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REVIEW ARTICLE

Non-coding RNAs underlying the pathophysiological links between type 2 diabetes and pancreatic cancer: A systematic review

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ABSTRACT

Type 2 diabetes is known as a risk factor for pancreatic cancer (PC). Various genetic and environmental factors cause both these global chronic diseases. The mechanisms that define their relationships are complex and poorly understood. Recent studies have implicated that metabolic abnormalities, including hyperglycemia and hyperinsulinemia, could lead to cell damage responses, cell transformation, and increased cancer risk. Hence, these kinds of abnormalities following molecular events could be essential to develop our understanding of this complicated link. Among different molecular events, focusing on shared signaling pathways including metabolic (PI3K/Akt/mTOR) and mitogenic (MAPK) pathways in addition to regulatory mechanisms of gene expression such as those involved in non-coding RNAs (miRNAs, circRNAs, and lncRNAs) could be considered as powerful tools to describe this association. A better understanding of the molecular mechanisms involved in the development of type 2 diabetes and pancreatic cancer would help us to find a new research area for developing therapeutic and preventive strategies. For this purpose, in this review, we focused on the shared molecular events resulting in type 2 diabetes and pancreatic cancer. First, a comprehensive literature review was performed to determine similar molecular pathways and non-coding RNAs; then, the final results were discussed in more detail.

BACKGROUND

Diabetes mellitus is a severe and worldwide health problem that develops due to changes in the environment and lifestyle. The global number of patients with diabetes will increase to 552 million by 2030. Previous studies have indicated that the incidence of different cancers, including liver, biliary tract, colorectum, kidney, breast, pancreas, etc., is increased in diabetic patients through abnormalities in glucose metabolism[1]. Pancreatic cancer (PC) is one of the most lethal malignancies among the different kinds of cancers and is the seventh leading cause of global cancer deaths in industrialized countries. The etiology of pancreatic cancer is complex and includes both genetic and environmental factors[2]. Type 2 diabetes is the third risk factor for pancreatic cancer after cigarette smoking and obesity. According to the American Cancer Society's Cancer Facts and Figures 2013, at diagnosis, 25% and 40% of pancreatic cancer patients have diabetes and prediabetes, respectively. A 50% increased risk of pancreatic cancer has been shown in long-term (>5 years) type 2 diabetes patients, and vice versa pancreatic cancer can be a cause of diabetes. Furthermore, in some cases, diabetes could be considered to be an early sign of a tumor. However, the association between type 2 diabetes and pancreatic cancer is complicated. On the one hand, diabetes can be considered as an early prognostic tool for pancreatic cancer, and on the other hand, it could be a predisposing factor for pancreatic cancer[2]. This review aims to improve our understanding of the association between type 2 diabetes and pancreatic cancer, mainly focusing on the molecular mechanisms underlying this association. This approach would greatly aid in developing

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novel tools for the prevention, prognosis, diagnosis, and treatment of this cancer.

TYPE 2 DIABETES

Type 2 diabetes is caused by resistance to insulin in target tissues, insulin secretion deficiency, or both of them, leading to hyperglycemia[3]. Polyuria, polydipsia, polyphagia, and weight loss are different symptoms of type 2 diabetes[4]. According to the International Diabetes Federation (IDF), about one in eleven adults had diabetes mellitus worldwide, of which 90% of them have type 2 diabetes. In addition, Asia is a significant region with rapid growth in the type 2 diabetes epidemic[5]. The risk of type 2 diabetes is determined by the interaction of genetic, epigenetic, and lifestyle factors. Ethnicity, family history, obesity, and overweight, unhealthy diets, low physical activity, and smoking increase the risk of disease[5].

PANCREATIC CANCER

Pancreatic cancer ranks fourth globally among all malignant tumors, with early metastasis, high invasiveness, lack of specific symptoms, and a high mortality rate[6]. Globally, aging is associated with an increased incidence and mortality rate of pancreatic cancer. The disease is slightly more common in men than in women, and the incidence worldwide is 5.5 per 100,000 for men and 4.0 per 100,000 for women. Environmental risk factors and lifestyles such as high alcohol intake and heavy smoking habits in men could lead to pancreatic cancer. However, undiscovered genetic factors may be potential influencers of cancer incidence and mortality in males and females[2]. Pancreatic cancer can be classified into two types: exocrine pancreatic cancer, which includes adenocarcinoma and is the most common type (85% of cases), and neuroendocrine pancreatic cancer, which comprises less than 5% of patients[7]. Several risk factors may increase the chance of developing pancreatic cancer. Smokers have more than twice the risk of developing cancer[8], although unlike other smoking-related diseases[9], an apparent mutation signature has not been detected[10]. Heavy alcohol drinking is undoubtedly related to the risk of pancreatic cancer, whereas there is no association with low-to-moderate alcohol intake[11]. According to an American Cancer Society (ACR) study, the risk of pancreatic cancer among overweight people is higher compared with those with a normal BMI (18.5–24.9 kg/m^2)[12]. Family history has a significant role in developing pancreatic cancer, and approximately 10% of individuals with pancreatic cancer have a family history of the disease[13]. Germline pathogenic variants in hereditary breast and ovarian cancer genes (BRCA1 or BRCA2 and PALB2) may pose an increased risk of pancreatic cancer[14]. Finally, defective DNA mismatch repair genes MLH1, MSH2, MSH6, and PMS2 could increase cancer[15]. Other genetic factors contributing to pancreatic cancer have been identified but are rare and often personal variants[16].

Hence, apart from the clinical staging of disease, there is no clinical feature to inform decision-making for pancreatic cancer. Possibly, due to the lack of patient numbers and the lack of desire among surgeons, very few clinical trials are being carried out to control the disease. Inadequate diagnostic tests may miss patients in the early stages of the disease[17]. Surgery, chemotherapy, and radiotherapy have been used traditionally to help increase patients' survival and to relieve their pain. However, there is still no definite treatment for the advanced stage of cancer cases. There is a need for further research for novel therapies and to assess the outcomes of these approaches. Therefore, examining different patients to identify the genes and variants involved in the disease is a straightforward way to treat the disease[18].

DIFFERENT ASPECTS OF THE ASSOCIATION BETWEEN TYPE 2 DIABETES AND PANCREATIC CANCER

Assessing the association between the presence of diabetes and the progression of pancreatic cancer faces many challenges. A possible explanation for the observed relationship between type 2 diabetes mellitus and pancreatic cancer could be the shared risk factors and metabolic abnormalities, including high cholesterol intake, hyperglycemia, insulin resistance (IR), and chronic inflammation[19]. A population-based study in British Columbia and Canada found that people with type 1 diabetes mellitus are at increased risk of pancreatic cancer[20]. Additionally, a meta-analysis had considered eleven studies with a total of 14,399 patients, of whom 4,080 were type 2 diabetes-positive and 9,721 were non-diabetic. Their results showed that a plausible manifestation of pancreatic cancer is recent-onset type 1 diabetes mellitus, whereas long-term type 1 diabetes mellitus is probably a risk factor for this cancer[21]. A large number of patients with pancreatic cancer show impaired metabolism of glucose[22]. Tumor formation and progression are possibly correlated with metabolic factors contributing to the long-term insulin resistance[23]. A specific environment is necessary for tumor formation. Overproduction of insulin, which usually occurs in type 1 diabetes mellitus, provides an appropriate environment for cells and blood vessels to proliferate in the pancreas[24]. Since exogenous administration is the only source of insulin in type 1 diabetes mellitus, the risk of developing pancreatic cancer in this disease can be low[25]. Diabetes mellitus could occur due to developing pancreatic cancer or could be a consequence of this disease[26]. The correlation between type 1 diabetes mellitus and pancreatic cancer is not yet definite[27]. However, it has been reported that the progression of tumor status is affected by type 1 diabetes mellitus, which contributes to increasing the size of the tumor and the pancreatic ducts[28]. Hyperinsulinemia causes insulin resistance, which in turn increases the risk of malignancy. It is reported that pancreatic cancer is correlated with obesity and the insulin pathway. The link between the reports and the hypothesis shows that obesity increases insulin levels and the risk of hyperinsulinemia. This condition leads to decreased levels of insulin-like growth factor-binding proteins (IGFBPs), and increased levels of circulating insulin-like growth factor 1 (IGF1)[29]. Insulin and IGF1 both promote inhibition of cancer cell apoptosis and contribute to the cell proliferation[24].

