospective cohort study, all studies were controlled for cigarette smoking, and 13 studies also adjusted for DM. One cohort study including 63,000

individuals and 166 PC cases was excluded because BMI was classified by two categories only (high versus low BMI: >25.2 vs. ≤ 25.2 kg/m² in men; >24.7 vs. ≤ 24.7 kg/m² in women) [35]. The results show that the estimated summary risk ratio (RR) per 5 kg/m² increase in BMI was 1.12 (95% CI, 1.06–1.17) in men and women combined. There was no significant difference of summary RR between men and women. Therefore, the authors have concluded that there was a positive association between BMI and risk of PC in both men and women. Overall, a 5 kg/m² increase in BMI was associated with a 12% increased risk of PC. In 2008, another meta-analysis from 221 datasets, including 282,137 incidence of cancer cases [39]. For analysis of high BMI associated with the risk of PC, the total sample size was 3,338,001 subjects (2,390 PC cases in men and 2,053 PC cases in women). Like the 2003 findings, results also show a weak association of high BMI with the risk of PC (RR, 1.12; CI, 1.02–1.22).

Recently, one large prospective cohort study including 138,503 postmenopausal women in the Women's Health Initiative study in the United States was conducted. This study examined obesity, especially central obesity, in relation to PC (n=251) for the duration of an average of 7.7 years of follow-up [40]. The results show that women in the highest quintile of waist-to-hip ratio have a 70 percent (95% CI, 10–160%) greater risk of PC compared with women in the lowest quintile. This suggests that obesity, especially central adiposity, is positively associated with the increased risk of PC. Another new case-control study included 841 PC patients and 754 healthy individuals and the purpose of this study was to examine the association of high BMI across an age cohort to determine at what age an individual became at risk, age of onset and overall survival of PC [41]. Individuals who were overweight from the ages of 14 to 39 years (highest odds ratio [OR], 1.67; 95% CI, 1.20–2.34) or obese from the ages of 20 to 49 years (highest OR, 2.58; 95% CI, 1.70–3.90) had an associated increased risk of PC, independent of DM status. This association was stronger in men (adjusted OR, 1.80; 95% CI, 1.45–2.23) from the ages of 14 to 59 years than in women (adjusted OR, 1.32; 95% CI, 1.02–1.70). Individuals with high BMI ($\geq$ or > 25) from the ages of 20 to 49 years had an earlier onset of PC by 2 to 6 years. Individuals who were overweight or obese from the ages of 30 to 79 years or were overweight or obese in the year prior to recruitment had reduced overall survival of PC regardless of disease stage and tumor resection status (overweight patients: hazard ratio, 1.26, 95% CI, 0.94–1.69; obese patients: hazard ratio, 1.86, 95% CI, 1.35–2.56). Similarly, the authors concluded that being overweight or obese during early adulthood was associated with a greater risk of PC and a younger age of disease onset, whereas obesity at an older age was associated with a lower overall survival in patients diagnosed with PC.

More recently, several large prospective cohort studies with a long duration of follow-up has been conducted in the U.S. showing a positive association between high BMI and the risk of PC (adjusted RR 1.13–1.54) [42,43], suggesting the role of obesity and overweight with higher risk in the development and eventual death due to PC. Although the role of smoking and gender in the association of obesity and PC is not clear, the new evidence strongly supports a positive association of high BMI with increased risk of PC, consistent with the majority of early findings; however, all recent studies strongly suggest that obesity and overweight are independent risk factor of PC.

2. Obesity, insulin resistance, hyperinsulinemia, and the risk of PC

Obesity, especially central obesity, or central adiposity, has been well documented to be related to insulin resistance, hyperinsulinemia, glucose intolerance, and with subsequent development of type 2 DM [44–46]. A metabolic consequence of obesity, especially central adiposity, is the development of insulin resistance, which induces an increase in the secretion of insulin from the pancreas. Increased insulin production leads to compensatory hyperinsulinemia, which leads to insulin resistance [43,44,46]. The development of insulin

resistance is one of the earliest negative effects of obesity, and is associated with the early altered glucose metabolism, chronic inflammation, oxidative stress and decreased levels of adipose hormone adiponectin and PPAR- γ , key regulators for adipogenesis [46–49]. Moreover, altered regulations in the expression of inflammatory cytokines, adipose hormones such as adipokines, and PPAR- γ also leads to enhance the development of insulin resistance in obese subjects [50]. Consequently, insulin resistance and abnormal glucose metabolism, even in the absence of diabetes, is associated with increased risk for the development of PC [27,51–53]. Several studies have demonstrated that the levels of fasting plasma glucose, insulin, and the degree of insulin resistance, are linearly associated with the risk for the development of PC after 10 or more years [27,54,55].

