Noncoding miRNAs as key controllers of pancreatic β-cell functions

Pascal Lovis and Romano Regazzi†

miRNAs, a recently discovered family of small noncoding RNAs, are emerging as major controllers of gene expression and key determinants of pancreatic β-cell function. These 19-22-nucleotide molecules govern gene expression by partially pairing to 3’-untranslated regions of target mRNAs and by inhibiting their translation. The elucidation of the role of miRNAs promises to unravel new aspects of β-cell biology and to clarify the mechanisms leading to defective insulin secretion in diabetes mellitus. This information is expected to favor the design of new approaches for preserving functional β-cells in prediabetic stages and the development of strategies for engineering insulin-secreting cells capable of replacing endogenous β-cells in diabetic patients.


Diabetes mellitus

With approximately 170 million cases worldwide, diabetes mellitus is the most common metabolic disorder. Owing to aging populations and increasing trends towards obesity and sedentary lifestyles, the number of affected individuals is increasing rapidly and is expected to double within the next 25 years. In industrialized countries, diabetes is already the leading cause of blindness, renal failure and lower limb amputations, and is a major risk factor for cardiovascular disease and stroke. The pancreatic β-cell and insulin, its secretory product, play a central role in the pathophysiology of diabetes. Indeed, the release of insulin is an essential factor in the achievement of blood glucose homeostasis and insufficient supply of this hormone causes hyperglycemia and, ultimately, diabetes. Type 1 diabetes mellitus (T1DM) results from an absolute deficiency of insulin due to autoimmune destruction of pancreatic β-cells. Type 2 diabetes mellitus (T2DM) is characterized by impaired insulin sensitivity of target tissues and variable degrees of β-cell dysfunction. Environmental factors, such as inappropriate diet and lack of exercise, play a central role in the pathogenesis of T2DM. A rise in glucose and free fatty acid concentration in the blood stimulates insulin release. However, prolonged exposure to supraphysiological concentrations of glucose and lipids leads to deleterious effects on β-cell function [1,2]. Impairment of β-cell activity results in loss of glucose-induced insulin secretion, sensitization to apoptosis and, possibly, reduction of proliferation of β-cells. Euglycemia is usually maintained by a feedback loop between insulin sensitivity and insulin secretion, since changes in sensitivity of peripheral tissues are accompanied by inverse adaptations in secretion. However, if β-cell function is impaired because of environmental or predisposing genetic factors, the quantity of insulin released fails to counterbalance the degree of insulin resistance, and thus progression to diabetes occurs [3].

The pancreatic β-cell

Pancreatic β-cells are highly specialized cells characterized by the unique capacity to synthesize and release insulin in response to circulating levels of glucose and other nutrients. The secretory response to nutrients is modulated by a large array of hormones and neurotransmitters permitting a moment-to-moment control of blood glucose levels and its adaptation to the organism demands. β-cell-specific functions are insured through
the expression of a distinct set of genes. This is achieved through a complex regulatory network acting both at transcriptional and translational level. A number of transcription factors playing an essential role in achieving and maintaining the unique phenotypic traits of β-cells have been identified [4]. The central role of some of these proteins in β-cell development and function is emphasized by the finding that mutations in genes encoding the transcription factors HNF-4α, HNF-1α, HNF-1β, IPF-1 and NeuroD1/BETA2 are responsible for the appearance of monogenic forms of T2DM, known as maturity onset diabetes of the young (MODY) [5]. In addition, variants in two transcription factor genes, transcription factor 7-like 2 (TCF7L2) and homeobox gene HHEX (H HEX) were found to increase the risk of developing T2DM in genome-wide association studies [6,7]. Besides transcriptional control, the expression of several β-cell genes, including insulin, is submitted to extensive regulation at the translational level. This regulatory mechanism plays an essential role in preserving β-cell functions under stressful conditions as those imposed by high-fat diets and loss of mRNA translational control can favor the development of diabetes [8].

