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

Fariba Dehghanian¹*, Zahra Azhir¹, Sheyda Khalilian¹, Björn Grüning²

¹Department of Cell and Molecular Biology and Microbiology, Faculty of Biological Science and Technology, University of Isfahan, Isfahan, Iran, and ²Department of Computer Science, Bioinformatics Group, University of Freiburg, Freiburg, Germany

Keywords
Non-coding RNAs, Pancreatic cancer, Type 2 diabetes

*Correspondence
Fariba Dehghanian
Tel: (+98) 31 37934155
Fax (+98) 31 37932456
E-mail address: fd.dehghanian@gmail.com; fa.dehghanian@sci.ui.ac.ir

Björn Grüning
Tel: (+49)9139169706
E-mail address: bjoern.gruening@gmail.com

J Diabetes Investig 2022; 13: 405–428
doi: 10.1111/jdi.13727

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 metabolism¹. 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 factors². 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 cancer². 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...
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. Polyuria, polydipsia, polyphagia, and weight loss are different symptoms of type 2 diabetes. 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. 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. 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. 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.

**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. 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. 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. Several risk factors may increase the chance of developing pancreatic cancer. Smokers have more than twice the risk of developing cancer, although unlike other smoking-related diseases, an apparent mutation signature has not been detected. Heavy alcohol drinking is undoubtedly related to the risk of pancreatic cancer, whereas there is no association with low-to-moderate alcohol intake. 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/m²). 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. Germine pathogenic variants in hereditary breast and ovarian cancer genes (BRCA1 or BRCA2 and PALB2) may pose an increased risk of pancreatic cancer. Finally, defective DNA mismatch repair genes MLH1, MSH2, MSH6, and PMS2 could increase cancer. Other genetic factors contributing to pancreatic cancer have been identified but are rare and often personal variants.

Hence, apart from the clinical staging of disease, there is no clinical feature to inform decision-making for pancreatic cancer.

**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. A population-based study in British Columbia and Canada found that people with type 1 diabetes mellitus are at increased risk of pancreatic cancer. 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. A large number of patients with pancreatic cancer show impaired metabolism of glucose and 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. 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. Diabetes mellitus could occur due to developing pancreatic cancer or could be a consequence of this disease. The correlation between type 1 diabetes mellitus and pancreatic cancer is not yet definite. 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. 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). Insulin and IGF1 both promote inhibition of cancer cell apoptosis and contribute to the cell proliferation.
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)\textsuperscript{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\textsuperscript{31}. Q6 and K117 are also other mutations that account for extra hotspots associated with activated KRAS in PDAC\textsuperscript{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\textsuperscript{33}. Mutation in KRAS leads to an increase in glucose uptake, which ultimately results in glycolytic flux\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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.

Mitogenic pathway
The activated insulin receptor also triggers the mitogenic-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. 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. 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. 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.

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. 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. Many studies have reported that a small change in their expression can lead to various diseases and cancer progression. miR-25 is suggested as a candidate biomarker for pancreatic cancer and miR-128a has an essential role in regulating the target genes involved in significant insulin signaling cascades. 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. According to studies, LncRNAs play significant roles in regulating chromatin modification, gene expression, and protein function. Besides, they possibly have a role in controlling miRNA level and function, suggesting that LncRNAs have a negative correlation with the expression of miRNAs. Mounting evidence suggests that dysregulated LncRNAs have been involved in several diseases, such as pancreatic cancer and diabetes. 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. Recently, circRNA expressions were found in eukaryotic cells, and they are considered erroneous splicing products. The results obtained from different experiments have indicated that the circRNAs role is disorder in various diseases, including cancer and diabetes. 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. Additionally, it is suggested that they could act as potential biomarkers for the prognosis and early diagnosis of pancreatic cancer. 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. 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. 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. In pancreatic cancer, they participate in tumor invasion, metastasis, apoptosis, and cell proliferation. 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. CircRNA_100782 also regulates pancreatic carcinoma proliferation through the IL-6/STAT3 pathway by acting as a sponge for miR-124. Circular RNA cRS-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. 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. In both diseases, these non-coding RNAs have been reported as potential biomarkers, consisting of CircRNA0054633 in type 2 diabetes, hsa_circ_0001649, and circ-LDLRAD3 in pancreatic cancer.

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. Maternally expressed 3 (MEG3) is an imprinted maternally lncRNA, 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). Its overexpression acts as a
tumor suppressor by regulating PI3K/AKT/Bcl-2/Bax/Cyclin D1/P53 and PI3K/AKT/MMP-2/MMP-9 signaling pathways. The increased expression levels of MEG3 were also reported in the PBMCs of type 2 diabetes patients, hi g h f a t d i e t , a n d o b / o b mice hepatocytes. It increases hepatic insulin resistance through enhanced FOXO1 expression. 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.

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. 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. PVT1 regulates SERBP1 by acting as a miR-448 sponge which leads to the proliferation and migration of PC cells. It involves EMT, cell proliferation, and migration by deregulating P21 and TGFβ/Smad signaling pathways. In another study related to diabetic nephropathy, the knockdown of PVT1 results in the significant reduction of FN1, COL4A1 (major ECM proteins) and TGFβ, PaI1 (regulators of ECM proteins), indicating that PVT1 may be involved in the progression of diabetic nephropathy by mechanisms within ECM accumulation. In diabetes, PVT1 may also be involved in the susceptibility of end-stage renal disease (ESRD) (Figure 4).

**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                   |                    |                 | miR-335-5p       |
|                 | hsa_circ_0007534           | Increased tissue   | JMD2C           | miR-625          |
|                 | circRNA_100782             | Increased tissue   | IL6R            | miR-892b         |
|                 | hsa_circ_0001649           | Decreased tissue   | STAT3           | microRNA-124     |
|                 | circ-FDE8A                 | Increased tissue   | caspase-9       |                  |
|                 | hsa_circ_0006215           | Increased tissue   | caspase-3       |                  |
|                 | circRHOT1                  | Increased tissue   | MET             | miR-338          |
|                 | circ-IARS                  | Increased tissue   | MACC1           |                  |
|                 | circ-LDLRAD3               | Increased tissue   | EGFR/STAT3      | miR-7            |
|                 | circ_0030235               | Increased tissue   | SERPINA4        | miR-378a-3p      |
| Type 2 diabetes  | has-circRNA11783-2         | Decreased peripheral blood |                  | miR-1253         |
|                 | has-circRNA0054633         | Increased plasma   |                 | miR-608          |
|                 | cirCANKRD36                | Increased peripheral blood leucocytes | IL-6 | miR-3907         |
|                 | hsa_circRNA_404457        | Increased serum    |                 |                  |
|                 | hsa_circRNA_063981        |                  |                 |                  |
|                 | hsa_circRNA_100750        |                  |                 |                  |
|                 | hsa-circRNA-406918        |                  |                 |                  |
|                 | hsa_circRNA_104387        |                  |                 |                  |
|                 | Hsa-circRNA-103410        |                  |                 |                  |
|                 | hsa-circRNA-100192        |                  |                 |                  |

© 2021 The Authors. Journal of Diabetes Investigation published by AASD and John Wiley & Sons Australia, Ltd
This lncRNA regulates CD24 and integrin expression, which results in sphere formation and invasion in pancreatic cancer cells. 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. 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.