Insulin acts as a growth-promoting mitogen by binding to insulin receptor and causing activation of insulin signaling cascades, and its growth promoting effects in the pancreas have been shown by *in vitro* studies [56]. High levels of insulin can enhance insulin-like growth factor-1 (IGF-1) synthesis as well and down-regulate IGF-1 binding proteins in the liver, leading to an increase in the bioavailability of free or active IGF-1, which transducer its downstream signaling through binding to its receptor (IGF-R). IGF-1 has been shown to be associated with cell proliferation and the risk of PC [53,57]. Both insulin and IGF-1 stimulate anabolic processes as a function of available energy and elementary substrates (e.g. amino acids). The anabolic signals produced by insulin and IGF-1 can promote tumor development by inhibiting apoptosis, stimulating cell proliferation and enhancing angiogenesis [58–62]. Thus, one major biological contribution of obesity to the development of PC might be due to the development of insulin resistance, and its secondary impact on increased activity of IGF-1.

3. Alterations of adipocyte hormone in obesity and PC

Obesity, especially central adiposity, can alter the secretion and regulation of polypeptide hormones secreted by adipocytes in adipose tissues. Such hormones are known as adipokines, which plays important roles in the secretion, regulation and maintenance of normal metabolic and immune function [50,63,64]. Currently, there are more than 50 different types of adipokines such as adiponectin, leptin, resistin, and ghrelin, etc. Emerging evidence suggests that adipokines plays a greater role in the regulation of insulin sensitivity, glucose and lipid metabolisms, immune response, and angiogenesis [50].

Adiponectin and leptin are the most abundantly expressed adipokines secreted by adipocytes. Adiponectin, a 244 amino acid polypeptide, is exclusively expressed and secreted by adipose tissue, which is present at high concentration in the blood (from 5 to 10 $\mu\text{g/mL}$) [50]. Moreover, it has been found to improve insulin sensitivity, decrease insulin resistance and possibly reduce the risk of type 2 DM [65,66], suggesting that adiponectin is an endogenous negative regulator of diabetes. Contrary to other adipokines that are increased in obesity, the level of adiponectin is decreased in obesity and DM patients along with those that are insulin resistant [67,68]. Therefore, it has been suggested that adiponectin is down-regulated in obesity, and thus higher levels of adiponectin is associated with decreased risk of DM in older men and women [66,69], suggesting that the replacement of adiponectin could be useful for reverting the severity of diabetes although it may not be curative. Interestingly, it has been documented that interventions that reduce adipose mass percentage and overall body weight leads to increased levels of adiponectin with a concomitant improvement in insulin sensitivity [65,70,71], further suggesting that low levels of adiponectin may lead to the development of insulin resistance in obesity, which is mechanistically associated with diabetes, resulting in the development of PC.

A number of studies demonstrate that adiponectin is similarly linked with the risk of cancers such as colon, breast, and PC [72–76]. Increased levels of adiponectin decrease the risk of

cancer, while its low levels increases the risk of cancer [75]. Although the molecular mechanism of adiponectin action against tumor development is not clear, its potential role in the development of PC may be implicated by several direct and indirect mechanisms. First, adiponectin can directly increase insulin sensitivity and reduce insulin resistance through tyrosine phosphorylation of insulin receptors in muscle tissue [77], leading to the down-regulation of insulin/IGF-1 signaling. Secondly, adiponectin is also known as an anti-inflammatory cytokine, thus it can down-regulate the expression of inflammatory cytokines, such as TNF- α and IL-6, and inhibit NF- κ B activation [78], which is likely to be the molecular mechanism involved in these chronic diseases. Therefore, the low levels of adiponectin will induce the expression of inflammatory cytokines in obese subjects, which will lead to subsequent development of diabetes and cancers. Moreover, the *in vitro* and *in vivo* studies have shown that adiponectin could affect cancer development more directly through the activation of the AMPK pathway at a local tissue level [79,80]. Adiponectin has also been shown to directly inhibit angiogenesis through the activation of PPAR- γ and by promoting apoptosis *in vivo* through the activation of the caspase cascade [81], which could be responsible for the anti-diabetes and anti-cancer effects of adiponectin. Collectively, these studies suggest that decreased levels of adiponectin in obesity may contribute to the development of PC by complex mechanisms.

