# MicroRNAs in β-Cell Biology, Insulin Resistance, Diabetes and Its Complications

**Selene L. Fernandez-Valverde, Ryan J. Taft, and John S. Mattick**

MicroRNAs (miRNAs) are small 19–23 nucleotide RNA molecules that act as regulators of protein expression in eukaryotic cells by inducing the translational arrest and degradation of messenger RNAs (1). They are potent drivers of differentiation and development (1), and their dysregulation has been linked to many diseases. Here, we present an overview of the known and proposed roles and effects of miRNAs in type 1 and type 2 diabetes (T1D and T2D), focusing on β-cell biology, insulin resistance, and diabetes complications. Specifically, we discuss miRNAs in β-cell biology, altered expression of miRNAs in adipose tissue in response to obesity, and miRNA dysfunction in organs and tissues that may be affected in later stages of the disease. Additionally, we propose a set of research directions that may yield novel diagnostic and therapeutic approaches for this chronic illness.

T2D is characterized by hyperglycemia resultant from impaired insulin secretion and/or impaired insulin action in peripheral tissues (2). T2D constitutes one of the greatest pandemics of our time, with 220 million people currently diagnosed (3), and 366 million people expected to be affected by 2030 (4). A number of lines of evidence support a key role for pancreatic β-cell dysfunction in T2D (in addition to T1D), in which it is the major pathology. For example, recent genome-wide association studies have strongly implicated genes involved in insulin secretion as etiological factors in the development of T2D (5).

A role for miRNAs in T2D was first established in 2004 by Poy et al. (6) who showed that miR-375 is directly involved in the regulation of insulin secretion. This study was one of the first to demonstrate that a miRNA could be tightly linked to a disease phenotype. In recent years, dozens of additional miRNAs have been identified as components of pathways triggered by, or contributing to, the pathology of both T1D and T2D (Table 1). Because of the multifactorial and polysystemic nature of this disease and the increased interest in miRNAs, it seems likely that many more miRNAs, and perhaps other small regulatory RNA species, will be identified as factors in diabetes. This will undoubtedly lead to a greater understanding of the genetic basis of the disease and provide novel diagnostic, prognostic, and treatment alternatives.

From the Institute for Molecular Bioscience, University of Queensland, St Lucia, Queensland, Australia.
Corresponding author: John S. Mattick, j.mattick@imb.uq.edu.au.
Received 9 February 2011 and accepted 12 April 2011.
DOI: 10.2337/db11-0171


**See accompanying perspective, p. 1832.**

## miRNAS IN β-CELL BIOLOGY

Pancreatic β-cells play a fundamental role in glucose homeostasis, releasing insulin in response to glucose levels in the bloodstream. Insulin then triggers glucose uptake in its target tissues, such as the liver, kidney, skeletal muscle, and cardiac muscle. Absence or malfunction of β-cells leads to diabetes due to lack of insulin producing cells (T1D), or to the inability to increase insulin levels to sufficiently stimulate glucose uptake in the face of insulin resistance (T2D).

In T1D, the lack of insulin is primarily caused by the absence or destruction of pancreatic β-cells, which is driven by developmental errors or immune malfunction, respectively. A large suite of miRNAs has been implicated in pancreas (and therefore β-cell) development including miR-15a/b, miR-16, miR-195 (7), miR-503, miR-541, miR-214 (8), miR-9 (9), miR-124a (10), miR-7 (9,11), miR-376 (9) and miR-375 (9,12), among others. There remains a need for detailed studies of the role of these miRNAs in diabetes, but it is clear that mutations or misexpression of these species could lead to β-cell pathologies (see below).

Likewise, miRNAs have been implicated in the autoimmune destruction of β-cells, also leading to T1D. Recently, Hezova et al. (13) measured changes in miRNA expression in regulatory T cells (T-reg cells) of T1D-affected individuals. These cells are of special interest as they are critical regulators of autoimmune disease. They found that miR-510 was significantly upregulated, and miR-191 and miR-342 were significantly downregulated in adult peripheral T-reg cells of diabetic patients compared with healthy individuals (13). miR-342 is also known to show altered expression profiles in hematological disease (14,15). These observations suggest a role for these miRNAs in the autoimmune destruction of β-cells.

The role of miRNAs in the function of β-cells in T2D patients has been extensively studied but is not yet fully understood, as exemplified by miR-375. In adult β-cell islets miR-375 levels are decreased when high levels of glucose are available (6). Low levels of miR-375 induce insulin secretion by de-repression of its targets Mtpn (6,16) and PDK1 (17,18), while overexpression of miR-375 attenuates proliferation and insulin gene transcription while reducing glucose-induced insulin secretion (16,18,19). Indeed, ectopic expression of miR-375 in diabetic pancreatic β-cells results in increased susceptibility to fatty acid induced apoptosis (16). Consistent with these studies, high levels of miR-375 are present in pancreatic islets of obese diabetic mouse models (*ob/ob*) (20) and T2D affected individuals (21). Additionally, when miR-375 is deleted in *ob/ob* mice, they develop a marked decrease in β-cell mass, which results in a severe insulin-deficient diabetes not found in *ob/ob* mice (20). Overall, it is becoming clear that miR-375 targets a suite of genes that negatively regulate cellular growth and proliferation (20), and that aberrant loss of this miRNA leads to dramatic reduction of β-cell

