Review Article

miRNAs provide mechanisms for integrated control of endocrine pancreas homeostasis and metabolic disease pathogenesis: a narrative review

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Background and Objective: microRNAs (miRNAs) are short non-coding RNAs that have emerged to be the novel post-transcriptional regulators of gene expression, contributing to the development of metabolic diseases such as diabetes. Also, new and more precise high-throughput analytical tools have made it possible to study miRNAs' complex causative roles and targets. Here, we summarise the available evidence for the roles of miRNAs in the endocrine pancreas regulating fundamental cellular processes in beta-cells and the pathology of diabetes.

Methods: We searched PubMed for research conducted and published before June 2022 using classical Boolean expressions. Only manuscripts written in English were considered.

Key Content and Findings: Numerous miRNAs in the endocrine pancreas have been reported to regulate the fundamental cellular processes in beta-cells, such as proliferation, differentiation, apoptosis, and insulin biosynthesis and secretion by post-transcriptionally repressing their targets, as well as contributing to the pathology of diabetes. Also, many miRNAs, as molecular cargo of exosomes-mediate the crosstalk between the pancreas and other peripheral organs, unravelling new pathophysiological mechanisms related to the onset and worsening of diabetes.

Conclusions: This review summarised the existing evidence of the complex network of miRNAs regulating the endocrine pancreas function and pathology of diabetes, providing the theoretical base for a future scientific study revealing the mechanism of diabetes and facilitating the discovery of new therapeutical targets in clinical practise.

Keywords: microRNA (miRNA); pancreas; beta-cell; insulin; type 2 diabetes (T2D)

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Introduction

In a healthy individual, insulin secretion accurately matches the insulin demand of target tissues such as skeletal muscle and white adipose tissue, therefore maintaining glucose homeostasis. However, in models of insulin resistance or type 2 diabetes (T2D), compensatory responses to increase insulin secretion and/or expand beta-cell mass occur until beta-cell failure ensues (1,2). The initial adaptive responses are part of allostatic mechanisms to maintain adequate

glucose homeostasis, whereas the latest is a deleterious end-point characterised by insufficient/inadequate insulin secretion and beta-cell destruction. These allostatic adaptations to maintain energy homeostasis integrate beta-cell mass and associated insulin levels and secretion with the function of other organs. The adaptation at the level of the pancreatic islets is controlled by multiple biological processes coordinating proliferation, differentiation, and ultimately the death of beta-cells, involving the regulation of insulin gene expression, protein translation, and the mechanisms responsible for insulin secretion (3,4). Our understanding of endocrine pancreas pathobiology in T2D and T1D has been enriched by the contribution of miRNAs to these diseases.

microRNAs (miRNAs) are endogenous short non-coding RNAs, usually containing 19–22 nucleotides, that repress translation or initiate mRNA degradation through binding (mostly) to the 3'UTR of mRNAs (5,6). During the last decades, miRNAs have emerged as novel and regulatory effectors on gene transcription at the intracellular level. Moreover, the origin of these miRNAs might be in distant organs from where they are transported as targeted cargo in exosomes (7). The discovery of miRNAs and their "endocrine/paracrine" role has opened exciting new avenues for metabolic research aimed at understanding how and where they originated, which genes they target, when that occurs, and what (patho)physiological outcomes are associated with their dysregulation.

The current interest in miRNAs in health and disease has been fuelled by technologies such as genetic engineering and advanced analytical tools to dissect their contributions to physiological and pathophysiological outcomes (8,9). A compelling example of miRNA network dysregulation in diabetes comes from the research by Melkman-Zehavi and colleagues that showed how a beta-cell-specific deletion of *Dicer1 in vivo* prevents pre-miRNAs' cleavage, leading to impaired insulin secretion and recapitulating the natural progression of diabetes (10).

The study of miRNAs in metabolism is novel and promising but not without significant challenges and unsolved questions: (I) the majority of studies focus on the role or association of individual miRNA with the onset or natural history of the disease; (II) there is evidence that a unique miRNA can target multiple targets genes (as a coordinated effect) or conversely, multiple miRNAs can target the same gene limiting our understanding of the real-size effect of miRNAs and the synergies among them in the pathogenesis of T2D; (III) there is still limited information about the transcriptional regulation of the miRNA; and (IV) lack of integrative approaches to investigate the crosstalk between different organs using miRNAs as proxy information molecule at the organismal level. Some of these limitations have been recently addressed by several comprehensive investigations (I) using data from T2D cohorts and miRNA-mRNA network-based approaches, confirming some classical and newly identified miRNAs linked to T2D and identifying clusters of target genes associated with functional aspects of islets and insulin secretion (11) and (II) taking advantage of machine learning workflows and identifying specific miRNA signatures associated with insulin transcription (12).

In this review, we focus on the roles of miRNAs in pancreas endocrine biology and integrate the knowledge of well-established and recent discoveries using genetically modified organisms (mostly mouse models) and *in vitro* models. We summarise how miRNAs affect islet function in the context of insulin resistance and T2D (and also, to a lesser extent, T1D) with a focus on functional roles in beta-cell proliferation, differentiation, apoptosis, insulin biosynthesis and secretion (*Table 1*).

The role of miRNAs on pancreatic cancer or other pancreatic pathologies falls out of the remit of this review and will not be addressed here. We remit the readers to previous excellent reviews on that subject (113-115). We present the following article in accordance with the Narrative Review reporting checklist (available at https://exrna.amegroups.com/article/view/10.21037/exrna-22-17/rc).

Methods

We used the PubMed database and restricted our search to manuscripts written in English until June 2022. We used general Boolean expressions as follows: (I) (microRNA OR miRNA OR miR) AND (pancreas OR islet OR beta cell); (II) (microRNA OR miRNA OR miR) AND pancreas AND crosstalk. Then, we applied several exclusion criteria (manually curated), such as (I) manuscripts unrelated to the specific topic of the review; (II) manuscripts related to tumours or cancer-related processes; (III) manuscripts that lacked novelty based on the authors' discretion. Authors independently selected and ranked manuscripts based on their originality and the robustness of their findings, and a final selection of manuscripts was agreed. Several manuscripts were added to the review following reviewers' suggestions. Our research strategy is outlined in *Table 2*.

Table 1 Summary of miRNAs and their targets in beta-cells

miRNAs ID	Expression profile	Phenotype	Target(s)	Model(s)	References
miR-101a	Increased by inflammatory cytokines	Increases β-cell apoptosis; decreases GSIS; decreases insulin biosynthesis	*NeuroD1*, *Onecut2*	MIN6 (mouse)	(13)
miR-124a	Increased in T2D patients	Decreases insulin biosynthesis; decreases GSIS	*NeuroD1*, *Mtpn*, *Foxa2*	MIN6 (mouse)	(14,15)
miR-125b	Increased by high glucose	Decreases insulin biosynthesis; decreases GSIS	*M6pr*, *Mtfp1*	MIN6 (mouse) human islets; mouse	(16)
miR-126	Increased by high glucose	Decreases β-cell proliferation	*Irs2*	INS-1 (rat)	(17)
miR-127	Decreased in obese mice; increased by high glucose	Decreases β-cell proliferation; decreases GSIS	*Kif3b*	MIN6 (mouse)	(18)
miR-130	Increased in T2D patients and rats	Decreases insulin biosynthesis; decreases GSIS		INS-1 (rat)	(19)
miR-132	Increased in T2D mice	Increases GSIS		INS-1 (rat)E; mouse	(20,21)
miR-133a	Increased in T2D patients	Decreases insulin biosynthesis	*Ptbp*	Human islets	(22,23)
miR-139-5p		Decreases GSIS	*Pick1*	MIN6 (mouse); mouse	(24)
miR-141	Increased in diabetic mice and human	Decreases β-cell proliferation; decreases GSIS	*Foxa2*	INS-1 (rat), MIN6 (mouse)	(25)
miR-145	Decreased in T2D rat	Increases β-cell apoptosis; decreases β-cell differentiation; decreases GSIS	*Xbp1*, *Sox2*, *Abca1*	MIN6 (mouse); HuAEC-derived β islet-like cells mouse islets; rat	(26-28)
miR-146	Increased in T2D patients; increased in obese mice; increased by high glucose	Increases β-cell apoptosis		MIN6 (mouse); rat islets	(29,30)
miR-149-5p	Decreased by high glucose	Decreases β-cell apoptosis; increases GSIS	*Bim*	MIN6 (mouse)	(31)
miR-15a		Increases insulin biosynthesis; increases GSIS	*Ucp2*	MIN6 (mouse)	(32)
miR-152	Decreased in T2D patients	Increases β-cell proliferation; increases GSIS	*PI3Kα*, *Pdha1*	INS-1 (rat) MIN6 (mouse)	(19,33)
miR-153	Increased in T2D patients and mice	Decreases GSIS	*Vamp2*, *Snap25*, *Stx1a*, *Cacna1c*	INS-1 (rat) MIN6 (mouse); mouse islets; mouse	(34,35)
miR-155-5p	Increased by hyperlipidemia in mice	Increases insulin biosynthesis	*Mafb*	MIN6 (mouse); mouse	(36)
miR-17	Increased by high glucose	Increases β-cell proliferation	*Menin*	MIN6 (mouse)	(37)
miR-17-92	Increased in obese mice; increased by high glucose	Increases β-cell proliferation; decreases GSIS; decreases insulin biosynthesis	*NeuroD1*	MIN6 (mouse); mouse	(38,39)
miR-181a-5p		Increases β-cell apoptosis		INS-1 (rat)	(40)
miR-181c-5p		Increases β-cell differentiation	*Smad7*, *Tgif2*	hiPSC	(41)
miR-184	Decreased in T2D patients and mice	Decreases β-cell proliferation; decreases GSIS	*Ago2*	MIN6 (mouse)	(42)
miR-185	Decreased in T2D patients and mice	Increases β-cell proliferation; increases GSIS; decreases β-cell apoptosis	*Socs3*	MIN6 (mouse)	(43)
miR-187	Increased in T2D patients	Decreases GSIS	*Hipk3*	INS-1 (rat)at islets	(44)
miR-19a-3p	Increased in T2D patients	Increases β-cell proliferation; increases GSIS	*Socs3*	INS-1 (rat) MIN6 (mouse)	(45)
miR-190b		Decreases β-cell proliferation; decreases GSIS	*Nkx6.1*	MIN6 (mouse)	(46)
miR-196b	Increased by high glucose	Increases insulin biosynthesis	*insulin 2*	βTC6 (mouse)	(47)
miR-199b-5p	Increased in pancreas regeneration rodent model	Increases β-cell proliferation	*Mlk3*	Rat islets	(48)
miR-200 family	Increased in T2D patients and mice	Increases β-cell apoptosis; decreases GSIS	*Dnajc3*, *Xiap*, *Jazf1*, *Ypel2*, *Rps6kb1*, *Etv5*	MIN6 (mouse); INS-1E (rat) EndoC-βH1 (human); human islets; mouse	(49,50)
miR-204	Increased in obese mice	Decreases insulin biosynthesis	*Mafa* (controversial)	INS-1 (rat) EndoC-βH1 (human); human islets; mouse islets	(51,52)
miR-205-5p	Increased in T2D mice	Increases insulin biosynthesis	*Tcf7l2*	INS-1 (rat)	(53)
miR-21	Increased in T2D mice	Decreases β-cell differentiation; increases GSIS	*Sox6*, *Rbpj*	Embryonic pancreas (chick); mouse	(54,55)
miR-212		Increases GSIS	*Crct1*	INS-1 (rat); mouse	(56)
miR-217	Increased in T2D patients and mice	Decreases β-cell proliferation; increases β-cell apoptosis	*Mafb*	β-TC-tet (mouse)	(57)
miR-218	Decreased by high glucose	Decreases GSIS	*Stxbp1*	MIN6 (mouse); mouse islets	(58)
miR-221/222	Increased in obese mice	Increases β-cell proliferation; decreases β-cell apoptosis; decreases insulin biosynthesis	*Nfatc3*, *Pak1*	MIN6 (mouse); INS-1 (rat); mouse	(59,60)
miR-223	Increased in obese and diabetic mice and human	Increases β-cell proliferation; increases GSIS	*Foxo*, *Sox6*	MIN6 (mouse); mouse	(61)