Leptin is expressed and secreted by adipocytes, which is positively associated with adiposity and insulin [82]. Specifically, leptin binds to its receptors in the hypothalamus, thereby activating signals to suppress appetite and increasing energy expenditure. Insulin acts as a positive feedback on leptin gene expression and it has been shown that leptin and insulin levels are increased in obesity [82]. Interestingly, epidemiological and xenograft mouse model studies have shown that leptin is positively associated with increased risk of cancer, and in particular promotes PC growth [65,83–85]. Leptin has also been shown to act as a mitogen for various types of cells, including cancer cells [69,83]. *In vitro* studies show that leptin exerts its anti-apoptotic and pro-angiogenic activity mediated by the activation of vascular endothelial growth factor (VEGF), and thus may potentially function as a pro-inflammatory agent. In addition, leptin when binds to its receptor is known to activate PI3K/Akt/MAP kinase and STAT signaling pathways, and these signaling pathways are critical for cell survival, growth, proliferation and differentiation [82,86]. Therefore, leptin may play a key role in the development of PC; however, further in-depth studies are warranted in order to fully recognize the mechanistic role of leptin in obesity, diabetes and cancer.

4. Obesity, chronic inflammation, and PC

Chronic inflammation is well known to be involved in the initiation and progression of tumors including PC [18,87,88]. For example, chronic pancreatitis is directly linked with increased risk of PC [5,7,18]. Similarly, obesity has been found to be positively associated with low-grade chronic inflammation [89–91]. Consequently, obesity-induced chronic inflammation represents one of the key features of adipose tissue dysfunction. Local inflammatory responses include macrophage infiltration and resistance to hormones such as insulin and leptin. Systemic inflammatory responses such as increased production of TNF- α , IL-6, IL-1, CRP, plasminogen activator inhibitor-1 (PAI-1), fibrinogen and tissue specific hormone activity mediated through the activation of NF- κ B and PPAR- γ pathways, appears to be mechanistically linked with chronic inflammation and obesity [90,92,93]. The loss of body weight leads to decreased levels of inflammatory markers whereas weight gain leads to an increase in these markers [94], suggesting that controlling body weight may reduce chronic inflammation, and thus will reduce the risk for the development of PC.

Although the causes of inflammation in obesity are not fully understood, existing evidence suggests that increased levels of inflammatory cytokines and proteins such as matrix metalloproteinases (MMPs), key mediators of cancer cell invasion and metastasis, are

correlated with the high risk of cancers including PC [87,88,95–101]. Chronic inflammation also induces the development of insulin resistance [102], which may eventually contribute to the increased risk of PC mediated through insulin/IGF-1 signaling cascades. Therefore, obesity-induced chronic inflammation appears to contribute to the development of PC.

5. Obesity, oxidative stress, and PC

Oxidative stress is caused by an imbalance between the production of reactive oxygen species (ROS) such as, peroxides and free radicals, and the detoxification of reactive intermediates in a biological system. The maintenance of homeostasis is therefore important for maintaining normal health. Evidence suggests that obesity may induce systemic oxidative stress, which if unresolved, could lead to the development of PC. The oxidative stress created by chronic high exposure to glucose and lipids, and decreased activity of antioxidants in the accumulated adipose tissue leads to dysfunction of adipose tissues such as altered expression of adipokines and cytokines [103]. Several observations from human and animal models have suggested that obesity is involved in lipid peroxidation, which is an oxidative stress marker [50]. For example, one study showed that obese, non-diabetic subjects have increased levels of lipid peroxidation [103]. Obese mouse models show similar increase along with a decrease in the activity of antioxidants [103]. These studies suggest that obesity could induce oxidative stress, which in turn, could induce a series of alterations in the biological processes such as DNA damage, inflammation, apoptosis, and insulin resistance, resulting in the development of cancer [104,105]. ROS can also induce chronic inflammation by activation of NF- κ B, and could alter the regulation of adiponectin in adipose tissue [50,106,107]. Thus, obesity-induced oxidative stress may contribute to the increased risk of PC; however, the exact mechanism requires further investigation.

6. Altered regulation of sex hormones in obesity and PC

Sex hormones are known to maintain homeostasis between cellular differentiation, proliferation and apoptosis, and deregulated functioning may promote cancer cell growth [15,108]. The altered regulation of sex hormones is also another key feature of obesity. Obesity-induced high levels of insulin along with IGF-1 can inhibit the synthesis of hormone binding globulin (SHBG) in the liver, the only source of SHBG synthesis [109]. SHBG is a major carrier protein for sex hormones such as testosterone and estradiol in the blood. Thus, a decreased level of SHBG gives rise to an increase in the levels of unbound sex hormones, resulting in increased bioavailability of these hormones to activate signaling cascades [110]. Furthermore, adipose tissue is a major site for the synthesis of estrogens from androgenic precursors [111].

Epidemiological studies have demonstrated that increased risk of breast, endometrial, colon, and prostate cancers are associated with high BMI or obesity, especially central adiposity, is probably mediated by the alterations in the free levels of sex hormones in obesity [65,112,113]. For example, increased risk of postmenopausal breast cancer is associated with a low plasma level of SHBG and an increased level of total and free androgens and estrogens [114]. Although the alterations in the levels of sex hormones have been observed in PC patients, there is no consistent data showing any significant difference in the risk for the development of PC between obese women and men. Thus, the role of sex hormones such as estrogen and testosterone in the development of PC can not be established based on existing evidence, and thus further rigorous studies are required for establishing the role of sex hormones in the context of obesity for the development of PC.