TABLE 1
miRNAs involved in diabetes

| miRNA | Tissue | Relevance to diabetes | References |
|---|---|---|---|
| miR-375 | Pancreas | Expressed in pancreatic development. Regulates insulin secretion in β-cells and increases their death by lipoapoptosis, as it regulates this cell viability and proliferation. Upregulated in β-cells of T2D patients. Its deletion causes severe insulin-deficient diabetes in *ob/ob* mice. | (6,8,9,12,16,18–21,69) |
| miR-29(a/b/c) | Adipose | Induced by high glucose and high insulin. Overexpression leads to insulin resistance. | (31,32,70) |
| miR-143 | Adipose | Participates in adipocyte differentiation and is induced in adipogenesis and downregulated in obesity. | (41,42) |
| miR-9 | Pancreas, cardiac muscle | Expressed in pancreatic development. Impairs insulin secretion in β-cells and is upregulated in cardiomyocytes of STZ-induced diabetic mice. | (9,22) |
| miR-124a | Pancreas | Upregulated by glucose. Regulates the insulin exocytosis pathway, causing exaggerated insulin release when no glucose is available but reduced glucose-induced insulin secretion. | (10,23,24) |
| miR-195 | Pancreas, liver | Expressed in pancreatic development and upregulated in liver of diabetic rats. | (7,32) |
| miR-192 | Kidney | Induced by transforming growth factor-β and highly expressed in glomeruli of STZ-induced diabetic mice. Targets SIP1. | (59) |
| miR-222 | Adipose | Upregulated in response to high glucose in adipose tissue of diabetic rats. | (32) |
| miR-126 | Pancreas, skeletal muscle | Expressed in pancreatic development. Upregulated in skeletal muscle of GK rats and in livers of *ob/ob* mice compared with STZ mice. | (8,56,71) |
| miR-133a | Cardiac and skeletal muscle | Overexpressed in rabbit diabetic heart, where it induces prolongation of QT interval. Downregulated in cardiac hypertrophy in mouse and human hearts and in hearts of STZ-induced diabetic mice. Also reduced in human skeletal muscle in T2D. High fasting glucose associates with lower expression of this miRNA. | (45,46,48,53,54,72) |
| miR-296 | Pancreas | Expressed in β-cell islets and upregulated by glucose. | (18) |
| miR-96 | Pancreas | Negatively regulates insulin exocytosis through upregulation of granuphilin. | (23) |
| miR-34a | Pancreas, liver | Increases in β-cells in response to palmitate, making them more susceptible to death by apoptosis and inhibiting nutrient-induced insulin secretion. Upregulated in the livers of STZ-induced diabetic mice. Found in the bloodstream and can differentiate between nondiabetic and early T2D patients. | (23,56,73,74) |
| miR-146b | Pancreas | Contributes to increased apoptosis of β-cells. Expression induced by cytokines and sodium palmitate. | (72,74) |
| miR-657 | Liver | Regulates insulin-like growth factor 2 receptor, and variants in its regulation site (changes in regulation) give predisposition to diabetes. | (75) |
| miR-30d | Adipose | Upregulated in presence of high glucose, upregulates insulin gene transcription. | (24) |
| miR-320 | Cardiac vascular endothelium | Upregulated in GK rats with impaired angiogenesis. | (76) |

*Continued on facing page*

TABLE 1
Continued

| miRNA | Tissue | Relevance to diabetes | References |
|---|---|---|---|
| miR-103 | Pancreas, liver | Overexpression accelerates adipogenesis. Reduced in response to TNF-α. Downregulated in obesity. Upregulated in liver of *ob/ob* mice (vs. STZ-induced diabetic mice) and diabetic rats. | (32,41,56) |
| miR-107 | Pancreas, adipose | Overexpression accelerates adipogenesis. Reduced in response to TNF-α. Upregulated in β-cells in presence of high glucose. | (24,41) |
| miR-1 | Cardiac and skeletal muscle | Regulates cardiac arritmogenic potential. Upregulated by high glucose in cardiomyocytes, where it accelerates apoptosis. High levels found in ventricle of diabetic patients. Impaired insulin response in skeletal muscle of T2D patients. Significantly downregulated in the heart of STZ-induced diabetic mice. | (45,51,53,55,77) |
| miR-223 | Heart | Upregulated in the insulin-resistant heart, where it increases glucose uptake through increase of Glut4. | (78) |
| miR-125(a/b) | Liver, vascular tissue | Upregulated in liver of hyperglycemic rats. Increase of this miRNA results in a proinflammatory diabetic phenotype in vascular smooth muscle cells. | (31,79) |
| miR-27(a/b) | Adipose | Impairs human adipocyte differentiation and targets peroxisome proliferator–activated receptor γ. Upregulated in adipose tissue of diabetic rats and by glucose in 3T3 adipocytes. | (32,34) |
| miR-216a, miR-217 | Kidney | Highly expressed in kidney and upregulated by transforming growth factor-β. Activates Akt signaling through targeting of PTEN. | (60,80) |
| miR-122 | Liver | Suppression in liver results in reduced fatty acid accumulation. Downregulated in liver of STZ-induced diabetic mice. | (56,57) |
| miR-320 | Adipose, vascular endothelium | Highly upregulated in insulin-resistant adipocytes. Targets p85, leading to increased insulin resistance in adipocytes. Upregulated in myocardial microvascular cells in GK rats, where it impairs angiogenesis. | (33,76) |
| miR-21 | Pancreas, liver | Upregulated by nuclear factor-κB and fatty acids in liver, leading to downregulation of its target PTEN. Induced by interleukin-1β and TNF-α in pancreatic islets. Expression increased in rats on high-fat diet and in liver of T2D patients. Overexpression reduces maximal glucose-induced insulin release in β-cells. | (58,74) |
| miR-206 | Cardiac and skeletal muscle | Upregulated in skeletal muscle of diabetic and prediabetic patients. Upregulated by high glucose in cardiomyocytes. Accelerates cardiomyocyte apoptosis. | (48,55) |
| miR-93 | Vascular endothelium | Downregulated by high glucose through downregulation of its host gene *MCM7*. | (81) |
| miR-30a* | Adipose | Downregulated in T2D individuals, independent of obesity. | (68) |
| miR-181d | Liver | Most effective miRNA at reducing intracellular lipid content of hepatocytes. | (82) |

