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The small RNA miR-375 – a pancreatic islet abundant miRNA with multiple roles in endocrine beta cell function

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ABSTRACT

The pathophysiology of diabetes is complex and recent research put focus on the pancreatic islets of Langerhans and the insulin-secreting beta cells as central in the development of the disease. MicroRNAs (miRNAs), the small non-coding RNAs regulating post-transcriptional gene expression, are significant regulators of beta cell function. One of the most abundant miRNAs in the islets is miR-375. This review focus on the role of miR-375 in beta cell function, including effects in development and differentiation, proliferation and regulation of insulin secretion. It also discusses the regulation of miR-375 expression, miR-375 as a potential circulating biomarker in type 1 and type 2 diabetes, and the need for the beta cell to keep expression of miR-375 within optimal levels. The summed picture of miR-375 is a miRNA with multiple functions with importance in the formation of beta cell identity, control of beta cell mass and regulation of insulin secretion.

1. Introduction

Diabetes is a prevalent endocrine disease with an almost exponential worldwide increase. It has become a major burden on health care systems globally, causing suffering for patients and their families. Roughly, there are two major subtypes of the disease, type 1 diabetes (T1D) and type 2 diabetes (T2D). The pathogenesis of T1D includes an autoimmune beta cell destruction, lack of insulin secretion and hyperglycemia (Mathis et al., 2001). T2D is a more complex disease, and in most cases insulin resistance in target tissues increases the demand on the pancreatic beta cells to secrete more insulin (Halban et al., 2014). Therefore, one of the key factors in the development of T2D is impaired insulin secretion from the beta cells, where first phase insulin secretion is absent and second phase insulin secretion reduced. The progression of T2D requires complex beta cell adaptation to meet the increasing demand to produce and secrete more insulin. MicroRNAs (miRNAs) are small non-coding RNAs that have the capacity to take part in such adaptions, and prior to the diseased state, expression of several miRNAs is altered (Bolmeson et al., 2011; Erener et al., 2013).

The endocrine part of the pancreas constitutes the islets of Langerhans. The islets are cell clusters spread out through the pancreas and the number of islets within one pancreas is approximately 1 million. The major cell types within the islets are insulin-secreting beta cell (~60%), glucagon-secreting alpha cells (~30%) and somatostatin-secreting delta cells (~10%). High glucose condition stimulates the release of insulin, which in turn facilitates the uptake of glucose into target tissues. The uptake of glucose into the beta cell initiates a cascade involving increased metabolism with elevated intracellular ATP as a result, closure of the ATP-dependent K^+ channel (K_{ATP} channel), opening of voltage-sensitive Ca^{2+} channel, influx of Ca^{2+} and exocytosis of insulin-containing granules (Ashcroft and Rorsman, 2012). Important for the formation of beta cell identity are key transcriptions factors such as *PDX1*, and the presence of certain miRNAs. MiRNAs are ~22 nt non-coding RNAs that suppress the expression of genes by mRNA degradation, mRNA deadenylation and/or translational repression (Winter et al., 2009). In 2004, we published the first paper describing an islet-abundant miRNA (Poy et al., 2004). At that time miR-375 was thought to be a beta cell specific miRNA, but later research also

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identified miR-375 in other (neuro)-endocrine cells in the islets (alpha cells), adrenal gland, thyroid, pituitary, lungs and gastrointestinal tract (Latreille et al., 2015). Still, miR-375 has several important functions in the beta cell and takes part in generating the beta cell identity. Lately, it has also been widely discussed if circulating levels of miR-375 can be a valuable biomarker in diabetes prediction (Latreille et al., 2015). Hence, miR-375 is a prime example of a miRNA important for insulin secretion, and thereby in diabetes development.

Here, I summarize current knowledge of the role of miR-375 in beta cells from different angles. The first part presents a plausible role of miR-375 in diabetes development and it describes currently available miR-375 mouse models. Thereafter follows a description of the current view on the regulation of miR-375 expression and biogenesis in the islet. This is followed by a summary of the role of miR-375 in the beta cell: in proliferation, redifferentiation, upregulation of beta cell transcription factors, insulin biogenesis, and regulation of beta cell insulin secretion. Finally, the review discuss miR-375 as a potential circulating biomarker for diabetes prediction.

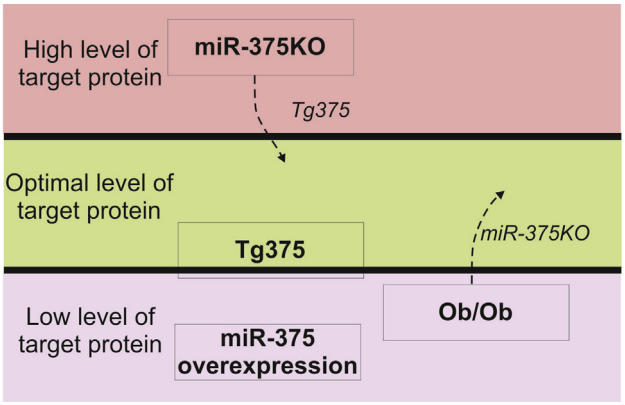

Fig. 1. Target protein levels in different miR-375 models. The idea of miR-375 being a rheostat keeping miR-375 target protein levels at an optimal level is from the review by Bartel (Bartel, 2009). This image demonstrates how the levels of miR-375 target proteins in the different models of miR-375 only comes out of the optimal zone of expression in extreme conditions of miR-375 overexpression and knockout.