Table 1 (*continued*)

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miRNAs ID	Expression profile	Phenotype	Target(s)	Model(s)	References
miR-23	Decreased by inflammation	Decreases β-cell apoptosis		EndoC-βH1 (human)	(62)
miR-24	Increased in obese mice	Decreases β-cell proliferation; decreases GSIS	*Sp1*, *Hnf1α*, *NeuroD1*	MIN6 (mouse); mouse islets	(63,64)
miR-25	Increased in T2D mice	Decreases insulin biosynthesis	*Ins1*	INS-1 (rat)	(65)
miR-26		Increases β-cell differentiation	*Tet1/2/3*, *Tdg*	Mouse	(66)
miR-27a	Increased in obese mice	Increases β-cell apoptosis		INS-1 (rat)	(67)
miR-29a	Increased by high glucose	Decreases GSIS	*Stx1a*	INS-1E (rat)	(68)
miR-296-3p	Decreased in diabetic; patients	Decreases β-cell apoptosis	*Pten*	MIN6 (mouse)	(69)
miR-297b-5p	Decreased by stearic acid in mice	Decreases β-cell apoptosis	*Lats2*	β-TC6 (mouse); mouse islets	(70)
miR-299-5p	Decreased by glucolipotoxicity in primary human islets	Decreases β-cell apoptosis	*Perp*, *Siah1*, *Rassf6*, *Sgk1*	β-TC6 (mouse); MIN6 (mouse); mouse islets; human islets	(71)
miR-30a-5p	Increased in obese mice; increased by high glucose	Increases insulin biosynthesis	*NeuroD1*	INS-1 (rat); mouse	(72)
miR-30b	Increased by inflammatory cytokines	Increases β-cell apoptosis; decreases insulin biosynthesis	*Bcl2*, *NeuroD1*	MIN6 (mouse)	(13)
miR-30d	Decreased in T2D patients and mice	Decreases β-cell proliferation; increases β-cell apoptosis; increases insulin biosynthesis	*Map4k4*	MIN6 (mouse); mouse islets; mouse	(73-75)
miR-32		Increases β-cell differentiation	*Wwp2*		(76)
miR-322	Decreased by high glucose	Decreases GSIS	*Stxbp1*	MIN6 (mouse); mouse islets	(58)
miR-335-5p	Increased in T2D patients and rat	Decreases β-cell proliferation; increases β-cell apoptosis; decreases GSIS	*Glut-4*, *Snap25*, *Stxbp1*, *Syt11*	MIN6 (mouse); INS-1 (rat) EndoC-βH1 (human)	(77,78)
miR-338-3p	Decreased in obese and diabetic mice	Decreases β-cell proliferation; increases β-cell apoptosis		INS832/13 (rat); rat islets human islets; mouse	(79,80)
miR-34a	Increased in T2D patients and mice	Increases β-cell apoptosis; decreases GSIS	*Vamp2*, *Bcl2*, *Sirt1*	INS-1 (rat)	(81)
miR-344-5p	Decreased by lipotoxicity	Decreases β-cell apoptosis	*Cav1*	INS-1 (rat)	(82)
miR-375	Increased in T2D patients; increased obese mice	Decreases β-cell proliferation; increases β-cell apoptosis; increases β-cell differentiation; decreases GSIS; decreases insulin biosynthesis	*Psen1*, *Mtpn*, *Yap1*, *Pdk1*, *Hnf1βb*, *Pax6*, *Insm1*, *Gata6*, *Pdpk1*, *Insr*	NIT-1 (mouse) MIN6 (mouse); INS-1 (rat); mouse islets; rat islet; human islets; mouse	(83-90)
miR-383	Decreased by high glucose	Decreases β-cell apoptosis	*Tlr4*, *ApoC3*	MIN6 (mouse); mouse	(91)
miR-409-3p		Decreases β-cell apoptosis; increases GSIS	*Casp8*	NES2Y (human)	(92)
miR-433	Decreased by high glucose	Increases β-cell proliferation; decreases β-cell apoptosis	*Cox2*	MIN6 (mouse)	(93)
miR-455	Increased in obese mice	Increases β-cell proliferation	*Cpeb1*	MIN6 (mouse); EndoC-βH1 (human); human islets; mouse islets; mouse	(94)
miR-463-3p	Increased in T2D patients	Decreases GSIS	*Abcg4*	MIN6 (mouse); mouse islets; human islets	(95)
miR-483	Increased in T2D mice; increased by high glucose	Increases insulin biosynthesis; decreases β-cell apoptosis	*Socs3*, *Aldh1a3*	βTC3 (mouse) MIN6 (mouse); mouse islets; mouse	(96,97)
miR-532-5p	Decreased by high glucose	Decreases β-cell apoptosis; increases GSIS	*Ccnd1*	MIN6 (mouse)	(98)
miR-552-3p	Decreased in T2D patients	Decreases β-cell apoptosis	*Jak1*	INS-1 (rat)	(99)
miR-577	Increased in T1D patients	Decreases insulin biosynthesis; decreases GSIS	*Fgf21*	INS-1 (rat) Embryonic pancreatic beta-cells	(100)
miR-7		Increases β-cell differentiation	*Gata6*, *Irs-2*, *Irs-1*, *Pax6*, *Pax4*, *NeuroD1*, *Nkx2.2*	hiPSC	(101)
miR-7a	Decreased in T2D patients and mice	Decreases β-cell proliferation	*p70S6K*, *eIF4E*, *Mknk1*, *Mknk2*, *Mapkap1* …	MIN6 (mouse); mouse islets human islets; mouse	(102-104)
miR-708	Increased in obese mice	Increases β-cell apoptosis; decreases GSIS	*Nnat*	MIN6 (mouse); mouse islets	(105)
miR-802	Increased in obese mice	Decreases GSIS; decreases insulin biosynthesis	*NeuroD1*, *Fzd5*	MIN6 (mouse); mouse islets; Mouse	(106)
miR-9		Decreases GSIS	*Sirt1*, *Oc2*, *Stxbp1*	MIN6 (mouse); INS-1 (rat)	(107,108)
miR-92a	Increased in T2D mice; decreased by high glucose	Decreases β-cell apoptosis; decreases insulin biosynthesis; increases GSIS	*Klf2*, *Ins1*	MIN6 (mouse); INS-1 (rat)	(65,109)
miR-96	Increased in T2D patients and mice	Increases β-cell proliferation; decreases β-cell apoptosis	*Foxo1*, *Sox6*	MIN6 (mouse); mouse	(110)
Let7b-5p	Increased in T2D patients	Decreases β-cell proliferation; increases insulin biosynthesis; decreases GSIS	*Ccnd1*, *Ccnd2*	INS-1 (rat); mouse	(111,112)

miRNA, microRNA; T2D, type 2 diabetes; GSIS, glucose-stimulated insulin secretion; hiPSC, human induced pluripotent stem cell; INS, insulin gene.

Table 2 Summary of the search strategy

Items	Specification
Date of search	May to June 2022
Databases and other sources searched	PubMed
Search terms used	(I) (microRNA OR miRNA OR miR) AND (pancreas OR islet OR beta cell); (II) (microRNA OR miRNA OR miR) AND pancreas AND crosstalk
Timeframe	Manuscripts published before June 2022
Inclusion and exclusion criteria	Inclusion criteria: (I) English only; (II) research manuscripts; (III) review manuscripts were only mentioned when referring to an area/field not addressed in the present review Exclusion criteria: (I) manuscripts unrelated to the specific topic of the review; (II) manuscripts related to tumours or cancer related processes; (III) manuscripts that lacked novelty based on authors' discretion
Selection process	Authors independently selected and ranked manuscripts based on their originality and the robustness of their findings and a final selection of manuscripts was agreed

Evidence that miRNAs are essential for beta-cell proliferation

One of the first pieces of evidence of the role of miRNAs in pancreas biology came from studies showing that miRNAs target the expression of genes regulating beta-cell proliferation affecting insulin levels (83). The number of targeted genes, the regulation effect of the diabetic/glycemic status on the expression of a particular miRNA, and the outcome promoting or repressing beta-cell proliferation are surprisingly diverse (*Figure 1*). Globally considered, these studies evidence the complex regulation of miRNAs. Some of these miRNAs seem to operate as part of homeostatic responses aimed at maintaining appropriate levels of insulin and insulin secretion in the context of obese and insulin-resistant states by controlling beta-cell proliferation and beta-cell mass where the dysregulation of others *a priori* could worsen and exacerbate the T2D phenotype.

Several examples of miRNAs induced in T2D can be considered homeostatic regulatory events aimed at restoring glycemic levels. One of these miRNAs, described to exert positive effects on beta-cell proliferation, is miR-455, whose expression is induced in obese and diabetic models and mediated by the activation of *Erg2*. miR-455 inhibits the expression of *Cpeb1* by directly targeting its 3'UTR. The decreased *Cpeb1* suppresses the elongation of the poly(A) tail and the subsequent *Xdkn1b* translation, removing the inhibition of G1-S transition and promoting beta-cell proliferation (94). Another homeostatic miRNA upregulated by a high concentration of glucose is miR-17. Here, beta-cells overexpressing miR-17 proliferate driven by the inhibitory effect of miR-17 on *Menin* (a tumour suppressor) expression and the concomitant reduction of the downstream factors p21 and p27 (37). Following a similar regulatory pattern, miR-19a-3p is upregulated in the plasma of T2D patients, inducing the downregulation of *Socs3*—a negative regulator of cytokine signalling—via binding its 3'UTR enhancing beta-cell proliferation and insulin secretion (45). Other examples of miRNAs induced in T2D to promote beta-cell proliferation are miR-199b-5p and miR-223. miR-199b-5p directly interacts with *Mlk3* and downregulates its expression (48). On the other hand, the knockout mouse of miR-223 shows impaired beta-cell proliferation and insulin secretion *in vitro* and glucose intolerance, but interestingly also, insulin resistance *in vivo*. The ablation of miR-223 triggers the activation of *Foxo1* and *Sox6* signalling cascades, which regulate the expression of beta-cell markers (*Pdx1*, *Nkx6.1*, *Ucn3*), and cell cycle-related genes (cyclin D1, cyclin E1, and P27), suggesting that miR-223 is a critical factor for maintaining functional beta-cell mass and adaptation during metabolic stress (61).