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. 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. A feedback loop between MALAT1 and miR-200-3p promotes cell invasion and migration in PDAC. It also increases pancreatic cancer proliferation and metastasis through stimulation of autophagy. In PDAC, MALAT1 regulates KRAS by sponging miR-217 and inhibiting its translocation from the nucleus to the cytoplasm. On the contrary, the expression levels of MALAT1 were downregulated in the serum of patients with type 2 diabetes. 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), non-proliferative 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. The expression level of MALAT1 was also upregulated in the PBMCs of type 2 diabetes patients compared with controls.

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 cell line inhibits cell proliferation, and its inhibition leads to a decrease in G0/G1 phase and an increase in S phase. GAS5 could inhibit PC metastasis by positive regulation of PTEN through miR-32-5p. 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. In addition, GAS5 regulates the miR-221/SOCS pathway, which results in the suppression of metastasis, cell growth, and resistance to gemcitabine. 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 nephropathy.
The expression level of GAS5 was decreased in the tissue of db/db mice, the serum, and plasma of patients with type 2 diabetes, which is considered to be a biomarker of type 2 diabetes in Egypt. In contrast, the elevated expression of GAS5 was demonstrated in the PBMCs of patients with type 2 diabetes. GAS5 regulates the expression of insulin receptors by binding to its promoter, in which its depletion suppresses glucose uptake and insulin signaling.

HOTAIR transcript antisense RNA (HOTAIR) is considered to be a negative prognostic factor with pro-oncogenic activity in pancreatic cancer. Its functional polymorphisms (SNP rs4759314 and rs200349340) have been demonstrated to have strong associations with susceptibility to pancreatic cancer. 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. It also sponges miR-613, which results in notch3 expression regulation and pro-oncogenic functions by regulating different sets of genes in Panc1 cells. miR-663b is another target of this IncRNA in which its inhibition causes pancreatic cancer cell proliferation by increased levels of insulin-like growth factor 2 (IGF2). 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. 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. HOTAIR could promote energy metabolism in pancreatic adenocarcinoma cells by upregulating hexokinase-2 (HK2), which leads to increased tumor cell proliferation. 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. It develops hepatic insulin resistance by suppressing the AKT/GSK pathway and the expression of SIRT1. In contrast, its expression did not show significant changes in the serum of type 2 diabetes patients compared with healthy controls. HOTAIR is a critical regulator in diabetic retinopathy and promotes diabetic cardiomyopathy through PI3K/AKT pathway activation. 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.

IncRNA nuclear-enriched abundant transcript 1 (NEAT1) is another upregulated IncRNA 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. 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. Another study also showed that NEAT1 sponges miR-23c and develops diabetic nephropathy.

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. Furthermore, the aberrant expression of miRNAs has
been reported in the tissue\textsuperscript{118}, plasma\textsuperscript{119}, serum\textsuperscript{120}, and PBMC\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{125}. In diabetic nephropathy, the serum levels of miR-21 could also be a diagnostic biomarker\textsuperscript{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\textsuperscript{127}. In addition, the plasma miR-221 may be a valuable biomarker for the diagnosis and prediction of malignant outcomes in pancreatic cancer patients\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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 adenyl cyclase 1 (Adcy1) and exchanges protein directly activated by cAMP 2 (Epac2). Both proteins are involved in insulin secretion\textsuperscript{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\textsuperscript{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\textsuperscript{135}. Metformin also inhibits human pancreatic cancer proliferation and tumor growth through altering miRNAs related to cell cycle-related proteins\textsuperscript{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 dose dependent\textsuperscript{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 alterations. 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)\textsuperscript{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.

**FUNDING INFORMATION**

This study was performed at the University of Isfahan (Isfahan, Iran) and was supported by the Graduate Studies Office at this university.

**DISCLOSURE**

The authors declare no conflict of interest.

Approval of the research protocol: N/A.

Informed consent: N/A.

Approval date of registry and the registration no. of the study/-trial: N/A.