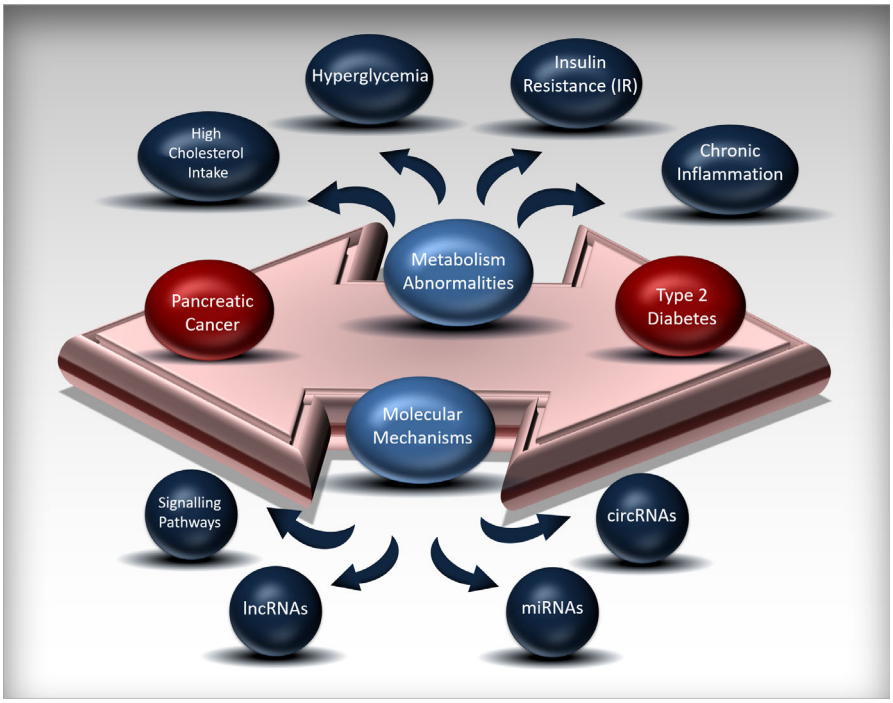

Figure 1 | Schematic representation of different aspects of the association between type 2 diabetes and pancreatic cancer. Metabolism abnormalities and molecular mechanisms are identified as two significant aspects of the association between type 2 diabetes and pancreatic cancer.

As a result, increased IGF-1 due to hyperinsulinemia will cause tumor progression. IGF-1 and IGF-1 receptor (IGF-1R) have a strong tendency to prevent apoptosis, and hyperinsulinemia in an insulin resistance environment will potentiate this effect. In tumor cells, the high receptor expression for IGF-1 and insulin led to an increase in the circulating levels of active IGF-1 and decreased hepatic production of IGFBP-1 and -2. Therefore, hyperinsulinemia following insulin resistance may enhance tumor cell growth via the IGF-1R and lead to the hypothesis for the connection between type 1 diabetes mellitus and pancreatic cancer(Figure 1)[30].

MOLECULAR ASPECTS OF THE ASSOCIATION BETWEEN TYPE 2 DIABETES AND PANCREATIC CANCER

Signaling pathways

KRAS mutations constitute 86% of all somatic alterations in PDAC. G12D and G12V are the predominant mutations accounting for 80% of all KRAS mutations and initiate most PDAC cases[31]. Q6 and K117 are also other mutations that account for extra hotspots associated with activated KRAS in PDAC[32]. The *KRAS* is a proto-oncogene that encodes a GTPase as a molecular switch, which is bound with GTP in an active form and bound with GDP in the inactive state. Guanine nucleotide exchange factor (GEF) regulates the KRAS-GDP to KRAS-GTP conversion, and the GTPase-activating protein (GAP) promotes hydrolysis of GTP that keeps most of the KRAS in an inactive form[33]. Mutation in KRAS leads to an increase in glucose uptake, which ultimately results in glycolytic flux[34]. Changes in the tumor microenvironment, including inflammation and insulin resistance, which are associated with obesity and type 2 diabetes, can augment the KRAS activation. A high-fat diet with stimulation of KRAS activation can lead to the transformation of normal pancreatic cells into pancreatic intraepithelial neoplasm lesions. Actually, a fatty diet helps KRAS to activate more inflammatory factors in the pancreas that leads to the formation of neoplasm lesions leading to PDAC with high penetrance[35]. Additionally, previous studies have reported that mutant KRAS mice are more susceptible to a high-fat diet, leading to an increase in the oncogenic KRAS-mediated progression of invasive PDAC[36]. Activated KRAS promotes different downstream signaling pathways, such as the MAPK pathway and the PI3K pathway, leading to a cascade of cellular responses and enhancing the proliferation, and invasion of cancer cells[37]. These two different signaling pathways, including metabolic (PI3K/Akt/mTOR) and mitogenic (MAPK) pathways, will become activated when insulin binds to its receptor (Figure 2).

Metabolic pathway

The metabolic pathway is the one through which glucose, lipid, and protein metabolism is regulated[38]. Insulin binding to its

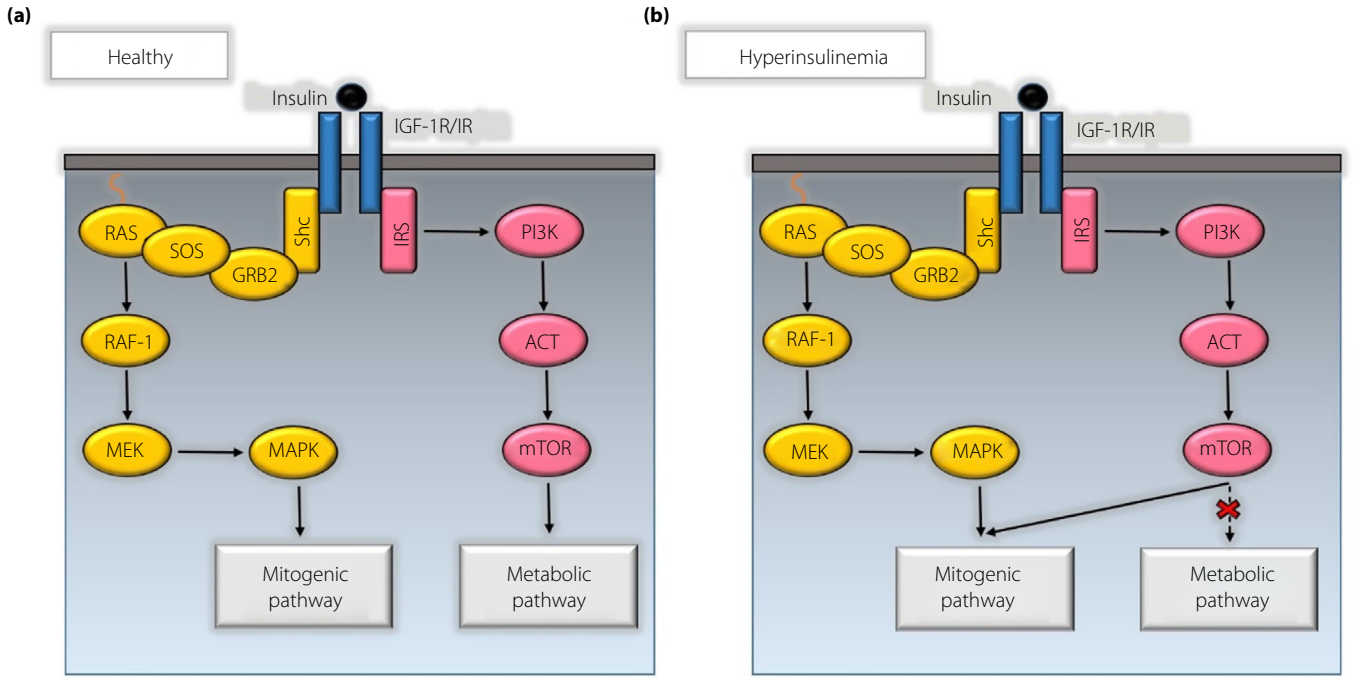

Figure 2 | Involvement of metabolic (PI3K/Akt/mTOR) and mitogenic (MAPK) pathways induced by insulin binding to its receptor in the development of pancreatic cancer in healthy (a) and hyperinsulinemia (b) conditions.

receptor causes phosphorylation and activation of the receptor by the insulin receptor substrate (IRS) adapter proteins. This connection also activates the phosphatidylinositol 3-kinase (PI3K). Afterward, the phosphatidylinositol-3,4,5- triphosphate (PIP3) synthesis is increased, and consequently, the three phosphoinositide-dependent protein kinase 1 (PDK1) and Ser/Thr kinase Akt are activated. After that, by phosphorylating and inhibiting TSC1/2, a critical negative regulator of mTORC1, AKT increases protein synthesis and cell growth through the mTOR pathway. AKT is also involved in other pathways. For example, inhibiting glycogen synthetase kinase 3 (GSK3) regulates glucose metabolism and glycogen synthesis. AKT also can trigger the nuclear export of forkhead box O transcription factors (FOXO) that are significant for apoptosis. PIP3 is dephosphorylated by PTEN phosphatase, and thus the metabolic pathway is negatively regulated[39].