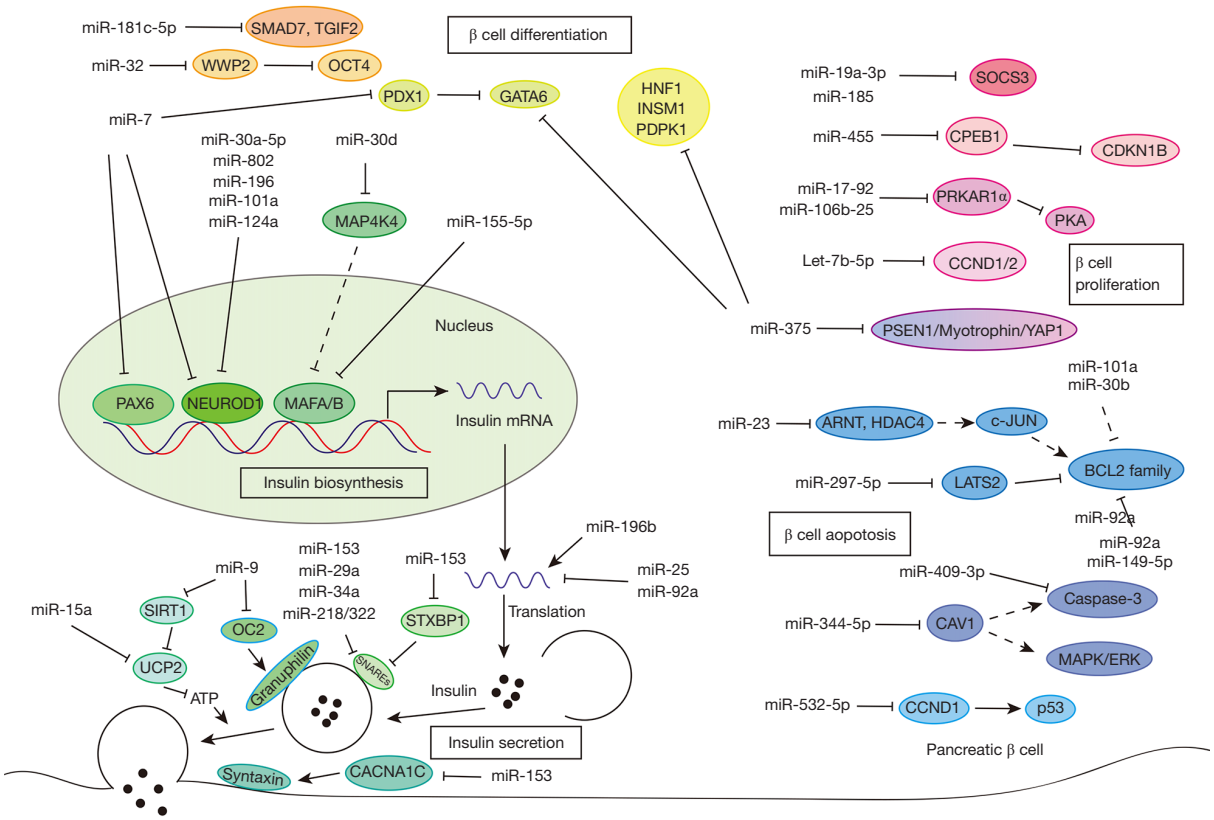

Figure 1 Diagram representing described mechanisms by which miRNAs lead to altered beta-cell function, including pathways associated to beta-cell proliferation, apoptosis, differentiation, insulin biosynthesis and secretion. miRNA, microRNA.

Interestingly, some examples of miRNA are also upregulated in hyperglycemic/T2D conditions that conversely impair beta-cell proliferation and contribute negatively to the pathogenesis of T2D. This is the case for miR-126, whose expression is upregulated in response to high glucose and insulin and suppresses beta-cell proliferation by directly targeting insulin receptor substrate 2 (*Irs-2*) (17). It is also worth mentioning the miR-190b, which impairs beta-cell proliferation and insulin secretion by targeting *Nkx6.1*, a mechanism that could mediate gestational diabetes mellitus (46). Similar outcomes have been described for miR-141. miR-141 is upregulated in T2D patients' serum and mice islets. *In vitro* overexpression of miR-141 in rat insulinoma cells (INS-1) beta-cells leads to impaired cell proliferation and reduced glucose-stimulated insulin secretion (GSIS) by targeting the 3'UTR of *Foxa2* transcript (25).

Other examples of how inappropriate levels of miRNA cause harmful effects on beta-cell proliferation come from models such as transgenic mice. This is the case of Let7b-5p, which is upregulated in the serum of T2D patients (111). At the cellular level, Let7b-5p-TG mice present a decreased expression of the proliferation marker Ki67, with smaller beta-cells and beta-cell mass, by regulating *Ccnd1* and *Ccnd2* mRNA (112).

Similarly, miR-17-92 is highly expressed in pancreatic islets and beta-cell lines, and its expression is upregulated *in vivo* in response to high-fat diet (HFD) and *in vitro* in response to high glucose. The beta-cell-specific knockout (KO) mice for miR-17-92 show a decreased beta-cell number and increased beta-cell size compared to the wildtype (WT) mice. In line with these data, the KO mice exhibit impaired glucose tolerance with a reduced insulin level. At the gene expression level, the KO mice present an upregulation of cell proliferation (*Pten*), cell cycle (*Cdk1a*, *Rbl2*) and transforming growth factor (TGF)-beta signalling (*Tgfbr2*, *Smad2*, *Smad4*) related genes, as well as the expression of several inhibitors of insulin production such as *Sox6* and *Crem* likely as an attempt to compensate for the primary dysfunction caused by the genetic ablation of miR-17-92 (38).

On another note, several miRNAs exert beneficial effects

whose expression is compromised in T2D, potentially contributing to its pathogenesis. For instance, miR-185 is downregulated in the islets of T2D patients and mice. Overexpression of miR-185 in beta-cells enhances cell proliferation and insulin secretion and protects beta-cells from apoptosis by directly targeting 3'UTR of *Socs3* mRNA and positively regulates the STAT-3 signalling pathway (43). Another miRNA physiologically promoting beta-cell proliferation is miR-152, whose expression is negatively correlated with blood glucose levels in T2D patients. Its overexpression promotes beta-cell proliferation and insulin secretion by directly targeting 3'UTR of the PI3K catalytic subunit α (PI3Kα) and inhibiting its expression (33).

These results contrast with the adverse effects exerted by other miRNAs that contribute negatively to the pathogenesis of T2D and whose expression is downregulated in diabetes, such as miR-127. miR-127 is highly expressed in mouse beta-cells and downregulated in islets of mice fed with HFD and in beta-cell lines treated with high glucose concentrations. Interestingly, its overexpression attenuates beta-cell proliferation and inhibits insulin secretion by directly targeting and downregulating the expression of *Kif3b* (a kinesin family member) while having no impact on beta-cell apoptosis (18). miR-184, whose expression is also downregulated in islets of obese mice and T2D patients, directly targets *Ago2*, inhibiting the compensation of beta-cell proliferation and insulin secretion during insulin resistance (42). miR-7a is enriched in mouse beta-cells and directly targets some components of mTOR signalling pathway. Thus, inhibition of miR-7a activates mTOR signalling, including TORC1 and its downstream effectors p70S6 and *eIF4E*, and two MAPK-interacting kinases *Mknk1* and *Mknk2*, but also *Pax6*, promoting beta-cell replication in mouse islets, which the treatment with rapamycin can reverse. These data evidence that miR-7a acts as a brake on adult beta-cell proliferation (103).

Another exciting example is miR-338-3p, whose expression is decreased in islets of obese and insulin-resistant mice. Interestingly, the use of miRNA sponges to inhibit the activity of this miRNA results in increased beta-cell proliferation without any significant change in beta-cell mass and GSIS. Curiously, its hosting gene, apoptosis-associated tyrosine kinase (AATK) has a similar impact as miR-338-3p on beta-cells (80).

miRNAs as gatekeepers for beta-cell apoptosis

An alternative strategy to maintain beta-cell mass is to prevent beta-cell apoptotic death. In the context of obesity, diabetes and a high-fat diet, we find associated changes in miRNAs in blood and islets. Their functional interpretation is complex since they might represent allostatic responses trying to maintain metabolic homeostasis or disease effectors. Moreover, these functions might be accomplished through increased levels and/or repression, and the analysis of the targets of these miRNAs also reveals heterogeneous mechanisms leading to similar pro/anti-apoptotic effects (*Figure 1*).

Several miRNAs protect against beta-cell apoptosis by directly or indirectly regulating *Bcl2* family members and/or other independent targets. For instance, the miR-23 family, miR-23a-3p or miR-23b-3p are downregulated in beta-cells in response to pro-inflammatory cytokines. Their physiological role is to protect human beta-cells from inflammatory cytokine-induced cell death by downregulating the expression of pro-apoptotic *Bcl2* family members, including *Dp5*, *Puma*, *Bax* and *Bim*, through a mechanism dependent on the activation of c-JUN pathway (62). Also, miR-92a and miR-149-5p inhibit cell apoptosis and reactive oxygen species (ROS) release and increase insulin secretion when beta-cell cultured with high glucose via directly targeting *Klf2* and BCL2 like 11 (*Bim*), a BCL-2 protein family member, respectively. Both, miR-92a and miR-149-5p decrease their levels in beta-cells treated with high glucose (31,109). Another apoptosis protector is miR-297b-5p, which targets *Lats2*, a novel tumour suppressor reported to promote Bcl2 degradation (70), which is recently described as reducing the expression of the serum amyloid A3 (*Saa3*) (116). Also what relevant is that miR-297b-5p expression is downregulated in both beta-cell lines and islets of mice when treated with high levels of stearic fatty acid (70,116).

Anti-apoptotic miRNAs fail in their homeostatic role when their expression is downregulated in glucolipotoxic environments. This is the case for miR-299-5p, whose expression is downregulated *in vivo* and *in vitro* in glucolipotoxicity environments. However, its overexpression is sufficient to protect beta-cells from high glucose/palmitate-induced cell death by downregulating the expression of its target genes, including some apoptosis-related genes *Perp*, *Siah1*, *Rassf6*, and *Sgk1*. Conversely, the selective inhibition of miR-299-5p results in a dramatic beta-cell dysfunction with impaired GSIS and significantly increased expression of apoptosis markers (71). miR-344-5p is another protective miRNA whose levels is downregulated in hypercholesterolaemia, and palmitate-induced lipotoxic diabetic beta-cells. Overexpression of

miR-344-5p in beta-cells attenuates the lipotoxicity-induced beta-cell dysfunction and lipid accumulation and decreases cell apoptosis. Its inhibition aggravates the beta-cell dysfunction. miR-344-5p directly targets *Cav1*, initiating lipotoxicity-induced beta-cell death through caspase-3/Bax, MAPK/ERK and AKT signalling pathways (82).