7. Adipose tissue hypoxia and PC

Hypoxia is one of the fundamental features associated with solid tumors including PC [115–118]. Hypoxia-inducible factor-(HIF)-1 α , a key transcription factor for hypoxia responsive

genes, plays a critical role in increased cell proliferation, survival, angiogenesis and metastasis by primarily regulating the VEGF expression. Tumor hypoxia and over-expression of HIF-1 α have been reported to be associated with radiation and chemotherapy resistance, risk of invasion and metastasis, and poor prognosis of solid tumors, all of which lead to higher mortality [118–120]. Hypoxia has been observed in the white adipose tissue in obese mouse models [121–123]. Obesity-induced hypoxia, especially in adipose tissue, is involved in the development of local and systemic insulin resistance, the up-regulation of chronic inflammation, reduced adiponectin and increased leptin gene expressions [122–124]. Thus, adipose tissue hypoxia might play a key role in increased risk for the development and chronicity of cancers including PC.

Recent studies have shown that HIF-1 α is involved in the up-regulation of leptin in colorectal and breast tumors [83,89,125]. Hyperinsulinemia might induce HIF-1 α -mediated over-expression of leptin in breast cancer cells, contributing to disease progression [83,126]. Furthermore, obesity-induced hypoxia and HIF-1 α increases the expression of MMPs and VEGF, suggesting that obesity-induced hypoxia and HIF-1 α could be involved in the angiogenic and metastatic processes of tumors [124]. These findings are consistent with clinical data showing that the level of VEGF, regulated mainly by HIF-1 α and NF- κ B, increases with high BMI [127]. Furthermore, it is well known that VEGF plays an important role in tumor angiogenesis [128]. Thus, increased levels of VEGF, known as a key endothelial mitogen, in obesity may contribute to the development and progression of PC, suggesting that obesity-induced hypoxia and HIF-1 α may play a key role in the development and progression of PC.

8. Diabetes Mellitus (DM) and the risk of PC

DM is a very common metabolic disorder with hyperglycemia, eventually affecting all systems in the body, and is highly prevalent in the world. There are two types of DM, type-1 and type-2. In adults, type-2 DM accounts for 90–95 percent of all diagnosed cases of DM. There are more than 1.5 million of people newly diagnosed with DM each year in the U.S. This number is expected to double in the next 15–20 years [129]. It is known that one of the main consequences attributed to DM is the impairment of multiple tissues and systems, including the cardiovascular and immune response systems. Moreover, the relationship between DM and cancer risk has been investigated for more than a decade as briefly stated under obesity and the risk of PC.

Emerging evidence indicates that DM, particularly type-2 DM, is positively associated with an increased risk of certain cancers including PC [130–134]. This association is complex because DM may be the cause of PC or often the precursor to the onset of its symptoms and signs. In addition, PC induced DM could also exist which is usually characterized by a short duration of course (several months to several years), a negative family history, the absence of obesity, and rapid progression to insulin dependence [135] whereas DM mediated development of PC has a longer duration (>4 years) before its onset [54,135–137]. Therefore, the examination of the duration of DM prior to the onset of PC is important to elucidate the cause and effect relationship between DM and PC so that appropriate customize management could be discovered.

A large number of epidemiological data supports the hypothesis that DM is positively associated with increased risk of PC as summarized earlier in this chapter. In 1995, a meta-analysis of 20 retrospective cohort studies demonstrates that longstanding DM (5 years or more) increased pancreatic cancer risk by two-fold (RR, 2.0; 95% CI: 1.2–3.2) [138]. In 2005, a meta-analysis of 17 case-control and 19 cohort or nested case-control studies including 9,220 cases of PC shows a modest association between DM and PC (the combined summary OR, 1.82; 95% CI, 1.66–1.89). Individuals with DM history less than four years

had a 50 percent greater risk of PC compared with individuals who had DM history for more than 5 years (OR 2.1 vs 1.5) [139], suggesting a modest causal association between DM and PC. In 2007, another meta-analysis of three cohort and six case-control studies specifically conducted in type-1 and young-onset DM patients, confirmed that even in this population a two fold higher risk of PC was observed compared with individuals without DM (RR, 2.0; 95% CI 1.37–3.01) [140]. Recently, one large case-control cohort study including 278,761 DM and 836,283 control subjects was conducted to investigate the association of DM with PC and biliary cancer. The results demonstrate that DM has a three-fold increased risk for the development of PC and a two-fold risk for biliary cancer [141]. Other recent studies also provide supportive evidence documenting that DM is positively associated with increased risk of PC [54,142–144].