mass, leading to low levels of insulin, hyperglycemia, and thus diabetes.

At least three additional miRNAs play a critical role in insulin exocytosis in β-cells. For example, miR-9 positively regulates glucose-induced insulin secretion in β-cells by directly repressing Onecut-2, the granuphilin (synaptotagmin-like 4) repressor, a protein that significantly enhances basal, but strongly inhibits $K^+$-induced insulin secretion (22). Likewise, miR-96 also negatively regulates insulin exocytosis by targeting synaptotagmin-like 4 (23), and reduces levels of Noc2, which impairs β-cell ability to respond to secretagogues (23). The third well-described β-cell miRNA, miR-124a, intriguingly, appears to link β-cell and neural biology through the exocytosis pathway. miR-124a is

upregulated in β-cells in the presence of glucose (24), but was first described as a brain-specific miRNA implicated in neurogenesis (25). High levels of miR-124a in β-cells lead to exaggerated insulin release at low-glucose concentrations but reduced glucose-induced secretion (24). This is likely to the result of targeting of Foxa2, which in turn downregulates Sur-1, Kir6.2, and Pdx1, the latter of which directly regulates the expression of the insulin gene (10). miR-124a also decreases levels of Rab27a and Noc2 and upregulates Snap25, Rab3a, and Synapsin1a, facilitating tight regulation of the insulin exocytosis pathway (23).

Interestingly, two other miRNAs, miR-7 (26) and miR-375 (12), are expressed both in brain and in β-cell islets. Both β-cells and neurons share similar secretion mechanisms and are responsive to signals in the bloodstream including glucose and insulin. Taking into account the fact that insulin stimulates glucose metabolism in the brain, mainly in the cerebral cortex (27), it is likely that miRNA expression in the brain is affected by diabetes, which could therefore have profound neurologic consequences.

## miRNAS IN OBESITY AND ADIPOSE TISSUE

Obesity, hyperlipidemia (elevated levels of blood lipids), and insulin resistance (reduced glucose uptake in response to the insulin signal) are strongly associated with the onset of T2D (28). Obesity itself is characterized by adipocyte dysfunction with abnormalities in adipokine secretion and in energy metabolism. Adipogenic abnormalities lead to an adipocyte phenotype distinct from the "ideal" which stores excess energy benignly in the triglyceride droplet. Among other downstream effects, this leads to an accumulation of fat in ectopic sites, such as liver, muscle, pancreas, and kidneys (29). It also leads to the secretion of chemoattractants that promote macrophage infiltration of adipose tissue, leading to inflammation and excessive release of free fatty acids into the bloodstream (29,30).

miRNAs in adipose tissue are strongly dysregulated in response to obesity-induced molecular changes and environmental signals. For instance, the expression of the miR-29 family is induced by hyperglycemia and hyperinsulinemia in adipose tissue (31), and miR-29a is highly upregulated in 3T3-L1 adipocytes in response to high glucose (32). Likewise, miR-320 increases insulin sensitivity of insulin resistant adipocytes (33) and miR-27b impairs human adipocyte differentiation (34). These miRNAs target conserved core cell-regulatory pathways that are affected both locally and systematically by obesity and by diabetes generally. Indeed, miR-320 targets p85, which plays a critical role in cell growth by increasing Akt phosphorylation and thus the level of Glut4 (33). Similarly, miR-29 targets p85α in HeLa cells, and is thus likely to affect Akt signaling in adipocytes (35). Additionally, miR-27b targets peroxisome proliferator–activated receptor γ (34), the nuclear receptor targeted by thiazolidinediones, an insulin-sensitizing agent used for treating T2D (36). Just as miRNAs are diagnostic of broad changes in cancer (37,38), they also reflect the degree of disturbance in diabetes.

