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Islet microRNAs in health and type-2 diabetes

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Failure of the β-cell to secrete enough insulin is a major contributing factor in the pathogenesis of type-2 diabetes (T2D). MicroRNAs provide an extra layer in the regulation of protein expression, and are thus involved in β-cell compensation during development of the disease. In this review, we discuss how microRNAs can regulate their target protein expression and phenotypic output, present the status of nutritional regulation of microRNA expression, and summarize work on microRNA expression in human islets. In conclusion, current data lend support to microRNAs being essential regulators of insulin secretion. Future work will describe microRNAs in α-cell function, details of the microRNA–mRNA network, and possibilities to use microRNAs as biomarkers and in therapeutic treatment of T2D and complications.

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Introduction

Diabetes is a group of diseases all characterized by chronic hyperglycemia. The World Health Organization (WHO) reports diabetes to be the seventh leading cause of death globally year 2016 with rapidly increasing prevalence worldwide and is expected to reach 700 million cases in 2045 [1]. The absolute majority (~90%) of all diabetic patients suffer from type-2 diabetes (T2D). T2D further divides into four different subgroups as recently published from Lund University Diabetes Centre [2]. The interplay between genetic and lifestyle factors are causative to the development of T2D but how this occurs is not yet fully elucidated. However, among the main contributing lifestyle factors are reduced physical activity and increased obesity. T2D increases the risk for complications such as cardiovascular disease, nephropathy, retinopathy and neuropathy. Interestingly, the individual T2D subgroups have different risks of developing the specific complications [2].

Both increased insulin resistance in target tissues (mainly liver, muscle and adipose tissue) and impaired insulin secretion from pancreatic β-cells characterize T2D. Still, recent evidence strongly supports that failure of the β-cells to respond to the increased metabolic demand defines the pathogenesis of the disease [3]. The β-cells are organized together with other hormone secreting cells, most notably the glucagon-secreting α-cells, in the islets of Langerhans within the pancreas. Preservation of sufficient insulin secretion, require β-cell compensation and is dependent on the number and size of β-cells (referred to as β-cell mass) and the function of each individual β-cell [3,4]. Changes in β-cell mass occurs in T2D, and proliferation of β-cells have been demonstrated to involve microRNAs [5••]. However, this change in β-cell mass is too small to account for the full reduction in insulin secretion [6]. The main trigger for insulin release is glucose and elevated blood glucose levels leads to the release of insulin through a series of events referred to as the stimulus-secretion coupling pathway of the β-cell (reviewed in Ref. [4]). The end-result of this pathway is insulin release through Ca^{2+}-dependent exocytosis of insulin-containing vesicles. T2D is associated with a loss of first phase insulin secretion, which has been coupled with reduced exocytosis. Indeed, exocytotic genes show reduced expression in human T2D islets [7,8]. Several aspects of β-cell identity and physiology, including the release of insulin, is under the regulation of microRNAs [9]. Moreover, several studies demonstrate differential microRNA expression in islets from T2D donors or diabetic animal models [5••,9,10•,11,12••].

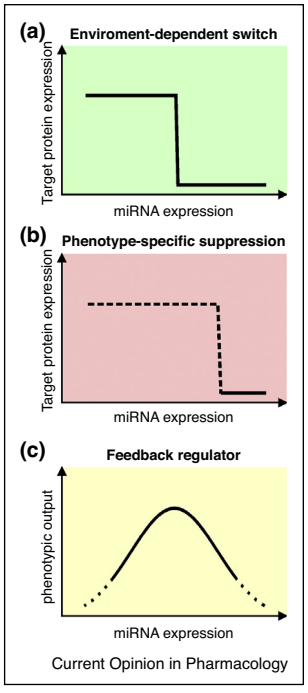
Function of microRNAs

MicroRNAs are short (21–23 nt) RNAs that do not code for proteins. Instead they regulate protein expression by binding to their complementary mRNA(s) causing translational inhibition or mRNA destabilization [13]. For a more detailed description regarding microRNA biogenesis, target recognition and biological function see [14••]. Post-transcriptional regulation of gene output by microRNAs is intricate. The output repression of a single microRNA is modest, and often several different microRNAs regulate the expression one gene. In short, the nature of microRNAs is to complement and extend the gene-regulation by transcription and other nuclear events [14••]. Hence, the network of microRNA–mRNA interaction gives an extra layer to post-transcriptional gene

regulation, and frequently microRNAs are termed rheostats [15], which can act within the β-cell compensatory network [9].