9. DM, insulin/IGF-1R signaling pathways and the risk of PC

Accumulating evidence clearly suggests that DM is positively associated with increased risk of PC (RR, 1.4–2.2). However, the exact molecular mechanism(s) has not been fully understood. Similar to the role of obesity in the development of PC, insulin resistance and induced compensatory hyperinsulinemia are widely considered to be mechanisms underlying the causal association of DM and cancers, including PC.

Insulin resistance and altered glucose metabolism are common features for both obesity and type-2 DM. Moreover, DM has a more extensive degree of insulin resistance, hyperinsulinemia and hyperglycemia, which may contribute to the development of PC. Emerging evidence has shown that high levels of insulin, increased fasting and postprandial blood glucose increases the risk of PC [27,145,146]. A high level of insulin stimulates the insulin/IGF-1R signaling pathway via insulin receptor substrates (IRS). In most cell types, these substrates mediate the PI3K/Akt/mTOR signaling pathway [147], which is known to play a pivotal role in the proliferation and survival of PC cells [148,149]. Human insulin users have been found to have an increased risk for the development of cancers including PC [150,151]. It is known that hyperinsulinemia increases IGF-1 by increasing its synthesis and inhibiting its binding protein. Thus, the increased level of insulin and consequently higher levels of IGF-1 promotes cell proliferation, inhibits apoptosis and enhances angiogenesis, all are involved in the development and progression of PC [60,60,152]. Insulin/IGF-1 could also activate PI3K/Akt/mTOR signaling pathway by activation of insulin receptor substrate 1–4 [153], which will contribute to the development of cancers including PC. Moreover, the activation of insulin/IGF-1 receptors by insulin can interplay positively with the hedgehog signaling pathway, which is involved in the regulation of cancer cell growth by regulating cell proliferation and differentiation [154]. It is well known that PC cells express insulin and IGF-1 receptors and IRS-1,2 in large amounts [153,155], suggesting that insulin/IGF-1R signaling pathway may play an important role in the development and progression of PC. Further evidence showed that intrapancreatic insulin/IGF-1 in combination with the activation of K-Ras, a known oncogene for the development of PC, can stimulate PI3K/Akt signaling pathway, which contributes to the development and conferring aggressiveness of PC. Likewise, the inhibition of IGF-1R has been shown to increase the sensitivity of colon cancer stem-like cells to chemotherapeutic drugs [156]. However, the signaling pathways activated by insulin/IGF-1 receptors in PC have not been fully elucidated, suggesting that further mechanistic studies are required to elucidate the role of this signaling pathway in the development and progression of PC.

10. The role of anti-diabetic drugs in PC

Anti-diabetic drugs are known to lower blood insulin levels and increases insulin sensitivity. Due to the positive association of DM with PC, and existing knowledge on the role of insulin/IGF-1R signaling pathways in the development and progression of PC, anti-diabetic

drugs have been investigated for their use in prevention and treatment of cancers such as PC for more than a decade. Currently, extensive attention has been given to the anti-diabetic drugs metformin and thiazolidinediones (TZD).

10.1. The role of Metformin in PC—Metformin (1,1-dimethylbiguanide hydrochloride) is a biguanide class of oral hypoglycemic agents and it is the world's most widely used anti-diabetic drug for the treatment of type-2 DM. Although it has been in clinical use for decades, its precise molecular mechanism of action is still not fully understood. The primary systemic effect of metformin is to decrease blood glucose levels through reduced hepatic gluconeogenesis and increased glucose uptake in peripheral tissues, including skeletal muscles and adipose tissue [157]. It also increases insulin sensitivity which results in decreased insulinemia. Metformin is a very safe drug, which is also well tolerated although it is associated with very low incidence of lactic acidosis ($<1/10,000$), which is seen predominantly in patients with poor renal function [158,159]. Numerous epidemiological studies have demonstrated that the administration of metformin in DM patients exhibits a protective effect by decreasing incidence of different tumors and improving prognosis of patients with cancer [160–164]. These protective roles of metformin in the development and progression of tumors prompted an investigation into its anti-tumor effect on site-specific tumors. Specifically, clinical studies in both diabetic and non-diabetic patients clearly suggest that metformin may decrease the risk of developing cancers such as breast cancer and PC. Furthermore, several randomized trials have demonstrated its protective role when used as adjuvant therapy and for the prevention of breast and colorectal cancers [165–168].

