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REVIEW

MiRNA dysregulation underlying common pathways in type 2 diabetes and cancer development: an Italian Association of Medical Oncology (AIOM)/ Italian Association of Medical Diabetologists (AMD)/Italian Society of Diabetology (SID)/Italian Society of Endocrinology (SIE)/Italian Society of Pharmacology (SIF) multidisciplinary critical view

A. Natalicchio[1], M. Montagnani[2], M. Gallo[3], N. Marrano[1], A. Faggiano[4], M. C. Zatelli[5], R. Mazzilli[4], A. Argentiero[6], R. Danesi[7], S. D'Oronzo[8], S. Fogli[7], D. Giuffrida[9], S. Gori[10], A. Ragni[3], V. Renzelli[11], A. Russo[12], T. Franchina[13], E. Tuveri[14], L. Sciacca[15], M. Monami[16], G. Cirino[17], G. Di Cianni[18], A. Colao[19,20], A. Avogaro[21], S. Cinieri[22], N. Silvestris[13†] & F. Giorgino[1*†]

[1]Department of Precision and Regenerative Medicine and Ionian Area, Section of Internal Medicine, Endocrinology, Andrology and Metabolic Diseases, University of Bari Aldo Moro, Bari; [2]Department of Precision and Regenerative Medicine and Ionian Area, Section of Pharmacology, Medical School, University of Bari Aldo Moro, Bari; [3]Endocrinology and Metabolic Diseases Unit, AO SS Antonio e Biagio e Cesare Arrigo of Alessandria, Alessandria; [4]Endocrinology Unit, Department of Clinical and Molecular Medicine, Sant'Andrea Hospital, ENETS Center of Excellence, Sapienza University of Rome, Rome; [5]Section of Endocrinology, Geriatrics, and Internal Medicine, Department of Medical Sciences, University of Ferrara, Ferrara; [6]Medical Oncology Unit, IRCCS Istituto Tumori "Giovanni Paolo II", Bari; [7]Unit of Clinical Pharmacology and Pharmacogenetics, Department of Clinical and Experimental Medicine, University of Pisa, Pisa; [8]Interdisciplinary Department of Medicine, University of Bari Aldo Moro, Bari; [9]Department of Oncology, Istituto Oncologico del Mediterraneo, Viagrande, Catania; [10]Oncologia Medica, IRCCS Ospedale Don Calabria-Sacro Cuore di Negrar, Verona; [11]Diabetologist and Endocrinologist, Italian Association of Clinical Diabetologists, Rome; [12]Department of Surgical, Oncological and Oral Sciences, Section of Medical Oncology, University of Palermo, Palermo; [13]Medical Oncology Unit, Department of Human Pathology "G. Barresi", University of Messina, Messina; [14]Diabetology, Endocrinology and Metabolic Diseases Service, ASL-Sulcis, Carbonia, Sardinia; [15]Department of Clinical and Experimental Medicine, Endocrinology Section, University of Catania, Catania; [16]Diabetology, Careggi Hospital and University of Florence, Firenze; [17]Department of Pharmacy, School of Medicine and Surgery, University of Naples Federico II, Naples; [18]Diabetes Unit, Livorno Hospital, Livorno; [19]Endocrinology, Diabetology and Andrology Unit, Department of Clinical Medicine and Surgery, Federico II University of Naples, Naples; [20]UNESCO Chair, Education for Health and Sustainable Development, Federico II University, Naples; [21]Department of Medicine, University of Padova, Padua; [22]Medical Oncology Division and Breast Unit, Senatore Antonio Perrino Hospital, ASL Brindisi, Brindisi, Italy

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Increasing evidence suggests that patients with diabetes, particularly type 2 diabetes (T2D), are characterized by an increased risk of developing different types of cancer, so cancer could be proposed as a new T2D-related complication. On the other hand, cancer may also increase the risk of developing new-onset diabetes, mainly caused by anticancer therapies. Hyperinsulinemia, hyperglycemia, and chronic inflammation typical of T2D could represent possible mechanisms involved in cancer development in diabetic patients. MicroRNAs (miRNAs) are a subset of non-coding RNAs, ~22 nucleotides in length, which control the post-transcriptional regulation of gene expression through both translational repression and messenger RNA degradation. Of note, miRNAs have multiple target genes and alteration of their expression has been reported in multiple diseases, including T2D and cancer. Accordingly, specific miRNA-regulated pathways are involved in the pathogenesis of both conditions. In this review, a panel of experts from the Italian Association of Medical Oncology (AIOM), Italian Association of Medical Diabetologists (AMD), Italian Society of Diabetology (SID), Italian Society of Endocrinology (SIE), and Italian Society of Pharmacology (SIF) provide a critical view of the evidence about the involvement of miRNAs in the pathophysiology of both T2D and cancer, trying to identify the shared miRNA signature and pathways able to explain the strong correlation between the two conditions, as well as to envision new common pharmacological approaches.

Key words: type 2 diabetes, cancer, miRNAs, miRNA-based drugs

*Correspondence to: Prof. Francesco Giorgino, Department of Precision and Regenerative Medicine and Ionian Area, Section of Internal Medicine, Endocrinology, Andrology and Metabolic Diseases, University of Bari Aldo Moro, Piazza Giulio Cesare 11, 70124 Bari, Italy. Tel: +39-080-5593522

E-mail: francesco.giorgino@uniba.it (F. Giorgino).

†Co-last authors.

INTRODUCTION

Diabetes mellitus (DM) involves a group of metabolic disorders characterized by chronically elevated glycemia. In its two main forms, DM is caused by almost complete immune-mediated β-cell destruction [type 1 diabetes mellitus (T1D)] or by reduced β-cell functional mass [type 2 diabetes mellitus (T2D)]. The number of people with DM has quadrupled in the past three decades, representing one of the fastest-growing health challenges of the 21st century.[1,2] According to the International Diabetes Federation (IDF), ∼463 million adults between the ages of 20 and 79 years have DM, 90% being T2D.[3]

Increasing evidence suggests that patients with DM, particularly T2D, are characterized by an increased risk of developing different types of cancer:[4] at the time of cancer diagnosis, ∼18% of patients have pre-existing DM and the incidence of DM is approximately six times higher in cancer patients than in the general population.[5] Accordingly, the increase in the incidence of cancer appears to parallel the increasing incidence of metabolic disorders, including T2D.[6] On the other hand, cancer may also increase the risk of developing DM, mainly caused by anticancer therapies (i.e. corticosteroids, chemotherapy, radiotherapy, immunosuppressive therapies).[4,7] T2D and cancer share many risk factors: obesity, sedentary lifestyle, unbalanced diet, cigarette smoking, and excessive alcohol consumption.[8,9] Hyperinsulinemia, hyperglycemia, and chronic inflammation typical of T2D could be possible mechanisms involved in cancer development. Many cancer cells overexpress insulin receptors and therefore are more responsive to the mitogenic effects of insulin.[9] In addition, since glucose excess is an important source of energy for cancer cells ('Warburg effect'), hyperglycemia could promote tumor growth.[8,9] Hyperglycemia could also cause oxidative stress and DNA damage, thus triggering or enhancing the tumorigenic process.[9] Lastly, inflammation further promotes neoplastic transformation, cancer cell proliferation, and metastasization.[9] On the other hand, tumor cachexia is often associated with glucose intolerance, insulin resistance, and inflammation that predispose to T2D development.[7] Cancer-related stress can also induce hyperglycemia and worsen inflammation.[7] Finally, DM can occur when cancer affects organs involved in glycemic homeostasis, such as the pancreas and liver.

MicroRNAs (miRNAs) are a subset of non-coding RNAs, ∼22 nucleotides in length, that control the post-transcriptional regulation of gene expression through either translational repression or messenger RNA (mRNA) degradation.[10] Importantly, it has been shown that an individual miRNA can control the expression of more than one target mRNA and that each mRNA may be regulated by multiple miRNAs.[10] Growing evidence suggests that miRNAs operate in all organs and tissues, and play significant roles in various regulatory mechanisms, including cell differentiation, proliferation, apoptosis, and many others.[10] Under various conditions, cells can also release miRNAs, either in free form or complexed with extracellular vesicles, that can be taken up by other cell types, thereby mediating cell-to-cell communication and coordinating multiple biological functions.[11] Indeed, circulating miRNAs have been detected in different human biofluids including plasma, serum, urine, breast milk, cerebrospinal fluid, and saliva.[12] It should be noted that recent research on circulating miRNAs highlights their usefulness as biomarkers of diseases; however, this aspect is beyond the scope of the current manuscript. Of note, miRNAs have multiple target genes and alteration of their expression has been reported in multiple diseases, including T2D and cancer.[13] Interestingly, specific miRNA-regulated pathways are involved in the pathogenesis of both conditions.