Mitogenic pathway

The activated insulin receptor also triggers the mitogen-activated protein kinase (MAPK) pathway that causes cell proliferation. Upon insulin binding to its receptor, growth factor receptor-binding protein 2 (Grb2) binds to the activated receptor and engages with the son of sevenless (SOS) to produce the complex of receptor-Grb2-SOS. It facilitates the activation of GTPase Ras and then RAF and MEK1/2 and MAPKs. The active MAPKs translocate to the nucleus and regulate the activity of genes, cell growth, differentiation, and apoptosis by phosphorylating different transcription factors. Thus, the increased activation of the MAPK signaling pathway can promote the development of tumor cells[40]. Overall, upon insulin/IGF-1 binding to their receptors, they can trigger signaling pathways, including metabolic (PI3K/Akt/mTOR) or mitogenic (MAPK) pathways, therefore increasing cell growth and decreasing cancer cell apoptosis[41]. Hyperinsulinemia in type 1 diabetes mellitus, through an insulin resistance environment, blocks the metabolic pathway. Stimulation of glucose transportation into cells and induction of glycogen synthesis are the consequences of this signaling pathway[42]. On the other hand, insulin resistance cannot block the mitogenic pathway activity. AKT and mTOR affect both the metabolic and mitogenic pathways. But in the hyperinsulinemia condition, AKT and mTOR are driven towards the mitogenic pathway, which leads to the cell growth and the proliferation of normal and tumor cells, which contribute to the development of pancreatic cancer (Figure 2)[43].

Roles of molecular biomarkers including circRNAs, lncRNAs, and miRNAs in type 2 diabetes and pancreatic cancer

Previous studies have shown that the prevalence of type 1 diabetes mellitus is very high among people with pancreatic cancer. It is also reported that people with pancreatic cancer have more evidence of type 1 diabetes mellitus than healthy people[44]. According to these results, type 1 diabetes mellitus and pancreatic cancer are associated with each other, and finding the

biomarkers that are common in these two diseases would help in the prognosis or even in the treatment of the disease. Recently, several molecular biomarkers have been reported, including microRNAs (miRNAs), long non-coding RNAs (LncRNAs), and circular RNAs (circRNAs). In this review, we tried to gather all information about the roles of non-coding RNAs related to diabetes and pancreatic cancer, and we focused on the studies that aimed to describe these non-coding RNAs. So, in these studies, the samples or the models are specifically associated with these two diseases. But because of the numerous functions and regulatory effects of non-coding RNAs and shared pathways involved in different cancers, it is possible that a specific non-coding RNA discussed in this study could also be involved in other cancers or even in other diseases as well.

miRNAs are a class of small non-coding RNAs (ncRNAs) of 20–24 nucleotides in length, which have a significant role in the cellular process control via regulating the gene expressions. miRNAs bind to the 3' UTR of target mRNAs to prevent mRNA translation and to silence target expression[45]. Many studies have reported that a small change in their expression can lead to various diseases and cancer progression[46]. miR-25 is suggested as a candidate biomarker for pancreatic cancer[47], and miR-128a has an essential role in regulating the target genes involved in significant insulin signaling cascades[48]. Among these, a number of miRNAs are common between these two diseases, and knowing them will help us to discover the molecular connection of these two diseases.

LncRNAs belong to RNA species of at least 200 nucleotides in length and are molecularly similar to mRNAs[49]. According to studies, lncRNAs play significant roles in regulating chromatin modification, gene expression, and protein function[50]. Besides, they possibly have a role in controlling miRNA level and function, suggesting that lncRNAs have a negative correlation with the expression of miRNAs[51]. Mounting evidence suggests that dysregulated lncRNAs have been involved in several diseases, such as pancreatic cancer and diabetes[52]. Furthermore, some studies have reported lncRNA alterations between patients with diabetic pancreatic cancer and non-diabetic pancreatic cancer.

Another class of ncRNAs are the circRNAs that were primarily discovered in plant viroids[53]. Recently, circRNA expressions were found in eukaryotic cells, and they are considered erroneous splicing products[54]. The results obtained from different experiments have indicated that the circRNAs role is disordered in various diseases, including cancer and diabetes[55]. The circRNA functions in diabetes are not yet fully understood, but many studies have suggested that they may play a significant role in the development of type 1 diabetes mellitus[56]. Additionally, it is suggested that they could act as potential biomarkers for the prognosis and early diagnosis of pancreatic cancer[57]. For this reason, we were encouraged to collect different studies that introduced potential miRNAs, lncRNAs, and circRNAs in type 1 diabetes mellitus and pancreatic cancer. Then, we tried to find common biomarkers among them to provide a molecular reason for the relationship between these two diseases. In the following, we will discuss these biomarkers separately.

Circular RNAs

Circular RNAs (CircRNAs) are known to be a widespread endogenous class of non-coding RNAs that are produced from back splicing[58]. CircRNAs act as microRNA (miRNA) and protein sponges or decoys and are involved in protein scaffolding, translation, splicing, and transcription. They are associated with various diseases, including many types of cancers, cardiovascular diseases, and type 2 diabetes[59]. In recent years, the differential expression of circRNAs has been reported in pancreatic cancer and in type 2 diabetes, some of which are illustrated in Table 1. CircRNAs are involved in the β-cell function, inflammation, and complications related to type 2 diabetes[60]. In pancreatic cancer, they participate in tumor invasion, metastasis, apoptosis, and cell proliferation[61]. Among them, circANKRD36 is elevated in the peripheral leukocytes of type 2 diabetes patients and correlated with chronic inflammation, probably through interactions with miRNAs such as hsa-miR-3614-3p, hsa-miR-498, and hsa-miR-501-5p. The expression of IL-6 was associated with circANKRD36[59]. CircRNA_100782 also regulates pancreatic carcinoma proliferation through the IL-6/STAT3 pathway by acting as a sponge for miR-124[62]. Circular RNA ciRS-7 plays a vital role as an oncogene in pancreatic ductal adenocarcinoma (PDAC) through targeting miR-7, and regulation of the EGFR/STAT3 pathway regulation leads to cell proliferation and metastasis[63]. It also regulates β-cell proliferation and insulin secretion and has demonstrated decreased expression in the islets of diabetic mice, leading to reduced β-cell proliferation and survival along with impaired insulin secretion[64]. In both diseases, these non-coding RNAs have been reported as potential biomarkers, consisting of CircRNA0054633 in type 2 diabetes[65,66], hsa_circ_0001649, and circ-LDLRAD3 in pancreatic cancer[67].

LncRNAs

LncRNAs are another group of ncRNAs that are longer than 200 nts and involved in almost every gene expression regulation stage. There is growing evidence that highlights their role in different kinds of diseases. The venn diagram below illustrates various lncRNAs in pancreatic cancer and in type 2 diabetes as well as shared lncRNAs involved in the development of both pancreatic cancer and type 2 diabetes (Figure 3). In the following, the molecular mechanisms of the most important shared lncRNAs in both diseases will be discussed[68].

Maternally expressed 3 (MEG3) is an imprinted maternally lncRNA[69], which is significantly decreased in microdissected pancreatic cancer samples and cancer cell lines compared with normal controls and has a prognostic value in the prediction of pancreatic cancer. MEG3 knockdown leads to elevated cell proliferation, migration, and invasion and induced epithelial-mesenchymal transition (EMT)[70]. Its overexpression acts as a

Table 1 | The list of circRNAs related to type 2 diabetes and pancreatic cancer

Disease	Name	Expression	sample	Gene association	miRNA association
Pancreatic cancer	hsa_circ_0000977	Decreased	Tissue	PLK1	miR-874-3p
	CircZMYM2	Increased	Tissues/cell line	JMJD2C	miR-335-5p
	circ_0007534	Increased	PDAC tissues/cell lines		miR-625, miR-892b
	circRNA_100782	Increased	PDAC tissue	IL6R STAT3	microRNA-124
	hsa_circ_0001649	Decreased	PDAC tissues/cell lines	caspase-9 caspase-3	
	circ-PDE8A	Increased	PDAC cells Plasma	MET MACC1	miR-338
	ciRS-7	Increased	PDAC tissues	EGFR/STAT3	miR-7
	hsa_circ_0006215	Increased	Tissue	SERPINA4	miR-378a-3p
	circRHOT1	Increased	Cell line		miR-26b, miR-125a, miR-330, miR-382
	circ-IARS	Increased	Tissue/plasma	ZO1, RhoA, RhoA-GTP F-actin	miR-122
	circ-LDLRAD3	Increased	Tissue/plasma/cell line		
	circ_0030235	Increased	PDAC tissues/cell line		miR-1253 miR-1294
Type 2 diabetes	hsa-circRNA11783-2	Decreased	Peripheral blood		miR-608 miR-3907
	hsa-CircRNA0054633	Increased	Plasma		
	circANKRD36	Increased	Peripheral blood leucocytes	IL-6	hsa-miR-3614-3p hsa-miR-498 hsa-miR-501-5p
	hsa_circRNA_ 404457 hsa_circRNA_063981 hsa_circRNA_100750 Hsa-circRNA-406918 hsa_ circRNA_104387 Hsa-circRNA-103410 hsa-circRNA-100192_	Increased	Serum		

tumor suppressor by regulating PI3K/AKT/Bcl-2/Bax/Cyclin D1/P53 and PI3K/AKT/MMP-2/MMP-9 signaling pathways[71]. The increased expression levels of MEG3 were also reported in the PBMCs of type 2 diabetes patients[72], high fat diet, and ob/ob mice hepatocytes. It increases hepatic insulin resistance through enhanced FOXO1 expression[73]. In contrast, MEG3 expression was downregulated in the islets of type 2 diabetes models (db/db mice) and was shown to be a regulator of beta cells by impact on insulin production and cell apoptosis[74].