One recent study showed that women taking metformin had a pathologic complete response rate of 24 percent as compared to 8 percent of women who were not [169]. An additional new, large case-control clinical trial regarding the use of metformin for the treatment of PC was conducted from 2004 to 2008 involving 973 PC patients (including 259 DM patients) and 863 controls (including 109 DM patients) [170]. The results showed that DM patients who were administered metformin had a significantly lower risk of PC compared to those who did not receive metformin. In contrast, DM patients administered insulin had a significantly higher risk of PC compared to those without insulin. These recent findings clearly suggest that the administration of metformin is positively associated with the decreased risk of PC in DM patients while the use of insulin or other agents is associated with an increased risk. Therefore, metformin appears to exert a protective role against the development and progression of PC.

Animal studies have also demonstrated that metformin can inhibit tumor growth in xenograft models [171–174]. The anti-tumor effect of metformin is probably related to its direct and indirect mechanisms although the detailed molecular mechanisms in support of these findings are not fully understood, several mechanisms have been proposed. It has been shown that increasing insulin sensitivity and decreasing insulin level by metformin could inhibit cancer cell growth by activation of AMP kinase (AMPK), which in turn inhibits mTOR signaling [175,176]. AMPK is usually activated when the ratio of AMP/ATP is increased and the activation of AMPK results in the down-regulation of the PI3K/Akt/mTOR signaling pathway by phosphorylation of mTOR. The mTOR is usually activated by mitogenic-responsive pathways such as Ras/ERK and PI3K/Akt as well as pathways that signal the availability of intracellular energy and nutrients including amino acids. However, the inhibition of mTOR pathway by metformin through activation of AMPK leads to a rapid inhibition of cellular protein synthesis and growth [165–167]. Moreover, metformin can directly inhibit cancer cell growth and proliferation through the regulation of cyclin D1-mediated cell cycle, p53 expression and phosphorylation in breast cancer and prostate cancer cells [177–182]. Metformin has also been found to inhibit the production of inflammatory cytokines such as TNF- α and IL-6 as well as VEGF, probably by inactivation of NF- κ B and

HIF-1 α [183–185]. *In vitro and in vivo* studies show that metformin can block tumor growth by inactivation of breast cancer stem-like cells and epithelial-mesenchymal transition (EMT) phenotype, and these cells are believed to be the root cause of tumor recurrence and metastasis [186,187].

The first animal study using metformin on pancreatic tumors showed that metformin can prevent the growth of carcinogen-induced pancreatic tumors in hamsters maintained on a high-fat diet [188]. It has also been found that metformin could induce apoptosis in PC cells, and also inhibited tumor growth in xenograft model of tumors induced by PANC-1 and MIAPaCa-2 cell lines [189,190]. Additional evidence showed that metformin can inhibit PC cell growth and proliferation by disruption of insulin/IGF-1R and GPCR crosstalk through the activation of AMPK [189,191]. These results suggest that metformin could be useful anti-tumor agent for the treatment of PC by targeting AMPK/mTOR, insulin/IGF-1R, GPCR, and other signaling pathways.

10.2. PPAR- γ ligands, thiazolidinediones, and PC treatment—Peroxisome proliferator-activated receptor- γ (PPAR- γ), expressed predominantly in adipose tissue and in the immune system [161,192,193], is a ligand-activated transcription factor involved in the regulation of lipid and glucose homeostasis, and also control of inflammation [194]. Upon the binding of the ligand, PPAR- γ translocates to the nucleus where it heterodimerizes with RXR [161,195,196] and activate genes with a peroxisome proliferator response element (PPRE) in their promoter regions initiating their transcription [197,198]. Altered regulations of PPAR- γ have been implicated in a number of disease processes, including obesity, type-2 DM, and carcinogenesis [161,199–201]. Thiazolidinediones (TZD), an agonist of PPAR- γ have been used effectively to mediate insulin sensitivity and decrease high insulin levels through the activation PPAR- γ however, the molecular mechanism has not fully established. Currently, two TZD classes of synthetic PPAR- γ agonist (ligand), pioglitazone and rosiglitazone, have been approved by the United States Food and Drug Administration (FDA) as anti-diabetic drugs for the treatment of type-2 DM although the use of pioglitazone in more safer than rosiglitazone.

Because TZD has the ability to modulate insulin signaling, the use of TZD has been proposed as a potential anti-tumor agent for the treatment of cancers [202,203]. A number of clinical studies have been conducted for assessing the efficacy of the TZD class of PPAR- γ agonists. The majority of the studies showed inconsistent or inconclusive results [164,204]. This is probably due to the short duration of treatment, study design bias, residual confounders, or cell- or tissue-specific targeting [203]. In recent years, several clinical studies have suggested that the treatment of DM patients with PPAR- γ agonist may have preventive effects on the development of cancer. As a result, PPAR- γ agonist could be useful as adjuvant therapy with conventional chemotherapeutics [205–207]. There has been no clinical report regarding the use of PPAR- γ ligands in PC patients. However, the over-expression of PPAR- γ activation has been found to be positively correlated with higher tumor stage and grade, and associated with shorter patient survival, suggesting its potential role in PC progression [131,208]. Although the biological role of PPAR- γ in the development of PC is not clear, the TZD class of PPAR- γ ligands have been shown to have activity in pre-clinical cell culture and xenograft mouse models [209–212]. One animal study, using Syrian golden hamsters, demonstrated that dietary intake of 800 ppm pioglitazone for 22 weeks correlated with a decreased incidence and multiplicity of carcinogen-induced pancreatic tumors, implicating the potential chemopreventive role of TZD in the development of PC [213].