As mentioned above, obesity triggers macrophage infiltration and cytokine release in adipose tissue. This is closely followed by changes in miRNA expression, which in turn affect lipid levels and adipogenesis. Indeed, many cytokines, such as tumor necrosis factor (TNF)-α, interfere with insulin signaling and inhibit adipogenesis (39,40) and several miRNAs that are induced during adipogenesis are downregulated in obesity (41). For example, inhibition of miR-143 has been shown to regulate adipocyte differentiation and results in reduced adipogenesis (42). Similarly, miR-103 and miR-107 have been shown to accelerate adipogenesis (43), and are predicted to target pathways that regulate cellular acetyl-CoA and lipid levels (44). Levels of miR-143, miR-103 and miR-107 are reduced after one-day treatment with TNF-α in adipocytes (43), suggesting that macrophage infiltration and cytokine release are a contributing factor to reduced adipogenesis in obesity. The connection between miRNA expression and cytokine exposure may eventually be leveraged into treatment options for morbidly obese diabetic patients.

## miRNAS IN DIABETES COMPLICATIONS

Tissues adversely affected by diabetes may include cardiac and skeletal muscle, liver, kidney, and endothelium. Hyperglycemia and hyperlipedemia damage these tissues causing conditions such as fatty liver, stroke, kidney failure, neuropathy, and blindness. Not surprisingly, the expression of miRNAs is altered in these tissues in diabetic individuals.

A precondition for the onset of T2D is insulin resistance of skeletal muscle. Abnormally circulating fatty acids accumulate in skeletal muscle and disrupt important signaling pathways (29). Normally, insulin activates the transcription of sterol regulatory element–binding protein 1, which represses transcription of miR-1 and miR-133 by inhibiting muscle specific factor myocyte enhancer factor (MEF) 2C (45,46). The repression of miR-133a and miR-1 in response to insulin levels is impaired in T2D patients (45), which contributes to impaired muscle function (47). Indeed, a recent study has shown that the expression of miR-133a is strongly downregulated in this tissue in T2D-affected individuals (48).

The miRNAs miR-1 and miR-133 also play a primordial role in normal cardiac function and cardiogenesis (49,50). In the normal heart, cardiomyocytes exposed to high levels of glucose develop hypertrophy and, similar to skeletal muscle, have low levels of miR-133a (51). Indeed, glucose-induced cardiomyocyte hypertrophy is associated with increased levels of MEF2A and MEF2C (52). In diabetes, however, the relationship between MEF2A/C is impaired. miR-133 is in fact overexpressed in the rabbit diabetic heart, where it induces prolongation of the QT interval, a known phenotype of T2D (53). However, and surprisingly, both miR-1 and miR-133a are downregulated in the hearts of mice with insulin-deficiency induced by streptozotocin (STZ), and in cardiac-hypertrophy and heart failure (54). This strongly suggests that the relationship between miR-133 and miR-1 and cardiomyocte responses to insulin and glucose is complex. Indeed, a recent study has shown that these miRNAs are upregulated in cardiomyocytes after high-glucose exposure (55), which accelerates cardiomyocyte apoptosis (55), a key factor in the development of diabetic cardiomyopathy. These observations suggest that miR-1 and miR-133 are excellent candidates for further functional studies. Unraveling their seemingly contradictory behavior will undoubtedly shed light on the complicated biology underpinning muscle cell responses to physiological stimuli.

In the late stages of diabetes, liver and kidney function may be impaired, and this is reflected in several abnormal miRNA expression profiles. For example, inhibition of

a miRNA crucial for liver function, miR-122, which is downregulated in the livers of STZ-induced diabetic mice (56), results in low plasma cholesterol levels, increased hepatic fatty acid oxidation, and decreased hepatic fatty acid and cholesterol synthesis rate (57). miR-21 also plays an important role in hepatocytes, where it is induced by nuclear factor-κB, leading to the downregulation of phosphatase and tensin homolog (PTEN), a protein that inhibits Akt activation (58). High-fat diets result in the upregulation of miR-21 in rats (58), and liver biopsies of obese human patients also show an increase in the expression of miR-21 and a decreased level of PTEN expression in comparison with normal controls (58). In the diabetic kidney, tranforming growth factor-β and miR-192 induce expression of miR-216a and miR-217 (59,60), which leads to activation of Akt through targeting of PTEN (60).

A tissue that has recently come to attention in diabetes is vascular endothelium, which changes in response to diabetic inflammatory signals. There is a strong negative correlation between miR-126 levels and the onset of diabetic vascular complications (61). However, this miRNA is significantly increased in patients suffering of coronary artery disease (62). Interestingly, delivery of this miRNA by apoptotic bodies protects against diet-induced atherosclerosis (62). This indicates that miR-126 can be used as both a biomarker for early detection of vascular complications of diabetes, and as a possible RNA-based therapeutic for diabetes-induced atherosclerosis.