Despite recent progress in understanding β-cell gene expression, it is clear that functional defects in the factors identified so far cannot account for the development of T2DM in all diabetic patients. This implies the existence of additional regulatory mechanisms possibly acting upstream or in conjunction with the already known factors. The identification of these regulatory molecules is of primary importance to gain new insight into β-cell specific activities, including insulin expression and/or secretion, and to unravel the causes of T2DM. In addition, the elucidation of the mechanisms determining the phenotypic traits of β-cells is an essential prerequisite for the engineering of an unlimited source of insulin-secreting cells that may possibly be used to reconstitute β-cell function in diabetic patients [9].

miRNAs as important regulators of gene expression
At the beginning of this century, a new paradigm of RNA-directed control of gene expression emerged. Eukaryotic cells were found to express hundreds of short (19–22 nucleotides) noncoding RNAs termed miRNAs [10–13]. Almost all human miRNAs are conserved in mouse and approximately a third of Caenorhabditis elegans miRNAs possess vertebrate homologs. Some of these molecules are ubiquitously expressed, while others are restricted to specific tissues. It was rapidly recognized that miRNAs form a new class of regulators of gene expression that direct translational repression of a large number of mRNA targets [10–13]. Indeed, according to recent estimates, up to a third of all human genes could be subjected to miRNA translational control. In view of this immense regulatory potential, the involvement of miRNAs in a variety of cellular functions was anticipated. Indeed, we now know that miRNAs guide most aspects of plant and animal development [10–14]. Moreover, in mammals, they play important roles in a variety of physiological processes including cell proliferation, apoptosis and vesicular trafficking [10–13,15]. miRNA dysfunction has also turned out to be a potential culprit in several human diseases, including spinal muscular atrophy, fragile X syndrome and cancer [12,16,17].

miRNA synthesis & maturation
miRNA precursor sequences can be generated from intronic regions of known protein coding or noncoding genes [11,13]. In this case, miRNAs and host genes share similar expression patterns [18]. miRNAs can also be produced from independent transcription units located outside protein coding genes. Like conventional miRNAs, miRNAs are transcribed by RNA polymerase II as long primary transcripts (pri-miRNAs) that are capped, polyadenylated and spliced [11,13]. They are then processed to stem-loop precursors of approximately 70 nucleotides (pre-miRNAs) by a nuclear RNase III-like enzyme called Drosha. Pre-miRNAs are exported from the nucleus to the cytoplasm by Exportin-5 and its cofactor, Ran GTPase [11,13]. In the cytoplasm, 19–22 nucleotide duplexes are excised from pre-miRNAs by Dicer, another RNase III-like enzyme. The RNA duplex produced in this reaction is then loaded into a ribonucleoprotein complex called miRNP (miRNA–protein complex), which shares many components with the RNA-induced silencing complex (RISC).
involved in the process of RNA interference. One of the two strands is discarded while the other, the mature miRNA, engages in imperfect base pairing with target mRNAs.

**miRNA mode of action**

miRNAs inhibit gene expression by pairing to sequences in the 3′-untranslated region (UTR) of their target mRNAs (Figure 1) [10,11]. In mammals, base pairing of miRNAs with their targets is usually imperfect and typically involves several mismatched bulges in the central region and at the miRNA 3′-end. This enables each miRNA to control the expression of more than 100 different mRNAs. In general, in mammals, the interaction between the miRNA and its targets does not lead to drastic changes in the mRNA level, but translation of the messenger is strongly reduced. The precise mechanism by which miRNAs affect translation is still unclear, and evidence for inhibition of both initiation and post-initiation steps, including elongation and termination, has been provided [19,20]. Thus, it is possible that miRNAs repress protein synthesis by interfering with multiple stages of the translational process. mRNAs targeted by miRNAs accumulate in discrete cytoplasmic foci, called P-bodies, that can be readily visualized using GFP-tagged proteins of the argonaute family (Figure 2) [21,22]. These dynamic structures are enriched in factors involved in mRNA decay and translational repression [23]. Interestingly, mRNAs associated with P-bodies are not necessarily destined for degradation and under certain circumstances the messengers can exit these structures and re-enter the translational process (Figure 1).

Indeed, in liver cells subjected to starvation or other stressful conditions, miR-122-mediated repression of the cation amino acid transporter CAT-1 is relieved [24]. The rescue of the translational process requires the association of HuR, an AU-rich-element-binding protein belonging to the embryonic lethal abnormal vision (ELAV) family, to the 3′-UTR of CAT-1 mRNA [24]. How stress and HuR mobilize the mRNAs from P-bodies and make them available again for translation is still unclear. We do not know yet whether the reversal of the translational block is a phenomenon restricted to miR-122 or if it is just an example of a much more general regulatory mechanism. Additional experiments are needed to establish whether miRNAs are involved in a dynamic control of mRNA translation rather than in a continuous selective inhibition of gene expression.