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-κB target genes such as IL-6, IL-8, IL-1β, and TNFα, which leads to inflammation | PBMC       | Down                     | Downregulation of EGFR and the NF-κB regulatory kinase IRAK1 | 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-γ (IFN-γ), and TNF-α     | PBMC       | Up                       | Promotes pancreatic cancer development and invasion by targeting TP53/INP1 | 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 involved in the PPAR-γ-P3K/AKT-GLUT4 signaling axis, thus leading to increased glucose uptake and decreased IR | Serum      | Down                     | Inhibits proliferation by phosphorylation of p53                       | Tissue    |
| hsa-miR-27a    | Up                       | Reduce insulin gene expression suggesting its role in defective insulin biosynthesis | Serum      | Up                       | Promotes growth, colony formation and migration                        | Tissue    |
| hsa-miR-30d    | Up                       | Targeting IL1A and IRS2                               | Serum      | Down                     | Tumor suppressor or an oncogene in the progression of different tumor types | Tissue    |
| hsa-miR-30e    | Down                     |                                              | Serum      | Down                     | No report                                                               | Tissue    |
| miRNA    | Type 2 diabetes | Pancreatic cancer |
|----------|-----------------|------------------|
|          | Change of        | Function and       | Cell origin | Change of        | Function and       | Cell origin |
|          | expression      | importance         |            | expression      | importance         |            |
| miR-221  | Up              | Positively         | Serum       | Up              | Enhances the       | Tissue      |
|          |                 | correlated with    |             |                 | progression of     |             |
|          |                 | the insulin        |             |                 | the cell           |             |
|          |                 | resistance index   |             |                 | cycle and         |             |
| miR-424  | Down            | Repression of INSR | Cell line   | Up              | Negatively         | Tissue      |
|          |                 | in the insulin     |             |                 | regulates the      |             |
|          |                 | signaling pathway  |             |                 | downstream         |             |
| miR-100  | Down            | Reduced expression | Blood       | Up              | a multitude of     | Tissue      |
|          |                 | of mammalian       |             |                 | genes involved    |             |
|          |                 | target of rapamycin|             |                 | in the inhibition  |             |
|          |                 | (mTOR) and Insulin  |             |                 | of p53 and DNA    |             |
|          |                 | Growth Factor      |             |                 | damage response    |             |
|          |                 | Receptor (IGFR)    |             |                 | pathways, affects  |             |
| miR-181a | Up              | Role in TNFa-induced IR downregulates | Serum | Up              | Targets PTEN which | Tissue      |
|          |                 | SIRT1 protein      |             |                 | negatively regulates |             |
|          |                 |                   |             |                 | the PI3K-AKT path-  |             |
|          |                 |                   |             |                 | way, leading to   |             |
|          |                 |                   |             |                 | cell proliferation |             |
|          |                 |                   |             |                 | and induces       |             |
|          |                 |                   |             |                 | migration of       |             |
|          |                 |                   |             |                 | pancreatic cancer  |             |
| hsa-miR-375 | Up | Decrease proliferation and insulin gene | -- | Down | In PI3K/AKT signaling, function as a | Tissue |
|          |                 | transcription and  |           |                 | tumor suppressor,  |             |
|          |                 | decrease secretion |           |                 | inhibits the       |             |
|          |                 | of glucose-induced |           |                 | malignant phenotype|             |
| miR-148a | Up              | Directly target     | Bovine milk | Down | Inhibits proliferation and | Tissue |
|          |                 | cholecystokinin     |             |                 | metastasis of     |             |
|          |                 | receptor 2 (CCKBR), |             |                 | ASPC-1 cells       |             |
|          |                 | which leads to     |             |                 |                   |             |
|          |                 | increased           |             |                 |                   |             |
|          |                 | hypothalamic        |             |                 |                   |             |
|          |                 | neuropeptide Y (NPY)|             |                 |                   |             |
| miR-29c  | Up              | Inhibits insulin-     | Skeletal muscle | Down | Inhibits cell growth, | Tissue |
|          |                 | stimulated glucose    |             |                 | invasion, and      |             |
|          |                 | uptake and           |             |                 | migration         |             |
|          |                 | negatively regulates|             |                 |                   |             |
|          |                 | gluconeogenesis and  |             |                 |                   |             |
|          |                 | insulin signaling    |             |                 |                   |             |
|           |                 | in hepatocytes       |             |                 |                   |             |
| miR-130b | up              | Negatively influence | Cell line   | Down | Targets STAT3 and inhibits | Tissue |
|          |                 | ATP production via  |             |                 | proliferation and  |             |
|          |                 | downregulation of    |             |                 | invasion          |             |
|          |                 | mitochondrial genes  |             |                 |                   |             |
|          |                 | (PDHA1 and GCK)      |             |                 |                   |             |
| MiR-148b | up              | Targets DNMT1, an    | Serum       | Down | By targeting AMPKα1, | Tissue |
|          |                 | enzyme for DNA       |             |                 | arrests cell cycle |             |
|          |                 | methylation, which   |             |                 | and inhibits cell  |             |
|          |                 | is involved in       |             |                 | growth            |             |
|          |                 | regulating the β-cell formation | | | | |
| miR-335  | Up              | Regulate final stages | Islets from the | Down | Inhibits progression and | Tissue |
|          |                 | of insulin secretion | diabetic GK-rat |     | stem cell           |             |
|          |                 | and Ca2+-dependent exocytosis through | model |     | properties by        |             |
|          |                 | effects on granular priming | |     | targeting OCT4    |             |
| miR-10a  | Down            | Target TNFα and      | Tissue      | Up              | Involved in the    | Tissue      |
|          |                 | reduces glucose      |             |                 | invasive potential |             |
|          |                 | transporter 4 in     |             |                 | of PDAC cells      |             |
|          |                 | cells and decreases  |             |                 | partially via      |             |
|          |                 | glucose uptake       |             |                 | suppression of HOXA1 |             |
| miRNA    | Type 2 diabetes                                                                                                                                  | Pancreatic cancer                                                                                                                                            |
|----------|--------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|
|          | Change of expression | Function and importance                                                                                                                                  | 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                                                                                                                                     | 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, \( \beta \)-cell apoptosis and proliferation, and insulin biosynthesis and secretion | Cell line              | Promotes migration by targeting PTEN, MAP2K4                                                                                                          |
|          |                        |                                                                                                                                                    |                        | Tissue                                                                                                                                                 |
| miR-214  | Down                   | Suppress glucose production, involved in the regulation of hepatic gluconeogenesis via targeting ATF4                                             | Up                    | Decreases the sensitivity of tumor cells to gemcitabine                                                                                               |
|          |                        |                                                                                                                                                    |                        | Cell line                                                                                                                                               |
| let-7i    | Up                     | Involved in pathways of chronic stress response                                                                                                   | Plasma                 | No report                                                                                                                                            |
|          |                        |                                                                                                                                                    |                        | Tissue                                                                                                                                                 |
| miR-23b  | Up                     | Regulates high-glucose-induced cellular metabolic memory through a SIRT1-dependent signaling pathway                                               | Human retinal endothelial cells | Regulates autophagy associated with radioresistance by targeting ATG12                                                                             |
|          |                        |                                                                                                                                                    |                        | Cell line                                                                                                                                               |
| miR-24   | Down                   | Lead to a fall of circulating glucose and insulin levels                                                                                          | Tissue                 | 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              | Promotes proliferation and migration by targeting NFkB1                                                                                               |
|          |                        |                                                                                                                                                    |                        | 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                  | Inhibited pancreatic cancer growth by decreasing Snail1 and Notch1 expression                                                                       |
|          |                        |                                                                                                                                                    |                        | Cell line                                                                                                                                               |
| 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 P3K/AKT/NF-kB 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’UTR 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 GPC153A, 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 |
| 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-486 | Down                  | 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-483-3p | Up                    | 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 PAN-1 cells | Cell line |
| hsa-miR-486 | Down                  | 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-571 | Up                    | No report               | Plasma       | Up                   | No report                                                      | Cell line |
| hsa-miR-572 | Up                    | 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        |                   |
|           | 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 |
| 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 metalloproteinase 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 |
| 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 |
| miRNA     | Type 2 diabetes                                      | Pancreatic cancer                                      | Cell origin          |
|-----------|------------------------------------------------------|--------------------------------------------------------|----------------------|
|           | Change of expression | Function and importance                                      | 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) |
| miR-1260a | Down          | No report                                              | Plasma               | Up            | Potential mediators of SMAD family member 4 (SMAD4)-associated deregulated calcium fluxes, create an immunosuppressive myeloid cell background in PDAC cells |
|           |               |                                                        |                      |               | Cell line |
| miR-1275  | Up            | No report                                              | Plasma               | Down          | Depresses growth and invasion of pancreatic cancer cells |
| miR-1291  | Up/Down       | No report                                              | Plasma               | Down          | Lower migration and invasion capacity as well as suppresses tumorigenesis |
| miR-1825  | Up            | No report                                              | Plasma               | Up            | Influences pancreatic cancer cell proliferation and invasive ability |
| miR-76S   | Down          | --                                                     | Plasma, rat islets and INS-1 cells                       | Up            | -- |
| miR-30a-5p| Up            | Modulates beta cell function and involved in the suppression of BETA2/NeuroD | Urinary exosomes, ectosomes                                  | Down          | Targets FOXD1 and increases the sensitivity to gemcitabine in PC |
| miR-30b-5p| Down          | Related to impaired renal function proangiogenic       | Ectosomes            | Up            | -- |
| miR-30c-5p| Up            | Targets the mRNA transcripts of two genes involved in angiogenesis, namely, MTDH and POCD10 | Urinary exosomes, ectosomes                                  | Down          | Attenuates cancer cell proliferation, migration and invasion |
| miR-564   | Up            | --                                                     | Plasma               | Down          | -- |
| 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 |
| miR-64S   | Up            | --                                                     | Plasma               | Up            | -- |

