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Micro-managing the pancreatic β cell

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In his writings on the milieu intérieur, Claude Bernard first hypothesized on the presence of feedback mechanisms within the cell to maintain its steady-state physiology.[1] Walter Bradford Cannon would subsequently build on this concept and coin the term homeostasis. To date, numerous counter-regulatory mechanisms have been characterized in the cell, illustrating the dynamic nature of the intracellular environment. Among the more recently discovered is the microRNA (miRNA) pathway, and as of this writing, 2578 mature human miRNAs have been annotated in the miRBase database V20, which now catalogs 206 different plant and animal species.[2] Importantly, since their identification in *C. elegans*, a canonical pathway has now been identified to describe how miRNAs are processed and incorporated into Argonaute-containing complexes to maintain their effect on gene expression (**Fig. 1**). Many insights into the functional role of miRNAs have been recently made, improving our understanding of how these small RNAs integrate into the already complex landscape of regulating gene expression. Most notably, based on a number of miRNA-knockout mouse models showing subtle phenotypes under steady-state conditions, a hypothesis has gradually emerged suggesting the miRNA pathway contributes to cellular stress responses.[3] Moreover, these observations are further supported by our recent study focusing on the role of Argonaute2 (Ago2) in the compensatory proliferation of the pancreatic β cell during insulin resistance.[4] These recent findings culminate over 10 y since our initial study, which identified *miR-375*, a miRNA now established among the highest expressed sequences in this cell type.[5]

The very first loss- and gain-of-function studies revealed this miRNA as a negative regulator of insulin release via the direct targeting of the gene *myotrophin*. The role of *miR-375* in insulin release was further confirmed in vivo using the total mouse knockout (375KO).[6] Furthermore, this model facilitated the identification of several additional targets of *miR-375*, including *Elavl4*/*HuD*, *Cadm1*, *Gphn*, and *Rasd1*. Moreover, 375KO mice exhibited hyperglycemia and decreased β-cell mass, and these effects were further exacerbated after crossing the knockout onto the *leptin*-deficient *ob/ob* background. This result indicated that *miR-375* plays an essential role in the compensatory β-cell proliferation induced by insulin-resistance in *ob/ob* mice. Moreover, our recent observations showing loss of Ago2 also blocked proliferation during insulin resistance further support a role for the miRNA pathway in mediating cellular stress responses. Importantly, we showed that Ago2 is upregulated in the pancreatic islets of both genetic and diet-induced models of insulin resistance and obesity as a result of the silencing of *miR-184*. Furthermore, the inverse relationship between *Ago2* and *miR-184* was confirmed in islets of human subjects, further underlining the relevance of studying β-cell function in these mouse models. Of note, *miR-184* was shown to target the gene *Slc25a22*, a mitochondrial glutamate transporter, indicating that miRNAs may regulate many stages of the canonical pathway in the β cell leading to insulin secretion.[7]

While *miR-184* has been shown to potently regulate both growth and secretion of the β cell, it remains to be determined how changes in insulin sensitivity, as shown in the models of obesity, may contribute to the direct regulation and function of all miRNAs in this cell type. Meanwhile, it is unclear whether miRNA function in the β cell may also change in response to alterations within its metabolic environment, such as levels of extracellular nutrients (glucose, amino acids, or fatty acids), signaling hormones, neurotransmitters, or perturbations in cell-to-cell contact with neighboring endocrine, endothelial, mesenchymal, or neuronal cells. Moreover, key transcriptional regulators of miRNAs in the β cell as well as RNA-binding proteins that may specifically bind *miR-184* and target it for degradation remain unidentified. It is unclear how the additional abundant β-cell miRNAs may coordinately target genes to promote insulin release as well as facilitate compensatory expansion of the β cell as metabolic demand increases. While *miR-184* was the most significantly regulated miRNA in the islets of insulin-resistant mice, additional miRNAs have been shown to participate in β-cell growth using human islet cells.[8] It will presumably be determined that numerous miRNAs act in a concerted fashion to regulate multiple targets that mediate cell growth and the continual recruitment of insulin-containing granules to the plasma membrane. Interestingly, it is still not known whether the same miRNAs perform an identical regulatory function in different cell types. As Ago2-associated sequences such as *miR-375* are expressed in several unique tissues, such as the pituitary and adrenal gland, it is unclear how this miRNA may regulate growth and secretion in these other neuroendocrine cell types.

In summary, in light of recent findings identifying components of the RNAi machinery in the nucleus, including Ago2, Dicer, and GW182, it appears only a matter of time before new mechanistic insights into the role of this pathway are discovered. While the identification of

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direct targets of the miRNAs and their biological significance remains to be studied in greater detail, the role of small RNAs in the nucleus also remains to be described. The story of non-coding RNAs and their functional role in the pancreatic β cell is far from complete. In an exciting time of rapidly evolving technologies, the next 10 y are certain to bring clarity to this expanding narrative.

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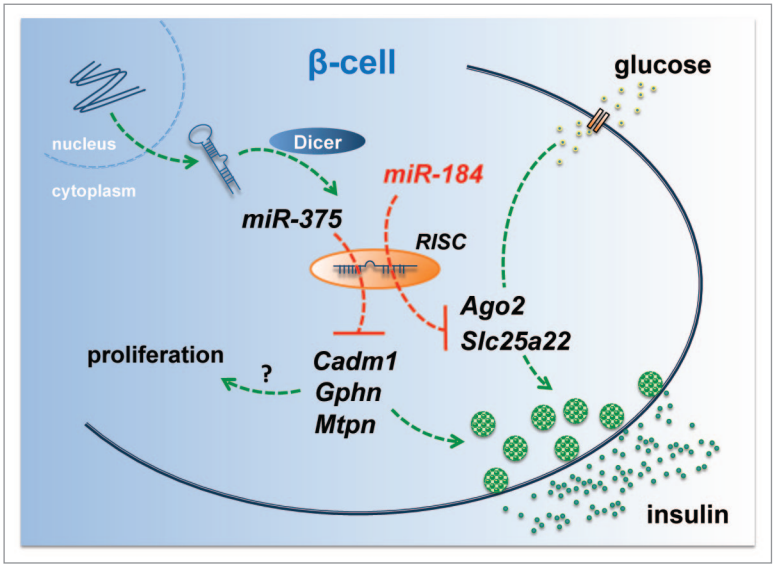

Figure 1. Regulation of β-cell growth and function by the microRNA pathway. *miR-184* and *miR-375* coordinately regulate β-cell proliferation and insulin secretion. Silencing of *miR-184* alleviates inhibition of its targets *Ago2* and *Slc25a22* during insulin resistance. *Ago2* mediates *miR-375* function on several target genes to regulate the release of insulin and β-cell proliferation.