**Identification of miRNA targets**

The procedure through which miRNAs recognize their targets is not fully understood. In mammalian cells, mRNA binding sites are selected through complementarities over very short (seven to eight nucleotides) sequences, rendering the identification of putative miRNA target sites arduous. Additional sequences surrounding the binding sites are thought to contribute to the specificity of the miRNA interaction, but the underlying mechanism remains unclear [25]. Several algorithms designed to identify putative miRNA target genes have been developed, but the prediction has only been experimentally validated for a very small number of them [26-30]. In addition, most of the putative interactions were tested by coexpression of the miRNA with a reporter construct fused to the 3′-UTR of the target mRNA. Thus, the data available so far have to be interpreted with caution, and it is conceivable that many of the described miRNA-target interactions can only occur in specific cellular contexts. A new promising method to detect functional miRNA targets has been recently described [31]. This technique uses the naturally occurring double-stranded miRNA/mRNA complexes present in the cells as primers for initiating cDNA synthesis on the messenger template. The miRNA and the target can then be identified by sequencing the molecules amplified in a PCR reaction. This methodology avoids several of the problems mentioned above, but more data are needed to establish the extent of functional interactions occurring in the cells that are missed using this approach.

**miRNAs as regulators of pancreatic β-cell function**

As is the case for other mammalian cells, pancreatic β-cells express a large set of miRNAs. The targets predicted for these miRNAs are enriched in genes involved in transcriptional regulation and include several transcription factors that play pivotal roles in β-cell differentiation and function, such as HNF-3β (FOXA2), HNF-6, HES-1, ID2 and Sp1 cofactors [26-30]. Thus, the miRNAs are likely to modulate several aspects of β-cell physiology and to be instrumental in defining the specific properties of insulin-secreting cells. Using a cloning strategy, Stoffel and collaborators identified 67 miRNAs expressed in the murine pancreatic β-cell line MIN6 [32]. Most of these miRNAs were already identified in other cells, but some of
them were unknown. Two of the newly discovered RNAs were of particular interest because they turned out to be specifically expressed in the endocrine pancreas. In fact, miR-375 expression was found to be restricted to pancreatic islets and miR-376 was only detected in β-cells. The recent development of microarray tools specifically devoted to miRNA quantification has greatly facilitated the analysis of miRNAs. Using this approach, we detected approximately 150 miRNAs in MIN6 cells (UNPUBLISHED DATA). The most abundant miRNAs present in these cells and their general characteristics are summarized in Table 1. In agreement with the data of Poy and colleagues [32], we found that miR-375 is one of the most abundant miRNAs in insulin-secreting cells. The level of this molecule is crucial to permit the accomplishment of specific pancreatic β-cell tasks. Indeed, overexpression of miR-375 led to impairment in glucose-induced insulin release, while functional inactivation of this small RNA has an opposite effect [32]. Insulin-release triggered by glucose can be altered either by a modification of the complex signaling cascades elicited by the sugar and/or by effecting the activity of the machinery controlling exocytosis. Detailed analysis of the mechanism underlying the action of miR-375 points to a defect in a distal step in the exocytotic process rather than a perturbation of glucose signaling. In fact, inhibition of insulin secretion is observed also when exocytosis is triggered by directly depolarizing the plasma membrane, a maneuver that bypasses glucose metabolism and directly activates the exocytotic machinery. miR-375 was found to target the mRNA of myotrophin/V1 [29], a small cytoplasmic protein first identified in cardiomyocytes [33]. Interestingly, silencing of myotrophin in β-cells by RNA interference mimicked the effect of miR-375 on glucose-stimulated insulin secretion [32], suggesting that at least part of the effect of the miRNA is exerted through translational repression of this protein. The precise role of myotrophin/V1 in the exocytotic process of β-cells is unclear at present. Myotrophin/V1 possesses two important features that could potentially explain the effect on insulin secretion. First, it is able to inhibit actin polymerization by binding to the capping protein CapZ [34]. Modification of actin dynamics resulting from miR-375-mediated reduction in myotrophin/V1 expression could negatively impact on the final delivery of secretory granule to the plasma membrane and decrease exocytosis. Second, myotrophin/V1 binds to the transcription factor NF-κB, stimulates its translocation to the nucleus and enhances its transcriptional activity [35]. Attenuation of the activity of NF-κB has been reported to generate mice with perturbed expression of genes involved in insulin exocytosis and displaying impaired glucose-induced insulin secretion [36]. More experiments are needed to elucidate the precise role of myotrophin/V1 in β-cells and to identify other functional targets of miR-375.