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 targeting FOXO3A | Cancer cell line |
| miR-15a   | Down | Targets 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 | Serum | — | Inversely correlates with metastasis formation | Serum |
| miR-492   | — | Contributed to insulin resistance and endothelial dysfunction caused by high glucose | Serum | Down | — | — |
| 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 | — | — | Down | Targets SOX12 and DNMT3b and suppresses proliferation and mobility Antimetastatic potential, tumor suppressive properties mTOR regulation | Cell line |
| miR-29    | Up | Important regulator of insulin-stimulated glucose metabolism and lipid oxidation | Skeletal muscle | Down | Anti-metastatic potential, tumor suppressive properties mTOR regulation | Cancer cells |
| miR-99b   | Up | — | Tissue | Up | Involved in cell cycle, proliferation, and apoptosis plays an oncogenic role | Cell line |
| miR-125a-5p | Down | Targets STAT3 and regulates glycolipid metabolism | Cell lines and rat livers | Up | — | Tissue |
| miR-151-5p | Up | — | Whole blood | Up | Induces cell proliferation, migration, and invasion by regulating PDCD4 expression | PanIN-3 lesions |
| miR-183   | Up | Effects on diabetic retinopathy by inactivating BTG1-mediated PKB/Akt/VEGF signaling pathway | Whole blood | Up | — | 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 cell proliferation | Cancer tissue |
| 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                                 | 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 FOXC3 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                                 | 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                                 | Serum       | Down                  | Targets MDM2 and induces PC cell apoptosis | Tissue cell culture |
| miR-133a     | Up                                 | Serum       | Down                  | Directly targets FSCN1 and considered as a tumor suppressor | Tissue samples and cell line |
| miR-152      | Up                                 | 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                               | Skeletal muscle | Down                  | Positively correlates with chemoresistance Suppresses the expression of SOCS6 | Tissue cell line |
| miR-424      | Down                               | –           | Up                    | –                                   | Tissue samples and cell lines |
| 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              | Serum             | Down                 | Impair insulin signaling | Tissue samples and cell lines | Serum     | Up                    | Targeting pancreatic carcinoma results in cell death and apoptosis induction | Tissue and cell lines |
| miR-96-5p   | Up              | Serum             | Down                 | Suppresses CACNA1E which results in impaired insulin secretion | Tissue and cell line | Serum     | Up                    | Inhibits BCL-2 and stimulates cell proliferation, migration, and invasion | Cell line |
| miR-34c-5p  | Up              | Monocytes         | Up                   | May have played a mechanistic role in the phenomenon of down-regulated inflammation | Monocytes   | Monocytes | Up                    | Regulates TLR4 pathway that is involved in PANC-1 cell migration and invasion | Monocytes |
| miR-200b    | Down            | Islet             | Up                   | Involves in beta cell survival | Tissue and cell line | Islet     | Down                 | Regulates BCL-2 and induces apoptosis | Islet |
| miR-204     | Down            | Monocytes         | Down                 | Feedback regulation has been noted | Human skin | Monocytes | Down                 | Regulates BCL-2 and induces apoptosis | Monocytes |
| miR-124     | Up              | Keratinocytes     | Up                   | Affects genes involved in MAPK pathway | Human skin | Monocytes | Up                    | Involved in cell migration and invasion | Monocytes |
| miR-345     | Down            | Rat liver         | Up                   | Affects genes involved in MAPK pathway | Human skin | Rat liver  | Down                 | Involved in cell migration and invasion | Rat liver |
| miR-217     | Up              | Islets            | Down                 | Involved in migration and invasion | Human skin | Islets     | Down                 | Involved in cell migration and invasion | Islets |
| miR-200c    | Up              | Adipose tissue    | Down                 | May have a correlation with the development of proteinuria and diabetes kidney disease | Human skin | Adipose tissue | Down                 | May have a correlation with the development of proteinuria and diabetes kidney disease | Adipose tissue |
| miR-371     | Down            | Plasma             | Down                 | Involves in beta cell survival | Human skin | Plasma     | Down                 | Involves in beta cell survival | Plasma |
| miR-210     | Up              | Blood             | Down                 | Related to obesity | Human skin | Blood     | Up                    | Related to obesity | Blood |
| miR-15b     | Up              | Skeletal muscle    | Down                 | Affects GLUT4 expression and cell migration | Human skin | Skeletal muscle | Up                    | Affects GLUT4 expression and cell migration | Skeletal muscle |

© 2021 The Authors. Journal of Diabetes Investigation published by AASD and John Wiley & Sons Australia, Ltd
INSTITUTIONAL REVIEW BOARD STATEMENT
Not applicable.

DATA AVAILABILITY STATEMENT
Data sharing not applicable.

REFERENCES
1. Ogura Y, Fukatsu A. Exfoliative cytology of oral mucosa epithelium: cytochemical study and morphologic analysis of patients with type 2 diabetes. Open J Stomatol 2019; 9: 281–294.
2. Saremi MA, Esfahani VR. IL7 receptor polymorphisms and multiple sclerosis in Western Provinces of Iran. Pers Med J 2020; 1: 18–20.
3. Chaudhury A, Duvoor C, Reddy Dendi VS, et al. Clinical review of antidiabetic drugs: Implications for type 2 diabetes mellitus management. Front Endocrinol 2017; 8: 6.
4. Olokoba AB, Obateru OA, Olokoba LB. Type 2 diabetes mellitus: a review of current trends. Oman Med J 2012; 27: 269.
5. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol 2018; 14: 88.
6. Lv Y, Huang S. Role of non-coding RNA in pancreatic cancer. Oncol Lett 2019; 18: 3963–3973.
7. Hidalgo M, Cascinu S, Kleeff J, et al. Addressing the challenges of pancreatic cancer: future directions for improving outcomes. Pancreatology 2015; 15: 8–18.
8. Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. N Engl J Med 2014; 371: 1039–1049.
9. Network CGAR. Comprehensive molecular profiling of lung adenocarcinoma. Nature 2014; 511: 543–550.
10. Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Erratum: signatures of mutational processes in human cancer (Nature (2013) 500 (415–421). Nature 2013; 502: 258.
11. Wang Y-T, Gou Y-W, Jin W-W, et al. Association between alcohol intake and the risk of pancreatic cancer: a dose–response meta-analysis of cohort studies. BMC Cancer 2016; 16: 212.
12. Rawla P, Sunkara T, Gaduputi V. Epidemiology of pancreatic cancer: global trends, etiology and risk factors. World J Oncol 2019; 10: 10.
13. Matsubayashi H, Takaori K, Morizane C, et al. Familial pancreatic cancer and surveillance of high-risk individuals. Gut Liv 2019; 13: 498.
14. Molho RB, Zalmanoviz S, Laitman Y, et al. De novo pathogenic germline variant in PALB2 in a patient with pancreatic cancer. Fam Cancer 2019; 19: 193–196.
15. Hu ZI, Shia J, Stadler ZK, et al. Evaluating mismatch repair deficiency in pancreatic adenocarcinoma: challenges and recommendations. Clin Cancer Res 2018; 24: 1326–1336.
16. Childs EJ, Chaffee KG, Gallinger S, et al. Association of common susceptibility variants of pancreatic cancer in
higher-risk patients: a PACGENE study. Cancer Epidemiol Biomarkers Prev 2016; 25: 1185–1191.