In this review, a panel of experts from the Italian Association of Medical Oncology (AIOM), Italian Association of Medical Diabetologists (AMD), Italian Society of Diabetology (SID), Italian Society of Endocrinology (SIE), and Italian Society of Pharmacology (SIF) provide a critical view of the evidence about the involvement of miRNAs in the pathophysiology of both T2D and cancer, trying to identify the shared miRNA signature and pathways able to explain the strong correlation between the two conditions, as well as to envision new common pharmacological approaches.

THE ROLE OF miRNAS IN THE PATHOGENESIS OF TYPE 2 DIABETES

In the past two decades, a growing number of evidence demonstrated the crucial role of miRNAs in the regulation of glucose homeostasis, insulin secretion, and action.[14,15] The metabolic effects of miRNAs are exerted at various levels, both in the pancreatic islets and in peripheral tissues. Accordingly, miRNAs can regulate the two hallmarks of T2D pathogenesis: β-cell failure (Table 1) and peripheral insulin resistance (Table 2).

β-Cell failure

Recent studies have shown that certain miRNAs can regulate the expression of genes that are important for the maintenance of pancreatic β-cell homeostasis.[14] Accordingly, miRNAs could exert important physiological roles in compensatory response of β-cells to stressful stimuli, regulation of insulin secretion mechanisms, maintenance of β-cell mass, and maturation process of β-cells.[15,16]

Compensatory response of β-cells to stressful stimuli. MiR-375 is the most highly expressed miRNA in pancreatic islets (10% of β-cell miRNAs are miR-375).[17,18] It regulates β-cell adaptation to metabolic stress and insulin resistance;[19] therefore, mice with global miR-375 knockout show progressive hyperglycemia with lower numbers of β-cells and impaired compensatory β-cell proliferation.[20,21] Similarly, miR-223 and miR-455 expression is increased in islets of diabetic and obese mice, respectively, and drive the compensatory β-cell expansion and the maintenance of functional β-cell mass during metabolic stress.[22,23] In addition, the miR-17-92 cluster regulates β-cell restoration and adaptation after streptozotocin treatment in mice.[24] MiR-216a (a conserved, pancreas-specific miRNA) also plays important roles in pancreatic islet compensatory response, since its knockout in mice leads to a reduction in islet size,

Table 1. MiRNAs of importance for β-cell failure

β-Cell failure	
miRNAs	Effects
miR-7	Represses β-cell function,[34] regulates GLP-1-mediated insulin release.[49]
miR-9	Represses β-cell function.[37]
miR-15a	Regulates insulin synthesis.[33]
miR-17-92 cluster	Regulates β-cell replication, restoration and adaptation, and GSIS.[24]
miR-24	Reduces insulin promoter activity and insulin mRNA levels and consequently insulin content.[33,39]
miR-25	Its overexpression leads to inhibition of insulin biosynthesis and increased β-cell apoptosis.[27]
miR-26	Reduces insulin promoter activity and insulin mRNA levels and consequently insulin content.[33,39]
miR-29 family	Its overexpression negatively affects GSIS and β-cell proliferation.[45]
miR-30d	Increases insulin gene expression.[32]
miR-34a	Its overexpression results in sensitization to apoptosis and impaired nutrient-induced insulin secretion.[26]
miR-92b	Its overexpression leads to inhibition of insulin biosynthesis and increased β-cell apoptosis.[27]
miR-96	Represses β-cell function.[38]
miR-124a	Promotes β-cell dysfunction and death.[43]
miR-125b-5p	Its down-regulation reduces insulin sensitivity and deregulates β-cell function.[46]
miR-130a/b	Negatively correlated with insulin exocytosis.[15]
miR-132	Controls β-cell identity,[48] proliferation and survival,[51] regulates GLP-1-mediated insulin release.[50]
miR-146	Its overexpression results in sensitization to apoptosis and impaired nutrient-induced insulin secretion.[26]
miR-148	Reduces insulin promoter activity and insulin mRNA levels and consequently insulin content.[33,39]
miR-152	Negatively correlated with insulin exocytosis.[15]
miR-153	Its overexpression induces insulin secretion defects.[28]
miR-181b	Regulates β-cell replication and GSIS.[24]
miR-182	Reduces insulin promoter activity and insulin mRNA levels and consequently insulin content.[33,39]
miR-187	Negatively correlated with GSIS.[42]
miR-200 family	Represses β-cell function.[35,166]
miR-204	Blocks insulin production,[47] promotes β-cell ER stress.[52]
miR-212	Regulates GLP-1-mediated insulin release.[50]
miR-216a	Its knockout leads to a reduction in islet size, β-cell mass, and insulin levels.[25]
miR-223	Its overexpression drives the compensatory β-cell expansion and the maintenance of functional β-cell mass during metabolic stress.[22]
miR-299-5p	Its reduction promotes β-cell dysfunction and loss.[31]
miR-320a	Its overexpression initiates pancreatic islet dysfunction by increasing the ROS level, inhibiting proliferation, and inducing apoptosis.[29]
miR-335	Negatively correlated with insulin exocytosis.[41]
miR-375	Regulates β-cell adaptation to metabolic stress and insulin resistance[19] and promotes GSIS[33]
miR-383	Its overexpression reverses β-cell apoptosis and oxidative stress.[30]
miR-455	Its overexpression drives the compensatory β-cell expansion and the maintenance of functional β-cell mass during metabolic stress.[23]
miR-770-5p	Promotes β-cell dysfunction and death.[44]

ER, endoplasmic reticulum; GLP-1, glucagon-like peptide-1; GSIS, glucose-stimulated insulin secretion; miRNA, microRNA; mRNA, messenger RNA; ROS, reactive oxygen species.

β-cell mass, and insulin levels.[25] MiR-34a and miR-146 levels are increased in islets of diabetic *db/db* mice or in the MIN6 β-cell line exposed to palmitate and this increase results in sensitization to apoptosis and impaired nutrient-induced insulin secretion.[26] Likewise, miR-25 and miR-92b expression is up-regulated by palmitate and pro-inflammatory cytokines, leading to inhibition of insulin biosynthesis and increased β-cell apoptosis.[27] Similarly, the miR-153 expression level is increased in interleukin-1β-treated β-cells and induces insulin secretion defects.[28] Furthermore, miR-320a is increased in the pancreatic β-cells from high-fat-diet (HFD)-treated mice and its overexpression in cultured β-cells initiates pancreatic islet dysfunction by increasing the reactive oxygen species level, inhibiting proliferation, and inducing apoptosis.[29] On the contrary, miR-383 expression is reduced in T2D patients and its overexpression reversed cell apoptosis and oxidative stress in β-cell lines exposed to high glucose levels, and ameliorated hyperglycemia and pancreatic apoptosis in HFD-induced diabetic mice.[30] Similarly, miR-299-5p expression is reduced by glucolipotoxicity in healthy human islets and this inhibition promotes β-cell dysfunction and loss.[31]

Regulation of insulin biosynthesis and secretion. Several miRNAs are able to regulate insulin biosynthesis and glucose-stimulated insulin secretion (GSIS). In particular, it has been demonstrated that miR-30d, miR-15a, and miR-375 play a constitutive role in insulin gene expression,[32] insulin synthesis,[33] and GSIS,[33] respectively. On the contrary, miR-7, miR-9, miR-96, and miR-200 family (which consists of miR-200a/141 and miR-200b/miR-200c/miR-429 clusters, and account for up to two-thirds of all miRNAs in β-cells) appear to constitutively repress β-cell function, since their deletion or overexpression promotes or suppresses, respectively, insulin secretion.[15,33-38] Likewise, miR-24, miR-26, miR-148, and miR-182 reduce insulin promoter activity and insulin mRNA levels and consequently insulin content.[33,39] In addition, miR-335, miR-152, and miR-130a/b are increased in pancreatic islets isolated from Goto-Kakizaki rats, a model of T2D with β-cell dysfunction,[40] and their expression is negatively correlated with insulin exocytosis.[15,41] Similarly, miR-187, miR-124a, and miR-770-5p expression is increased in human T2D islets and negatively correlated with β-cell function.[42-44] Similarly, the transient overexpression of miR-29a negatively affects GSIS in MIN6 cells.[45] On the contrary, miR-125b-5p is down-regulated in β-cells of diabetic mice and this results in reduced insulin sensitivity and deregulated β-cell function.[46] Interestingly, it has been demonstrated that miR-204 is able to reduce the expression of MafA, a key transcription factor controlling insulin expression, thus blocking insulin production.[47] MafA expression is also indirectly and positively influenced by miR-132.[48] Finally, it has been recently demonstrated that miR-7, miR-132, and miR-212 expression in β-cells is regulated by glucagon-like peptide-1 (GLP-1) and they play a functional role in the regulation of GLP-1-mediated insulin release.[49,50]

Regulation of β-cell mass. It has been demonstrated that several miRNAs are able to constitutively control β-cell mass. It is the case of miR-132 that controls pancreatic β-cell proliferation and survival through phosphatase and tensin homolog (PTEN)/protein kinase B (AKT)/forkhead box O3 (FOXO3) signaling.[51] On the contrary, miR-7, miR-9, miR-96, and miR-200 family deletion or overexpression