## FUTURE CHALLENGES AND POSSIBILITIES

There are many areas of research that remain unexplored in relation to miRNAs and diabetes. One is the interplay between the brain and insulin target tissues. It is known that the brain is fueled by glucose and, despite previous reports that this tissue is insulin insensitive, recent articles have shown insulin-induced glucose uptake in specific brain regions (27). Indeed, the similarities between β-cell and neuronal exocytosis systems are remarkable (see above). Due to the fact that the brain is responsible for behavioral control, it is likely that it reacts directly to the availability or depletion of glucose in the bloodstream by regulating caloric uptake. miRNAs have already been shown to carry out important regulatory functions in the brain, and therefore a study focusing on the miRNA changes in brain in response to hyperglycemia and hyperlipidemia is essential for a complete systemic understanding of diabetes.

It is now clear that the miRNA profile of insulin resistance tissues changes years before the onset and/or diagnosis of T2D. Indeed, a study by Zampetaki et al. (61) has shown that a plasma signature of five miRNAs (miR-15a, miR-29b, miR-126, miR-223, and miR-28–3p) can accurately differentiate patients with a high likelihood of developing diabetes from healthy controls. In a review, Regazzi (63) proposed that these miRNAs might not only be indicators of early disease onset but are also responsible for its progression and thus a good target for early intervention. One possibility is that these miRNAs actually act distant from their sites of biogenesis, and are transmitted from one tissue to another (64). The recent observation of miR-150 transmission through the bloodstream and uptake by target endothelial cells (65) makes this possibility likely. If diabetes-related miRNAs are trafficked in *trans*, it may be possible to interfere in the progression of the disease with minimally invasive RNA therapeutics.

Because of the high genetic predisposition of some individuals to develop T2D, identification of genetic variants that alter the levels of key miRNAs may become a clinically powerful tool, undoubtedly aided by the increasing affordability of personal genomic sequencing. We predict that the availability of this technology will provide clinicians with an invaluable tool to identify at-risk individuals, to prompt their patients to take preventive action, and, eventually, to prescribe tailored therapeutics (66). It will also provide a baseline for beginning to rigorously identify environmental factors that promote epigenetic variations, particularly for genetically susceptible individuals.

It is important to emphasize the need for integrating current and future miRNA studies into existing resources like the Beta Cell Biology Consortium (http://www.betacell.org/). Many recent genome-wide studies have provided a snapshot of the miRNA content of different tissues involved in this disease, including the developing pancreas (67) and subcutaneous adipocytes of T2D patients (68). However, it is difficult to integrate this information if it is not summarized in a central repository. As highlighted by Gallagher et al. (48), even though the community hoped to gain insight into miRNA mechanisms of action by studying them in isolated model systems, it is now clear that this information must be centralized and integrated with clinical data in order to obtain the insights necessary to conquer this illness.

## ACKNOWLEDGMENTS

This work was supported by the Australian National Health and Medical Research Council (Australia Fellowship 631668 to J.S.M.), the Australian Research Council (Australian Postgraduate Awards Fellowship to S.L.F.-V.), and the University of Queensland (University of Queensland Postdoctoral Fellowship to R.J.T.).

No potential conflicts of interest relevant to this article were reported.

S.L.F.-V. surveyed the literature and wrote and developed the manuscript. R.J.T. and J.S.M. wrote sections of the manuscript and provided editorial feedback on its structure and text.

The authors apologize to those colleagues whose work could not be cited because of space constraints. The authors thank John Prins (University of Queensland Centre for Diabetes and Endocrine Research) and Brad Marsh (Institute for Molecular Bioscience, University of Queensland) for insightful comments and criticisms.

## REFERENCES

1. Fabian MR, Sonenberg N, Filipowicz W. Regulation of mRNA translation and stability by microRNAs. Annu Rev Biochem 2010;79:351–379
2. McCarthy MI. Genomics, type 2 diabetes, and obesity. N Engl J Med 2010; 363:2339–2350
3. World Health Organization. Diabetes Fact Sheet N°312 [article online], 2010. Available from http://www.who.int/mediacentre/factsheets/fs312/en/index.html. Accessed December 2010
4. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004; 27:1047–1053
5. McCarthy MI, Zeggini E. Genome-wide association studies in type 2 diabetes. Curr Diab Rep 2009;9:164–171
6. Poy MN, Eliasson L, Krutzfeldt J, et al. A pancreatic islet-specific microRNA regulates insulin secretion. Nature 2004;432:226–230
7. Joglekar MV, Parekh VS, Mehta S, Bhonde RR, Hardikar AA. MicroRNA profiling of developing and regenerating pancreas reveal post-transcriptional regulation of neurogenin3. Dev Biol 2007;311:603–612
8. Lynn FC, Skewes-Cox P, Kosaka Y, McManus MT, Harfe BD, German MS. MicroRNA expression is required for pancreatic islet cell genesis in the mouse. Diabetes 2007;56:2938–2945