Other interesting examples of anti-apoptotic miRNAs include miR-296-3p-whose expression is reduced in the serum of T2D, which protects against uric acid-induced apoptosis and beta-cell dysfunction by targeting *Pten* (69). miR-433, downregulated in the beta-cells treated with high glucose, also exerts a protective effect. miR-433 overexpression protects beta-cell viability from high glucose levels by inhibiting cell apoptosis and promoting cell proliferation. Mechanistically, miR-433 directly targets the 3'UTR of *Cox2*, suppressing its expression (93). miR-552-3p is also downregulated in the serum of T2D patients, exerting a homeostatic role by targeting and suppressing the expression of *Jak1*, and subsequently inhibiting the phosphorylation of STAT3, restraining the inflammation and apoptosis of beta-cells. Curiously, miR-552-3p is sponged by CircPIP5K1A. Thus, low levels of CircPIP5K1A decrease ROS, inflammation and apoptosis in cells exposed to glucolipotoxic stimuli, and the effect is reversed by the silencing of miR-552-3p (99).

Other miRNAs downregulated by hyperglycemia contributing to beta-cell failure include miR-532-5p, miR-383 and miR-409-3p. Specifically, miR-532-5p alleviates oxidative stress and inhibits cell apoptosis when cultured with high glucose, improving GSIS. These effects are mediated by directly targeting *Ccnd1* and subsequent downregulation of p53 (98). miR-383 protects beta-cells from glucose-induced apoptosis and oxidative stress, and its overexpression in diabetic mice reverses HFD-induced hyperglycemia and pancreatic apoptosis. At the molecular level, miR-383 targets *Tlr4*, an nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway upstream activator, and *ApoC3*, a regulator of lipid metabolism (91). Another miRNA, miR-409-3p inhibits pancreatic beta-cell apoptosis by directly targeting the pro-apoptotic gene caspase-8. Interestingly, the Hsa_circ_0054633, whose expression is upregulated by high glucose, has been identified as a sponge for miR-409-3p (92).

Other miRNAs are upregulated in obesity and diabetes, but this does not imply their pathogenic contribution. For instance, miR-96 is a miRNA whose expression is upregulated in the islets of obese and diabetic patients or obese mice. However, upregulation seems to contribute to maintaining the system's homeostasis since its overexpression in beta-cells promotes cell proliferation and inhibits apoptosis due to the negative direct regulation of beta-cell homeostasis regulators *Foxo1* and *Sox6* expression. In line with these findings, miR-96 KO mice show impaired beta-cell function in response to HFD (110).

There are also other miRNAs whose expressions are pathogenically relevant, causing a harmful phenotype promoting cell death, mediated or not by the regulation of BCL2 family members. This is the case for miR-101a, and miR-30b. Both are upregulated in beta-cells in response to interleukin (IL)-1b, promoting IL-1b-induced beta-cell dysfunction and apoptosis. These effects are mediated by downregulating the expression of the anti-apoptotic protein BCL2 by two different mechanisms: (I) miR-30b directly targets the 3'UTR in *Bcl2* mRNA, and (II) miR-101a downregulates the expression of *Bcl2* through the suppression of STAT3 (13).

miRNAs can promote beta-cell apoptosis through a pleiotropic repertoire of mechanisms. For instance, miR-375 is selectively expressed in human and mouse pancreatic islet cells and is upregulated in the pancreas and serum of T2D patients (117). Its direct targets are *Psen1*, myotrophin (V1) and *Yap1* (45,84,86,87,89). Also, recent studies have shown that beta-cells export miR-375-3p into high-density lipoprotein (HDL) (88). Overexpression studies demonstrate that miR-375 induces apoptosis in beta-cells and inhibits cell proliferation. Conversely, loss of function protects beta-cells from glucolipotoxicity-induced cell death. The mechanism of miR-375 is diverse as it is positively correlated with islet amyloid and negatively correlated with islet mitochondria density (90). Moreover, the overexpression of miR-375 also reduces glucose-induced insulin gene expression and secretion by directly targeting *Pdk1*, decreasing the phosphorylation of PKB and GSK3α/β, downstream of PDK1 in the beta-cell insulin signalling pathway (83,85). miR-375 overexpression *in vitro* promotes beta-cell differentiation by targeting genes in several pathways, including some transcription factors such as *Hnf1βb*, *Pax6*, *Insm1*, *Gata6*, *Pdpk1* and *Insr* (85). These are examples of miRNAs that exert control over the expression of genes responsible for different aspects of beta-cell function, synergising in their detrimental/beneficial effects on global beta-cell homeostasis.

miR-200 family miRNA coordinates the expression of multiple genes—this family consists of five members miR-141, miR-200c, miR-200a, miR-200b and miR-429. Curiously, the expression of miR-200 family members

in mouse islets is not altered at prediabetic stages but significantly upregulated late in the natural history of the disease, when mice become severely diabetic. Interestingly, in human islets from T2D, only miR-200c is upregulated. The beta-cell-specific overexpression of miR-141/200c mice exhibits a diabetic phenotype with beta-cell dysfunction and apoptosis. Conversely, beta-cell-specific ablation of miR-141/200c protects from streptozotocin (STZ)-induced beta-cell death ameliorating T2D. At the molecular level, miR-200c directly binds and downregulates *multiple genes* such as the chaperone *Dnajc3*, the caspase inhibitor *Xiap*, *Jazf1* (has a locus related to T2D), *Rps6kb1*(a downstream effector of mTOR and Bax inhibitor) and *Ypel2*, also positively controls tumour suppressor *Trp53* activation, inducing the transcription of genes involved in pro-apoptosis pathways (49). Of note, inhibiting miR-200c biogenesis by the small molecule TGP-200c reverses its pro-apoptosis effect in beta-cells (118). Curiously, miR-200c has also been reported to regulate GSIS (see the section below). Another example of miRNA upregulated by diabetes is miR-335-5p, which inhibits pancreas beta-cell proliferation and promotes beta-cell apoptosis. miR-335-5p directly targets *Slc2a4* (*Glut-4*) (77). Other researchers have also found that miR-335-5p suppresses pancreatic islet beta-cell secretion by directly inhibiting *Vash1*, and subsequently activating TGF-β signalling pathway in an *in vivo* model of gestational diabetes (119).

miR-30d is another miRNA that promotes beta-cell apoptosis while inhibiting proliferation and is downregulated in diabetic individuals and mice models. Its overexpression in beta-cells leads to hyperglycemia, reduced insulin level and glucose intolerance in mice fed HFD. Interestingly, miR-30d negatively affects beta-cells identity by downregulating beta-cell markers and inducing the expression of alpha-cell markers (73).

All in all, there is growing evidence of the promiscuity exerted by single miRNAs regulating the expression of multiple genes that control specific but complementary regulatory nodes or end effectors related to beta-cell physiology.

Another example of miRNA promoting beta-cell apoptosis is miR-146, which is upregulated in beta-cell lines treated with palmitate and the islet of db/db mice (30) and in T2D patients with poor blood glucose control (29). miR-146 overexpression promotes beta-cell apoptosis (30). miR-770-5p targets *Triap1*, a Tp53-regulated inhibitor of apoptosis, although this latter has only been found in association with gestational diabetes for the moment (120). miR-217 is upregulated in the serum of T2D patients and mouse islet beta-cells treated with high glucose. Overexpression of miR-217 in beta-cells inhibits cell proliferation and promotes high glucose-induced cell apoptosis, while depletion of miR-217 protects beta-cell from glucotoxicity and represses NF-κB signalling pathway. miR-217 directly targets *Mafb* (57). miR-708, whose expression is upregulated by endoplasmic reticulum (ER) stress and obesity, impairs beta-cell function and induces cell death in an effect mediated by the direct dysregulation of *Nnat*, an intracellular Ca^{2+} regulator on ER membrane (105).

Other interesting examples of detrimental miRNA are miR-338-3p and miR-27a, causing apoptosis, whose expression seems to be regulated at the molecular level by glucagon-like peptide 1 (GLP-1). The inhibition of miR-338-3p (whose expression is downregulated in genetically and dietary-induced obese mice) promotes beta-cell proliferation and protects beta-cell from apoptosis, while its overexpression has opposite effects, mimicking the effect of diabetes. Mechanistically, GLP-1 negatively controls the expression of miR-338-3p (79). Similar is the case for miR-27a, whose overexpression reverses the beneficial effects of GLP-1 on protecting beta-cells from cholesterol-induced cell apoptosis and lipid accumulation (67).

Lastly, some examples of miRNAs acting as CirRNA or lncRNAs' intermediates promoting beta-cell apoptosis. Hence, miR-145-whose expression is decreased in the serum of T2D rodents-mediates the effect of CircANKRD36 inducing apoptosis. The downstream target of miR-145 is *Xbp1*, and silencing CircANKRD36 in diabetic mice results in the upregulation of the serum levels of miR-145 (27). miR-181a-5p also mediates the effects of the lncRNA PVT1 in INS-1 cells damaged by STZ (40).

miRNAs regulate beta-cell differentiation

The optimal differentiation from stem cells to beta-cells is critical for their mature functionality in maintaining glucose homeostasis. There is growing interest in cell therapy approaches transplanting stem cell differentiated beta-cells to restore pancreatic endocrine function in diabetes (121,122). Thus, understanding the early and late processes controlling beta-cell differentiation is an attractive research topic, including miRNAs' contribution to homeostatic and pathological processes.

Specific miRNAs contribute to the early and late stages of differentiation (*Figure 1*). For instance, miR-7 is involved

in the early stages of beta-like cell differentiation from human induced pluripotent stem cell (hiPSC) by targeting *Gata6*, *Irs-2*, *Irs-1*, *Pax6*, *Pax4*, *NeuroD1*, and *Nkx2.2*. The overexpression of miR-7 rapidly induces the expression of pancreatic transcription factors (insulin, *Ngn3*, *Glut2*, *Pax4*, *Pax6*, *Kir6.2*, *Nkx6.1*, *Pdx1*, glucagon, and *Oct4*) (101). Conversely, miR-181c-5p is more relevant at late hiPSC-derived beta-cell differentiation stages. The overexpression of miR-181c-5p increases PDX1 and NKX6.1 expression in pancreatic progenitors and increases the number of differentiated insulin-positive beta-like cells. miR-181c-5p directly binds to the 3'UTR of *Smad*7 and *Tgif2* mRNA, repressing their expression and subsequently increasing the phosphorylation of SMAD2/3 and activating the TGF-β-SMAD2/3 signalling pathway. In line with these positive effects on beta-cell differentiation, mice transplanted with miR-181c-5p overexpressed hiPSC presents increased C-peptide secretion and improved glucose tolerance (41).