Plasmacytoma variant translocation 1 (PVT1) is another lncRNA that has been reported in relation to both diseases. The salivary expression of PVT1 was increased significantly in patients with pancreatic cancer and considered to be a potential non-invasive biomarker[75]. It also showed elevated expression in PDAC tissues and was related to tumor progression, making it a potential biomarker for the prognosis prediction of patients[76]. PVT1 regulates SERBP1 by acting as a miR-448 sponge which leads to the proliferation and migration of PC cells[77]. It involves EMT, cell proliferation, and migration by deregulating P21 and TGFβ/Smad signaling pathways[78]. In another study related to diabetic nephropathy, the knockdown of PVT1 results in the significant reduction of FN1, COL4A1 (major ECM proteins) and TGFβ1, Pal1 (regulators of ECM proteins), indicating that PVT1 may be involved in the progression of diabetic nephropathy by mechanisms within ECM accumulation[79]. In diabetes, PVT1 may also be involved in the susceptibility of end-stage renal disease (ESRD) (Figure 4)[80]. H19 is another elevated maternally expressed lncRNA in PDAC tissues which was demonstrated to promote pancreatic cancer metastasis by antagonizing Let-7 and increased HMGA2-mediated EMT[81]. In addition, the axis of H19/miR is involved in PDAC cell proliferation and migration by means of PFTK1 and downstream wnt signaling pathway[82]. Upregulation of E2F-1 is another way in which H19 could be involved in PDAC cell proliferation. E2F-1 is a direct target of miR-675 and there may be a regulatory loop of H19/miR-675/E2F-1 that modulates the cell cycle[83]. SOCS5 (the inhibitor of the STAT3 pathway) is another direct target of miR-675-3p, so the H19/miR-675-3p axis has a vital role in the EMT and pancreatic cancer cell stemness maintenance through activating the STAT3

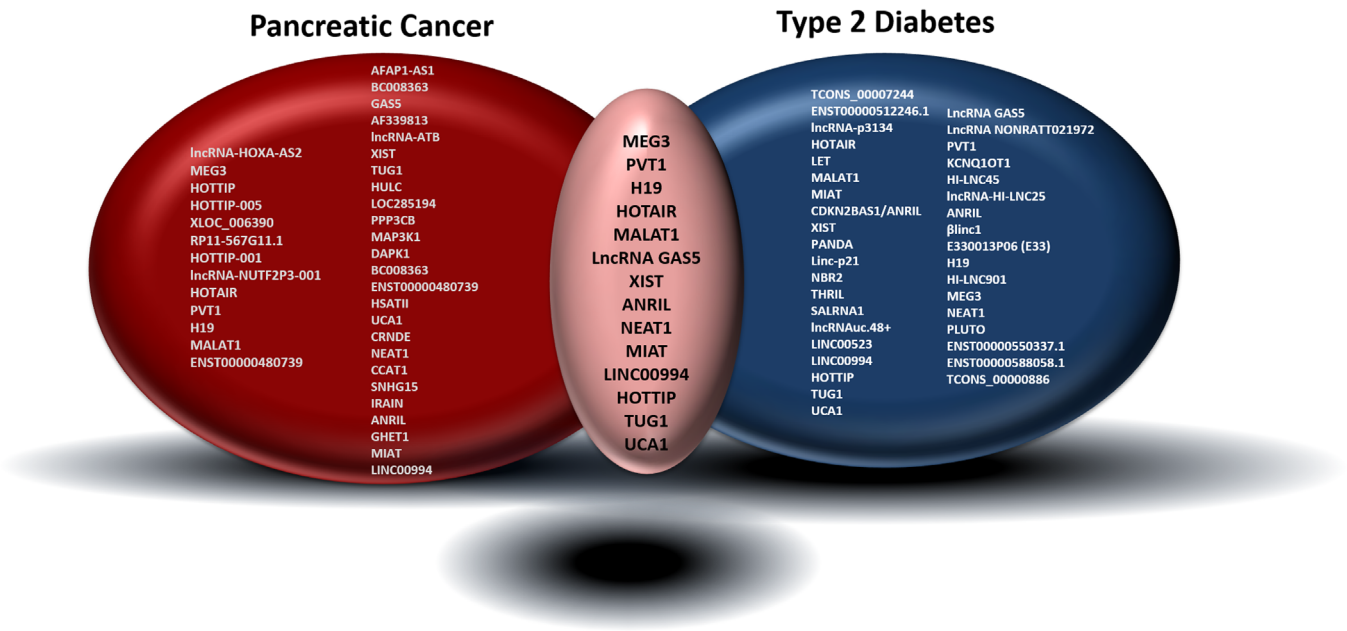

Figure 3 | Venn diagram of lncRNAs in type 2 diabetes and pancreatic cancer. The involved lncRNAs in pancreatic cancer and type 2 diabetes are shown in red and blue, respectively. The shared lncRNAs which are involved in both diseases are represented in pink.

pathway[84]. This lncRNA regulates CD24 and integrin expression, which results in sphere formation and invasion in pancreatic cancer cells[85]. Consistent with studies in pancreatic cancer, the elevated expression of H19 has been reported in the diabetic liver, patients with type 2 diabetes with poor glycemic control, and its increased hepatic expression is involved in diabetic hyperglycemia[86,87]. The downregulation of H19 by five times in the muscles of patients with type 2 diabetes and mice with insulin resistance suggests that more Let-7 (as a target of H19) contributes to insulin resistance and type 2 diabetes[88].

Metastasis-associated lung adenocarcinoma transcript-1 (MALAT1) is an overexpressed lncRNA in pancreatic cancer tissues and cell lines involved in cell proliferation, migration, apoptosis, and invasion through regulating the Hippo-YAP signaling pathway[89]. In addition, six hub genes, including CCND1, MAPK8, and VEGFA may be its targets. Several pathways consist of mTOR, and MAPK signaling pathways are suggested as being critical pathways in pancreatic cancer disease[90]. A feedback loop between MALAT1 and miR-200-3p promotes cell invasion and migration in PDAC[91]. It also increases pancreatic cancer proliferation and metastasis through stimulation of autophagy[92]. In PDAC, MALAT1 regulates KRAS by sponging miR-217 and inhibiting its translocation from the nucleus to the cytoplasm[93]. On the contrary, the expression levels of MALAT1 were downregulated in the serum of patients with type 2 diabetes[86]. In another study, with different groups of patients with type 2 diabetes and healthy controls, the expression level of MALAT1 showed upregulation in the serum of groups of patients with nondiabetic retinopathy (NDR), nonproliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR), comparing each with healthy subjects. Furthermore, the expression level of this lncRNA was increased in diabetic retinopathy (DR) and PDR groups compared with NDR, and NPDR compared with NDR patients. All together these results showed that MALAT1 could be used as a potential biomarker for screening diabetic retinopathy and proliferative diabetic retinopathy early diagnosis[94]. The expression level of MALAT1 was also upregulated in the PBMCs of type 2 diabetes patients compared with controls[72].

LncRNA Growth Arrest-specific transcript 5 (GAS5) has been studied in both diseases. Gas5 expression is significantly downregulated in pancreatic cancer tissues compared with normal controls and negatively regulates the expression of CDK6 (cyclin-dependent kinase 6). Its overexpression in PC cells prohibits cell proliferation, and its inhibition leads to a decrease in G0/G1 phase and an increase in S phase[95]. GAS5 could inhibit PC metastasis by positive regulation of PTEN through miR-32-5p[96]. It is involved in Hippo pathway regulation by negative regulation of miR-181c-5p and antagonizes the development of multidrug resistance in pancreatic cancer cells[97]. In addition, GAS5 regulates the miR-221/SOCS pathway, which results in the suppression of metastasis, cell growth, and resistance to gemcitabine[98]. In diabetic nephropathy (DN), GAS5 also acts as a miR-221 sponge and increases its target, SIRT1, inhibiting cell proliferation and fibrosis. The expression levels of GAS5 have been reported in type 2 diabetes patients with diabetic