17. Barry K. Chronic pancreatitis: diagnosis and treatment. Am Fam Physician 2018; 97: 385–393.

18. McGuigan A, Kelly P, Turkington RC, et al. Pancreatic cancer: a review of clinical diagnosis, epidemiology, treatment and outcomes. World J Gastroenterol 2018; 24: 4846.

19. Xia B, He Q, Pan Y, et al. Metabolic syndrome and risk of pancreatic cancer: a population-based prospective cohort study. Int J Cancer 2020; 147: 3384–3393.

20. Johnson JA, Bowker SL, Richardson K, et al. Time-varying incidence of cancer after the onset of type 2 diabetes: evidence of potential detection bias. Diabetologia 2011; 54: 2263–2271.

21. Tan J, You Y, Guo F, et al. Association of elevated risk of pancreatic cancer in diabetic patients: a systematic review and meta-analysis. Oncol Lett 2017; 13: 1247–1255.

22. Biadgo A, Abebe M. Type 2 diabetes mellitus and its association with the risk of pancreatic carcinogenesis: a review. Korean J Gastroenterol 2016; 67: 168–177.

23. Shen H, Zhan M, Wang W, et al. Impact of diabetes mellitus on the survival of pancreatic cancer: a meta-analysis. Onco Targets Ther 2016; 9: 1679.

24. Mutgan AC, Besikcioglu HE, Wang S, et al. Insulin/IGF-driven cancer cell-stroma crosstalk as a novel therapeutic target in pancreatic cancer. Mol Cancer 2018; 17: 1–11.

25. Szablewski L. Diabetes mellitus: influences on cancer risk. Diabetes Metab Res Rev 2014; 30: 543–553.

26. Li W, Zhang L, Chen X, et al. Hyperglycemia promotes the epithelial-mesenchymal transition of pancreatic cancer via hydrogen peroxide. Oxid Med Cell Long 2016; 2016: 1–9.

27. Stolzenberg-Solomon RZ, Graubard BI, Chari S, et al. Insulin, glucose, insulin resistance, and pancreatic cancer in male smokers. JAMA 2005; 294: 2872–2878.

28. Pothuraju R, Rachagani S, Junker WM, et al. Pancreatic cancer associated with obesity and diabetes: an alternative approach for its targeting. J Exp Clin Cancer Res 2018; 37: 1–15.

29. Zhang AMY, Magrill J, de Winter TJJ, et al. Endogenous hyperinsulinaemia contributes to pancreatic cancer development. Cell Metab 2019; 30: 403–404.

30. Du C, da Silva A, Morales-Oyarvide V, et al. Insulin-like growth factor-1 receptor expression and disease recurrence and survival in patients with resected pancreatic ductal adenocarcinoma. Cancer Epidemiol Biomarkers Prev 2020; 29: 1586–1595.

31. Consortium APG. AACR Project GENIE: powering precision medicine through an international consortium. Cancer Discov 2017; 7: 818–831.

32. Cicenas J, Kvedaraviciute K, Mesknyte I, et al. KRAS, TP53, CDKN2A, SMAD4, BRCA1, and BRCA2 mutations in pancreatic cancer. Cancers 2017; 9: 42.

33. Zeitouni D, Pylaev-Gupta Y, Der CJ, et al. KRAS mutant pancreatic cancer: no lone path to an effective treatment. Cancers 2016; 8: 45.

34. Ying H, Kimmelman A, Lyssiotis C, et al. Oncogenic Kras maintains pancreatic tumors through regulation of anabolic glucose metabolism. Cell 2012; 149: 656–670.

35. Philip B, Roland CL, Daniluk J, et al. A high-fat diet activates oncogenic Kras and COX2 to induce development of pancreatic ductal adenocarcinoma in mice. Gastroenterology 2013; 145: 1449–1458.

36. Wang D, Bi Y, Hu L, et al. Obesogenic high-fat diet heights aerobic glycolysis through hyperactivation of oncogenic KRAS. Cell Commun Signal 2019; 17: 1–9.

37. Jonckheere N, Vasseur R, Van Seuningen I. The cornerstone K-RAS mutation in pancreatic adenocarcinoma: from cell signaling network, target genes, biological processes to therapeutic targeting. Crit Rev Oncol/Hematol 2011; 77: 7–19.

38. Yang Q, Vijayakumar A, Kahn BB. Metabolites as regulators of insulin sensitivity and metabolism. Nat Rev Mol Cell Biol 2018; 19: 654–672.

39. Świderska E, Strzycharz J, Wróblewska A, et al. Role of PI3K/AKT pathway in insulin-mediated glucose uptake. In: Blood Glucose Levels. London: IntechOpen, 2018.

40. Guo YJ, Pan WW, Liu SB, et al. ERK/MAPK signalling pathway and tumorigenesis. Exp Ther Med 2020; 19: 1997–2007.

41. Emangholipour S, Ebrahimli R, Bahiaee A, et al. Acetylation and insulin resistance: a focus on metabolic and mitogenic cascades of insulin signaling. Crit Rev Clin Lab Sci 2020; 57: 196–214.

42. Czech MP. Insulin action and resistance in obesity and type 2 diabetes. Nat Med 2017; 23: 804–814.

43. Sun G, Kashyap SR. Cancer risk in type 2 diabetes mellitus: metabolic links and therapeutic considerations. J Nutr Metab 2011; 2011: 1–11.

44. Khadka R, Tian W, Hao X, et al. Risk factor, early diagnosis and overall survival on outcome of association between pancreatic cancer and diabetes mellitus: changes and advances, a review. Int J Surg 2018; 52: 342–346.