9. Joglekar MV, Joglekar VM, Hardikar AA. Expression of islet-specific microRNAs during human pancreatic development. Gene Expr Patterns 2009; 9:109–113
10. Baroukh N, Ravier MA, Loder MK, et al. MicroRNA-124a regulates Foxa2 expression and intracellular signaling in pancreatic beta-cell lines. J Biol Chem 2007;282:19575–19588
11. Correa-Medina M, Bravo-Egana V, Rosero S, et al. MicroRNA miR-7 is preferentially expressed in endocrine cells of the developing and adult human pancreas. Gene Expr Patterns 2009;9:193–199
12. Kloosterman WP, Lagendijk AK, Ketting RF, Moulton JD, Plasterk RH. Targeted inhibition of miRNA maturation with morpholinos reveals a role for miR-375 in pancreatic islet development. PLoS Biol 2007;5:e203
13. Hezova R, Slaby O, Faltejskova P, et al. microRNA-342, microRNA-191 and microRNA-510 are differentially expressed in T regulatory cells of type 1 diabetic patients. Cell Immunol 2010;260:70–74
14. Schmidt WM, Spiel AO, Jilma B, Wolzt M, Müller M. In vivo profile of the human leukocyte microRNA response to endotoxemia. Biochem Biophys Res Commun 2009;380:437–441
15. Garzon R, Pichiorri F, Palumbo T, et al. MicroRNA gene expression during retinoic acid-induced differentiation of human acute promyelocytic leukemia. Oncogene 2007;26:4148–4157
16. Li Y, Xu X, Liang Y, et al. miR-375 enhances palmitate-induced lipoapoptosis in insulin-secreting NIT-1 cells by repressing myotrophin (V1) protein expression. Int J Clin Exp Pathol 2010;3:254–264
17. Hashimoto N, Kido Y, Uchida T, et al. Ablation of PDK1 in pancreatic beta cells induces diabetes as a result of loss of beta cell mass. Nat Genet 2006; 38:589–593
18. El Ouaamari A, Baroukh N, Martens GA, Lebrun P, Pipeleers D, van Obberghen E. miR-375 targets 3′-phosphoinositide-dependent protein kinase-1 and regulates glucose-induced biological responses in pancreatic beta-cells. Diabetes 2008;57:2708–2717
19. Xia HQ, Pan Y, Peng J, Lu GX. Over-expression of miR375 reduces glucose-induced insulin secretion in Nit-1 cells. Mol Biol Rep 2010 [Epub ahead of print] DOI: 10.1007/s11033-010-9973-9
20. Poy MN, Hausser J, Trajkovski M, et al. miR-375 maintains normal pancreatic alpha- and beta-cell mass. Proc Natl Acad Sci USA 2009;106:5813–5818
21. Zhao H, Guan J, Lee HM, et al. Upregulated pancreatic tissue microRNA-375 associates with human type 2 diabetes through beta-cell deficit and islet amyloid deposition. Pancreas 2010;39:843–846
22. Plaisance V, Abderrahmani A, Perret-Menoud V, Jacquemin P, Lemaigre F, Regazzi R. MicroRNA-9 controls the expression of Granuphilin/Slp4 and the secretory response of insulin-producing cells. J Biol Chem 2006;281: 26932–26942
23. Lovis P, Gattesco S, Regazzi R. Regulation of the expression of components of the exocytotic machinery of insulin-secreting cells by microRNAs. Biol Chem 2008;389:305–312
24. Tang X, Muniappan L, Tang G, Ozcan S. Identification of glucose-regulated miRNAs from pancreatic beta cells reveals a role for miR-30d in insulin transcription. RNA 2009;15:287–293
25. Cheng LC, Pastrana E, Tavazoie M, Doetsch F. miR-124 regulates adult neurogenesis in the subventricular zone stem cell niche. Nat Neurosci 2009;12:399–408
26. Bravo-Egana V, Rosero S, Molano RD, et al. Quantitative differential expression analysis reveals miR-7 as major islet microRNA. Biochem Biophys Res Commun 2008;366:922–926
27. Bingham EM, Hopkins D, Smith D, et al. The role of insulin in human brain glucose metabolism: an 18fluoro-deoxyglucose positron emission tomography study. Diabetes 2002;51:3384–3390
28. Goossens GH. The role of adipose tissue dysfunction in the pathogenesis of obesity-related insulin resistance. Physiol Behav 2008;94:206–218
29. Guilherme A, Virbasius JV, Puri V, Czech MP. Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. Nat Rev Mol Cell Biol 2008;9:367–377
30. Cancello R, Henegar C, Viguerie N, et al. Reduction of macrophage infiltration and chemoattractant gene expression changes in white adipose tissue of morbidly obese subjects after surgery-induced weight loss. Diabetes 2005;54:2277–2286
31. Herrera BM, Lockstone HE, Taylor JM, et al. MicroRNA-125a is over-expressed in insulin target tissues in a spontaneous rat model of type 2 diabetes. BMC Med Genomics 2009;2:54
32. Herrera BM, Lockstone HE, Taylor JM, et al. Global microRNA expression profiles in insulin target tissues in a spontaneous rat model of type 2 diabetes. Diabetologia 2010;53:1099–1109
33. Ling HY, Ou HS, Feng SD, et al. Changes in microRNA profile and effects of miR-320 in insulin-resistant 3T3-L1 adipocytes. Clin Exp Pharmacol Physiol 2009;36:e32–e39