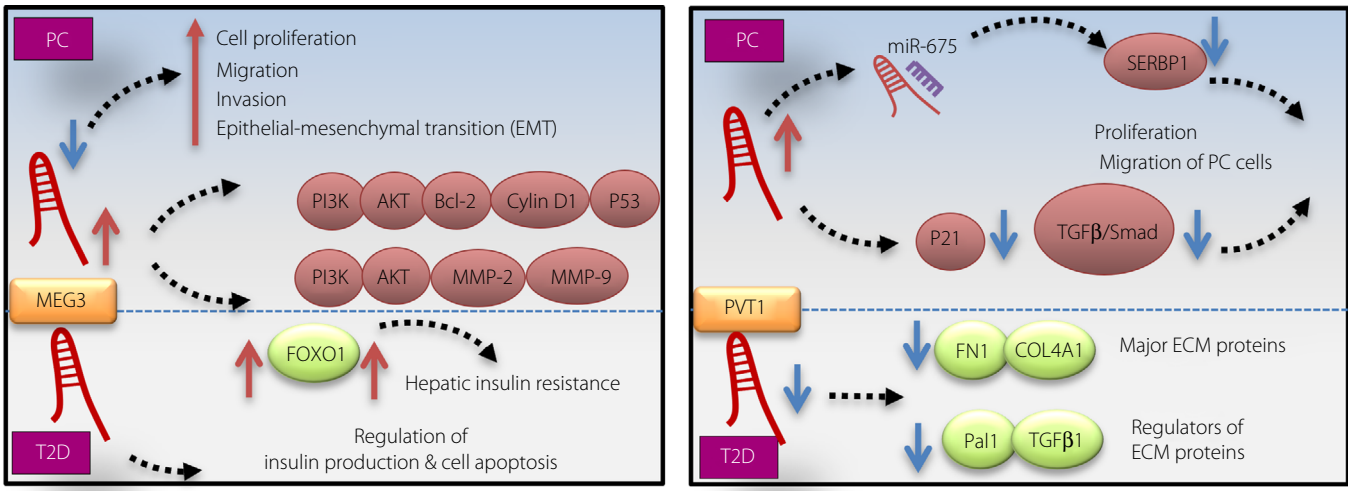

Figure 4 | The schematic representation of molecular mechanisms of MEG3 and PVT1 lncRNAs in the development of pancreatic cancer and type 2 diabetes.

nephropathy compared with patients without diabetic nephropathy[99]. The expression level of GAS5 was decreased in the tissue of db/db mice[100], the serum[101], and plasma of patients with type 2 diabetes, which is considered to be a biomarker of type 2 diabetes in Egypt[102]. In contrast, the elevated expression of GAS5 was demonstrated in the PBMCs of patients with type 2 diabetes[72]. GAS5 regulates the expression of insulin receptors by binding to its promoter, in which its depletion suppresses glucose uptake and insulin signaling[103].

HOX transcript antisense RNA (HOTAIR) is considered to be a negative prognostic factor with pro-oncogenic activity in pancreatic cancer[104]. Its functional polymorphisms (SNP rs4759314 and rs200349340) have been demonstrated to have strong associations with susceptibility to pancreatic cancer[105]. HOTAIR was elevated in PC tissues, PC cell lines, and the saliva of pancreatic cancer patients in which its salivary expression could be considered to be a novel biomarker for early pancreatic cancer[75,106]. It also sponges miR-613, which results in notch3 expression regulation and pro-oncogenic functions by regulating different sets of genes in Panc1 cells[106]. miR-663b is another target of this lncRNA in which its inhibition causes pancreatic cancer cell proliferation by increased levels of insulin-like growth factor 2 (IGF2)[107]. Elevated HOTAIR levels lead to increased resistance of PC cells to TRAIL-induced apoptosis by regulating death receptor 5 (DR5), making it a potential therapeutic target[108]. In pancreatic cancer cells, the knockdown of HOTAIR increased radiosensitivity and the effects of autophagy by overexpressing ATG7, which is more evidence of its potential as a therapeutic target[109]. HOTAIR could promote energy metabolism in pancreatic adenocarcinoma cells by upregulating hexokinase-2 (HK2), which leads to increased tumor cell proliferation[110]. Consistent with the mentioned studies in pancreatic cancer, an elevated expression of HOTAIR was reported in the liver tissues of C57BL/6J mice fed with a high-fat diet, db/db mice, and the PBMCs and liver tissue of type 2 diabetes patients[111]. It develops hepatic insulin resistance by suppressing the AKT/GSK pathway and the expression of SIRT1[111]. In contrast, its expression did not show significant changes in the serum of type 2 diabetes patients compared with healthy controls[101]. HOTAIR is a critical regulator in diabetic retinopathy and promotes diabetic cardiomyopathy through PI3K/AKT pathway activation[112]. The expression of glomerular HOTAIR was reported to be upregulated in human diabetic kidney disease (DKD) and db/db mouse model of diabetes, but surprisingly its knockdown did not change the development of kidney damage in diabetic mice[113].

lncRNA nuclear-enriched abundant transcript 1 (NEAT1) is another upregulated lncRNA in PC tissues and cell line which binds to E74 like ETS transcription factor 3 (ELF3) mRNA and suppressing its degradation leading to develop PC cell growth and metastasis[114]. The expression levels of NEAT1 were also reported to be overexpressed in streptozotocin-induced rat models of diabetic nephropathy and high-glucose-induced mice mesangial cells. It targets miR-27b-3p and ZEB1, which results in the promotion of extracellular matrix accumulation and epithelial to mesenchymal transition in diabetic nephropathy[115]. Another study also showed that NEAT1 sponges miR-23c and develops diabetic nephropathy[116].

MicroRNAs

In recent years, there has been growing evidence indicating that miRNAs are involved in the pathogenesis of both type 2 diabetes and pancreatic cancer. MiRNAs are involved in different pathways related to pancreatic cancer, including MAPK/KRAS, PI3K/AKT, JAK/STAT, and Wnt/β-Catenin signaling pathways[117]. Furthermore, the aberrant expression of miRNAs has

been reported in the tissue[118], plasma[119], serum[120], and PBMC[121] of type 2 diabetes and pancreatic cancer patients, which highlights their disruption in these diseases. Circulating-free miRNAs have been identified in the biofluids of type 2 diabetes and pancreatic cancer patients, which leads to their application to non-invasive tests[122]. As a consequence, the diagnostic and prognostic potential of these non-coding RNAs has been widely investigated, and various numbers of them have been identified as biomarkers in relation to type 2 diabetes and pancreatic cancer. MiR-21 is one of the best examples in which previous studies reported its possible role as a biomarker[123]. Circulating miR-21-5p could be a promising non-invasive biomarker in pancreatic cancer patients, and serum levels of miR-21 are a predictor for the chemosensitivity of advanced pancreatic cancer[124]. The elevated tissue levels of miR-21 were correlated with shorter pancreatic cancer disease-free survival and overall survival and were proposed as a diagnostic and prognostic biomarker for pancreatic ductal adenocarcinoma[125]. In diabetic nephropathy, the serum levels of miR-21 could also be a diagnostic biomarker[126]. MiR-221 is another potential biomarker for both diseases. In pancreatic cancer, miR-221-3p induces cell proliferation, suppresses apoptosis, and its serum level is proposed as a biomarker[127]. In addition, the plasma miR-221 may be a valuable biomarker for the diagnosis and prediction of malignant outcomes in pancreatic cancer patients[128]. The serum levels of this miRNA serve as a potential biomarker for both the occurrence and progression of diabetic retinopathy in type 2 diabetes patients[129]. MiR-23a, as an oncogenic regulator of pancreatic cancer, is a potential biomarker in pancreatic cancer diagnosis and treatment. Its serum level is also a valuable biomarker for early diagnosis of pre-diabetic and type 2 diabetes patients[130,131]. Our literature review demonstrates that more than 149 common miRNAs are commonly involved in the development of both type 2 diabetes and pancreatic cancer diseases. The pattern of each miRNA expression and its molecular function in type 2 diabetes and pancreatic cancer are reported in Table 2.

Several studies aimed to determine the role of miRNAs related to recent-onset diabetes associated with pancreatic cancer, which could also be considered as potential biomarkers. Six serum miRNAs (miR-483-5p, miR-19a, miR-29a, miR-20a, miR-24, miR-25) have been differentially expressed in PC-associated new-onset diabetes mellitus (PaC-DM) samples and could be considered as potential biomarkers for the accurate discrimination of PaC-DM from healthy controls and non-cancer new-onset type 2 diabetes[132]. In another study, the exosomal miRNAs and their potential in PaC-induced β-cell dysfunction were explored by treating pancreatic β cells with exosomes from PaC cell lines. The results highlight that exosomes could be essential mediators in the pathogenesis of paC-DM. In addition, exogenous miR-19a can be a crucial mediator which directly targets adenylyl cyclase 1 (Adcy1) and exchanges protein directly activated by cAMP 2 (Epac2). Both proteins are involved in insulin secretion[133]. MiR-18a-5p is also associated with early diabetes, and it is suggested that miR-20b-5p and miR-29 could have a role in the identification of early diabetes in pancreatic cancer[134]. Another study was performed based on the reduced risk of pancreatic cancer in patients with diabetes by oral administration of metformin. Metformin suppresses cell proliferation, migration, and invasion through reexpression of miRNAs ((let-7a,let-7b, miR-26a, miR-101, miR-200b, and miR-200c), as their loss is typical in pancreatic cancer. These miRNAs are reported to target cancer stem cell (CSC) genes suggesting that metformin could be useful in overcoming the resistance to therapeutic approaches for pancreatic cancer[135]. Metformin also inhibits human pancreatic cancer proliferation and tumor growth through altering miRNAs related to cell cycle-related proteins[136]. Nine miRNAs were significantly upregulated in metformin treated pancreatic cancer cells, and among them, the expression of miR-26a, miR-192, and let-7c is dos dependent[137]. A Panc02 pancreatic tumor cell transplant model in diet-induced obese (DIO) C57BL/6 mice was also used to explore the effect of metformin and rapamycin on miRNA alternations. Rapamycin results in the increased expression of let-7b and miRNAs involved in cell cycle regulation, while metformin (but not rapamycin) leads to reduced glucose and insulin levels. Metformin also caused decreased expression of miR-34a and its direct targets (Notch, Slug, and Snail)[138].