Other miRNAs reported to exert beneficial effects on beta-cell differentiation are miR-32 and miR-26. Overexpression of miR-32 promotes the expression of islet beta-liked cell markers and embryonic stem cell markers by directly downregulating the 3'UTR of *Wwp2*—an E3 ubiquitin ligase family member and subsequently inhibits ubiquitination and degradation of the embryonic stem cell transcription factor OCT4 (76). Concerning miR-26, it also promotes pancreatic endocrine cells differentiation, by targeting *Tet1/2/3* and *Tdg*-and its overexpression *in vivo* results in increased postnatal islet numbers with higher expression of differentiation (*Ngn3*, *Nkx6.1* and *Pdx1*) and endocrine markers (*Ins1*, *Ins2*, *Gcg*, *Ppy*, and *Sst*) (66).

miRNAs can also inhibit beta-cell differentiation. For instance, miR-21—whose expression is downregulated in insulin-producing cells (IPC) compared to pancreatic progenitor cells (PPC)—inhibits the differentiation from PPC into IPC and reduces insulin secretion by targeting *Sox6*—a negative IPC differentiation and function regulator, and *Rbpj*—a NOTCH signalling pathway downstream effector, and subsequently downregulating *Rbpj*'s target *Hes1*—a repressor of beta endocrine cell development (54). Another negative regulator is miR-145 which binds and silences the expression of lncRNA-ROR and *Sox2*. IncRNA-ROR competitively binds to miR-145, therefore maintaining the expression of *Sox2*. Interestingly, the reduction of IncRNA-ROR suppresses the pluripotency of stem cells, caused by the decreased expression of *Sox2*, *Oct4*, and *Nanog* and also impaired the differentiation and function of HuAEC-derived β islet-like cells, leading to beta-cell impaired functionality and lower glucose-induced C-peptide secretion (28).

miRNAs control insulin biosynthesis

miRNAs can also regulate the expression of the insulin gene. Specific miRNAs can alter (I) the transcription of the insulin gene to mRNA and/or (II) affect the transcription of genes relevant for the transcriptional regulation of the insulin mRNA or (III) the stabilisation of the mRNA transcript levels contributing to the fine-tuning of the insulin biosynthesis in healthy stages and also to the pathophysiological adaptations to disease.

One example is miR-30a-5p, whose expression is induced in the islets of db/db mice and beta-cells exposed to glucotoxicity conditions. *In vitro* overexpression of miR-30a-5p decreases the expression of the insulin gene, while its inhibition reverses the negative effect of glucotoxicity on insulin levels. Inhibiting miR-30a-5p in the pancreas of db/db mice increases insulin gene expression and insulin content, improving glucose tolerance. Mechanistically, miR-30a-5p directly targets the 3'UTR of the transcription factor *NeuroD1* (72). Interestingly, another miR-30 family member, miR-30d, has the opposite effect of increasing glucose-induced insulin-gene transcription when overexpressed *in vitro*. The molecular mechanism for this opposite effect to miR-30a-5p is unknown, but *NeuroD1* and *Pdx1* seem to be discarded (74).

Another miRNA with a deleterious effect on beta-cell function is miR-802. This miRNA increases its expression in the islets of obese mouse models and impairs insulin transcription by targeting *NeuroD1* and insulin secretion by targeting *Fzd5*, which is involved in calcium signalling (106). miR-19b, miR-101a, miR-30b and miR-124a are other miRNA known to negatively regulate the insulin gene transcription by directly interacting with the transcription factor *NeuroD1* (13,14,39). Interestingly for miR-124, the transcription factor *Ets2* has been shown to mediate the effects of epidermal growth factor (EGF) inhibiting miR-124a expression (15).

The cluster of miR-221/222 also exerts a negative effect on insulin biosynthesis. Their overexpression targets the 3'UTR of *Nfatc3*, causing impaired insulin production due to reduced insulin mRNA, protein content, and insulin vesicles (59). This contradicts other results in INS-1 cells showing that the overexpression of miRNA-221 stimulated insulin secretion and cell proliferation and suppressed apoptosis by directly targeting *Pak1* (60).

Similar discrepancies have been found for miR-204, which has been reported to suppress insulin biosynthesis by directly targeting *Mafa* (52). Nevertheless, Marzinotto *et al.* found no correlation between miR-204, *Mafa* and insulin expression. Moreover, the 3'UTR of *Mafa* is not predicted as a target of miR-204 (51). More research would be needed to clarify these contradictory results.

Other miRNAs directly increase insulin mRNA expression by altering the expression of signalling molecules and transcription factors (*Figure 1*). For instance, miR-483 targets 3'UTR of *Socs3*, repressing its expression and provoking an increase in insulin mRNA levels in beta-cells (96). In addition, miR-483 targets *Aldh1a3*, a marker of beta-cell differentiation protecting beta-cell function (97). Similarly, miR-30d increases the expression of the insulin transcription factor *Mafa* by interacting with *Map4k4* 3'UTR and inhibiting its expression, therefore inducing insulin expression and protecting beta-cells from inflammatory cytokine-induced dysfunction (75). The overexpression of miR-155-5p also increases insulin mRNA expression and improves glucose and insulin sensitivity. The mechanism of miR-155-5p involves in is binding the 3'UTR and inhibiting *Mafb* expression, which (I) promotes β-cell function; (II) induces the transcription of IL-6 in beta-cells; and (III) increases GLP-1 production in α-cells. Interestingly, miR-155-5p is upregulated in the islets of mice by hyperlipidemia-associated endotoxemia. The KO of miR-155-5p in hyperlipidemic mice causes beta-cell dysfunction (e.g., decrease in fasting insulin levels, decreased insulin content and decreased GLP-1 level) (36). Another exciting example is miR-205-5p, a miRNA whose expression is upregulated in the islets of the obese and diabetes-susceptible NZO mice (a polygenic model of obesity and diabetes). The overexpression of miR-205-5p increases insulin 1 mRNA expression and intracellular insulin content. Mechanistically, miR-205-5p directly interacts with the *Tcf7l2* gene, a transcription factor that regulates genes involved in Wnt signalling and beta-cell function. Other predicted targets for miR-205-5p include *Plcb1*, *Nphp1* and *Cxxc4*, and *Plcb1*, whose expression is significantly downregulated in beta-cells when miR-205-5p is overexpressed (53).

miRNAs directly binding to the insulin gene have also been described. One is miR-196b, which positively regulates the biosynthesis of insulin 2 by directly targeting the 5'UTR of insulin 2 mRNA and activating the translation of insulin 2 in the presence of *Ago2*. It is worth mentioning that miR-196b can displace the RNA binding protein HuD by competing for the same binding site, thus abolishing the inhibitory impact of HuD on insulin 2 translation (47). This reinforces previous evidence that miRNAs can compete or synergise with other RNA regulators and miRNA over the same targets.

The opposite effect has been described for miR-25 and miR-92a. The overexpression of these two miRNAs decreases the expression of proinsulin, insulin content and secreted insulin, superseding the inhibitory effect of miR-9 in insulin secretion. Both bind directly to 3'UTR of *Ins1* mRNA, overlapping with the one for *Ptbp1*, a protein that stabilises insulin mRNA (65). Another interesting example is the miR-133a, whose expression is upregulated in the blood of prediabetic and T2D patients (22). miR-133a also directly targets *Ptbp*. Remarkably, human islet cells treated with the miR-133a precursor presents reduced insulin levels (23).

miRNAs control insulin secretion

The last process involving insulin production is insulin protein being transported in vesicles to the plasma membrane and released. A significant number of miRNAs (*Figure 1*) regulate insulin exocytosis by modulating the expression of genes responsible for the transport, the process of docking and the fusion of vesicles to the plasma membrane, or intermediate hubs that control the expression of these genes (123).

miR-212 and miR-132 positively regulate GSIS under the regulation of GLP1 (20). Increased intracellular cAMP elevates the expression of miR-212 and miR-132 in a cAMP-SIKs-CRCT1 dependent manner. *Crct1* is predicted to be the direct target of these two miRNAs, as part of negative feedback in beta-cells to maintain intracellular homeostasis. *In vivo* beta-cell-specific overexpression of miR-212 or miR-132 improves insulin secretion and glucose homeostasis and enhances the proliferation of beta-cells in the mice when fed HFD (miR-312 only) (21). Of relevance, their expression is upregulated in the islets of obese, prediabetic and diabetic mice models and in beta-cells cultured with high glucose and palmitate, which can be interpreted as part of the regulatory system ensuring appropriate levels of insulin to counteract the insulin resistance stage (56,124).

Another miRNA recently reported to stimulate GSIS is miR-21. This miRNA is upregulated in islets of diabetic db/db mice and mice fed with high fat and high glucose diets. Notably, it promotes GSIS by upregulating the expression of *Glut2* via a miR-21-Pdcd4-AP-1 axis. Thus, miR-21 specifically delivered into the pancreas of diabetic db/db

mice seems to improve blood glucose and insulin secretion, and conversely, the beta-cell-specific KO mice for miR-21 shows glucose intolerance and decreases GSIS (55).

Overexpression of miR-139-5p in beta-cells decreases beta-cell function. miR-139-5p acts as an upstream negative regulator of PICK1, a membrane protein involved in insulin granules formation and maturation (125), interacting with its 3'UTR. Overexpression of *Pick1* could reverse the adverse effect of miR-139-5p on beta-cell, as *Pick1* contributes to the activation of the PI3K/Akt pathway and increases the expression of *Glut2* and also promotes insulin secretion (24).

Opposite to the previous miRNAs, miR-124a expression is elevated in T2DM patients' islets, and its overexpression impairs GSIS. Confirmed targets for miR-124a are *Mtpn* and *Foxa2*, two insulin secretion regulators (14). Similarly, miR-187 is upregulated in islets from T2D patients, and its expression negatively correlates with GSIS in non-diabetic human islets. *Hipk3*, an insulin secretion regulator, is identified as its direct target, and the overexpression of miR-187 has been shown to impair GSIS in rat primary islets and beta-cell lines (44).

miR-153 expression is also increased in islets of obese and diabetic mice, and its overexpression inhibits both basal and GSIS as a result of a significant decrease of docked insulin granules *in vitro*, resulting in impaired glucose tolerance *in vivo*. miR-153 directly targets the mRNAs of some SNARE proteins (including *Vamp2*, *Snap25* and *Stx1a*). Thus, the inhibition miR-153 or the overexpression of SNAREs family members could recover the insulin secretion in a diabetic setting (34). Similarly, miR-29a, whose expression is upregulated in beta-cells in response to high glucose concentrations, inhibits insulin exocytosis by decreasing *Stx1a* (a two-SNEARs protein) mRNA by directly targeting its 3'-UTR (68). Also, miR-34a expression is upregulated in beta-cell lines treated with palmitate, in the islet of *db/db* mice (30) and overweight/*obese* T2D patients (29). miR-34a overexpression impairs GSIS and induces beta-cell apoptosis by targeting the SNARE family member *Vamp2* and the anti-apoptotic factor *Bcl2*. Increased miR-34a is also linked to the activation of p53, which could contribute to apoptosis. miR-34a also targets *Sirt1* and exacerbates ROS accumulation and apoptosis. Conversely, the inhibition of miR-34a reduces apoptosis induced by high glucose and palmitate (81).