Table 2. MiRNAs of importance for insulin resistance

Peripheral insulin resistance	
miRNAs	Effects
miR-19a	Regulates PI3K activity in endothelial cells.[70]
miR-21	Its overexpression improves the insulin-induced phosphorylation in AKT and the translocation of the GLUT4 in insulin-resistant adipocytes.[87]
miR-27a	Its overexpression decreases glucose consumption and glucose uptake, and reduces the expression of GLUT4 and PI3K p85β.[83]
miR-29 family	Controls PI3K-p85α subunit expression;[67] its overexpression blunts insulin-stimulated AKT activation and glucose uptake in adipose tissue[72] and causes a decrease in levels of GLUT4 which partially induces a decrease in insulin-dependent glucose uptake in skeletal muscle.[84]
miR-30d	Its overexpression decreases glucose consumption and glucose uptake, and reduces the expression of GLUT4 and PI3K p85β.[83]
miR-33 family	Controls AKT phosphorylation and insulin signaling pathways in the liver;[73] increases IRS-2, PI3K levels, and AKT phosphorylation in liver, skeletal muscle, and subcutaneous adipocytes of IRS-1-deficient mice.[74]
miR-96	Decreases IRS-1 protein expression.[64]
miR-103	Affects insulin sensitivity.[55,56]
miR-106b	Its overexpression decreases glucose consumption and glucose uptake, and reduces the expression of GLUT4 and PI3K p85β.[83]
miR-107	Affects insulin sensitivity.[55,56]
miR-126	Decreases IRS-1 protein expression,[65] and controls PI3K-p85β subunit expression.[68]
miR-128 family	Negatively regulates insulin signaling;[60-62] its overexpression down-regulates INSR expression in adipocytes;[62] its inhibition mitigates myocardial insulin resistance.[63]
miR-133 family	Reduces the insulin-stimulated glucose uptake in adipose tissue and skeletal muscle.[81,82]
miR-135 family	Reduces the expression of IRS-2;[65] its overexpression reduces the expression of INSR and the glucose uptake in skeletal muscle.[66]
miR-143	Affects insulin sensitivity;[53] its overexpression impairs insulin-stimulated AKT activation and glucose homeostasis;[53,71] promotes GLUT4 protein expression in adipocytes.[86]
miR-144	Decreases IRS-1 protein expression.[65]
miR-181a	Affects insulin sensitivity.[54]
miR-194	Its knockdown induces an increase in basal and insulin-stimulated glucose uptake and glycogen synthesis, mediated by increased insulin-induced AKT and GSK3β phosphorylation in skeletal muscle.[85]
miR-199a-3p	Increases PI3K/AKT signaling pathway leading to reduced apoptosis and increased proliferation in endothelial cells.[80]
miR-200a-5p	Promotes glucose uptake in the cardiomyocytes.[89]
miR-205-5p	Increases AKT phosphorylation in hepatocytes and then decreases hepatocyte glucose production.[75]
miR-223	Promotes glucose uptake in the cardiomyocytes;[88] its overexpression is associated with a reduction in GLUT4 protein content and insulin-stimulated glucose uptake in human differentiated adipocytes.[90]
miR-320	Boosts insulin resistance in adipose tissue and endothelial cell by regulating IGF-1/IGF-1R expression and inulin pathway,[58] and controls PI3K-p85α subunit expression in the adipose tissue and skeletal muscle.[58]
miR-338-3p	Its reduction induces insulin resistance.[76]
miR-383	Its reduction stimulates AKT signaling through the regulation of IGF-1R.[59]
miR-384-5p	Controls PI3K-p110δ subunit expression.[69]
miR-449a	Promotes insulin-stimulated PI3K and AKT phosphorylation in skeletal muscle.[79]
miR-451	Negatively regulates hepatic gluconeogenesis in an AKT-dependent way.[78]
miR-499-5p	Its reduction induces insulin resistance.[77]
miR-802	Its reduction improves glucose tolerance and insulin action.[57]

AKT, protein kinase B; GLUT4, glucose transporter 4; GSK3β, glycogen synthase kinase-3β; IGF-1, insulin-like growth factor-1; IGF-1R, IGF-1 receptor; INSR, insulin receptor; IRS, INSR substrates; miRNA, microRNA.

promotes or suppresses, respectively, β-cell survival.[15,33-38] Similarly, the transient overexpression of miR-29a negatively affects MIN6 cell proliferation.[45] Likewise, miR-124a and miR-770-5p expression is increased in patients with T2D and promotes β-cell death.[43,44] In addition, many miRNAs can also affect the maturity state of β-cells: for example, the miR-29 family, miR-204, and miR-129 are up-regulated, whereas the miR-17-92 cluster, miR-181b, and miR-215 are suppressed, in young, immature, proliferating islets compared to adult, mature, non-proliferating islets.[15] In particular, the miR-17-92 cluster and miR-181b are able to regulate both β-cell replication and GSIS.[24] It has been demonstrated that miR-204 activates the unfolded protein response signaling, promoting endoplasmic reticulum stress and apoptosis in β-cell lines and human islets.[52]

Insulin resistance

MiRNAs also participate in the mechanisms underlying insulin resistance in peripheral tissues such as the liver, adipose tissue, skeletal muscle, and others.[14] Specifically, miR-143,[53] miR-181a,[54] miR-103, and miR-107[55,56] have all been shown to affect insulin sensitivity, and more recently, miR-802 has been shown to increase with obesity and its reduction improves glucose tolerance and insulin action.[57]

Several studies have demonstrated that miRNAs can affect each step of insulin and insulin-like growth factor (IGF)-(1/2) signaling: expression of insulin receptor (INSR), IGF receptor (IGF-R), and INSR substrates (IRS), intracellular pathways, glucose transporter 4 (GLUT4) translocation, and glucose uptake.

INSR, IGF-R, and IRS expression. MiR-320 plays an important role in boosting insulin resistance in adipose tissue and endothelial cells by regulating IGF-1/IGF-1R expression and insulin pathways.[58] Similarly, the reduction of miR-383 expression stimulates AKT signaling through the regulation of IGF-1R.[59] The miR-128a/b negatively regulates intracellular mediators that are associated with the insulin signaling protein cascades including INSR and IRS-1 at both mRNA and protein levels.[60,61] Accordingly, obesity promotes the

activation of miR-128 that reduces INSR expression in adipocytes.[62] Interestingly, miR-128-3p is overexpressed in the myocardium of mice manifesting severe cardiac dysfunction, together with IRS-1 degradation and insulin resistance, while its inhibition mitigates myocardial insulin resistance.[63] Likewise, miR-96, miR-126, and miR-144 are supposed to target IRS-1 and their expression causes a significant decrease in IRS-1 protein expression and consequent damage to insulin signaling.[64,65] On the other hand, miR-135a significantly reduces the expression of IRS-2 at both mRNA and protein levels.[65] Accordingly, murine skeletal muscle C2C12 cells overexpressing miR-135 show reduced expression of INSR and glucose uptake, similar to the insulin-resistant cell lines.[66]

Phosphatidylinositol 3-kinase/AKT signaling. Several miRNAs can regulate phosphatidylinositol 3-kinase (PI3K) activity. In particular, miR-320, miR-128a/b, and miR-29 control PI3K-p85α subunit expression in the adipose tissue and skeletal muscle,[58,60,67] while miR-126 regulates the subunit p85β,[68] and miR-384-5p regulates the catalytic subunit p110δ.[69] MiR-19a also regulates PI3K in endothelial cells under shear stress.[70] Furthermore, the activation of AKT can be modulated by miR-143: the overexpression of miR-143 in mice impairs insulin-stimulated AKT activation and glucose homeostasis.[53,71] In addition, miR-143 expression is increased in mouse models of obesity.[53,71]

In the adipose tissue cell-line 3T3-L1, the overexpression of miR-29 blunts insulin-stimulated AKT activation and glucose uptake.[72] Similarly, the miR-33 family (miR-33a and miR-33b) controls AKT phosphorylation and insulin signaling pathways in the liver.[73] In addition, IRS-1-deficient mice show reduced levels of miR-33, which compensates for insulin resistance by increasing IRS-2, PI3K levels, and AKT phosphorylation in the liver, skeletal muscle, and subcutaneous adipocytes.[74] Interestingly, miR-205-5p gain of function increases AKT phosphorylation in hepatocytes and then decreases hepatocyte glucose production and lowers glucose levels in mice.[75] Furthermore, in the liver of the *db/db*, HFD-fed, and tumor necrosis factor-α-treated mice, miR-338-3p and miR-499-5p levels are reduced and this induces insulin resistance, as indicated by altered glucose tolerance and insulin tolerance, and impairs AKT-mediated glycogen synthesis.[76,77] On the contrary, miR-451 is elevated in the liver of diabetic mice and negatively regulates hepatic gluconeogenesis in an AKT-dependent way, thus alleviating hyperglycemia.[78] Moreover, in C2C12 skeletal muscle cells, miR-449a promotes insulin-mediated PI3K/AKT signaling.[79] MiR-199a-3p levels are reduced in peripheral blood from patients with T2D compared to healthy subjects and this may be associated with vascular endothelial cell injury, since transfection with miR-199a-3p mimics activates the PI3K/AKT signaling pathway in human umbilical vein endothelial cells, leading to reduced apoptosis and increased proliferation.[80]