Type 2 diabetes is a known metabolic disorder with specific properties, including insulin resistance, and pancreatic cancer is the most common exocrine pancreas malignancy. Mounting evidence indicates a complex relationship between these two diseases. However, similar events such as shared risk factors, metabolic abnormalities, signaling pathways, and non-coding RNAs could be a cue to describe this association. This manuscript has highlighted the shared molecular events and similar non-coding RNAs in type 2 diabetes and pancreatic cancer. An increased understanding of the molecular mechanisms that explain this link could provide a powerful tool for prevention and therapy of this lethal cancer.

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DISCLOSURE

The authors declare no conflict of interest.
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Animal studies: N/A.

ETHICAL APPROVAL

The study is a systematic review, and no ethical or institutional approval is required.

Table 2 | miRNA expressions and molecular functions in type 2 diabetes and pancreatic cancer

miRNA	Type 2 diabetes			Pancreatic cancer		
	Change of expression	Function and importance	Cell origin	Change of expression	Function and importance	Cell origin
miR-145	Down	Targets several key regulators in insulin signaling, including IRS-1 and AKT	Plasma	Down	Suppressing the expression of oncogenes, such as angiopoietin-2 and NEDD9	Human umbilical cord mesenchyme stromal cells
hsa-let-7d	Up	Strongly predicted insulin resistance	Serum	Down	Enhanced expression of fibrosis-related genes	Serum
miR-130b	Up	Candidate by global serum miRNA profiling	Serum	Down	Activation of STAT3, which leads to promoted tumor cell growth and invasion	Serum
hsa-miR-146a	Down	Inhibit the expression of IRAK1 and TRAF6, and suppress the expression of NF-kB target genes such as IL-6, IL-8, IL-1b, and TNFa, which leads to inflammation	PBMC	Down	Downregulation of EGFR and the NF-κB regulatory kinase IRAK-1	Cell line
hsa-miR-155	Down	A component of macrophage and monocyte response to different types of inflammatory mediators, such as bacterial lipopolysaccharide (LPS), interferon-c (IFN-c), and TNF-a	PBMC	Up	Promotes pancreatic cancer development and invasion by targeting TP53INP1	Tissue
hsa-miR-21	Down	Development of the endocrine pancreas and the regulation of insulin secretion, glucose homeostasis, angiogenesis, inflammatory response modulation	Plasma	Up	Negatively regulates PTEN, a tumor suppressor gene	Tissue
hsa-miR-222	Up	Participate in the development of metabolic pathway	Tissue	Up	Promotes proliferation	Tissue
hsa-miR-223	Down	Inversely correlated to insulin resistance and glucose uptake by increasing GLUT-4 expression	Serum	Up	Acquires EMT phenotype	Tissue
hsa-miR-23a	Down	Regulating insulin-dependent glucose transport activity	Serum	Up	Promotes proliferation and reduces apoptosis	Tissue
hsa-miR-26a	Up	Implicated in the MAKP signaling pathway, responsible for the progression to type 1 diabetes mellitus	Serum	Down	Inhibits proliferation by phosphorylation of p53	Tissue
hsa-miR-27a	Up	Involved in the PPAR-γ-PI3K/AKT-GLUT4 signaling axis, thus leading to increased glucose uptake and decreased IR	Serum	Up	Promotes growth, colony formation and migration	Tissue
hsa-miR-30d	Up	Reduce insulin gene expression suggesting its role in defective insulin biosynthesis	Serum	Down	Tumor suppressor or an oncogene in the progression of different tumor types	Tissue
hsa-miR-30e	Down	Targeting *IL1A* and *IRS2*	Serum	Down	No report	Tissue

Table 2 (*Continued*)

miRNA	Type 2 diabetes			Pancreatic cancer		
	Change of expression	Function and importance	Cell origin	Change of expression	Function and importance	Cell origin
miR-221	Up	Positively correlated with the insulin resistance index	Serum	Up	Enhances the progression of the cell cycle and promotes proliferation	Tissue
miR-424	Down	Repression of INSR in the insulin signaling pathway	Cell line	Up	Negatively regulates the downstream suppressor of cytokine-induced signaling 6 (SOCS6)	Tissue
miR-100	Down	Reduced expression of mammalian target of rapamycin (mTOR) and Insulin Growth Factor Receptor (IGFR)	Blood	Up	Regulates a multitude of genes involved in the inhibition of p53 and DNA damage response pathways, affects the TGF-β-mediated response	Tissue
miR-181a	Up	Role in TNFa-induced IR downregulates SIRT1 protein	Serum	Up	Targets PTEN which negatively regulates the PI3K-AKT pathway, leading to cell proliferation and induces migration of pancreatic cancer cells	Tissue
hsa-miR-375	Up	Decrease proliferation and insulin gene transcription and decrease secretion of glucose-induced insulin	–	Down	In PI3K/AKT signaling, function as a tumor suppressor, inhibits the malignant phenotype of PDAC cells through the AKT signaling pathway rather than MAPK signaling pathways	Tissue
miR-148a	Up	Directly target cholecystokinin receptor 2 (CCKBR), which leads to increased hypothalamic neuropeptide Y (NPY) content and promoting diabesity	Bovine milk	Down	Inhibits proliferation and metastasis of ASPC-1 cells	Tissue
miR-29c	Up	Inhibits insulin-stimulated glucose uptake and negatively regulates gluconeogenesis and insulin signaling in hepatocytes	Skeletal muscle	Down	Inhibits cell growth, invasion, and migration	Tissue
miR-130b	up	Negatively influence ATP production via downregulation of mitochondrial genes (PDHA1 and GCK)	Cell line	Down	Targets STAT3 and inhibits proliferation and invasion	Tissue
MiR-148b	up	Targets DNMT1, an enzyme for DNA methylation, which is involved in regulating the β-cell formation	Serum	Down	By targeting AMPKα1, arrests cell cycle and inhibits cell growth	Tissue
miR-335	Up	Regulate final stages of insulin secretion and Ca2+-dependent exocytosis through effects on granular priming	Islets from the diabetic GK-rat model	Down	Inhibits progression and stem cell properties by targeting OCT4	Tissue
miR-10a	Down	Target TNF-α and reduces glucose transporter 4 in cells and decreases glucose uptake	Tissue	Up	Involved in the invasive potential of PDAC cells partially via suppression of HOXA1	Tissue

Table 2 (*Continued*)

miRNA	Type 2 diabetes			Pancreatic cancer		
	Change of expression	Function and importance	Cell origin	Change of expression	Function and importance	Cell origin
miR-107	Up	Impair glucose homeostasis by down-regulating caveolin-1, thereby inducing insulin resistance in the liver and adipose tissue	–	Down	Undergoes methylation in pancreatic cancer cells with chromatin-modifying agents and regulates cyclin-dependent kinase 6 (CDK6) levels, which leads to the cell cycle arrest	Cell line
miR-143	Down	Its inhibition suppresses adipocyte differentiation via altering glucose transporter type 4 (GLUT-4) expression, thus leading to insulin resistance	–	Down	Inhibits the migration, invasion, and liver metastasis by targeting ARHGEF1, ARHGEF2, K-RAS gene	Cell line
miR-150	Up	No report	Plasma	Down	Inhibits growth, clonogenicity, migration and invasion, and enhances intercellular by targeting MUC4	Tissue
miR-181a	Up	It decreases SIRT1 protein levels and activity and causes insulin resistance. Also associated with the regulation of immune responses, β-cell apoptosis and proliferation, and insulin biosynthesis and secretion	Cell line	Up	Promotes migration by targeting PTEN, MAP2K4	Tissue
miR-214	Down	Suppress glucose production, involved in the regulation of hepatic gluconeogenesis via targeting ATF4	Hepatocytes	Up	Decreases the sensitivity of tumor cells to gemcitabine	Cell line
let-7i	Up	Involved in pathways of chronic stress response	Plasma	Up	No report	Tissue
miR-23b	Up	Regulates high-glucose-induced cellular metabolic memory through a SIRT1-dependent signaling pathway	Human retinal endothelial cells	Up	Regulates autophagy associated with radioresistance by targeting ATG12	Cell line
miR-24	Down	Lead to a fall of circulating glucose and insulin levels	Tissue	Up	Promotes cell growth by targeting Bim	Cell line
hsa-miR-92a	Down	No report	–	Up	Promotes proliferation by targeting DUSP10	Cell line
miR-196a	Down	Regulating the insulin biosynthesis	Cell line	Up	Promotes proliferation and migration by targeting NFKBIA	Tissue
hsa-miR-34a	Up	Directly targets p53 and serves a crucial role in p53-mediated biological processes, such as cell cycle arrest, apoptosis, and senescence	PBMC	Down	Inhibited pancreatic cancer growth by decreasing Snail1 and Notch1 expression	Cell line