Another inhibitor of insulin secretion is miR-9, which is selectively expressed in islets and the brain. The overexpression of miR-9 in beta-cells decreases insulin exocytosis. The direct targets of miR-9 include three genes that span different roles related to insulin secretion *Sirt1*, *Oc2* and *Stxbp1*. Thus, *Sirt1* promotes insulin secretion by inhibiting UCP2 expression and *Oc2* that directly binds to the promoter of granuphilin, a Rab3/Rab27 effector that inhibits insulin secretion. Finally, *Stxbp1* plays a fundamental role in the fusion of the secretory granules containing insulin with the plasma membrane (107,108).

Interestingly, miR-335 is another miRNA negatively associated with insulin secretion in human islets from prediabetic individuals, and its expression is upregulated in the GK rat, a non-obese T2D model rodent model (126). The overexpression of miR-335 results in decreased GSIS due to decreased rapid exocytosis, despite having no effects on the docking or altering Ca^{2+} current. The molecular targets of miR-335 are three exocytotic proteins: SNAP25, STXBP1 and SYT11, whose expressions are downregulated by miR-335 (78).

miR-218 and miR-322 also target *Stxbp1* (as for miR-9 and miR-335). Their expression is downregulated after a prolonged glucose treatment, inhibiting insulin release (58). Another exciting example is miR-200c, previously discussed to regulate apoptosis. miR-200c targets *Etv5*, a transcription factor that regulates the expression of insulin exocytosis genes, including *Syt11*, *Aqp3* and *Cbfb*. The knockout of miR-200c in islets from T2D patients significantly improves GSIS (50).

miR-7a is another miRNA highly expressed in human and mouse islet cells whose expression is initially downregulated in the islets of genetic and diet-induced obese mice at early stages, although its expression seems to increase in advanced stages (102). Overexpression of miR-7 in islets beta-cells of mice leads to a diabetic phenotype by directly targeting the 3'UTR of *Myrip* mRNA and subsequently inhibiting insulin granule transportation and release (104) and by targeting *Reg1*, a gene associated with the prevention of apoptosis (127). miR-7a2, a dominant form of miR-7 in the pancreas, controls the late stages of insulin granule fusion with the plasma membrane and ternary SNARE complex activity. At the molecular level, the direct targets of miR-7a2 include vesicle fusion and SNARE activity (*Snca*, *Cspa*, *Cplx1*), calcium-regulated vesicular trafficking (*Pkcb*), cytoskeleton rearrangement (*Pfn2*, *Wipf2*, *Basp1*, *Phactr1*), and membrane targeting (*Zdhhc9*). Briefly, miR-7a2 binds 3'UTR of *Snca*, reducing its expression, disrupting the interaction between SNCA and VAMP complex, and decreasing SNARE activity (102).

miR-153, a miRNA located in the gene *Ia-2*β,

suppresses glucose-/potassium-induced insulin secretion in beta-cell line and primary mice islet cells by directly targeting the 3'UTR of the RNA that codes for the calcium channel gene *Cacna1c*, which is physically coupled to the genes related to vesicle release including RIMs, Snap-25 and Syntaxin-1. Interrupting the interaction between miR-153 and *Cacna1c* abolishes the effect of miR-153 in GSIS. Knockdown of the hosting gene *Ia-2* or/and *Ia-2*β mice beta-cells shows fewer dense-core vesicles (DCV) by decreasing their half-life and reducing insulin secretion (35).

miR-145 overexpression decreases GSIS and cholesterol efflux in beta-cells. miR-145 directly binds the 3'UTR of the cholesterol transporter *Abca1* and suppresses its expression. Other miRNAs such as miR-148, miR-27, miR-144, and miR-33a/33b also target and suppress the 3'UTR of *Abca1* mRNA. Interestingly, the specific Inhibition of *Abca1* in the pancreas causes impaired insulin secretion and higher insulin content in beta-cells, suggesting that the disturbances in cholesterol are the main effector of such disfunction (26,128). Interestingly the non-coding RNA lnc-DANCR has been shown to act as a sponge for miR-33a, a miRNA involved in gestational diabetes mellitus by inhibiting insulin production (26). miR-463-3p is upregulated in the islet of T2D patients and negatively correlates with GSIS. The direct target of miR-463-3p is *Abcg4* (95). miR-463-3p overexpression in beta-cell line and *in vivo* pancreas inhibits GSIS, while its inhibition promotes insulin secretion.

miR-24 expression is upregulated in response to oxidative stress and/or cholesterol accumulation, and it is present in high levels in islets from db/db and HFD-fed mice. Interestingly, when overexpressed in islets, it impairs GSIS. Mechanistically, miR-24 reduces the expression of *Sp1*, causing the inhibition of transcription of Scgn. Reduced levels of Scgn downregulate the phosphorylation of the focal adhesion kinase and paxillin, reducing the exocytosis of insulin granules. Also, miR-24 directly targets transcription factors *Hnf1*α and *Neurod1*, contributing to the impairment of GSIS and defects in beta-cell proliferation (64). Intriguingly, in the presence of high cholesterol, the inhibition of miR-24 rescues the insulin1 miRNA expression, but its mechanism remains unclear (63).

These findings evidence a crosstalk between the levels of cholesterol and miRNAs contributing to the impairment in insulin biosynthesis/secretion, raising the possibility that defective lipid metabolism, lipotoxicity—a hallmark of obesity and associated comorbidities such as diabetes and fatty liver—might do so through triggering the inappropriate expression of miRNAs.

Other miRNAs regulating insulin biosynthesis and secretion include miR-577, whose expression is upregulated in the blood of diabetic children. Interestingly, the overexpression of miR-577 in embryonic beta-cells blunts the effects of *Fgf21* inducing insulin biosynthesis and secretion by directly targeting *Fgf21* and inhibiting *Fgf21* mediated activation of ERK1/2 signal (100). miR-125b is another miRNA upregulated in mouse and human islets in response to high glucose, and its overexpression *in vivo* and *in vitro* has impaired insulin production and secretion from beta-cells. Interestingly, the targets of miR-125b include the genes encoding lysosomal protein M6PR and mitochondria homeostasis regulator MTFP1 (16), evidencing the role of this miRNA regulating organelle dynamics that contribute to beta cell function.

Let7b-5p also exert this dual effect, but in this case, biosynthesis and secretion are regulated in opposite directions. Let7b-5p is highly expressed in the serum of T2D patients, and its overexpression increases insulin biosynthesis but paradoxically inhibits GSIS, while let7b-5p inhibition decreases insulin content and partially restores GSIS. On a molecular level, let7b-5p plays a role in dysregulating the transcriptional level of Insulin, *Pdx1*, *Gck*, *Glut2* and *Insr* (111).

A very intriguing mechanism through which several miRNAs seem to control insulin secretion consists of regulating the intracellular bioenergetics. Specifically, miR-15a and miR-130a/miR-130b/miR-152 target intracellular adenosine triphosphate (ATP) production, causing impairment of ATP-dependent insulin production and secretion. Moreover, miR-15a downregulates *Ucp2* expression by targeting its 3'UTR directly, causing changes in mitochondrial performance, uncoupling ATP production from oxygen consumption in pancreatic beta-cells, and promoting insulin biosynthesis (32). miR-130a/miR-130b/miR-152 act differently, decreasing the ATP production by indirect (miR-130a/miR-130b)/direct (miR-152) interaction with ATP production protein *Pdha1*. These three miRNAs can also reduce *Gck* expression and negatively affect ATP-dependent insulin production and secretion (19).

miRNAs in type 1 diabetes

T1D is a chronic autoimmune disease characterised by infiltrated immune cells, eventually leading to beta-cell death (129). A priori, there are two ways how immune cells

cause adverse effects on beta-cells: (I) the pro-inflammatory mediators such as cytokines released from macrophages and T lymphocytes that induce ER stress and beta-cells apoptosis (130); (II) the release of exosomes produced by immune cells that target beta-cells (131). Recently, a growing body of evidence highlights the critical roles of miRNAs in regulating the autoimmune response in T1D, aiming to provide potential therapeutical targets to protect beta-cells against immune cell attacks.

Several miRNAs regulate immune cell activation in the context of T1D. Thus, for example, the expression of miR-20a and miR-326 are upregulated in peripheral blood mononuclear cells (PBMCs) of T1D patients. Interestingly, the predicted targets of miR-20a and miR-326 are genes classically associated with T1D and other autoimmune diseases (132). For example, miR-326 targets *Ets1* and is predicted to target *Vdr*, both genes involved in modulating the immune response (133).

miR-202-3p is upregulated in pancreas-infiltrating lymphocytes (PILs) compared to other immune cells such as thymocytes and peripheral T $CD3^+$ lymphocytes. Interestingly, miR-202-3p targets *Ccr*7 or *Cd24*7 mRNA in the PILs of non-obese diabetic (NOD)-mice, contributing to the regulation of autoimmune response in T1D (134). Similarly, miR-142-3p is upregulated in peripheral blood T cells from T1D human patients and NOD mice, an animal model for studying autoimmune diabetes. Thus, the miR-142-3p aggravates high glucose-induced inhibition of Treg cells induction, whereas a miR-142-3p inhibitor promotes Treg induction. Thus, the inhibition of miR-142-3p seems to attenuate the islet autoimmunity in NOD mice. The miR142-3p/*Tet2*/*Foxp3* axis is responsible for enhancing Treg induction and stability. miR-142-3p directly targets and negatively regulates *Tet2*, a regulator involved in Treg induction and maintenance, by activating demethylation of the *Foxp3* CNS2 (135). miR-216a is another example of miRNA whose expression is induced in NOD mice. Interestingly, miR-216 promotes pancreatic beta-cell proliferation by directly targeting and suppressing the *Pten* (136). miR-21 is another miRNA upregulated in islets of the NOD mice and inflammatory cytokine-treated beta-cells. miR-21 is transcriptionally activated by NF-κB family members c-Rel and p65 and prevents beta-cell apoptosis in the context of T1D by negatively controlling the expression of *Pdcd4*, an apoptosis inducer via Bax family (137). miR-203a is another example of miRNA upregulated in pancreatic beta-cells of NOD mice. Elevated miR-203a inhibits proliferation and promotes apoptosis in MING6 cells by targeting *Irs-2*. Conversely, a miR-203a inhibitor ameliorates the hyperglycemic phenotype of NOD mice (138).

The miR-17-92 family members promote lymphomagenesis disorders and autoimmunity (139). One of the family members, miR-92a, is highly expressed in $(CXCR5)^+$ $CD4^+$ T follicular helper (TFH) cells at the early onset of islet autoimmunity, and its levels correlate with insulin autoantibody (IAA). *In vitro*, miR-92a induces TFH precursor induction, while inhibition of miR-92a suppresses TFH precursor induction but increases Treg cells induction. Inhibition of miR-92a in the context of NOD mice shows decreased TFH precursors in peripheral blood or islet lymph nodes, limiting the activity of islet autoimmunity. The mechanism of miR-92a includes (I) *Klf2* as a direct target of miR-92a; (II) miR-92a inducing TFH precursor is abolished by PI3K inhibitor but is aggravated by PTEN inhibitor, evidencing the role of PTEN-PI3K signalling pathway in mediating miR-92a effects (140).