GLUT4 translocation and glucose uptake. Finally, several miRNAs can affect glucose uptake by modulating GLUT4 translocation in adipose tissue and skeletal muscle.[33] For instance, the miR-133 family (miR-133a-1, miR-133a-2, and miR-133b) reduces insulin-stimulated glucose uptake in both adipose tissue and skeletal muscle.[81,82] Similarly, the overexpression of miR-106b, miR-27a, and miR-30d in L6 cells decreases glucose consumption and glucose uptake and reduces the expression of GLUT4 and PI3K p85β.[83] Likewise, overexpression of miR-29a causes a decrease in levels of GLUT4 which partially induces a decrease in insulin-dependent glucose uptake in C2C12 cells.[84] Also, miR-194 knockdown in L6 skeletal muscle cells induces an increase in basal and insulin-stimulated glucose uptake and glycogen synthesis, mediated by increased insulin-induced AKT and glycogen synthase kinase-3β phosphorylation.[85]

Interestingly, miR-194 expression is significantly reduced by 25%-50% in humans with pre-DM and established DM, as an adaptive response to facilitate tissue glucose uptake and metabolism in the face of insulin resistance.[85] On the other hand, miR-143 promotes GLUT4 protein expression in adipocytes.[86] In insulin-resistant adipocytes, the overexpression of miR-21 improves the insulin-induced AKT phosphorylation and GLUT4 translocation.[87] Additionally, GLUT4 is also targeted by miR-223 and miR-200a-5p that promote glucose uptake in the cardiomyocytes.[88,89] Differently, overexpression of miR-223 in human differentiated adipocytes is associated with a reduction in GLUT4 protein content and insulin-stimulated glucose uptake.[90]

ARE MiRNAs INVOLVED IN THE PATHOGENESIS OF DIABETES MELLITUS ALSO INVOLVED IN THE PATHOGENESIS OF CANCER?

MiRNAs are known as critical regulators of gene expression and, in cancer, they play a role in oncogenesis, metastasis, and resistance to various therapies. MiRNAs can be classified as oncogenes (oncomiRs), tumor-suppressor genes, pro-metastatic (metastamiRs), and metastasis suppressors.[91] The importance of miRNAs in cancer, in general, is highlighted by the observation that half of all miRNA genes are located in cancer-associated genomic regions or fragile sites, which are frequently altered in cancer.[92,93] Interestingly, many of the miRNAs involved in the pathogenesis of T2D ("The role of miRNAs in the pathogenesis of type 2 diabetes" section, Tables 1 and 2) also participate in multiple biological processes related to cancer onset and progression. Here we focused on miRNAs recognized as intervening in the main tumorigenic processes, and therefore playing a role in the pathogenesis of multiple types of cancer, while excluding miRNAs that are involved only in specific cancers. The major genes or pathways targeted by these miRNAs are also summarized in Table 3.

miR-7

MiR-7 is one of the most conserved and oldest miRNAs and is engaged in numerous signaling circuits involved in differentiation, regulation of proliferation, apoptosis, and migration. Its dominant activity is tumor suppression by inhibition of cell proliferation and survival. Indeed, in most tumors, its expression is reduced, and in some cancer types,

Table 3. Major genes/pathways targeted by selected miRNAs in cancer

miRNAs	Major genes/pathways targeted in cancer
miR-7	Targets XRCC2 expression and EGFR signaling pathway.[95,167]
miR-9	Modulates the PI3K/AKT, JAK/STAT, Notch1, Wnt/β-catenin, Ras, and ERK signaling pathways.[98]
miR-15a	Targets the oncogenes BCL2, MCL1, CCND1, and Wnt3A.[99]
miR-17-92 cluster	Targets tumor-suppressive (PTEN, RB2, and TGF-β) and oncogenic (c-myc, Notch, and Sonic Hedgehog) signaling pathways.[102,103]
miR-21	Modulates PTEN, PDCD4, RECK, MAPK/ERK, PI3K/AKT, STAT3, and BCL2 gene expression.[106]
miR-24	Increases the oncogenes (c-myc, BCL2, HIF1) gene expression and reduces the tumor-suppressor (p21 and p53) protein expression.[108]
miR-25	Regulates E2F1 expression.[168]
miR-26	Targets caspase-3, caspase-9, and poly (ADP-ribose) polymerase.[111]
miR-27a	Increases PI3K/AKT/GSK3β, Wnt/β-catenin, Ras/MEK/ERK, and c-myc signaling pathways, while inhibiting TGF-β pathway.[112]
miR-34	Activates p53; inhibits vimentin and fibronectin expression; promotes E-cadherin expression; controls Wnt, TGF-β/Smad, and Notch signaling pathways.[115-117]
miR-96	Targets the structural proteins (involved in cell migration and adhesion) and the FOXO transcription factors.[119]
miR-125b	Suppresses the expression of BCL-2 family genes.[169]
miR-126	Reduces the PI3K, K-Ras, VEGF signaling pathways.[123]
miR-132	Modulates the PI3K, TGF-β, and Hippo signaling pathways; reduces the expression of oncogenes Ras, AKT, and mTOR.[125]
miR-135	Targets AKT and Wnt signaling pathways, and APC, FOXO1, FOXN1, RECK, some matrix metalloproteinases gene expression.[126]
miR-144	Modulates the Src/AKT/ERK, Notch, JAK2/STAT3, EGFR, and PTEN/PI3K/AKT signaling pathways.[127]
miR-153	Reduces PTEN expression.[130]
miR-181	Regulates the MAPK, ERK, Wnt, TGF-β, EGFR/Ras, PI3K/AKT, p53 signaling pathways.[132]
miR-212	Modulates the Wnt/β-catenin, Hedgehog, and Hippo/YAP signaling pathways.[136]
miR-320	Suppresses E-cadherin level and increases N-cadherin and vimentin expression by directly targeting FOXM1; regulates the Wnt, PI3K/AKT, TGF-β/Smad, CDK6, STAT3, and E2F1 signaling pathways.[139]
miR-335	Targets the Hedgehog, the PI3K/AKT/mTOR, and the Hippo/YAP signaling pathways.[140]
miR-375	Targets the AEG-1, YAP1, IGF-1R, PDK1, Wnt, NF-κB, Notch, and TGF-β/Smad signaling pathways.[141,142]
miR-449a	Targets the TAK1, Notch, NF-κB/p65/VEGF, RB-E2F, MAPKs, Wnt/β-catenin, p53, and androgen receptor signaling pathways.[143]
miR-802	Modulates the regulation of the Wnt, PI3K/AKT, ERK, and Hedgehog signaling pathways.[144]

AEG-1, astrocyte elevated gene 1; AKT, protein kinase B; APC, adenomatous polyposis coli; BCL2, B-cell lymphoma 2; CCND1, cyclin D1; CDK6, cyclin dependent kinase 6; EGFR, epidermal growth factor receptor; ERK, extracellular receptor kinase; FOX, forkhead box; GSK3β, glycogen synthase kinase-3β; HIF1, hypoxia-inducible factor 1; IGF-1R, insulin-like growth factor 1 receptor; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; MCL1, induced myeloid leukemia cell differentiation protein; miRNA, microRNA; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor-kappa B; PDCD4, programmed cell death protein 4; PDK1, phosphoinositide-dependent kinase-1; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog; Ras, rat sarcoma virus; RB, retinoblastoma-like protein; RECK, reversion-inducing cysteine-rich protein with Kazal motifs; Smad, small mother against decapentaplegic; Src, steroid receptor coactivator; STAT, signal transducer activator of transcription; TAK1, TGF-β activated kinase 1; TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor; XRCC2, X-ray repair complementing defective repair gene; YAP, yes-associated protein.

it acts as an oncomiR (Table 4).[94,95] Of note, its depletion affects the expression of various proteins involved in apoptosis, epidermal growth factor receptor signaling pathways, and multidrug resistance.[95] In most cases, its depletion limits the effectiveness of anticancer therapies, while its restoration sensitizes cells to the administered drugs. Therefore, miR-7 might be considered a potential adjuvant agent, which can increase the efficiency of standard chemotherapeutics.[95]

miR-9

MiR-9 plays a prominent role in tumorigenesis and its aberrant expression has been observed in many human cancer types (Table 4).[96,97] Of note, the role of miR-9 in cancer is dependent on cancer type, so miR-9 serves as a tumor-suppressor miRNA in some cancers and has an oncogenic role in others.[98] MiR-9 controls different biological processes, such as self-renewal, proliferation, and differentiation, and has been shown to play important regulatory roles in cancer biology regulating processes such as tumor initiation (apoptosis/proliferation), progression (angiogenesis/metastasization), and chemosensitivity.[97,98] Specifically, miR-9 expression affects many biochemical pathways commonly deregulated in human cancers (Table 3).