Table 2 (*Continued*)

miRNA	Type 2 diabetes			Pancreatic cancer		
	Change of expression	Function and importance	Cell origin	Change of expression	Function and importance	Cell origin
miR-140-3p	Down	Directly inhibit the expression of the FOXK2 that contribute to angiogenic dysfunction in DM	Endothelial cells	Down	Decreased pancreatic duct adenocarcinoma cell growth and invasion by directly down-regulating the inhibitor of apoptosis-stimulating protein of p53 (iASPP)	Cell line
miR-199a-3p	Down	Promoted the proliferation, migration, and autophagy of HUVECs (human umbilical vein endothelial cells), potentially by regulating the PI3K/AKT/NF-κB signaling pathway	Serum	Up	Activation of pancreatic stellate cells (PSCs) and PSC-induced pro-tumorigenic effects	Cancer-associated fibroblasts
miR-331-3p	Down	No report	–	Up	Proliferation and epithelial to mesenchymal transition-mediated metastasis by suppressing *ST7L* gene	Cell line
miR-342-3p	Down	Promote the transactivation of FGF11 which leads to vascular dysfunction in type 1 diabetes mellitus	Endothelial cells	Up	Pancreatic cell proliferation, migration and invasion	Tissues and cell lines
miR-708	Down	Low-glucose induction by impairing glucose-stimulated insulin secretion (GSIS)	Tissue	Up	Proliferation, invasion and metastasis of PDAC	Tissues and cell lines
miR-886-5p	Up	No report	Serum	Up	No report	Tissue
miR-96	Up	Targets 3′UTRs of *INSR* and *IRS-1* genes directly to suppress the expression of the INSR and IRS-1 protein, resulting in impaired insulin signaling and glycogen synthesis	Hepatocytes	Down	Inhibit KRAS, damp Akt signaling, and triggered apoptosis in cells	Tissues and cell lines
hsa-miR-103	Up	Impair glucose homeostasis by down-regulating caveolin-1, thereby inducing insulin resistance	–	Up	Reduces the expression levels of *GPRC5A*, a tumor suppressor	Tissue
hsa-miR-126	Up	Implicated in adipokine synthesis, directly targeted to IRS-1 (Insulin Receptor Substrate-1) 3′ UTR, significantly reduced IRS-1 protein synthesis, leading to insulin resistance	–	Down	Knockdown of ADAM9, which results in reduced cellular migration, invasion, and induction of epithelial marker E-cadherin	Cell line
hsa-miR-17-5p	Down	Suppressed inflammatory macrophage that is related to insulin resistance confers an anti-diabetic activity by its anti-inflammation effect on macrophage	Tissue	Up	Proliferation and invasion of pancreatic cancer cells	Cell line

Table 2 (*Continued*)

miRNA	Type 2 diabetes			Pancreatic cancer		
	Change of expression	Function and importance	Cell origin	Change of expression	Function and importance	Cell origin
hsa-miR-186	Down	No report	Serum	Up	Suppression of NR5A2, leading to the cancer cell invasion	Tissue
hsa-miR-191	Down	Positively associated with glycemic impairment	Plasma	Up	Inhibit protein levels of UPS10, which suppressed the proliferation and growth of cancer cells through stabilizing P53 protein	Tissue
hsa-miR-192	Up/Down	No report	Serum	Up	Regulating tumor angiogenesis	Cancer endothelial cells
hsa-miR-197	Down	Peripheral angiogenic signaling	Serum	Up	Downregulation of p120 catenin and recapitulates the induction of EMT in pancreatic cancer cells	Tissue
hsa-miR-195	Up	Down-regulates the expression of INSR without apparently changing IRS-1 expression in hepatocytes reduced the insulin-stimulated glycogen synthesis	Myocytes and hepatocytes	Down	Directly targets DCLK1, and its downregulation leads to proliferation, migration, and invasion of PC cells	Tissue
hsa-miR-20b	Up	Its overexpression reduced AKTIP abundance and insulin-stimulated glycogen accumulation	Serum	Up	No report	Cell line
hsa-miR-29a	Up	Regulate glucose uptake and insulin-stimulated glucose metabolism	Skeletal muscle	Down	Inhibit cell proliferation, cell migration, cell invasion	Cell lines and tissues
hsa-miR-423-5p	Down	Its inhibition suppressed gluconeogenesis and improved insulin resistance, hyperglycemia, and fatty liver	Tissue	Up	No report	Tissue
hsa-miR-483-3p	Up	Increased endothelial and macrophage apoptosis and impairs the vascular response to injury	Endothelial-supportive macrophages	Up	Significantly represses DPC4/Smad4 protein levels in pancreatic cancer cell lines and simultaneously promotes cell proliferation and colony formation in vitro	Plasma
hsa-miR-486	Down	Involved in the regulation of carbohydrate and lipid metabolism and insulin metabolism	Serum	Up	Its downregulation leads to inhibit the migration and invasion and induce apoptosis in PANC-1 cells	Cell line
hsa-miR-571	Up	May contribute to kidney fibrosis and highlight the role of some aspects of the EMT pathway in diabetic nephropathy	Serum	Up	Targets guanylate binding protein 2 (GBP2)	Serum and tissue
hsa-miR-572	Up	No report	Plasma	Up	No report	Cell line
hsa-miR-593	Down	Potentially targets Slc38a1 and CLIP3, which participates in insulin-regulated glucose energy metabolism	Serum	Up/Down	No report	Serum and tissue

Table 2 (*Continued*)

miRNA	Type 2 diabetes			Pancreatic cancer		
	Change of expression	Function and importance	Cell origin	Change of expression	Function and importance	Cell origin
miR-106b	Up	Regulates GLUT4 expression and glucose metabolism	Plasma	Down/Up	Promotion of cell survival and gemcitabine resistance by directly targeting TP53INP1	Cell line
miR-122	Up	Play a central role in the regulation of lipid and glucose metabolism, associated with obesity and insulin resistance	Serum	Down	Inhibits cell proliferation, migration, and invasion by targeting CCNG1	Tissues and cell lines
miR-132	Up	Play a role in insulin secretion and regulating blood glucose	Tissue	Up	Improve cell proliferation by reducing pRb protein in pancreatic cancer cells	Tissue
miR-18a	Up	Modulate central cell responsiveness to stress by targeting glucocorticoid receptor (GR), and leads to stress-related disorders including type 1 diabetes mellitus	PBMC	Up	No report	Plasma
miR-320	Down	Negatively regulates expression of ET-1, VEGF, and FN through ERK 1/2, demonstrated glucose-induced downregulation	Cell line	Up	Inhibits tumor proliferation	Cell line
miR-885-5p	Up	No report	Serum	Up	Activates the p53 pathway, causes downregulation of cyclin-dependent kinase and mini-chromosome maintenance protein, and suppresses matrix metallopeptidase 9 expression and caspase genes (a tumor suppressive function by triggering cell cycle arrest and senescence and/or apoptosis)	Serum
miR-1247-5p	Up/Down	No report	Serum	Down	Important tumor suppressor that inhibited tumor growth, migration, invasion, and associated with disease prognosis	Tissue
miR-16-5p	Up	Correlated with insulin resistance	Blood	Up	No report	Tissue
miR-320a	Up	Regulation of carbohydrate and lipid metabolism by targeting adipoR1	Tissue and cell lines	Up	Involved in the regulation of the PDAC cell phenotype and response to 5-FU	Cell line

Table 2 (*Continued*)

miRNA	Type 2 diabetes			Pancreatic cancer		
	Change of expression	Function and importance	Cell origin	Change of expression	Function and importance	Cell origin
miR-126-3p	Down	Contribute to the inflammatory and endothelial dysfunction in type 1 diabetes mellitus	PBMC	Down	By downregulating ADAM9 gene, decreases the expression of Ki67, VEGF, COX-2, and MMP-14, thus inhibiting proliferation, migration, and invasion and promoting apoptosis of pancreatic cancer cells	Bone marrow mesenchymal stem cell
miR-30c-5p	Up	Involved in glucose metabolism, insulin signaling and inflammation	Plasma	Up	Reduced Rac1, MEK1, and E2F3 levels, and are crucial to the anti-pancreatic cancer effects of dihydroartemisinin (DHA)	Cell line
miR-1260a	Down	No report	Plasma	Up	Potential mediators of SMAD family member 4 (SMAD4)-associated de-regulated calcium fluxes, create an immunosuppressive myeloid cell background in PDAC cells	Serum
miR-1275	Up	No report	Plasma	Down	Depresses growth and invasion of pancreatic cancer cells	Tissues and cell lines
miR-1291	Up/Down	No report	Plasma	Down	Lower migration and invasion capacity as well as suppresses tumorigenesis	PANC-1 cells
miR-1825	Up	No report	Plasma	Up	Influences pancreatic cancer cell proliferation and invasive ability	Serum
miR-765	Down	–	Plasma	Up	–	Plasma
miR-30a-5p	Up	Modulates beta cell function and involved in the suppression of BETA2/ NeuroD	Plasma, rat islets and INS-1 cells	Down	Targets FOXD1 and increases the sensitivity to gemcitabine in PC	Pancreatic cancer cell lines
miR-30b-5p	Down Up	Related to impaired renal function proangiogenic	Urinary exosomes, ectosomes	Up	–	Serum
miR-30c-5p	Up	Targets the mRNA transcripts of two genes involved in angiogenesis, namely, *MTDH* and *PDCD10*	Ectosomes	Down	Attenuates cancer cell proliferation, migration and invasion	Tumor tissues
miR-564	Up	–	Plasma	Down	–	Pancreatic cancer tissues
miR-10b	Down	Targets components of insulin signaling pathways	Serum	Up	Suppression of TIP30 expression and promoting EGF and TGFβ actions leading to PC cell invasion	Plasma cell lines tissues
miR-645	Up	–	Plasma	Up	–	Pancreatic cancer tissues