Interestingly, many miRNAs have been reported as cargo of exosomes released by immune cells acting on beta-cells in T1D. For instance, in NOD mice, miR-142-3p, miR-142-5p and miR-155 are expressed and released from T lymphocytes and transferred to islet beta-cells via exosomes. Mechanistically, these miRNAs trigger beta-cell apoptosis and increase the expression of genes involved in chemokine signalling, including *Ccl2*, *Ccl*7, and *Cxcl10*. In line with this evidence, exosomes produced by cultured T cells from NOD mice increase the translocation of NF-κB and promote apoptosis in beta-cells (141). Conversely, inhibiting these miRNAs *in vivo* reduces beta-cell dysfunction and inflammation and improves diabetes.

It is worth noting that several miRNAs are downregulated in both T1D patients and preclinical models of T1D. For instance, miR-16-5p expression is downregulated in the plasma of T1D patients. The overexpression of miR-16-5p in beta-cells increases cell proliferation and reduces apoptosis in response to high glucose. Mechanistically, miR-16-5p negatively regulates *Cxcl10*, and conversely, the treatment with CXCL10 reverts the beneficial effects of miR-16-5p overexpression. The overexpression of miR-16-5p also increases the expression of *Bcl2* and decreases *Bax* and cleaved *Caspase-3* levels (142). miR-150 is also downregulated in T1D patients' islet beta-cells. Moreover, NF-κB activates miR-150 via direct interaction between NF-κB and miR-150 promoters. Inhibition of miR-150 could reverse the effects of NF-κB, promoting beta-cell apoptosis and inflammation. miR-150 targets and suppresses *Puma* expression, inhibiting inflammation and

beta-cell apoptosis induced by T1D (143). miR-125b-5p is downregulated in an experimentally induced diabetes model using HFD + STZ. Interestingly, its overexpression promotes beta-cell proliferation and inhibits cell apoptosis. miR-125b-5p acts on *Dact1* and inhibits the JNK signalling pathway (144). Another example is miR-409-3p, a miRNA enriched in $CD8^+$ central memory T cells whose expression gradually declines in the blood and pancreas of T1D patients and T1D mouse models, which positively correlates with the severity of insulitis (145).

Of particular interest are miRNAs reported to play a role in both T1D and T2D pathogenesis, contributing to shared processes at the molecular level. One key example is the miR-29 and miR-26 family members. In T1D, miR-29a/b/c are upregulated in the beta-cells (not in infiltrated immune cells) of the islets of NOD mice and human and mouse islet beta-cells treated with pro-inflammatory cytokines. In T2D, miR-29 family members are upregulated in obese and diabetic mice, and glucose levels induce their expression in humans and rodents. The overexpression of miR-29 in beta-cells induces inflammation-induced apoptosis by directly targeting and reducing the expression of the *Bcl2* family member *Mcl1*. Moreover, *in vitro*, miR-29 impairs GSIS by targeting the transcription factor *Onecut2*, which causes an increase of the insulin exocytosis inhibitor granuphilin (146,147). Paradoxically, the miR-29a KO exhibits a phenotype of T1D during unfolded protein stress and decreased insulin exocytosis (148). This apparent contradiction between *in vivo* and *in vitro* evidence the complexity of investigating the mechanisms associated with altered levels of miRNAs in health and disease. Of note, miR-29 is also enriched in the liver and is upregulated in the livers of ob/ob mice (149). The miR-29 family acts as a negative regulator of hepatic insulin sensitivity, and the global or hepatic miR-29a or miR-29c knockout are protected from diet-induced obesity and insulin resistance (148) by increasing the insulin signalling pathway via directly regulating PI3K expression (149).

Another T1D mouse model with an increased level of miR-26a in islets and T lymphocytes shows a prolonged normoglycemic period before T1D ensues, exhibiting lower grades of insulitis mediated by the inhibition of autoreactive $CD4^+$ and $CD8^+$ T cells and the expansion of Treg (150). Of relevance, miR-26a is downregulated in the islets and serum of obese and T2D diabetic mice, and its overexpression alleviates the phenotype of T2D by improving beta-cell function and peripheral insulin sensitivity. Thus, the overexpression of miR-26a protects mice from hyperinsulinemia induced by HFD, maintaining adequate insulin secretion and signalling. Mechanistically, miR-26a directly targets genes involved in beta-cell proliferation and insulin secretion, such as *Pten*, *Cacna1c*, *Crebrf*, *Ctgf*, *Esr1*, *Ext1*, *Mtpn*, *Onecut2*, *Pfkfb2*, *Pja2*, *Plcb1*, *Rhoq* and *Sox5* (151,152). Moreover, miR-26a also enhances insulin sensitivity in peripheral organs transported in exosomes (see in section "miRNAs mediate cell to cell and organ to organ crosstalk").

miRNAs in diabetes linked to pancreatitis

Post-pancreatitis diabetes mellitus (PPDM) is a frequent complication of pancreatitis, as hyperinsulinemia during pancreatitis might be responsible for the development of insulin resistance (IR) (153). Acute pancreatitis is an acute abdominal inflammatory disease associated with necrosis of the pancreas, systemic inflammation, multiple organ dysfunction, and mechanistically related to a cytosolic calcium overload (154) whereas chronic pancreatitis is a progressive syndrome characterised by pancreatic inflammation, leading to extensive tissue fibrosis and deficiency of pancreatic exocrine and endocrine function (155). Recent investigations have shown that in pancreatic acinar cells, miR-26a targets *Trpc3* and *Trpc6* store-operated Ca^{2+} entry (SOCE) channels and attenuates physiological oscillations and pathological elevations of intracellular calcium alleviating experimental pancreatitis (156). On a different note, miR-153 has been described to aggravate acute pancreatitis in hypertriglyceridemia by targeting *Traf3* and delaying pancreatic repair. Interestingly, SREBP1c transcriptionally suppresses miR-153 and facilitates tissue regeneration *in vivo* (157), which opens a potential therapeutical window for these patients. In a similar line, chronic pancreatitis relates to chronic inflammatory and fibrotic phenotype with reduced beta-cell mass, where pancreatic stellate cells (PSC) are critical in the progression of fibrosis. In this case, several miRNAs mediate TGF-β1 effects in PSC. For instance, miR-34b mediates the induction of extracellular matrix accumulation (158), whereas miR-140-3p and miR-143-3p directly target *Bcl2* to increase beta-cell apoptosis (159).

miRNAs mediate cell to cell and organ to organ crosstalk

Over the last decades, a growing body of evidence shows that extracellular vesicles (EVs)-/exosome-derived

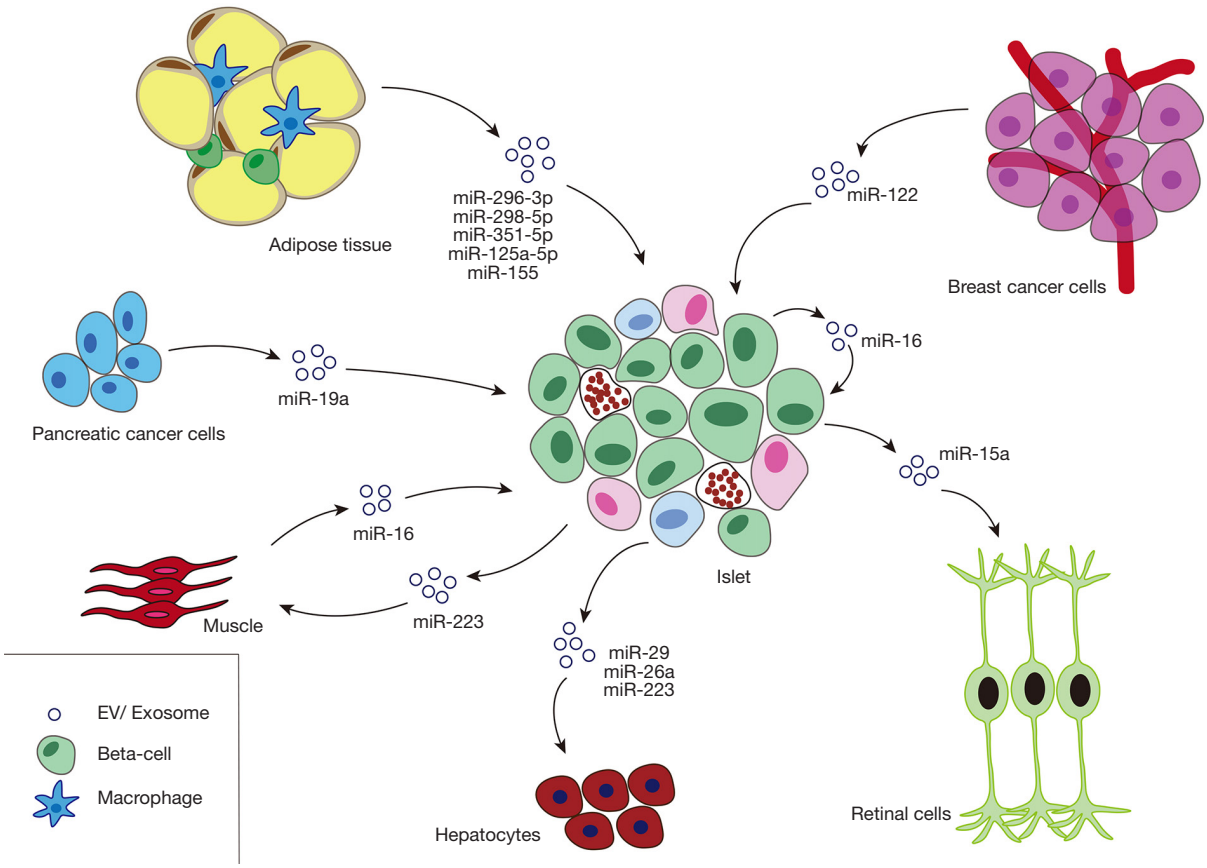

Figure 2 miRNAs contributing to the crosstalk between beta-cells and other peripheral cell types. miRNA, microRNA; EV, extracellular vesicle.

miRNAs mediate cell-to-cell crosstalk and organ-to-organ communication. This is also the case for the pancreas (160,161). However, the number of investigations focused on miRNAs' para/endocrine role is still limited. Also, there is evidence that the endocrine pancreas can release exosomes containing miRNAs into the bloodstream and target specific tissues modifying their metabolic activities and *vice-versa*. Other metabolic tissues and organs also secrete miRNAs that target the endocrine pancreas to regulate its viability and/or functionality (*Figure 2*).

miRNAs in beta-cell to beta-cell crosstalk

Pancreatic beta cell-derived exosomes have been reported to contain +200 miRNAs, among them miR-7, miR-29a, miR-146a, miR-451 and miR-142-3p are known to be secreted from beta-cells in response to pro-inflammatory cytokines and transferred to neighbouring beta-cells affecting basic processes such as apoptosis, proliferation and the activity of recipient beta-cells (162).

miRNAs connecting beta-cells to hepatocytes

miR-29 is one of the first miRNAs described to mediate the crosstalk between beta-cells and macrophages. Briefly, miR-29 released by beta-cells promotes inflammation by recruiting and activating circulating macrophages (163). miR-29 increases in the serum of obese subjects and mice fed HFD under fasting conditions and directly in response to free fatty acid (FFA) treatment *in vitro*. Briefly, exosomes enriched in miR-29 originated in beta-cells impair insulin sensitivity in isolated hepatocytes by downregulating AKT phosphorylation and increasing glucose output (164). Similarly, the overexpression of exosomal miR-29 *in vivo* attenuates insulin sensitivity and increases blood glucose levels. Of relevance, the beta-cell-specific depletion of miR-

29, by using a miRNA-sponge, reverses the HFD-induced insulin resistance phenotype *in vivo*.