miR-15a

MiR-15a is known to act as a tumor suppressor. Its expression inhibits cell proliferation, promotes apoptosis of cancer cells, and suppresses tumorigenicity [tumor survival, proliferation, migration, angiogenesis, invasion, and epithelial—mesenchymal transition (EMT)] both *in vitro* and *in vivo*, by targeting multiple oncogenes (Table 3).[99] MiR-15a is regulated by some important oncogenes or tumor suppressors (e.g. c-myc, p53), contributing to cancer initiation and insensitivity to chemotherapy.[100] MiR-15a expression is frequently reduced in many types of cancer (Table 4), and restoring its level has helped to enhance apoptosis, delay cell cycle of the cancer cells, and enhance chemosensitivity of tumor.[100,101]

miR-17-92 cluster (miR-17, miR-18a, miR-19a, miR-20a)

Overexpression of the miR-17-92 cluster is a key oncogenic event in various cancer types, as its members target tumor-suppressive proteins and pathways (Table 3).[102,103] In particular, the miR-17-92 cluster is remarkably increased in lung cancer, especially in the most aggressive form, small-cell lung cancer, and also enhances lung cancer cell growth.[104] Elevated expression of the miR-17-92 cluster was

Table 4. MiRNAs differentially expressed in diabetic and oncological patients, and profoundly involved in the pathogenesis of both type 2 diabetes (T2D) and cancer

miRNAs	Expression in T2D	Expression in cancer
hsa-miR-7	Increased[170]	Reduced in breast, lung, ovarian, prostate, gastric, and skin cancers, as well as in glioblastoma, hepatocellular carcinoma, melanoma, and leukemia.[94,95]
hsa-miR-9	Increased[171]	Aberrant expression in breast, cervical, colorectal, lung, gastric, bladder, and prostate cancers, as well as in glioblastoma, squamous cell carcinoma of skin and oral cavity, hematological malignancies, and uveal melanoma.[96,97]
hsa-miR-15a	Reduced[171-173]	Reduced in chronic lymphocytic leukemia, colorectal, bladder, and prostate cancers, as well as in human brain glioma, hepatoma, and different types of lymphoma or leukemia.[100,101]
miR-17-92 cluster (in particular hsa-miR-17, hsa-miR-18a, hsa-miR-19a, hsa-miR-20a)	Further studies required	Increased in lung cancer and human B-cell lymphomas.[104,105]
hsa-miR-21	Reduced[87,171,173]	Increased in gliomas, breast, and colorectal cancers.[106]
hsa-miR-24	Reduced[173]	Reduced in breast, colorectal, and non-small-cell lung cancers, as well as in hepatocellular, nasopharyngeal, laryngeal squamous cell, and esophageal squamous cell carcinomas.[107]
hsa-miR-27a	Increased[83,171,174]	Increased in ovarian, prostate, and gastric cancers, colorectal carcinoma, and esophageal tumors.[112]
hsa-miR-29	Increased[15,45,72,84,171,174]	Reduced in breast, ovary, gastric, colon, lung, pancreatic, prostate, cervix, and oral cancers, as well as in hepatocellular carcinoma, glioblastoma, glioma, melanoma, leukemia, lymphoma, osteosarcoma, rhabdomyosarcoma, and neuroblastoma.[113]
hsa-miR-34	Increased[26,171,173]	Dysregulated in colorectal, prostate, breast, lung, and liver cancers, as well as in osteosarcoma and hematological neoplasms.[115]
hsa-miR-106b	Further studies required	Increased in breast, prostate, lung, gastric, and colorectal cancers, as well as in hepatocellular and esophageal squamous cell carcinomas.[120]
hsa-miR-125b	Reduced[46]	Reduced in non-small-cell lung cancer, anaplastic thyroid cancer, bladder, ovarian, breast, gallbladder, colorectal, and endometrioid-endometrial cancers, as well as in hepatocellular and esophageal squamous cell carcinomas, melanoma, osteosarcoma, chondrosarcoma, multiple myeloma, and Ewing's sarcoma.[121] Increased in nasopharyngeal carcinoma, retinoblastoma, glioblastoma, poorly differentiated non-small-cell lung cancer, acute lymphoblastic leukemia, acute myeloid leukemia, and gastric cancer.[121]
hsa-miR-126	Reduced[173]	Lost in breast, lung, gastric, colorectal, cervix, bladder, oral, and prostate cancers.[123,124]
hsa-miR-132	Further studies required	Reduced in hepatocellular carcinoma, osteosarcoma, breast, colorectal, gastric, lung, prostate, pancreatic, and ovarian cancers.[125]
hsa-miR-135	Increased[66]	Reduced in prostate, renal, gallbladder, and nasopharyngeal cancers, as well as in glioma, impacting the enhancement of cell proliferation and aggressive behavior.[126] Increased in bladder, oral, colorectal, and liver cancers.[126] Dual role in in breast, gastric, lung, and pancreatic cancers, as well as in head and neck squamous cell carcinomas.[126]
hsa-miR-144	Further studies required	Reduced in lung, gastric, colorectal, thyroid, cervical, ovarian, prostate, bladder, esophageal, pancreatic, and breast cancers, as well as in osteosarcoma, glioblastoma, cholangiocarcinoma, hepatocellular, renal cell, head and neck squamous cell, and oral squamous cell carcinomas, leukemia, and lymphomas.[127,128]
hsa-miR-181	Further studies required	Aberrant expression in different solid tumors and hematological malignancies.[132]
hsa-miR-205	Reduced[75]	Reduced in breast, liver, prostate, skin, renal, and colorectal cancers, as well as in glioblastoma.[137] Increased in cervical, ovarian, endometrial, and lung cancers.[137]
hsa-miR-375	Further studies required	Reduced in hepatocellular carcinoma, gastric, esophagus, head and neck, and other cancers.[142]
hsa-miR-449a	Reduced[79]	Reduced in gastric, lung, breast, bladder, liver, cancer, prostate, ovarian, and endometrial cancers, as well as in glioma, neuroblastoma, and retinoblastoma.[143]
hsa-miR-802	Increased[57]	Reduced in gastric, colorectal, breast, cervical, and epithelial ovarian cancers, as well as in melanoma and tongue, oral, esophageal carcinoma, and laryngeal squamous cell carcinomas.[144] Increased in hepatocellular carcinoma, bladder urothelial cancer, osteosarcoma, and cholesteatoma tissue cells.[144]

miRNA, microRNA.

also found in several human B-cell lymphomas.[105] Of note, several studies have revealed the influence of oncogenic signaling pathways (Table 3) in the transcriptional regulation of miR-17-92 cluster in cancer.[102]

miR-21

MiR-21 is one of the first oncomiRs found to be up-regulated in a variety of cancers (Table 4).[106] Some of its target genes are associated with cell proliferation, migration, invasion, and apoptosis (Table 3).[106] As a result, miR-21 has been proposed as a plausible diagnostic and prognostic biomarker, as well as a therapeutic target for several types of cancer.

miR-24

MiR-24 targets and regulates numerous genes in various cancer types (Table 4).[107] In particular, it enhances the expression of several oncogenes (Table 3), while reducing the expression of several tumor-suppressor proteins (Table 3).[108] MiR-24 also regulates cell cycle and is associated with numerous cancer hallmarks such as apoptosis,

proliferation, metastasis, invasion, angiogenesis, autophagy, and drug resistance.[108]

miR-25 and miR-26

Similarly, miR-25 altered expression has been reported in many human malignant tumors.[109] It seems capable of regulating, via different targets, some of the most important pathways, including proliferation, invasion, differentiation, apoptosis, and autophagy.[109] Interestingly, it functions as both an oncogene and in some cases a tumor suppressor, depending on the type of cancer it is involved in.[109] Furthermore, the aberrant expression of miR-26 exists in various kinds of tumor tissues, where it participates in the regulation of tumor cell metabolism, proliferation, differentiation, apoptosis or autophagy, invasion, and metastasis through targeting gene expression at the post-transcriptional level.[110] It functions as either tumor suppressor or oncogene in different types of tumors.[110] For instance, miR-26b has been repeatedly found to decrease in colorectal specimens and cancer cell lines, whereas its overexpression is linked to the inhibition of colorectal cancer growth that is probably subsequent to enhanced levels of key apoptosis-related proteins (Table 3).[111]

miR-27a

MiR-27a is able to promote tumor proliferation and invasion (Table 3).[112] It has also been reported to be associated with chemotherapy resistance in several cancers, although the mechanisms remain unclear.[112] Accordingly, its expression is increased in several tumors (Table 4).[112]

miR-29 family

The miR-29 family is involved in important biological functions, such as cell growth, programmed death, differentiation, and proliferation, thereby playing a direct function in cancer progression.[113] Indeed, its expression is reduced in most cancers, which may be a sign of its role in inhibiting cancerous cells (Table 4).[113] MiR-29 intervenes in key processes, such as apoptosis, proliferation, metastasization, angiogenesis, EMT, and immunomodulation.[114]

miR-34

MiR-34 has been reported to be dysregulated in various human cancers (Table 4) and, at the same time, is also the first miRNA that has proven to be directly regulated by the tumor suppressor p53[115] and to induce p53 activation.[116] Thus, the miR-34 family is known to inhibit tumorigenesis. A large quantity of experimental data showed that miR-34 could influence EMT and then cell metastasis and invasion (Table 3).[115,117] In addition, miR-34a also appears to be involved in the regulation of apoptosis in colorectal cancer cell lines.[118]

miR-96

MiR-96 regulates cell motility, tumor initiation, progression, and invasion as an oncogene or tumor suppressor, mainly by targeting the structural proteins (involved in cell migration and adhesion) and the FOXO transcription factors, which are mainly considered tumor suppressors during tumor progression, regulating the expression of genes involved in cell proliferation, apoptosis, differentiation, and cell cycle regulation.[119]

miR-106b

MiR-106b overexpression has been identified in multiple tumor types (Table 4) and controls cell proliferation, migration, invasion, and metastasization.[120] Moreover, miR-106b overexpression is associated with aggressive clinical and pathological features (Table 3).