2. Development of diabetes and miR-375

MicroRNA expression analyses on islets from human donors have indicated miR-375 as one of the most abundant miRNAs (Bravo-Egana et al., 2008; van de Bunt et al., 2013). The expression level of miR-375 is stable, even leading one study to use this miRNA as an endogenous control in small RNA expression analysis (Pullen et al., 2011). As a key miRNA with a broad target network influencing many functions in the beta cell, it is not surprising that the levels of miR-375 levels are not differentially-expressed in islets from human T2D individuals as compared to non-diabetic (ND) controls (Sebastiani et al., 2015). However, as described below, miR-375 expression can increase under certain stress situations. Moreover, there is a slight indication, in a small number of human islet donors, of increased miR-375 expression in islets from glucose-intolerant donors (Bolmeson et al., 2011).

2.1. miR-375 and mouse models

The group of Markus Stoffel, who first discovered miR-375, has generated a general miR-375 knockout model (miR-375KO) and a beta cell specific transgenic model overexpression miR-375 (Tg375) (Poy et al., 2004; Latreille et al., 2015; Poy et al., 2009). The islets and other miR-375 expressing tissues are fully ablated of miR-375 in the miR-375KO (Poy et al., 2009), and the Tg375 overexpress miR-375 1.5 times specifically in the beta cells (Latreille et al., 2015).

The Tg375 mouse has no phenotype (Latreille et al., 2015), which differ from experiments using an adenovirus approach to overexpress miR-375 *in vitro* in islets. In the latter, insulin secretion was significantly reduced due to reduced exocytosis (Poy et al., 2004). The difference between Tg375 and the *in vitro* miR-375 overexpression is likely a dosage effect. The overexpression *in vitro* lead to higher expression levels of miR-375, than in the Tg375 mouse model, and thereby a stronger reduction of the target gene expression and a stronger phenotype (Fig. 1). It has been suggested that miRNAs have an optimal level of operation (Bartel, 2009). Both too high and to low levels can be detrimental for cell function. Hence, I suggest that the level of miR-375 in the Tg375 model could still be within the area of optimal miR-375 level, whereas the adenoviral overexpression pushes miR-375 out of this zone and thereby have stronger effects on miR-375 targets (Fig. 1).

The 375KO mice are hyperglycemic, have reduced beta cell and increased alpha cell mass (Poy et al., 2009). Measured glucose stimulated insulin secretion compensated for changes in insulin content was not different between the 375KO and control islets, but insulin exocytosis increased in the 375KO. Moreover, glucose-regulated glucagon secretion was reduced. Interestingly, combining the 375KO and the Tg375 rescued the 375KO phenotype and the mice became normoglycemic (Latreille et al., 2015) (Fig. 1).

2.2. Differential expression in islets of diabetic animal models

The Goto-Kakizaki (GK) rat, selectively bred from Wistar rats with high blood glucose levels, is a well-studied non-obese spontaneous T2D animal model (Goto et al., 1976; Portha et al., 2009). We have investigated miR-375 expression in this model and we found no significant difference in miR-375 expression between GK and Wistar control islets, when measured in freshly isolated islets (Esguerra et al., 2011). The diabetic phenotype of the GK rat most likely involve other differentially-regulated miRNAs.

The obese diabetes model the ob/ob mouse compensate for an increased metabolic demand, due to insulin resistance, by increasing the beta cell mass and thereby elevated release of insulin. Concomitant with the increase in beta cell mass, miR-375 levels are also increased in ob/ob islets as compared to control islets (Poy et al., 2009). That miR-375 is responsible for the beta cell expansion in the ob/ob model was elegantly demonstrated when ob/ob mice were crossed with the miR-375KO in the same study. This lead to a reduced beta cell mass and decreased release of insulin, most likely due to increased levels of key miR-375 target genes (Fig. 1). Moreover, ob/375KO had a much more severe diabetes development than the control ob/ob mice, most likely due to that the mice no longer could compensate for the increased demand from target tissue by increasing the beta cell mass.

3. Biogenesis of miR-375

The literature contain extensive and detailed descriptions of the biogenesis of miRNAs (See e.g (Bartel, 2009; Beermann et al., 2016)) and I will therefore only briefly go through this process. Genes encoding for miRNA precursors (pri-miRNAs) are present throughout the genome, and many of them organize in clusters. Often, genes coding for pri-miRNAs are within protein-coding regions and in a large portion of these, the protein-coding genes serve as host-genes for the miRNAs. Independent transcriptional elements also encode pri-miRNAs. One such example is the gene coding for the precursor of miR-375, which is located in an