The properties of microRNAs make them ideal factors in forming the phenotypic output of different cells in the body. In Figure 1, we describe microRNA functions and their effects on target protein expression and phenotypic output. First, a microRNA can act as an *environment-dependent switch* or off-switch. By this, the microRNA regulates the genes that are not expressed under certain conditions (Figure 1a). Second, some microRNAs can contribute in *phenotype-specific suppression* (Figure 1b). Here the expression of a specific microRNA is constitutively high to ensure suppression of specific target proteins belonging to so called 'disallowed genes', genes that will harm the function of a specific cell if expressed. In β-cells, we have the example of miR-29 that help ensure that MCT-1, a monocarboxylate transporter, is not expressed [16,17]. Finally, a microRNA can act as a *feedback regulator* (Figure 1c). Through this function, the microRNA fine-tunes the expression of their target genes to ensure that the protein output is within optimal range for optimal phenotypic output. Either too high or too low levels of microRNA expression can lead to impaired phenotypic function. In some cases, as with mir-375 [18], too high or too low levels of the microRNA is negative for the phenotypic output. There is also the possibility that the interaction is *neutral*, meaning that the microRNA repression serves no biological function or the repression is counteracted by other mechanisms [15].

Figure 1



Function of microRNAs. **(a)** MicroRNAs as an environmental switch, which is turning on and off target protein expression. High microRNA expression mostly results in low protein expression. **(b)** Phenotype-specific suppression is a version of the on-off switch in A. Here the level of the microRNA is high to suppress target protein expression of 'disallowed genes'. Once the expression of the microRNA is reduced under a certain level (dotted line), defective cellular output occurs, which can contribute to disease. **(c)** MicroRNAs as feedback regulator. MicroRNAs gives the extra layer of regulation to keep the cellular phenotypic output at an optimal level. MicroRNA expression thus have a window wherein the phenotypic output is kept within a normal range. Once microRNA expression becomes either too low or too high (dotted lines), the phenotypic output is reduced, which could lead to disease. In case of the β-cell; reduced insulin secretion leading to development of hyperglycemia.

Sometimes the regulation by one single microRNA of a direct target is strong with clear impact on cell function but small effects can be equally important, as they may be a part of a cumulative effect modifying cell function. This is not easy to investigate, but with the development of new genome-editing tools such as CRISPR or the possibility of viral infection of combinations of microRNAs this is conceivable.

Islet microRNA regulation by nutrients

Islet microRNAs are dysregulated in T2D, thus a potential deregulation caused by genetic variations is likely. There is currently limited information regarding genetic alterations in islet microRNA genes; however, other types of non-coding RNAs have recently been shown to regulate microRNAs [19•,20]. Here we focus on environmental factors to answer the questions how glucose and high fat diet (HFD) might affect microRNA expression. Effects by lifestyle factors such as diet can change microRNA expression as a compensatory mechanism to adjust the islet β-cell response to the metabolic demand. Alternatively, the modification of microRNA expression leads to impaired function.

Glucose regulated microRNAs

MicroRNAs are, like all transcripts, regulated by genetic and environmental factors. However, transcriptional regulation of islet microRNAs is still largely unexplored. Glucose is the main trigger for insulin secretion and a well-known regulator of gene expression, including microRNA expression. Glucose has been shown to decrease the levels of miR-375 [21,22], and miR-130a [22] in rat islets and increase the levels of miR-29a in human and rat islets [23]. Moreover, glucose-mediated variations in AMPK activity reduce miR-184 expression in both mouse and human islets [24], and glucose-regulation of thioredoxin-interacting protein (TXNIP) increases miR-204 expression and decreases expression of downstream targets, including the GLP-1 receptor (GLP1R) [10•,25].

In a study in islets from Wistar and Goto-Kakizaki (GK)-rat (a model of spontaneous T2D) islets, we found that