miR-125b

MiR-125b expression has been found to be both increased as an oncogene in various cancers and reduced as a tumor suppressor in others (Table 4).[121] At present, many genes have been confirmed as targets of miR-125b, covering a variety of biological signaling pathways and affecting the formation of many malignant phenotypes, such as proliferation, differentiation, migration, apoptosis, cell cycle, and drug resistance in different cancers.[121,122]

miR-126

Several studies have revealed the role of miR-126 as suppressor of tumor formation in various types of cancer, impairing cancer progression through the down-regulation of signaling pathways that control tumor cell proliferation, migration, invasion, survival, and especially angiogenesis (Table 3).[123] Accordingly, miR-126 was reported to be lost in various human cancers (Table 4).[123,124]

miR-132

Decreases in miR-132 level in various types of malignancies (Table 4) have been reported, indicating its function as a tumor suppressor.[125] MiR-132 is involved in cell proliferation, migration, and invasion, affecting cell cycle pathways, or reducing oncogene expression (Table 3).[125]

miR-135

MiR-135 is involved in the pathoetiology of several neoplastic conditions, with both tumor-suppressive and oncogenic roles.[126] Indeed, its expression is reduced or increased depending on the type of tumor in which it is involved (Table 4).[126] Studies in breast, gastric, lung, and pancreatic cancers, as well as head and neck squamous cell carcinomas, have reported dual roles for miR-135[126] (Table 3).

miR-144

MiR-144 has been identified as a tumor suppressor and its expression is reduced in many types of solid and hematological malignancies (Table 4).[127,128] Increasing evidence supports a crucial role for miR-144 in modulating physiopathologic processes, such as proliferation, apoptosis,

invasion, migration, and angiogenesis in different tumor cells (Table 3).[127] Besides these functions, miR-144 can also affect drug sensitivity, cancer treatment, and patient prognosis.[127]

miR-148/-152 family

The expression pattern of miR-148/-152 family members has been found to be reduced in various cancer cells, indicating a tumor-suppressive role for these miRNAs, regulating various pathways including malignant transformation and tumor initiation, growth, angiogenesis, migration, and invasion.[129]

miR-153

Previous studies have indicated that miR-153 functions as a tumor suppressor and as an oncogenic regulator. It is implicated in cancer pathophysiological processes, including proliferation, apoptosis, invasion, EMT and metastasis, angiogenesis, and chemo/radiotherapy resistance.[130,131] In this line, miR-153 suppresses tumor growth in epithelial cancer, glioblastoma, and leukemia. In contrast, miR-153 stimulates cell proliferation in prostate cancer cells.[130]

miR-181

The miR-181 family regulates many relevant biological processes such as cell proliferation, apoptosis, autophagy, angiogenesis, EMT, mitochondrial function, and immune response. Importantly, several studies have shown aberrant expression of these miRNAs in different solid tumors and hematological malignancies, where they act either as tumor suppressors or oncomiRs,[132] regulating several cancer-related pathways (Table 3).[132]

miR-200 family

The miR-200 family contributes to maintaining the epithelial phenotype by repressing the expression of factors that favor the process of EMT, a key hallmark of oncogenic transformation.[133] It also promotes resistance to chemotherapeutic drugs as well as radiotherapy during anticancer therapy.[134]

miR-204 and miR-212

MiR-204 has a dual function as a tumor-suppressive gene and/or an oncomiR in different cancers, by promoting apoptosis, conferring resistance of cancer cells to chemotherapy, and suppressing cancer stem cell self-renewal and EMT.[135] Similarly, miR-212 serves as an oncogene or a tumor suppressor by influencing different targets or pathways during the development and progression of cancer[136] (Table 3).

miR-205

MiR-205 is a highly conserved miRNA that can act as both an oncomiR and a tumor suppressor, although most reports confirm its emerging role as a tumor suppressor in many cancers.[137] Its expression can be both augmented and reduced in cancer (Table 4).[137] Accordingly, in specific cell types, miR-205 facilitates tumor initiation and proliferation acting as an oncogene; in others, it inhibits cell proliferation, invasion, and EMT, thus playing a tumor-suppressive role.[138] Interestingly, restoration of miR-205 makes cells more sensitive to drug treatments and mitigates drug resistance.[137]

miR-320

The miR-320 family is one of many tumor-suppressor families which has been demonstrated to be related to the repression of EMT and metastasization, cell proliferation, apoptosis, and drug resistance (Table 3).[139]

miR-335

The expression level of miR-335 in tissues and cancer cells varies according to cancer type. It may serve as an oncogene or a tumor suppressor by regulating different targets or pathways in tumor initiation, development, and metastasis (Table 3). Furthermore, miR-335 also influences tumor microenvironment and drug sensitivity.[140]

miR-375

MiR-375 is known to be involved in tumor cell proliferation, migration, and drug resistance. Previous studies have shown that miR-375 affects EMT of human tumor cells via some key transcription factors and signaling pathways (Table 3) and is vital for the development of cancer.[141] MiR-375 has been found to be significantly reduced in multiple types of cancer (Table 4), and suppresses core hallmarks of cancer by targeting several important oncogenes (Table 3).[142] Accordingly, reduced expression of miR-375 in tissue or circulation may indicate the presence of a neoplasia as well as a poor prognosis of many malignant cancers.[142]

miR-449a

MiR-449a has been reported to inhibit tumor growth, invasion, and metastasis, and to promote apoptosis and differentiation (Table 3).[143] This miRNA has a low expression level in several cancer cell lines and tumor patients (Table 4).[143]

miR-802

Lastly, current studies have found that miR-802 can target and regulate genes in different tumors (Table 3).[144] MiR-802 is abnormally expressed in many tumors (Table 4).[144]

Other miRNAs

Other miRNAs involved in the processes of tumor initiation, progression, and invasion are miR-107,[145] miR-187,[146] miR-223,[147] miR-338,[148] miR-383,[149] and miR-451.[150]

MiRNAs IN TYPE 2 DIABETES AND CANCER: COMMON PATHWAYS

With T2D and cancer independently representing two leading causes of death, the association between these two conditions further aggravates the socioeconomic burden on global public health. Beyond the epidemiological basis, the underlying molecular mechanisms mediating DM—cancer association are not yet fully understood. In this context, the role of specific miRNAs in both T2D and various cancer types individually, and the overlap between disease-specific regulatory miRNA networks, may be important to identify a conserved miRNA signature common to both diseases. In particular, in the previous sections, we have reported that 40 miRNAs are profoundly involved in the pathogenesis of both T2D and cancer.