The inhibitory effects of the TZD class of PPAR- γ ligands on the development and progression of cancer have been proposed, which involves PPAR- γ -dependent and

independent mechanisms. First, PPAR- γ ligands have been shown to increase insulin sensitivity and decrease the insulin level through the activation of PPAR- γ , leading to the inhibition of insulin/IGF-1R signaling pathways [209,210]. Secondly, the activation of PPAR- γ can inhibit TNF- α , IL-6, IL-8, PAI-1, VEGF, COX2, MMPs, uPA, NF- κ B, AP-1, STAT, and leptin [212,214–223]. PPAR- γ ligands can directly inhibit inflammatory response by the activation of AMPK through the regulation of mitochondrial function and ROS production in a PPAR- γ -independent pathways [224]. There is also evidence showing that PPAR- γ ligands can induce apoptosis and inhibit proliferation of brain cancer stem cells [225]. Furthermore, PPAR- γ ligands are also shown to increase the expression of PTEN, an oncogene suppressor, and could inhibit the activation of β -catenin, a positive modulator of cell growth through PPAR- γ -independent mechanism [211,222,226,227]. Based on these experimental evidences, it is important to note that the anti-tumor effects of TZD class of PPAR- γ ligand, which are anti-diabetic drugs, could be useful for the prevention and/or treatment of human malignancies especially PC.

11. The regulatory role of microRNAs (miRNAs) in obesity, DM and PC

MicroRNAs (miRNAs) are small non-protein-coding RNAs (around 21–24 nucleotides) that function as post-transcriptional gene regulators by specific binding to the 3' untranslated region (3'UTR) of target mRNAs to control protein synthesis or degradation of the mRNA. They are currently recognized as regulator of expression of most genes, and consequently they play critical roles in a wide array of biological processes, including cell differentiation, proliferation, death, metabolism and energy homeostasis [228,229]. A large number of miRNAs have been reported to be associated with chronic diseases such as obesity, DM and cancers, and are suspected to be mechanistically associated with these chronic diseases. However, their exact role in the pathogenesis of obesity, DM and PC are not fully understood.

A number of studies have demonstrated that miR-21 is a potential oncogene and it is up-regulated in PC cells [230–237]. Over-expression of miR-21 results in decreased expression of PTEN, a known tumor suppressor in PC [237]. The miR-21 has also been reported to show anti-apoptotic, proliferative, invasive and angiogenic properties in cancer cells [230,236,238]. Moreover, decreased expression of miR-200 has been observed in many cancer cells [230,236,238], suggesting that altered expression of these miRNAs may contribute to the invasiveness and metastatic characteristics of PC. The possible roles of these two miRNAs in obesity and DM associated with the development of PC require further studies.

Let7 family, especially let7b, is abundantly expressed in pancreatic islet cells and postulated to be important ribo-regulators of blood glucose [239–241]. Let7 has been found to regulate the expression of PPAR- γ 2 in adipocytes. In the pathogenesis of cancer, let7 has been found to be down-regulated thereby increasing the expression of Ras and c-Myc in malignant cells [234–236]. In addition, the altered regulation of let7 has been observed in DM and PC [234,235], suggesting that let7 may play a key role in the pathogenesis of obesity, DM and PC.

Another class of miRNA, miR-34a and miR-146a have been found to be highly expressed in obesity and DM [241–243], and over-expressions of miR-34a and miR-146a are known to cause alterations in glucose-stimulated insulin secretion and the induction apoptosis in β -cells [241,242]. In contrast, miR-34a has been shown to be induced by p53 and exhibit potent anti-proliferative and pro-apoptotic activities in cancer cells including PC cells [234]. Studies have also shown that miR-146a have angiogenic activity [241,242], and altered expression of miR-34a and miR-146a are typically found in PC cells [234,235,244] although the exact role of these miRNAs in obesity, DM and PC has not been fully elucidated.

The up-regulation of miR-143 has been found in obesity, DM and PC [232,235,240,241]. One identified target gene of miR-143a is MAPK7, which is involved in the regulation of MAPK signaling pathway. While, over-expression of miR-143 is related to altered regulation of PPAR- γ in adipose tissue of obese mice [240,241], the potential role of miR-143 in the development of PC associated with obesity and DM is not clear, suggesting that further in-depth mechanistic studies are warranted for elucidating the possible role of miR-143 in the development of PC in obese and DM patients.