miR-375 is not the only miRNA involved in the control of the secretory process of pancreatic β-cells. We found that in insulin-secreting cells, an increase in miR-9, a miRNA very abundant in brain and present in smaller amounts in pancreatic islets, causes a defect in exocytosis [37]. The effect of miR-9 on insulin secretion is indirect and results from the translational repression of the transcription factor Oectc 2 (OC2). In fact, we were able to show that, under normal conditions, OC2 controls the level of granuphilin/Sp4, a Rab GTase effector associated with secretory granules of β-cells that exerts a potent inhibitory action on insulin secretion [38,39]. When the concentration of miR-9 is raised, translation of OC2 mRNA is prevented, leading to a drop in the level of the transcription factor. This relieves the repression on the granuphilin promoter and causes an accumulation of the Rab effector in the cells. The presence of inappropriate levels of granuphilin is then at the origin of the defect in insulin secretion. Pancreatic β-cells and neurons share many components of the machinery of exocytosis [40]. Granuphilin represents one of the most striking exceptions because the expression of this protein is restricted to β-cells and is undetectable in neurons [38,41]. Our findings suggest that one of the reasons to maintain relatively low levels of miR-9 in β-cells is to avoid the presence of excessive amounts of granuphilin that would negatively affect insulin secretion.

The expression of another neuronal enriched miRNA, miR-124a, was recently shown to increase in the developing mouse pancreas between embryonic stage e14.5 and e18.5, suggesting an involvement in β-cell differentiation [42]. In insulin-secreting cell lines, miR-124a was found to modulate the expression of HNF-3β (FOXA2), a master regulator of pancreatic development [4] and of its downstream targets PDX-1 (pancreatic duodenum homeobox-1), Kir6.2 and SUR1. PDX-1 is a key element in the control of insulin transcription [4] while

### Table 1. miRNAs abundantly expressed in MIN6 B1 cells.

<table>
<thead>
<tr>
<th>miRNA</th>
<th>Relative abundance</th>
<th>Tissue distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Let-7 a, b, c, d, f</td>
<td>100</td>
<td>Ubiquitous</td>
</tr>
<tr>
<td>miR-30 b, c, d, e</td>
<td>41</td>
<td>Ubiquitous</td>
</tr>
<tr>
<td>miR-29 a, b, c</td>
<td>40</td>
<td>Ubiquitous</td>
</tr>
<tr>
<td>miR-200 a, b, c</td>
<td>37</td>
<td>Mainly expressed in prostate, lung and kidney</td>
</tr>
<tr>
<td>miR-23 a, b</td>
<td>32</td>
<td>Mainly expressed in lung and thymus</td>
</tr>
<tr>
<td>miR-375</td>
<td>31</td>
<td>Pancreatic islets and pituitary gland</td>
</tr>
<tr>
<td>miR-7</td>
<td>26</td>
<td>Highly expressed in brain and adrenal glands</td>
</tr>
<tr>
<td>miR-26 a, b</td>
<td>26</td>
<td>Ubiquitous</td>
</tr>
<tr>
<td>miR-27 a, b</td>
<td>26</td>
<td>Ubiquitous</td>
</tr>
<tr>
<td>miR-16</td>
<td>16</td>
<td>Ubiquitous</td>
</tr>
</tbody>
</table>

Global miRNA expression in MIN6 B1 cells was determined by microarray analysis [69]. The relative abundance of the miRNAs is given as a percentage of the expression level of the members of the Let-7 family.
accomplishment of highly specialized insulin-secreting cells would be instrumental for understanding the mechanisms permitting adaptation of the primary human cells and tumor cell lines [45,46]. The identified demonstrated to be involved in cell growth and apoptosis in hyperglycemia and diabetes. A number of miRNAs have been shown to down-regulate the expression of miRNAs in the regulation of the expression of components required for proper functioning of the insulin secretory apparatus. In view of the data gathered in other cell types, additional aspects of the biology of β-cells, including cell proliferation, apoptosis and metabolism are very likely to be influenced by the presence of a specific subset of miRNAs. The possible involvement of miRNAs in these processes will be briefly discussed in this section.

The islet β-cell mass in adults has to be adjusted to maintain an appropriate balance between insulin supply and the metabolic demand. Obesity is known to be associated with a diminished insulin sensitivity of peripheral tissues. In obese individuals, the augmented metabolic demand appears to be compensated by an increase in β-cell mass achieved through different mechanisms including β-cell replication, neogenesis, hypertrophy and survival [44]. In a subset of obese individuals, this adaptive process eventually fails, leading to chronic hyperglycemia and diabetes. A number of miRNAs have been demonstrated to be involved in cell growth and apoptosis in primary human cells and tumor cell lines [45,46]. The identification of the miRNAs governing replication and survival of insulin-secreting cells would be instrumental for understanding the mechanisms permitting adaptation of the β-cell mass to physiological conditions and those leading to cell death in disease states.