To evaluate functions of identified miRNAs, we carried out target prediction and functional annotation using the miRSystem database, which is a web-based system that integrates seven well-known miRNA target gene prediction programs: DIANA-microT web server v5.0 (http://www.microrna.gr/webServer), miRanda, miRBridge, PicTar, PITA, rna22, and TargetScan and two experimentally validated databases, TarBase and miRecords (http://mirsystem.cgm.ntu.edu.tw/).[151] The miRSystem can identify the biological functions/pathways regulated by miRNAs based on the enriched functions of their target genes.[151] The analysis parameters in the miRSystem were set as follows: hit frequency = 5; observed-to-expected (O/E) ratio = 2; minimal size of genes annotated by the ontology term for testing >50; pathways matched should be from Kyoto Encyclopedia of Genes and Genomes (KEGG), Biocarta, Pathway Interaction Database, and REACTOME databases.[151] As shown in Table 5, 28 of the queried miRNAs participate in pathways involved in cancer (KEGG database, 124 targeted mRNAs in the pathway). At the same time, 25 of the queried miRNAs participate in pathways involved in DM (REACTOME database, 38 targeted mRNAs in the pathway). The main pathways potentially involved in both DM and cancer included (Table 5): (i) mitogen-activated protein kinase (MAPK) signaling pathway (KEGG), (ii) INSR signaling cascade (KEGG), (iii) IRS-mediated signaling (REACTOME), (iv) IRS-related events (REACTOME), (v) signaling by INSR (REACTOME), (vi) insulin signaling pathway (KEGG), (vii) mammalian target of rapamycin (mTOR) signaling pathway (KEGG), (viii) PI3K cascade (REACTOME), (ix) phosphatidylinositol signaling system (KEGG), (x) apoptosis (KEGG), and (xi) caspase cascade in apoptosis (Pathway Interaction Database). Twenty-five of the 40 queried miRNAs were found to be involved in both DM and cancer pathways (Figure 1). This supports the hypothesis that these miRNAs should be taken into consideration to envision new pharmacological approaches common to both diseases (see "MiRNAs: a new molecular target for the simultaneous treatment of diabetes mellitus and cancer?" section). A more detailed analysis shows that insulin signaling is the most represented pathway, confirming the hypothesis that hyperinsulinemia and hyperglycemia could be possible shared mechanisms involved in both T2D and cancer development. Accordingly, as stated above, many cancer cells overexpress insulin receptors and therefore are more responsive to the mitogenic effects of insulin,[9] as well as hyperglycemia could cause oxidative stress and DNA damage and promote tumor growth.[8,9]

In addition, although the possible use of miRNAs as a biomarker is beyond the scope of the current manuscript, in Table 4 we have also summarized the evidence from literature on how most of these miRNAs are differentially expressed in both diabetic and oncological patients. Interestingly, many miRNAs are either down- or up-regulated in both pathological conditions (Table 4), suggesting their possible use as common biomarkers. Targeted studies are needed to understand whether the expression of these miRNAs in patients with both diseases is further modified compared to patients with diabetes or cancer alone. In addition, it should be noted that various regulatory mechanisms (including genetic polymorphisms, methylation of miRNA promoters, interactions with RNA-binding proteins or other coding/non-coding RNAs) control miRNA expression, activity, and/or bioavailability,[152] making it challenging to decipher the precise role of miRNAs as a biomarker in specific pathophysiological context.

MiRNAs: A NEW MOLECULAR TARGET FOR THE SIMULTANEOUS TREATMENT OF DIABETES MELLITUS AND CANCER?

MiRNA-based therapeutics is a growing field and advances have been made for a variety of disease states, including metabolic disorders and cancer (reviewed in Bajan and Hutvagner[153]). Dysregulation of miRNA expression in human diseases may provide opportunities for the development of miRNA-based therapies that utilize mimics to increase levels of an miRNA, or miRNA inhibitors (antagomiRs) to down-regulate or block miRNA expression and activity, depending on the type of alteration observed (hypoexpression or hyperexpression).[154] Unfortunately, there are still many challenges to the application of miRNA-based therapies, such as *in vivo* stability, incorrect distribution to the tissue sites of interest, breakdown or overload of endogenous RNA machinery, and in cases of viral vector delivery, toxicity and immunogenicity.[155] In addition, one miRNA can be both hyper- and hypoexpressed according to the disease or its stage, making it difficult to be used as a precise target.[156] Lastly, the possibility of off-target effects (as yet undiscovered mRNA targets) cannot be excluded and should be carefully considered since they may cause severe unanticipated responses.[156] Accordingly, several miRNA-targeted gene therapies have been terminated or withdrawn from clinical trials because of serious adverse effects. For example, the filrst miRNA replacement therapy clinical trial, which tested the efficacy of miR-34 (MRX34) in cancer, was terminated at phase I due to severe immune-related side-effects.[157] On the other hand, miRNAs, due to their ability to target numerous transcripts, often in the same

Table 5. Selected pathways involved in diabetes mellitus and cancer pathogenesis

Category	Term	Total gene of the term	Union target in the term	Union miRNAs in the term	Score
KEGG	PATHWAYS_IN_CANCER	325	124	28	2.839
KEGG	MAPK_SIGNALING_PATHWAY	272	101	27	2.452
PATHWAY_INTERACTION_DATABASE	DIRECT_P53_EFFECTORS	137	50	25	2.155
KEGG	TGF-BETA_SIGNALING_PATHWAY	84	39	25	1.929
PATHWAY_INTERACTION_DATABASE	E2F_TRANSCRIPTION_FACTOR_NETWORK	73	33	26	1.908
KEGG	WNT_SIGNALING_PATHWAY	150	63	26	1.720
KEGG	CELL_CYCLE	124	45	26	1.615
REACTOME	INSULIN_RECEPTOR_SIGNALING_CASCADE	86	35	24	1.582
PATHWAY_INTERACTION_DATABASE	REGULATION_OF_RETINOBLASTOMA_PROTEIN	64	32	24	1.543
REACTOME	IRS-MEDIATED_SIGNALING	81	32	24	1.459
REACTOME	IRS-RELATED_EVENTS	81	32	24	1.459
REACTOME	SIGNALING_BY_INSULIN_RECEPTOR	109	37	25	1.408
KEGG	INSULIN_SIGNALING_PATHWAY	137	45	24	1.397
KEGG	MTOR_SIGNALING_PATHWAY	52	21	23	1.390
REACTOME	SIGNALING_BY_INTERLEUKINS	106	40	25	1.314
REACTOME	CELL_CYCLE_MITOTIC	330	67	24	1.304
KEGG	P53_SIGNALING_PATHWAY	68	30	20	1.288
REACTOME	PI3K_CASCADE	70	26	23	1.275
KEGG	VEGF_SIGNALING_PATHWAY	76	26	24	1.218
PATHWAY_INTERACTION_DATABASE	INTEGRINS_IN_ANGIOGENESIS	74	27	23	1.207
PATHWAY_INTERACTION_DATABASE	HIF-1-ALPHA_TRANSCRIPTION_FACTOR_NETWORK	65	27	26	1.201
PATHWAY_INTERACTION_DATABASE	NOTCH_SIGNALING_PATHWAY	59	25	22	1.072
PATHWAY_INTERACTION_DATABASE	VALIDATED_TARGETS_OF_C-MYC_TRANSCRIPTIONAL_REPRESSION	63	26	24	1.014
KEGG	B_CELL_RECEPTOR_SIGNALING_PATHWAY	75	20	22	0.904
KEGG	PHOSPHATIDYLINOSITOL_SIGNALING_SYSTEM	78	23	20	0.895
KEGG	JAK-STAT_SIGNALING_PATHWAY	155	32	22	0.875
REACTOME	INTEGRATION_OF_ENERGY_METABOLISM	125	33	25	0.872
REACTOME	REGULATION_OF_INSULIN_SECRETION	98	26	25	0.823
KEGG	APOPTOSIS	88	24	22	0.794
KEGG	PANCREATIC_SECRETION	103	26	23	0.786
PATHWAY_INTERACTION_DATABASE	VALIDATED_TARGETS_OF_C-MYC_TRANSCRIPTIONAL_ACTIVATION	81	23	24	0.764
PATHWAY_INTERACTION_DATABASE	CASPASE_CASCADE_IN_APOPTOSIS	56	16	19	0.662
REACTOME	DIABETES_PATHWAYS	229	38	25	0.644
KEGG	INOSITOL_PHOSPHATE_METABOLISM	57	15	16	0.579
KEGG	CELL_ADHESION_MOLECULES_(CAMS)	133	26	20	0.557
PATHWAY_INTERACTION_DATABASE	P53_PATHWAY	58	20	18	0.526
KEGG	HEDGEHOG_SIGNALING_PATHWAY	56	22	16	0.504

KEGG, Kyoto Encyclopedia of Genes and Genomes; miRNA, microRNA.

biological process, have the potential to regulate an entire signaling pathway known to be misregulated in a pathogenic state, thereby increasing their desirability in clinical applications.[153]

To date, no miRNA-based antidiabetes and/or anticancer therapies have been approved by the Food and Drug Administration (FDA). Even though numerous miRNAs have been implicated in the pathogenesis of T2D, to the best of our knowledge, no miRNA-based therapy for the treatment of T2D has yet been envisioned or has entered a pre-clinical trial program. Conversely, several potential anticancer therapies have reached phase I and phase II clinical trials (reviewed in He et al.[158]), although none of them include the 25 miRNAs we identified in the "MiRNAs in type 2 diabetes and cancer: common pathways" section.