45. Eulalio A, Huntzinger E, Izaurralde E. Getting to the root of miRNA-mediated gene silencing. Cell 2008; 132: 9–14.

46. Ashir Z, Dehghanian F, Hojati Z. Increased expression of microRNAs, miR-20a and miR-326 in PBMCs of patients with type 1 diabetes. Mol Biol Rep 2018; 45: 1973–1980.

47. Deng T, Yuan Y, Zhang C, et al. Identification of circulating miR-25 as a potential biomarker for pancreatic cancer diagnosis. Cell Physiol Biochem 2016; 39: 1716–1722.

48. Motohashi N, Alexander MS, Shimizu-Motohashi Y, et al. Regulation of IRS1/Akt insulin signaling by microRNA-128a during myogenesis. J Cell Sci 2013; 126: 2678–2691.

49. Gil N, Ullitsky I. Regulation of gene expression by cis-acting long non-coding RNAs. Nat Rev Genet 2020; 21: 102–117.
50. Ulitsky I. Evolution to the rescue: using comparative genomics to understand long non-coding RNAs. Nat Rev Genet 2016; 17: 601–614.

51. Wang P, Liu Y-H, Yao Y-L, et al. Long non-coding RNA CASC2 suppresses malignancy in human gliomas by miR-21. Cell Signal 2015; 27: 275–282.

52. Wu M, Feng Y, Shi X. Advances with long non-coding RNAs in diabetic peripheral neuropathy. Diabetes Metab Syndr Obes 2020; 13: 1429.

53. Sanger HL, Klotz G, Riesner D, et al. Viroids are single-stranded covalently closed circular RNA molecules existing as highly base-paired rod-like structures. Proc Natl Acad Sci 1976; 73: 3852–3856.

54. Zhao W, Dong M, Pan J, et al. Circular RNAs: a novel target among non-coding RNAs with potential roles in malignant tumors. Mol Med Rep 2019; 20: 3463–3474.

55. Haque S, Harries LW. Circular RNAs (circRNAs) in health and disease. Genes 2017; 8: 353.

56. Abbaszadeh-Goudarzi K, Radbakhsh S, Pourhanifeh MH, et al. Circular RNA and diabetes: epigenetic regulator with diagnostic role. Curr Mol Med 2020; 20: 516–526.

57. Panda AC, Grammatikakis I, Munk R, et al. Emerging roles and context of circular RNAs. Wiley Interdiscip Rev RNA 2017; 8: e1386.

58. Kristensen LS, Andersen MS, Stagsted LV, et al. The biogenesis, biology and characterization of circular RNAs. Nat Rev Genet 2019; 20: 675–691.

59. Fang Y, Wang X, Li W, et al. Screening of circular RNAs and validation of circANKRD36 associated with inflammation in patients with type 2 diabetes mellitus. Int J Mol Med 2018; 42: 1865–1874.

60. Ghasemi H, Sabati Z, Ghaedi H, et al. Circular RNAs in β-cell function and type 2 diabetes-related complications: a potential diagnostic and therapeutic approach. Mol Biol Rep 2019; 1–13.

61. Wang Y-Z, An Y, Li B-Q, et al. Research progress on circularRNAs in pancreatic cancer: emerging but promising. Cancer Biol Ther 2019; 20: 1163–1171.

62. Chen G, Shi Y, Zhang Y, et al. CircRNA_100782 regulates pancreatic carcinoma proliferation through the IL6-STAT3 pathway. Onco Targets Ther 2017; 10: 5783.

63. Liu L, Liu F-B, Huang M, et al. Circular RNA cirs-7 promotes the proliferation and metastasis of pancreatic cancer by regulating miR-7-mediated EGFR/STAT3 signaling pathway. Hepatobiliary Pancreat Dis Int 2019; 18: 580–586.

64. Stoll L, Sobel J, Rodriguez-Trejo A, et al. Circular RNAs as novel regulators of β-cell functions in normal and disease conditions. Mol Metab 2018; 9: 69–83.

65. El-Hefnawy S, Al-sheikh N, Kasem H, et al. Plasma Circular RNA (0054633) expression as a biomarker for prediabetes and type 2 diabetes mellitus. Bull Egypt Soc Physiol Sci 2018; 38: 77–88.

66. Zhao Z, Li X, Jian D, et al. Hsa_circ_0054633 in peripheral blood can be used as a diagnostic biomarker of prediabetes and type 2 diabetes mellitus. Acta Diabetol 2017; 54: 237–245.

67. Jiang Y, Wang T, Yan L, et al. A novel prognostic biomarker for pancreatic ductal adenocarcinoma: hsa_circ_0001649. Gene 2018; 675: 88–93.

68. Li X, Wu Z, Fu X, et al. IncRNAs: insights into their function and mechanics in underlying disorders. Mutat Res/Rev Mutat Res 2014; 762: 1–21.

69. Leti F, DiStefano JK. Long noncoding RNAs as diagnostic and therapeutic targets in type 2 diabetes and related complications. Genes 2017; 8: 207.

70. Ma L, Wang F, Du C, et al. Long non-coding RNA MEG3 functions as a tumour suppressor and has prognostic predictive value in human pancreatic cancer. Oncol Rep 2018; 39: 1132–1140.

71. Gu L, Zhang J, Shi M, et al. IncRNA MEG3 had anti-cancer effects to suppress pancreatic cancer activity. Biomed Pharmacother 2017; 89: 1269–1276.

72. Sathishkumar C, Prabu P, Mohan V, et al. Linking a role of IncRNAs (long non-coding RNAs) with insulin resistance, accelerated senescence, and inflammation in patients with type 2 diabetes. Human Genomics 2018; 12: 41.

73. Zhu X, Wu Y-B, Zhou J, et al. Upregulation of IncRNA MEG3 promotes hepatic insulin resistance via increasing FoxO1 expression. Biochem Biophys Res Commun 2016; 469: 319–325.

74. You LiangHui, Wang N, Yin DanDan, et al. Downregulation of long noncoding RNA Meg3 affects insulin synthesis and secretion in mouse pancreatic beta cells. J Cell Physiol 2016; 231: 852–862.

75. Xie Z, Chen X, Li J, et al. Salivary HOTAIR and PVT1 as novel biomarkers for early pancreatic cancer. Oncotarget 2016; 7: 25408.

76. Huang C, Yu W, Wang Q, et al. Increased expression of the IncRNA PVT1 is associated with poor prognosis in pancreatic cancer patients. Minerva Med 2015; 106: 143–149.

77. Zhao L, Kong H, Sun H, et al. LncRNA-PVT1 promotes pancreatic cancer cells proliferation and migration through acting as a molecular sponge to regulate miR-448. J Cell Physiol 2018; 233: 4044–4055.

78. Zhang X, Feng W, Zhang J, et al. Long non-coding RNA PVT1 promotes epithelial-mesenchymal transition via the TGF-β/Smad pathway in pancreatic cancer cells. Oncol Rep 2018; 40: 1093–1102.