The expression of miR-29 has been found to be elevated in the insulin targeted tissues [239]. Over-expression of miR-29 represses insulin-stimulated glucose uptake, leading to the development of insulin resistance [239,241,242]. Moreover, high level of miR-29 has been observed in obesity and DM animals and DM patients [239–241,245]. Moreover, miR-29 was also found to be up-regulated in PC cells [235], suggesting the potential role of miR-29 in obesity, DM, and PC and thus, novel strategies by which specific miRNA could be down-regulated or up-regulated would become a novel approach for the treatment of chronic diseases including obesity, diabetes and PC. Further studies have shown that miR-375 is highly expressed in β -cells in pancreatic islet. It down-regulates glucose-stimulated insulin secretion by controlling the expressions of 3'-phosphoinositide-dependent protein kinase-1 (PDK1), a key regulator of β -cell function, and myotrophin, a regulator of insulin secretion [241,242]. An increased level of miR-375 has been found in obesity and type-2 DM patients [241,246] where it represses insulin secretion. Inhibition of miR-375 leads to an increase in insulin secretion [241,246]; however, miR-375 knockout mice display marked hyperglycemia, suggesting that miR-375 is essential to maintain normal pancreatic function [246]. Interestingly, miR-375 has been found to down-regulated in PC cells [235], suggesting the potential role of miR-375 in the development of PC associated with obesity and DM although mechanistic studies are lacking. The above sections underscore the importance of miRNA in chronic diseases; however, the field is still in its infancy and clearly more in-depth mechanistic studies are warranted in order to fully appreciate the roles and therapeutic regulations of miRNAs in obesity, diabetes and cancer especially PC.

12. Conclusions and Perspectives

A large number of epidemiological studies have documented a clear association between obesity and diabetes, which is also positively associated with increased risk of PC, suggesting that both obesity and diabetes are additional risk factors for PC. Insulin resistance and the induction of compensatory high levels of insulin, leading to the alteration of glucose and lipid metabolism, are common characteristics of obesity and type-2 DM. They appear to be primarily contributes to the development of PC by activation of insulin/IGF-1R signaling pathways. Increased levels of insulin, fasting and post-prandial blood glucose have also been reported to be related to the high risk of PC. Thus, targeting insulin/IGF-1 signaling by anti-diabetic drugs which will cause lowering of blood insulin level, could be useful for the prevention and/or treatment of PC although further novel well thought-out clinical trial design is warranted. A large number of studies have demonstrated that the administration of anti-diabetic drugs, such as metformin and the TZD class of PPAR- γ agonist decreases the risk of cancers, suggesting that these drugs could be useful anti-tumor agents for PC especially because metformin could effectively eliminate cancer stem cells which is the root cause of tumor recurrence and metastasis. *In vitro and in vivo* studies have also shown that these drugs can inhibit PC growth by different mechanisms including alterations in the expression of genes mediated by the regulation of miRNAs. Although the exact roles of miRNAs in the pathogenesis of obesity, DM and PC are not fully understood, selective up-regulation and down-regulation of important miRNAs such as miR-21, let7, miR-29, miR-34a, miR-134, miR-146a, and miR-375 could become novel and newer strategies for the treatment of obesity, DM and PC in the future. Overall, the future

looks brighter than ever before for exploration of targeting miRNAs by novel approaches for the management of chronic diseases such as obesity, diabetes and cancer especially in subjects who are at high risk for the development of PC.

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Figure 1.

Potential pathways directly linking obesity and diabetes to pancreatic cancer. Obesity and diabetes cause multiple alterations in glucose and lipid hemostasis, microenvironments, and immune responses, which result in the activation of several oncogenic signaling pathways. These deregulations increase cell survival and proliferation, eventually leading to the development and progression of pancreatic cancer. ROS, reactive oxygen species; IGF-1, insulin-like growth factor-1; IR, insulin receptors; IGF-1R, insulin-like growth factor-1 receptors; TNFR, tumor necrosis factor receptors; TLR, Toll-like receptors; HIF-1 α , hypoxia-inducible factor- α 1; AMPK, AMP kinase; IKK, I κ B kinase; PPAR- γ , peroxisome proliferator-activated receptor- γ ; VEGF, vascular endothelial growth factor; MAPK, MAP kinase; mTOR, mammalian target of rapamycin; TSC, tuberous sclerosis complex; Akt, protein kinase B. PI3K, phosphoinositide-3-kinase; STAT3, activator of transcription-3; JNK, c-Jun NH2-terminal kinase.