In the context of cancer, two studies described the possibility to co-deliver miR-7 and anticancer drugs loaded in nanovehicles, in order to sensitize cancer cells to the chemotherapeutics.[159,160] However, this possibility must undergo further investigation. On the other hand, the use of intravenous delivery of anti-miR-17-92 for the treatment of allograft medulloblastoma tumor has been tested in immune-compromised mice, resulting in the blockage of tumor growth.[161] Nevertheless, some issues regarding selective anti-miR delivery to cancer cells and its side-effects in animal models still require clarification.[102] Although there are no drugs that directly target miR-27, it has been demonstrated that GT-094 (a nitric oxide-releasing nonsteroidal anti-inflammatory drug) in colon cancer cell lines,[162] arsenic trioxide (a widely used anticancer drug in leukemia),[163] and liraglutide[164] in breast cancer cell lines are able to inhibit cancer proliferation through the reduction of miRNA-27a expression. Similarly, it has been demonstrated that several anticancer agents (e.g. 4-phenylbutyric acid, 5-aza-2′-deoxycytidine, olea europaea leaf extract, mifepristone) could induce the apoptosis of cancer cells (including breast cancer and glioblastoma cell lines) through the up-regulation of miR-153.[131] Several *in vitro* studies have shown that the up-regulation of miR-144-3p expression can increase the susceptibility of different cancer cell lines (gastric cancer cells, hepatocellular carcinoma cell lines, glioma and glioblastoma cells, non-small-cell lung cancer, cervical cancer cells,

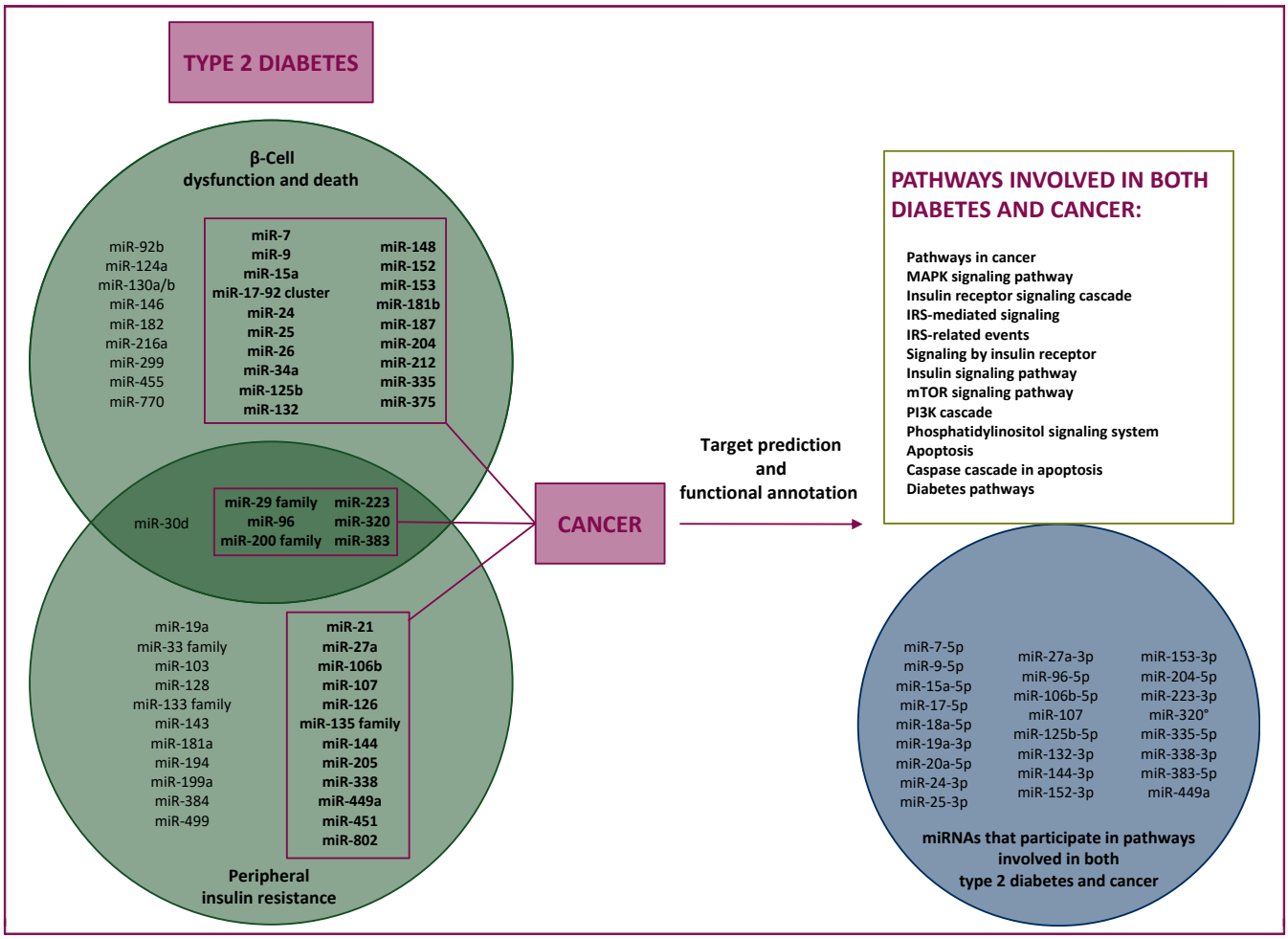

Figure 1. We identified the main microRNAs (miRNAs) involved in the pathophysiology of type 2 diabetes, for which a direct role has been shown in mediating pancreatic β-cell dysfunction and death and the onset of peripheral insulin resistance (green circles), the two hallmarks of type 2 diabetes pathogenesis. Among them, we have identified miRNAs also involved in cancer pathogenesis (miRNAs in bold in the pink boxes). We have then carried out target prediction and functional annotation using the miRSystem database, identifying 25 miRNAs (blue circle) that participate in pathways involved in both type 2 diabetes and cancer (olive green box). IRS, insulin receptor substrates; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase.

anaplastic thyroid carcinoma cell lines) to chemotherapy and radiotherapy.[127] Finally, an miR-383 mimic has been found to suppress proliferation and enhance chemosensitivity in ovarian cancer cells.[165]

Interestingly, a more detailed analysis of miRNAs in Table 4 shows that several miRNAs are down-regulated (i.e. miR-15a, miR-24, miR-125b, miR-126, miR-205, miR-449a) or up-regulated (i.e. miR-27a, miR-135, miR-802) in both diabetic and oncological patients. Accordingly, their hyperexpression or inhibition, respectively, could represent promising targets to simultaneously counteract T2D and cancer development.

CONCLUSIONS AND FUTURE PERSPECTIVES

Increasing evidence suggests that patients with DM, particularly T2D, are characterized by an increased risk of developing different types of cancer,[4,5] to the point that cancer could be proposed as a new T2D-related complication. On the other hand, cancer may also increase the risk of new cases of DM, mainly caused by the use of anticancer therapies (i.e. corticosteroids, chemotherapy, radiotherapy, immunosuppressive therapies).[4,7] Hyperinsulinemia, hyperglycemia, and chronic inflammation typical of T2D could represent possible mechanisms involved in cancer development in diabetic patients.

MiRNAs are a subset of non-coding RNAs, ~22 nucleotides in length, that control post-transcriptional regulation of gene expression through both translational repression or mRNA degradation.[10] Of note, miRNAs have multiple target genes and alteration of their expression has been reported in multiple diseases, including T2D and cancer.[13] Accordingly, specific miRNA-regulated pathways are involved in the pathogenesis of both conditions.

In this review, we have identified the main miRNAs involved in the pathophysiology of T2D ("The role of miRNAs in the pathogenesis of type 2 diabetes" section), for which a direct role has been shown in mediating pancreatic β-cell failure (Table 1) and the onset of peripheral insulin resistance (Table 2), the two hallmarks of T2D pathogenesis (Figure 1). Among them, we have tried to identify miRNAs also involved in cancer pathogenesis, finally focusing our attention on 40 miRNAs profoundly involved in the

pathogenesis of both diabetes and cancer (Figure 1). Some of them were also down- or up-regulated in both pathological conditions (Table 4). Interestingly, in cancer, these miRNAs play a role in cell proliferation and survival, autophagy, self-renewal, differentiation, angiogenesis, EMT, invasion, and sensitivity to various anticancer therapies ("Are miRNAs involved in the pathogenesis of diabetes mellitus also involved in the pathogenesis of cancer?" section). We then carried out target prediction and functional annotation using the miRSystem database, identifying 25 miRNAs that participate in pathways involved in both T2D and cancer ("MiRNAs in type 2 diabetes and cancer: common pathways" section, Table 5, and Figure 1). This supports the hypothesis that these miRNAs could represent a possible signature for the early diagnosis of T2D and cancer, and should be taken into consideration to envision new pharmacological approaches common to both diseases. Interestingly, insulin signaling was the most represented pathway, confirming the hypothesis that its impairment should be considered as a possible common mechanism in the pathogenesis of both T2D and cancer.

MiRNA-based drugs are the latest frontier in nucleic acid therapeutics, although there are still many challenges to their clinical application.[153-156] To date, no miRNA-based antidiabetes and/or anticancer therapies have been approved by the FDA. Several potential anticancer therapies have reached phase I and phase II clinical trials (reviewed in He et al.[158]); however, they do not include the 25 miRNAs we identified in "MiRNAs in type 2 diabetes and cancer: common pathways" section.

In conclusion, we believe that in the near future it may be possible to envision an miRNA-based drug able to treat both T2D and cancer, thus targeting two of the major causes of death of the 21st century, which are closely related to each other.

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DISCLOSURE

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