79. Alvarez ML, DiStefano JK. Functional characterization of the plasmacytoma variant translocation 1 gene (PVT1) in diabetic nephropathy. PLoS One 2011; 6: e18671.

80. Hanson RL, Craig DW, Millis MP, et al. Identification of PVT1 as a candidate gene for end-stage renal disease in type 2 diabetes using a pooling-based genome-wide single
nucleotide polymorphism association study. Diabetes 2007; 56: 975–983.
81. Yoshimura H, Matsuda Y, Yamamoto M, et al. Reduced expression of the H19 long non-coding RNA inhibits pancreatic cancer metastasis. Lab Invest 2018; 98: 814–824.
82. Sun Y, Zhu Q, Yang W, et al. LncRNA H19/miR-194/PFKT1 axis modulates the cell proliferation and migration of pancreatic cancer. J Cell Biochem 2019; 120: 3874–3886.
83. Ma L, Tian X, Guo H, et al. Long noncoding RNA H19 derived miR-675 regulates cell proliferation by down-regulating E2F–1 in human pancreatic ductal adenocarcinoma. J Cancer 2018; 9: 389.
84. Wang F, Rong L, Zhang Z, et al. LncRNA H19-derived miR-675–3p promotes epithelial-mesenchymal transition and stemness in human pancreatic cancer cells by targeting the STAT3 pathway. J Cancer 2020; 11: 4771–4782.
85. Sasaki N, Toyoda M, Yoshimura H, et al. H19 long non-coding RNA contributes to sphere formation and invasion through regulation of CD24 and integrin expression in pancreatic cancer cells. Oncotarget 2018; 9: 34719.
86. Tello-Flores VA, Valladares-Salgado A, Ramírez-Vargas MA, et al. Altered levels of MALAT1 and H19 derived from serum or serum exosomes associated with type-2 diabetes. Non-coding RNA Res 2020; 5: 71–76.
87. Zhang NA, Geng T, Wang Z, et al. Elevated hepatic expression of H19 long noncoding RNA contributes to diabetic hyperglycemia. JCI Insight 2018; 3: e120304.
88. Gao Y, Wu F, Zhou J, et al. The H19/let-7 double-negative feedback loop contributes to glucose metabolism in muscle cells. Nucleic Acids Res 2014; 42: 13799–13811.
89. Zhou Y, Shan T, Ding W, et al. Study on mechanism about long noncoding RNA MALAT1 affecting pancreatic cancer by regulating Hippo-YAP signalling. J Cell Physiol 2018; 233: 5805–5814.
90. Xie Z-C, Dang Y-W, Wei D-M, et al. Clinical significance and prospective molecular mechanism of MALAT1 in pancreatic cancer exploration: a comprehensive study based on the GeneChip, GEO, Oncomine, and TCGA databases. Onco Targets Ther 2017; 10: 3991.
91. Zhuo M, Yuan C, Han T, et al. A novel feedback loop between high MALAT-1 and low miR-200c-3p promotes cell migration and invasion in pancreatic ductal adenocarcinoma and is predictive of poor prognosis. BMC Cancer 2018; 18: 1–11.
92. Li LE, Chen H, Gao Y, et al. Long noncoding RNA MALAT1 promotes aggressive pancreatic cancer proliferation and metastasis via the stimulation of autophagy. Mol Cancer Ther 2016; 15: 2232–2243.
93. Liu P, Yang H, Zhang J, et al. The IncRNA MALAT1 acts as a competing endogenous RNA to regulate KRAS expression by sponging miR-217 in pancreatic ductal adenocarcinoma. Sci Rep 2017; 7: 1–14.
94. Shaker OG, Abdelaleem O, Mahmoud RH, et al. Diagnostic and prognostic role of serum miR-20b, miR-17-3p, HOTAIR, and MALAT1 in diabetic retinopathy. IUBMB Life 2019; 71: 310–320.
95. Lu X, Fang Y, Wang Z, et al. Downregulation of gas5 increases pancreatic cancer cell proliferation by regulating CDK6. Cell Tissue Res 2013; 354: 891–896.
96. Gao Z-Q, Wang J-F, Chen D-H, et al. Long non-coding RNA GASS suppresses pancreatic cancer metastasis through modulating miR-32-5p/PTEN axis. Cell Biosci 2017; 7: 1–12.
97. Gao Z-Q, Wang J-F, Chen D-H, et al. Long non-coding RNA GASS antagonizes the chemoresistance of pancreatic cancer cells through down-regulation of miR-181c-5p. Biomed Pharmacother 2018; 97: 809–817.
98. Liu B, Wu S, Ma J, et al. IncRNA GASS reverses EMT and tumor stem cell-mediated gemcitabine resistance and metastasis by targeting miR-221/SOCS3 in pancreatic cancer. Mol Ther Nucleic Acids 2018; 13: 472–482.
99. Ge X, Xu B, Xu W, et al. Long noncoding RNA GASS inhibits cell proliferation and fibrosis in diabetic nephropathy by sponging miR-221 and modulating SIRT1 expression. Aging 2019; 11: 8745.
100. Jin F, Wang N, Zhu Y, et al. Downregulation of long noncoding RNA Gas5 affects cell cycle and insulin secretion in mouse pancreatic β cells. Cell Physiol Biochem 2017; 43: 2062–2073.
101. Carter G, Miladinovic B, Patel AA, et al. Circulating long noncoding RNA GASS levels are correlated to prevalence of type 2 diabetes mellitus. BBA Clin 2015; 4: 102–107.
102. Saleh AA, Kasem HE, Zahran ES, et al. Cell-free long noncoding RNAs (LY86-AS1 & HCG27_201and GASS) as biomarkers for pre-diabetes and type 2 DM in Egypt. Biochem Biophys Rep 2020; 23: 100770.
103. Shi Y, Parag S, Patel R, et al. Stabilization of IncRNA GASS by a small molecule and its implications in diabetic adipocytes. Cell Chem Biol 2019; 26: 319–330.e6.
104. Kim K, Jutooru I, Chadalapaka G, et al. HOTAIR is a negative prognostic factor and exhibits pro-oncogenic activity in pancreatic cancer. Oncogene 2013; 32: 1616–1625.
105. Jiang D, Xu L, Ni J, et al. Functional polymorphisms in LncRNA HOTAIR contribute to susceptibility of pancreatic cancer. Cancer Cell Int 2019; 19: 47.
106. Cai H, Yao J, An Y, et al. LncRNA HOTAIR acts as competing endogenous RNA to control the expression of Notch3 via sponging miR-613 in pancreatic cancer. Oncotarget 2017; 8: 32905.
107. Cai H, An Y, Chen X, et al. Epigenetic inhibition of miR-663b by long non-coding RNA HOTAIR promotes pancreatic cancer cell proliferation via up-regulation of insulin-like growth factor 2. Oncotarget 2016; 7: 86857.
108. Yang S-Z, Xu F, Zhou T, et al. The long non-coding RNA HOTAIR enhances pancreatic cancer resistance to TNF-related apoptosis-inducing ligand. J Biol Chem 2017; 292: 10390–10397.
109. Wu C, Yang L, Qi X, et al. Inhibition of long non-coding RNA HOTAIR enhances radiosensitivity via regulating autophagy in pancreatic cancer. Cancer Manag Res 2018; 10: 5261.