Conversely, other miRNAs originating in the pancreas can play a beneficial role in liver metabolism. One of them is miR-26a, whose expression is downregulated in the serum of obese and T2D patients, in the islets of diet-induced or genetically obese mice, and in the liver of overweight humans. Interestingly, beta-cell-specific overexpression of miR-26a improves hepatic insulin sensitivity and glucose tolerance and decreases hepatic glucose production and fatty acid synthesis. Mechanistically, miR-26a targets the 3'UTR of critical regulators involved in liver fatty acid synthesis (*Acsl3*, *Acsl4*), gluconeogenesis (*Pck1*, *Tcf7l2*) and insulin signalling (mediating phosphorylation of IRS proteins *Gsk3b*, *Pkcd*, *Pkcq*) (152,165). Another exciting example is miR-223 which originates in beta-cells and whose expression is upregulated by high glucose. This miRNA has been reported to travel to the liver, and muscle in a mechanism mediated by exosomes and regulate the insulin signalling pathway of targeted organs by inducing the expression of *Glut4* (166).

Globally considered, these findings provide robust evidence of miRNA-mediated crosstalk between the endocrine pancreas and liver and reinforce the notion that failure in the pancreas could exacerbate the phenotype of other organs in the context of metabolic diseases.

miRNAs in muscle and beta-cell crosstalk

EVs secreted by muscles contain numerous miRNAs, including miR-16, whose expression is upregulated in response to high palmitate diet-induced insulin resistance. Interestingly, this miRNA can be taken up by the pancreas, thus promoting beta-cells proliferation. At the mechanistic level, miR-16 targets and inhibits *Ptch1*, an Hh receptor in Hedgehog signalling pathway involved in pancreas development (167,168).

miRNAs in Beta-cells crosstalk to retinal cells

It has been reported that miRNAs secreted from the pancreas can contribute to diabetic retinopathy, a common complication resulting from the late stages of diabetes. This is the case for miR-15a, whose expression is upregulated in diabetic patients and mice plasma. Thus, exosomal miR-15a secreted from beta-cells is increased in response to high glucose stimulation and transported to the circulatory system regulating retinal function. Overexpression of miR-15a in Muller cells either by being transfected with miR-15a precursor or culturing them with the exosomes released by high glucose-treated INS-1 cells results in oxidative stress, mediated by direct interaction between miR-15a and *Akt3*, a downstream factor of PI3K in insulin signalling pathway (169), and ultimately leading to cell apoptosis (170).

miRNAs in Adipose tissue crosstalk to beta-cells

Healthy adipocytes secrete EVs (Ad-EVs) that can be taken up by beta-cells promoting beta-cells survival and repressing cell death. In contrast, EVs produced by adipocytes treated with proinflammatory cytokines (CK-EVs) have opposite effects on recipient beta-cell viability by regulating the critical signalling pathways, including Akt-GSK-3β, ERK-eIF2α, and c-JUN pathways (171), which are involved in cell proliferation, survival and function (172). Interestingly, the miRNA cargos in Ad-EVs and CK-EVs are different and modulate the inflammatory fingerprint in beta-cells (171).

miRNAs in immune cells crosstalk to beta-cells

M1 macrophages that accumulate in the islet of diet-induced obese mice, secrete exosome enriched with miR-212-5p that can be taken up by beta-cells, inhibiting beta-cell GSIS. Interestingly, the transfer of M1 macrophage-derived exosomes (M1-exos) to the pancreas of living mice causes impaired glucose tolerance and insulin secretion. At the molecular level, miR-212-5p targets *Sirt2* 3'UTR, inhibiting its expression and impairing SIRT2-mediated AKT/GSK-3β/β-catenin signalling pathway. Blocking miR-212-5p in M1-exos *in vivo* improves glucose tolerance in HFD-induced obese mice by alleviating the impaired beta-cell GSIS (173). Interestingly, adipose tissue macrophages (ATM) have also been reported to release EVs that regulate pancreatic beta-cell adaptation and dysfunction in the context of obesity. Thus, miR-155, highly enriched in obese ATM EVs, has been shown to act on *Mafb* in beta-cells (36,174).

Another example of how miRNA secreted from immune cells affects beta-cell homeostasis comes from studies conducted by Guay *et al.* where exosomes derived from T lymphocytes containing miR-142-3p, miR-142-5p, and miR-155 can be taken by islet beta-cells, inducing beta-cell apoptosis. Mechanistically, this occurs by the upregulation of genes involved in chemokine signalling (including *Ccl2*, *Ccl7*, and *Cxcl10*). The inactivation of those miRNAs using a "miRNA sponge" prevents beta-cells from exosome-

induced cell death, thus preventing T1D development in pre-diabetic NOD mice (141).

On the other hand, bone marrow transplantation (BMT) promotes beta cell regeneration in STZ-induced diabetic mice in a mechanism mediated by bone marrow (BM) cells derived exosomes. Briefly, miR-106b-5p and miR-222-3p are secreted by BM cells and increased in pancreatic islet cells after transplantation. At the mechanistic level, these miRNAs suppress the expression of Cip/Kip family members p21Cip1 and p27Kip1, promoting post-injury beta-cells regeneration and improving glucose metabolism (175).

miRNAs mediate pancreatic cancer cells and beta-cells crosstalk

There is growing evidence showing how miRNA transported in exosomes derived from pancreatic cancer cells, or pancreatic cell lines can be transported and taken by beta-cells impairing GSIS. A relevant example is miR-19a which is enriched in pancreatic cells-derived exosomes. miR-19a directly targets 3'-UTR of *Adcy1* [a critical enzyme in insulin secretion by producing cAMP (176)] and *Epac2* [also known as cAMP-GEFII, mediates cAMP-dependent insulin secretion (177)] reducing cAMP and Ca^{2+} in recipient beta-cells (178). Of note, miR-19a also impairs beta-cell insulin secretion by directly targeting and inhibiting the expression of insulin gene transcription factor *Neurod1* (179). As a proof of concept, mice transplanted with pancreatic cancer cells where miR-19a has been knocked-down exhibit improved glucose tolerance and insulin sensitivity (178). This evidence is critical for understanding pancreatic cancer-associated diabetes and paving new avenues for the design of therapeutical strategies.

miRNAs in Breast cancer cells crosstalk to islet beta-cells

miR-122 in EVs correlates with high fasting blood glucose and low insulin levels in breast cancer patients. Interestingly, miR-122 is produced by breast cancer cells and taken by pancreatic islet beta-cells, negatively regulating beta-cell ATP-dependent insulin exocytosis by directly targeting pyruvate kinase (*Pkm*) (180).

Conclusions

The development of new and more precise high-throughput analytical tools in the field of bulk and single-cell transcriptomics along with exosome biology and the availability of integrative bioinformatics tools is expanding our understanding of the causative role of miRNAs, providing a more detailed map of the miRNA mediated crosstalk between cells and organs in health and disease.

In this review, we summarised relevant research studies from the last eighteen years that integrate our current knowledge of how miRNAs affect islet function in the context of diabetes. We also show the emerging evidences of the crosstalk mediated by exosomes between pancreas and other peripheral organs and its potential contribution to the complex pathophysiology of diabetes.

We believe that using genetically modified models to selectively increase or decrease pools of miRNAs in a particular time/spatial frame (conditional tools) and a specific cell type will help dissect the relevance of miRNAs on global organismal homeostasis and metabolism. These experimental models, combined with the development of more accurate prediction algorithms and machine learning-based analysis, will assist in understanding the abnormal miRNA profiles observed in multiple metabolic diseases such as obesity and diabetes (181-183). Nevertheless, despite the extreme value of animal models, a cautionary note is needed as there is a growing body of evidence showing significant species-specific differences in the development (184), microarchitecture and transcriptomics of the pancreatic islets (185-188) and functional differences such as susceptibility to injury (189) that could limit the value of animal models on reflecting certain aspects of human islets pathophysiology. Novel examples of some of these interspecies limitations have been recently highlighted by two excellent reviews reporting the species-specific evidence for de-differentiation/altered activity of islet beta cells as mechanisms of failure and recovery during maturation and T2D (190,191) or the work conducted by Keller and Perez, where they identified human *CREM* as a target gene of miR-375, where the predicted binding site was conserved in humans and other primates, but not in species like mice or rats (192).

Another critical area of research will be finding the molecular mechanisms responsible for the transcriptional regulation of miRNA in the context of disease. Understanding how, where, why and when miRNAs act is an unmet need to evaluate the value of miRNA as prognostic or diagnostic tools in clinical practice. Few examples of this are for instance the recent integration of cis-eQTLs and GWAS data as a promising approach to identifying signals associated with T2D; in the latter, five miRNAs, miR-7-5p, miR-126-3p, miR-1236, miR-130b-5p miR-1275 and miR-194-5p have been recently identified as potential signals for T2D and/

or insulin secretion rates (11), the discovery of SNPs in miR-196a and miR-423 linked to increased risk of T2D in Middle East regions (193) or the identification of "unique" signatures in the miRNA profile during the progression of T2D, where for instance, miR-222-3p and miR-148-3p were specifically modulated in diabetic patients and correlated with clinical parameters of glucose and lipid metabolism (194). Interestingly, miR-148-3p, also found to be increased in the serum of T1D (195), is highly present in human and cow milk exosomes and it has been hypothetised as a modulator of beta cell de-differentiation—at the transition that takes place during weaning process—and to play a pathogenic role in T2D during adulthood (196) adding a new perspective on the roles of dietary miRNAs as bioactive components of food and their relevance on health and disease (197).

Globally considered, we are confident that elucidating the regulatory networks controlling miRNAs and their targets will facilitate finding specific genes/signalling hubs of therapeutic significance. There are still significant limitations (e.g., promiscuity of targets, stability and target delivery) (198), and the limited number of clinical trials using miRNA. However, advances in engineering and refining miRNA therapeutics in metabolic diseases look promising and deserve further attention.

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Footnote

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