34. Karbiener M, Fischer C, Nowitsch S, et al. microRNA miR-27b impairs human adipocyte differentiation and targets PPARgamma. Biochem Biophys Res Commun 2009;390:247–251
35. Park SY, Lee JH, Ha M, Nam JW, Kim VN. miR-29 miRNAs activate p53 by targeting p85 alpha and CDC42. Nat Struct Mol Biol 2009;16:23–29
36. Krishnaswami A, Ravi-Kumar S, Lewis JM. Thiazolidinediones: a 2010 perspective. Perm J 2010;14:64–72
37. Fabbri M, Bottoni A, Shimizu M, et al. Association of a microRNA/TP53 feedback circuitry with pathogenesis and outcome of B-cell chronic lymphocytic leukemia. JAMA 2011;305:59–67
38. Liu R, Zhang C, Hu Z, et al. A five-microRNA signature identified from genome-wide serum microRNA expression profiling serves as a fingerprint for gastric cancer diagnosis. Eur J Cancer 2011;47:784–791
39. Hotamisligil GS, Murray DL, Choy LN, Spiegelman BM. Tumor necrosis factor alpha inhibits signaling from the insulin receptor. Proc Natl Acad Sci USA 1994;91:4854–4858
40. Warne JP. Tumour necrosis factor alpha: a key regulator of adipose tissue mass. J Endocrinol 2003;177:351–355
41. Xie H, Lim B, Lodish HF. MicroRNAs induced during adipogenesis that accelerate fat cell development are downregulated in obesity. Diabetes 2009;58:1050–1057
42. Esau C, Kang X, Peralta E, et al. MicroRNA-143 regulates adipocyte differentiation. J Biol Chem 2004;279:52361–52365
43. Xie H, Sun L, Lodish HF. Targeting microRNAs in obesity. Expert Opin Ther Targets 2009;13:1227–1238
44. Wilfred BR, Wang WX, Nelson PT. Energizing miRNA research: a review of the role of miRNAs in lipid metabolism, with a prediction that miR-103/107 regulates human metabolic pathways. Mol Genet Metab 2007;91:209–217
45. Granjon A, Gustin MP, Rieusset J, et al. The microRNA signature in response to insulin reveals its implication in the transcriptional action of insulin in human skeletal muscle and the role of a sterol regulatory element-binding protein-1c/myocyte enhancer factor 2C pathway. Diabetes 2009;58:2555–2564
46. Liu N, Williams AH, Kim Y, et al. An intragenic MEF2-dependent enhancer directs muscle-specific expression of microRNAs 1 and 133. Proc Natl Acad Sci USA 2007;104:20844–20849
47. Sayer AA, Dennison EM, Syddall HE, Gilbody HJ, Phillips DI, Cooper C. Type 2 diabetes, muscle strength, and impaired physical function: the tip of the iceberg? Diabetes Care 2005;28:2541–2542
48. Gallagher IJ, Scheele C, Keller P, et al. Integration of microRNA changes in vivo identifies novel molecular features of muscle insulin resistance in type 2 diabetes. Genome Med 2010;2:9
49. Carè A, Catalucci D, Felicetti F, et al. MicroRNA-133 controls cardiac hypertrophy. Nat Med 2007;13:613–618
50. Zhao Y, Ransom JF, Li A, et al. Dysregulation of cardiogenesis, cardiac conduction, and cell cycle in mice lacking miRNA-1-2. Cell 2007;129:303–317
51. Feng B, Chen S, George B, Feng Q, Chakrabarti S. miR133a regulates cardiomyocyte hypertrophy in diabetes. Diabetes Metab Res Rev 2010;26: 40–49
52. Feng B, Chen S, Chiu J, George B, Chakrabarti S. Regulation of cardiomyocyte hypertrophy in diabetes at the transcriptional level. Am J Physiol Endocrinol Metab 2008;294:E1119–E1126
53. Xiao J, Luo X, Lin H, et al. MicroRNA miR-133 represses HERG K+ channel expression contributing to QT prolongation in diabetic hearts. J Biol Chem 2007;282:12363–12367
54. Chen X, Wang K, Chen J, et al. In vitro evidence suggests that miR-133a-mediated regulation of uncoupling protein 2 (UCP2) is an indispensable step in myogenic differentiation. J Biol Chem 2009;284:5362–5369
55. Shan ZX, Lin QX, Deng CY, et al. miR-1/miR-206 regulate Hsp60 expression contributing to glucose-mediated apoptosis in cardiomyocytes. FEBS Lett 2010;584:3592–3600
56. Li S, Chen X, Zhang H, et al. Differential expression of microRNAs in mouse liver under aberrant energy metabolic status. J Lipid Res 2009;50: 1756–1765
57. Esau C, Davis S, Murray SF, et al. miR-122 regulation of lipid metabolism revealed by in vivo antisense targeting. Cell Metab 2006;3:87–98
58. Vinciguerra M, Sgroi A, Veyrat-Durebex C, Rubbia-Brandt L, Buhler LH, Foti M. Unsaturated fatty acids inhibit the expression of tumor suppressor phosphatase and tensin homolog (PTEN) via microRNA-21 upregulation in hepatocytes. Hepatology 2009;49:1176–1184
59. Kato M, Zhang J, Wang M, et al. MicroRNA-192 in diabetic kidney glomeruli and its function in TGF-beta-induced collagen expression via inhibition of E-box repressors. Proc Natl Acad Sci USA 2007;104:3432–3437
60. Kato M, Putta S, Wang M, et al. TGF-beta activates Akt kinase through a microRNA-dependent amplifying circuit targeting PTEN. Nat Cell Biol 2009;11:881–889