110. Ma YU, Hu M, Zhou L, et al. Long non-coding RNA HOTAIR promotes cancer cell energy metabolism in pancreatic adenocarcinoma by upregulating hexokinase-2. Oncol Lett 2019; 18: 2212–2219.

111. Liu H-N, Li X, Wu N, et al. Serum microRNA-221 as a biomarker for diabetic nephropathy in patients associated with type 2 diabetes. Int J Ophthalmol 2018; 11: 1889.

112. Yang Z, Chen H, Si H, et al. Serum miR-23a, a potential biomarker for diagnosis of pre-diabetes and type 2 diabetes. Acta Diabetol 2014; 51: 823–831.

113. Liu N, Sun Y-Y, Zhang X-W, et al. Oncogenic miR-23a in pancreatic ductal adenocarcinogenesis via inhibiting APAF1. Dig Dis Sci 2015; 60: 2000–2008.

114. Li M, Guo Y, Wang X, et al. Expression of long non-coding RNA HOTAIR enhances radiosensitivity via regulating SIRT1. Exp Clin Endocrinol Diabetes 2015; 103: 297-300.

115. Wang J, Duan L, Tian L, et al. Serum miR-21 may be a potential diagnostic biomarker for diabetic nephropathy. Exp Clin Endocrinol Diabetes 2016; 124: 417–423.

116. Li F, Xu J-W, Wang L, et al. MicroRNA-221-3p is upregulated and serves as a potential biomarker in pancreatic cancer. Artif Cells Nanomed Biotechnol 2018; 46: 482–487.

117. Majumder S, Hadden MJ, Thieme K, et al. Dysregulated expression but redundant function of the long non-coding RNA HOTAIR in diabetic kidney disease. Diabetologia 2019; 62: 2129–2142.

118. Wang X, Xu Y, Zhu Y-C, et al. Long non-coding RNA HOTAIR improves diabetic cardiomyopathy by increasing viability of cardiomyocytes through activation of the PI3K/Akt pathway. Exp Ther Med 2018; 16: 4817–4823.

119. Majumder S, Hadden MJ, Thieme K, et al. Dysregulated expression but redundant function of the long non-coding RNA HOTAIR in diabetic kidney disease. Diabetologia 2019; 62: 2129–2142.

120. Li M, Guo Y, Wang X, et al. Expression of long non-coding RNA HOTAIR enhances radiosensitivity via regulating SIRT1. Exp Clin Endocrinol Diabetes 2015; 103: 297-300.

121. Majumder S, Hadden MJ, Thieme K, et al. Dysregulated expression but redundant function of the long non-coding RNA HOTAIR in diabetic kidney disease. Diabetologia 2019; 62: 2129–2142.

122. Majumder S, Hadden MJ, Thieme K, et al. Dysregulated expression but redundant function of the long non-coding RNA HOTAIR in diabetic kidney disease. Diabetologia 2019; 62: 2129–2142.

123. Liu N, Sun Y-Y, Zhang X-W, et al. Oncogenic miR-23a in pancreatic ductal adenocarcinogenesis via inhibiting APAF1. Dig Dis Sci 2015; 60: 2000–2008.

124. Dai X, Pang W, Zhou Y, et al. Altered profile of serum microRNAs in pancreatic cancer-associated new-onset diabetes mellitus. J Diabetes 2016; 8: 422–433.

125. Vychytillova-Faltejskova P, Kiss I, Klusova S, et al. MiR-21, miR-34a, miR-198 and miR-217 as diagnostic and prognostic biomarkers for chronic pancreatitis and pancreatic ductal adenocarcinoma. Diagn Pathol 2015; 10: 38.

126. Wang J, Duan L, Tian L, et al. Serum miR-21 may be a potential diagnostic biomarker for diabetic nephropathy. Exp Clin Endocrinol Diabetes 2016; 124: 417–423.

127. Li F, Xu J-W, Wang L, et al. MicroRNA-221-3p is upregulated and serves as a potential biomarker in pancreatic cancer. Artif Cells Nanomed Biotechnol 2018; 46: 482–487.

128. Kawaguchi T, Komatsu S, Ichikawa D, et al. Clinical impact of circulating miR-221 in plasma of patients with pancreatic cancer. Br J Cancer 2013; 108: 361–369.

129. Liu N, Sun Y-Y, Zhang X-W, et al. Oncogenic miR-23a in pancreatic ductal adenocarcinogenesis via inhibiting APAF1. Dig Dis Sci 2015; 60: 2000–2008.

130. Yang Z, Chen H, Si H, et al. Serum miR-23a, a potential biomarker for diagnosis of pre-diabetes and type 2 diabetes. Acta Diabetol 2014; 51: 823–831.

131. Liu N, Sun Y-Y, Zhang X-W, et al. Oncogenic miR-23a in pancreatic ductal adenocarcinogenesis via inhibiting APAF1. Dig Dis Sci 2015; 60: 2000–2008.

132. Dai X, Pang W, Zhou Y, et al. Altered profile of serum microRNAs in pancreatic cancer-associated new-onset diabetes mellitus. J Diabetes 2016; 8: 422–433.

133. Liu N, Sun Y-Y, Zhang X-W, et al. Oncogenic miR-23a in pancreatic ductal adenocarcinogenesis via inhibiting APAF1. Dig Dis Sci 2015; 60: 2000–2008.

134. Tavano F, Fontana A, Mazza T, et al. Early-onset diabetes as risk factor for pancreatic cancer: miRNA expression profiling in plasma uncovers a role for miR-20b-5p, miR-29a, and miR-18a-5p in diabetes of recent diagnosis. Front Oncol 2020; 10: 1567.

135. Bao B, Wang Z, Ali S, et al. Metformin inhibits cell proliferation, migration and invasion by attenuating CSC function mediated by deregulating miRNAs in pancreatic cancer cells. Cancer Prev Res 2012; 5: 355–364.

136. Kato K, Iwama H, Yamashita T, et al. Inhibition of long non-coding RNA HOTAIR participates in hepatic steatosis through activation of the PI3K/Akt pathway. Exp Ther Med 2018; 16: 4817–4823.

137. Tavano F, Fontana A, Mazza T, et al. Early-onset diabetes as risk factor for pancreatic cancer: miRNA expression profiling in plasma uncovers a role for miR-20b-5p, miR-29a, and miR-18a-5p in diabetes of recent diagnosis. Front Oncol 2020; 10: 1567.