Table 2 (*Continued*)

miRNA	Type 2 diabetes			Pancreatic cancer		
	Change of expression	Function and importance	Cell origin	Change of expression	Function and importance	Cell origin
miR-126-3p	Down	Facilitates vascular endothelial growth factor (VEGF) signaling	Plasma	Down	Suppresses cell invasion and metastasis	Plasma
miR-150-5p	Down	Angiogenesis	Extracellular vesicles	Down	Involved in cell proliferation and apoptosis	Tissue
miR-223-5p	Down	–	Plasma	Up	Regulates CDDP resistance in pancreatic cancer through targetingFOXO3 A	Cancer cell line
miR-15a	Down	Targets endogenous uncoupling protein-2 gene expression endogenous uncoupling protein-2 gene expression and positively regulates insulin biosynthesis	Peripheral blood, Cell line	Down	Contributes in proliferation regulation	Pancreatic tissue
miR-7	Up	Activates mTOR signaling pathway and develops adult β cell proliferation	Serum	Down	Targets MAP3K9 Suppresses PC cell growth and mobility Suppresses autophagy	PC cells
miR-376	–	Pancreatic islet development		–		
miR-492	–	Contributes to insulin resistance and endothelial dysfunction caused by high glucose	Serum	Down	Inversely correlates with metastasis formation	Serum
miR-486-5p	Up	Regulates SIRT1, which is related to insulin sensitivity and energy expenditure	Plasma	Up	Promotes proliferation of PC cells	Tissue
miR-125b	Up	Inhibits insulin signaling pathway by targeting PIK3CD	PBMC serum cell line	Up	(5p strand) Promotes migration and invasion and associates with metastasis in PC	Pancreatic tissue cell line
miR-29b				Down	Targets SOX12 and DNMT3b and suppresses proliferation and mobility	Cell line
miR-29	Up	Important regulator of insulin-stimulated glucose metabolism and lipid oxidation	Skeletal muscle	Down	Anti-metastatic potential, tumor suppressive properties	Cancer cells
miR-99b	Up	–	Tissue		mTOR regulation	Cell line
miR-125a-5p	Down	Targets STAT3 and regulates glycolipid metabolism	Cell lines and rat livers	Up	Involved in cell cycle, proliferation, and apoptosis plays an oncogenic role	Tissue
miR-151-5p	Up	–	Whole blood	Up	–	PanIN-3 lesions
miR-183	Up	Effects on diabetic retinopathy by inactivating *BTG1*-mediated PI3K/Akt/VEGF signaling pathway	Whole blood	Up	Induces cell proliferation, migration, and invasion by regulating PDCD4 expression	Cancer cells
miR-185	Down	Targets SOCS3 and involves in the regulation of insulin secretion and β cell growth	Blood	Down	Targets TAZ and suppresses PC cells proliferation	Cancer tissue

Table 2 (*Continued*)

miRNA	Type 2 diabetes			Pancreatic cancer		
	Change of expression	Function and importance	Cell origin	Change of expression	Function and importance	Cell origin
miR-190	Up	–	Whole blood	Up	–	Cancer tissue, cell line
miR-194	Up	–	Urinary extracellular vesicles	Up	Involved in tumor growth and progression	Tissue
miR-299-3p	Up	–	Whole blood	Down	TUG1/miR-299-3p axis involved in PC malignant progression through Notch1 pathway	Tissue cell line
miR-335	Up	Induces insulin resistance and pancreatic islet β cell secretion	Mouse pancreatic islet β-cells	Down	Targets OCT4 and functions as a tumor suppressor	Tissue Cell line
miR-361-3p	Up	–	Whole blood	Up	Regulates ERK1/2 induced EMT through targeting DUSP2 and promotes metastasis	Cell line
miR-550	Up	–	Whole blood	Up	–	Blood
miR-629	Up	–	Whole blood	Up	Regulates FOXO3 results in enhanced cell proliferation and invasion	Cell line
miR-665	Down	–	Whole blood	Up	Has a tumor-suppressive role by targeting TGFBR1 and TGFBR2 through regulating the SMAD2/SMAD3 pathway	Cell line
miR-495	Up	Targets FTO leading to regulation of macrophage M1/M2 polarization and insulin resistant	Mouse peritoneal macrophages	Down	–	Cell line
miR-655	Down	–	Islet	Down	Involved in the EMT by targeting p120 catenin, ZEB1 and TGFBR2	Tissue
miR-95	Up	–	Ectosomes	Up	–	Cancer tissue cell line
miR-128	Up	Regulates IRS1/AKT insulin signaling	Serum	Down	Targets MDM2 and induces PC cell apoptosis	Tissue cell culture
miR-133a	Up	Clinical indicators of myocardial steatosis	Serum	Down	Directly targets FSCN1 and considered as a tumor suppressor	Tissue samples and cell line
miR-152	Up	Involved in glucose metabolism	Islet	Down	Reactivates tumor suppressor genes through suppression of DNMT-1	Cell line
miR-154	Up	–	Cell line	Up	–	Cancer tissue cell line
miR-374b				Down	Positively correlates with chemoresistance	Tissue cell line
miR-424	Down	–	Skeletal muscle	Up	Suppresses the expression of SOCS6	Tissue samples and cell lines

Table 2 (*Continued*)

miRNA	Type 2 diabetes			Pancreatic cancer		
	Change of expression	Function and importance	Cell origin	Change of expression	Function and importance	Cell origin
miR-144-3p	Up	Impair insulin signaling	Serum	Down	Targets PRR11via mitogen-activated protein kinase pathway results in cell cycle arrest and apoptosis induction	Tissue samples and cell lines
miR-96-5p	Up	Suppresses CACNA1E which results in impaired insulin secretion	Serum	Down	Inhibits GPC1 to suppress proliferation in PC cells	Tissue and cell line
miR-34c-5p	Up	May have played a mechanistic role in the phenomenon of down regulated inflammatory gene expression in monocytes	Monocytes	Up	-	Tissue and cell line
miR-200b	Down	Involves in beta cell survival	Islet	Up	Targets (–3p) ZEB1 and inhibit EMT and cell migration	Tissue and cell line
miR-19a	Down	Feedback regulation has been noted between PI3K and this miRNA	Human skin wound, keratinocytes	Up	Targets RHOB and stimulates cell proliferation, migration, and invasion	Tissue and cell line
miR-26b	Up	–	Rat liver	Down	–	Tissue samples
miR-204				Down	Targets BCL2	Cell line
miR-124				Down	Targets Rac1 and suppresses tumor cell growth, invasion, and metastasis	Cancer tissues
miR-125a	Up	Affects genes involved in MAPK pathway	Cell lines and rat livers	Up	miR-125a enhances the mitochondrial fission that is involved in PANC-1 cell apoptosis, metabolism and migration	Cell line
miR-345	Up	–	Islets	Down	Targets BCL2 and induces apoptosis	Cell line
miR-217	Up	May have a correlation with the development of proteinuria and involved in the development of diabetic kidney disease through promotion of chronic inflammation, renal fibrosis, and angiogenesis	Serum	Down	Regulate KRAS and functions as a tumor suppressor	Human tissues and cell line
miR-200c	Up	Involves in beta cell survival	Islet	Up	Involved in cell migration and angiogenesis	Tissue samples and cell culture
Let-7f	Down	Related to obesity	Adipose tissue	Down	May be involved in migration and invasion by regulating MMP-11	Cell line
miR-31	–	Targets GLUT4	Plasma	Up	Involved in cell migration and invasion	Cell line
miR-210	Up	Affects in the function of endothelial progenitor cells	Blood	Up	Targets E2F3, EFNA3, GIT2, MNT, ZNF462 and EGR3	Plasma, cell line
miR-15b	Down	Involves in insulin signaling pathway	Skeletal muscle	Up	Promotes EMT by targeting SMURF2	Cancer tissues and cell line

Table 2 (*Continued*)

miRNA	Type 2 diabetes			Pancreatic cancer		
	Change of expression	Function and importance	Cell origin	Change of expression	Function and importance	Cell origin
miR-181b		A key regulator of endothelial and beta-cell function, peripheral insulin sensitivity, and NFκB signaling	Plasma	Up	Increases the activity of NFκB by suppressing CYLD, leading to the resistance to gemcitabine	Plasma cell line
miR-199a-5p	Up	Involves in insulin secretory	Mice islet	Up	–	Cancer tissue

INSTITUTIONAL REVIEW BOARD STATEMENT

Not applicable.

DATA AVAILABILITY STATEMENT

Data sharing not applicable.

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