61. Zampetaki A, Kiechl S, Drozdov I, et al. Plasma microRNA profiling reveals loss of endothelial miR-126 and other microRNAs in type 2 diabetes. Circ Res 2010;107:810–817
62. Fichtlscherer S, De Rosa S, Fox H, et al. Circulating microRNAs in patients with coronary artery disease. Circ Res 2010;107:677–684
63. Regazzi R. Diabetes mellitus reveals its micro-signature. Circ Res 2010;107: 686–688
64. Dinger ME, Mercer TR, Mattick JS. RNAs as extracellular signaling molecules. J Mol Endocrinol 2008;40:151–159
65. Zhang Y, Liu D, Chen X, et al. Secreted monocytic miR-150 enhances targeted endothelial cell migration. Mol Cell 2010;39:133–144
66. Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403
67. Rosero S, Bravo-Egana V, Jiang Z, et al. MicroRNA signature of the human developing pancreas. BMC Genomics 2010;11:509
68. Ortega FJ, Moreno-Navarrete JM, Pardo G, et al. MiRNA expression profile of human subcutaneous adipose and during adipocyte differentiation. PLoS ONE 2010;5:e9022
69. Avnit-Sagi T, Kantorovich L, Kredo-Russo S, Hornstein E, Walker MD. The promoter of the pri-miR-375 gene directs expression selectively to the endocrine pancreas. PLoS ONE 2009;4:e5033
70. He A, Zhu L, Gupta N, Chang Y, Fang F. Overexpression of micro ribonucleic acid 29, highly upregulated in diabetic rats, leads to insulin resistance in 3T3-L1 adipocytes. Mol Endocrinol 2007;21:2785–2794
71. Huang B, Qin W, Zhao B, et al. MicroRNA expression profiling in diabetic GK rat model. Acta Biochim Biophys Sin (Shanghai) 2009;41:472–477
72. Fred RG, Bang-Berthelsen CH, Mandrup-Poulsen T, Grunnet LG, Welsh N. High glucose suppresses human islet insulin biosynthesis by inducing miR-133a leading to decreased polypyrimidine tract binding protein-expression. PLoS ONE 2010;5:e10843
73. Kong L, Zhu J, Han W, et al. Significance of serum microRNAs in pre-diabetes and newly diagnosed type 2 diabetes: a clinical study. Acta Diabetol 2011;48:61–69
74. Roggli E, Britan A, Gattesco S, et al. Involvement of microRNAs in the cytotoxic effects exerted by proinflammatory cytokines on pancreatic beta-cells. Diabetes 2010;59:978–986
75. Lv K, Guo Y, Zhang Y, Wang K, Jia Y, Sun S. Allele-specific targeting of hsa-miR-657 to human IGF2R creates a potential mechanism underlying the association of ACAA-insertion/deletion polymorphism with type 2 diabetes. Biochem Biophys Res Commun 2008;374:101–105
76. Wang XH, Qian RZ, Zhang W, Chen SF, Jin HM, Hu RM. MicroRNA-320 expression in myocardial microvascular endothelial cells and its relationship with insulin-like growth factor-1 in type 2 diabetic rats. Clin Exp Pharmacol Physiol 2009;36:181–188
77. Yang Z, Wu J. MicroRNAs and regenerative medicine. DNA Cell Biol 2007; 26:257–264
78. Lu H, Buchan RJ, Cook SA. MicroRNA-223 regulates Glut4 expression and cardiomyocyte glucose metabolism. Cardiovasc Res 2010;86:410–420
79. Villeneuve LM, Kato M, Reddy MA, Wang M, Lanting L, Natarajan R. Enhanced levels of microRNA-125b in vascular smooth muscle cells of diabetic db/db mice lead to increased inflammatory gene expression by targeting the histone methyltransferase Suv39h1. Diabetes 2010;59:2904–2915
80. Kato M, Wang L, Putta S, et al. Post-transcriptional upregulation of Tsc-22 by Ybx1, a target of miR-216a, mediates TGF-beta-induced collagen expression in kidney cells. J Biol Chem 2010;285:34004–34015
81. Long J, Wang Y, Wang W, Chang BH, Danesh FR. Identification of microRNA-93 as a novel regulator of vascular endothelial growth factor in hyperglycemic conditions. J Biol Chem 2010;285:23457–23465
82. Whittaker R, Loy PA, Sisman E, et al. Identification of microRNAs that control lipid droplet formation and growth in hepatocytes via high-content screening. J Biomol Screen 2010;15:798–805