The capacity to adjust most of their activities to changes in circulating levels of glucose and other nutrients constitutes one of the peculiarities of β-cells. The signaling pathways elicited by glucose and other nutrients involve the generation of ATP and other metabolic coupling factors derived from mitochondrial metabolism [47]. Consequently, in β-cells, any alteration in the metabolic state can have a severe functional impact. miR-14 was found to regulate adipocyte droplet size and triacylglycerol levels in the fruit fly Drosophila [48]. A direct homolog of miR-14 has not yet been identified in mammalian cells, but it is tempting to speculate that other miRNAs could accomplish analogous tasks in humans. The identification of miRNAs modulating glucose or lipid metabolism in β-cells would have a tremendous impact on the understanding of some essential aspects of the biology of insulin-secreting cells.

Impact of miRNAs on other β-cell functions

The results described above have highlighted the involvement of miRNAs in the regulation of the expression of components required for proper functioning of the insulin secretory apparatus. In view of the data gathered in other cell types, additional aspects of the biology of β-cells, including cell proliferation, apoptosis and metabolism are very likely to be influenced by the presence of a specific subset of miRNAs. The possible involvement of miRNAs in these processes will be briefly discussed in this section.

The islet β-cell mass in adults has to be adjusted to maintain an appropriate balance between insulin supply and the metabolic demand. Obesity is known to be associated with a diminished insulin sensitivity of peripheral tissues. In obese individuals, the augmented metabolic demand appears to be compensated by an increase in β-cell mass achieved through different mechanisms including β-cell replication, neogenesis, hypertrophy and survival [44]. In a subset of obese individuals, this adaptive process eventually fails, leading to chronic hyperglycemia and diabetes. A number of miRNAs have been demonstrated to be involved in cell growth and apoptosis in primary human cells and tumor cell lines [45,46]. The identification of the miRNAs governing replication and survival of insulin-secreting cells would be instrumental for understanding the mechanisms permitting adaptation of the β-cell mass to physiological conditions and those leading to cell death in disease states.

The capacity to adjust most of their activities to changes in circulating levels of glucose and other nutrients constitutes one of the peculiarities of β-cells. The signaling pathways elicited by glucose and other nutrients involve the generation of ATP and other metabolic coupling factors derived from mitochondrial metabolism [47]. Consequently, in β-cells, any alteration in the metabolic state can have a severe functional impact. miR-14 was found to regulate adipocyte droplet size and triacylglycerol levels in the fruit fly Drosophila [48]. A direct homolog of miR-14 has not yet been identified in mammalian cells, but it is tempting to speculate that other miRNAs could accomplish analogous tasks in humans. The identification of miRNAs modulating glucose or lipid metabolism in β-cells would have a tremendous impact on the understanding of some essential aspects of the biology of insulin-secreting cells.

Potential role of miRNAs in diabetes

An increasing number of studies have reported variations in the expression of miRNAs in different physiological or pathological conditions [49–51]. Prolonged exposures of β-cells to elevated levels of glucose and free fatty acids or to inflammatory cytokines have a strong impact on gene expression and are typically associated with de-differentiation and functional alterations of β-cells [52–55]. Changes in miRNA expression are likely to contribute to these phenomena but no published evidence is presently available. Technologies allowing global assessment of miRNA levels are now becoming broadly accessible and it can be anticipated that the impact of glucose, free fatty acids and inflammatory cytokines on β-cell miRNA expression will soon be unveiled. The signals that induce miRNA expression and regulate their transcription are poorly understood. This is particularly true for the miRNAs produced from transcription units that are located outside from protein-coding genes. Interestingly, the expression of some miRNAs has been shown to be modulated by the transcription factors cAMP-response-element-binding-protein (CREB) and REST (RE1 silencing transcription factor) [56–58]. Both of these transcription factors play important roles in pancreatic β-cells. CREB has been demonstrated to be involved in survival and proliferation of β-cells [59], while silencing of REST is necessary to allow the expression of specific phenotypic traits of β-cells [60] and to maintain their secretory functions [61]. This raises the possibility that at least part of the effects of these transcription factors may be exerted through changes in the level of a group of miRNAs.

T2DM results from a combination of unfavorable genetic and environmental factors that synergize to diminish sensitivity from insulin target tissues and insulin secretion from pancreatic β-cells. Although genetic susceptibility in T2DM is well established, only in a limited number of cases the causes of the disease have been determined. Genetic variants affecting miRNA function may constitute new factors predisposing to the development of diabetes. Indeed, polymorphisms in the 3′-UTR of miRNAs whose expression is controlled by miRNAs have been reported [62,63]. Some of these variants result in the destruction of evolutionary conserved miRNA target sites leading to expression of inappropriate levels of the gene product. Other mutations create illegitimate target sites in the 3′-UTR of miRNAs and can cause miRNA-mediated translational repression of the gene. Future studies will have to assess the potential impact of these genetic variants on pancreatic β-cell function and determine their possible role in predisposing individuals to T2DM.

Expert commentary

Mature miRNAs are small molecules that can be easily synthesized. In addition, each of these noncoding RNAs can be selectively and potently inactivated using modified antisense RNA molecules [64–66]. Because of these properties, once their contribution to the regulation of β-cell functions is established, it will become theoretically possible to favor β-cell replication, prevent β-cell death or improve insulin synthesis and secretion by manipulating the level of selected miRNAs. miRNAs and their antagonists are very similar in nature to small interfering RNAs. Thus, future strategies eventually developed to silence genes by RNA interference will be easily
adapted to allow the modification of the cellular levels of miRNAs [68]. Indeed, coupling of miRNA antagonists to cholesterol has already been demonstrated to allow efficient cellular delivery [67]. The coming years will certainly clarify the real potential of miRNAs as new tools for the prevention and/or treatment of diabetes.

Five-year view

The discovery of miRNAs has added a new unsuspected layer of complexity to the control of gene expression. Although so far we have probably obtained only a glimpse of the immense regulatory potential of these tiny molecules, miRNAs have already attracted the attention of a large cohort of molecular and cellular biologists. The number of studies devoted to the assessment of the role of miRNAs in a wide variety of processes and diseases is increasing exponentially. In the coming years, the results obtained are expected to revolutionize many of the current models in biomedical sciences. The elucidation of the precise role of miRNAs in pancreatic β-cells will be of particular importance since alterations in gene expression are associated with diabetes mellitus, a disease representing a major socio-economic burden in Western countries and for which the presently available treatments are not entirely satisfactory. Within the next 5 years, we can expect to have a global view of all the miRNAs present in pancreatic β-cells and of the alterations in the expression pattern elicited by environmental conditions with a deleterious impact on the function and survival of insulin-secreting cells. This knowledge would form the basis for future investigations aimed at assessing the precise role of selected miRNAs in β-cells and their possible contribution to the development of diabetes. This type of study could be envisaged either by taking advantage of the availability of molecules that specifically inactivate each miRNA in vitro and in vivo [64–67], or by genetically inactivating the miRNA genes in β-cells. These investigations will hopefully help in unraveling the causes of defective insulin secretion in T2DM patients and favor the design of new pharmacological principles to improve the treatment and prevention of diabetes.

Key issues

- Mammalian cells were recently found to contain several hundred small noncoding RNA molecules called miRNAs (miRNAs), capable of exerting a translational control on the expression of up to a third of human genes.
- miRNAs participate in the regulation of several cellular processes and are involved in an increasing number of human diseases including cancer.
- There is accumulating evidence that a subset of miRNAs governs the functional properties of pancreatic β-cells.
- Alterations in the level of a group of miRNAs or genetic variations that affect their functions may possibly contribute to β-cell dysfunction and predispose to diabetes mellitus.
- The definition of the role of individual miRNAs in β-cells may disclose new possible pharmacological approaches based on the manipulation of the endogenous level of these powerful noncoding RNAs.

References

Papers of special note have been highlighted as:

• of interest
•• of considerable interest

**MicroRNAs as regulators of β-cell functions**


- Demonstrates that under certain physiological or pathological conditions the translational repression exerted by microRNAs (miRNAs) can be relieved.


- First paper describing a role for miRNAs in the control of pancreatic β-cell functions.


- Shows that changes in miRNA level can alter the expression of one of the key components of the machinery of exocytosis of pancreatic β-cells.


Demonstrates that mutations affecting miRNA target sequences can be responsible for important phenotypic variations.


Shows the existence of human polymorphisms in miRNA sequences and in potential miRNA target sites.


Demonstrates that the level of miRNAs can be specifically reduced in vivo using oligonucleotide derivatives.