The Biochemical Cascades of the Human Pancreatic β-Cells: The Role of MicroRNAs

Joseph W Kim¹, John Z Luo¹,² and Luguang Luo¹*  
¹Department of Internal Medicine, Roger Williams Hospital, Boston University School of Medicine, Providence, RI, USA  
²Doctor’s Choice LLC, Warwick, RI, USA

Abstract

Diabetes mellitus is a disease that poses a burden to the health care system due to its prevalence and chronic nature. Understanding β cell pathophysiology may lead to future therapeutic options for diabetes mellitus type 1 and 2. MicroRNAs (MiR) fine-tune β cell biochemical cascades through specific protein targets. This review argues that miRs may play a critical role in human islet β cell biology and are potential candidates for a new pharmacological strategy. We have reviewed and presented how miRs fine tune four biochemical cascades in islet β cells: glucose stimulated insulin secretion, β cell replication, apoptosis, and development. Only studies that examine human pancreatic islets either in vitro or in vivo are included. The unveiling role of miR pathways in regulating human islet β cell biology could open the door for diagnostic and therapeutic methods for diabetes mellitus prevention and therapy.

Keywords: miRNAs (miR); Human islet; β cells; Diabetes; Metabolism

Introduction

Diabetes mellitus is a prevalent disease in the USA and worldwide. It has a significant burden on the health care system due to its chronic nature and its long-term complications [1-4]. Novel therapeutic and diagnostic strategies could potentially lower the cost to the health care system and ultimately lower the morbidity and mortality of diabetic patients. A better understanding of the physiological mechanisms of the pancreatic β cell could help develop new therapies. In spite of their different pathophysiologies, both diabetes mellitus type 1 and type 2 could benefit from therapies that focus on the β cells. One approach to understanding β cell physiology is the microRNA (miR). MiRs were discovered in the 1990s in Caenorhabditis elegans, and they epigenetically inhibit miRNA translation [5-8]. By inhibiting specific protein or enzyme targets, miRs can regulate a biochemical cascade within the β cell. Depending on which protein is targeted, the overall biochemical cascade can be inhibited or stimulated [6] miRs, by targeting specific enzymes or proteins, can uniquely “fine tune” the biochemical cascades of the β cells. miRs change subtle aspects of a cascade, affecting when, why, or how it occurs. Studies that examine the effect of miRs on biochemical cascades focus on four pathways: glucose stimulated insulin secretion (GSIS) [9-19], replication [20-24], apoptosis [25-32], and development [33-35].

Multiple miRs regulate each cascade and have unique ways of fine tuning them (Figure 1). This review argues that miRs could be the mechanism of a new form of regulating human islet β cell biology. Using pharmacologic agents that target miR pathways, human islet β cells may be fine-tuned. First, the article will demonstrate how β cell biochemical cascades are fine-tuned by miR; second, potential agents or special vectors carrying miRs can be used to target miR pathways modifying human islet β cell biological processes.

miRs Fine-Tune β Cell Biochemical Pathways

miRs affect subtle aspects of GSIS or the response of GSIS to a stimulus

GSIS is the special release of insulin from β cells in response to glucose [36,37]. It includes β cell glucose detection, insulin released by exocytosis after insulin translation, and insulin storage in vesicles. Multiple enzymes regulate these multiple biochemical cascades in GSIS, and miRs regulate these enzymes to fine tune the GSIS process in human islet β cell in response to glucose [38,39]. MiR-124 affects β cell responsiveness to glucose. miR-124 targets Foxa2, an insulin transcription factor. When Foxa2 is inhibited, the total insulin available for release increases [10].

MiR-124 also affects insulin exocytosis by targeting the protein Mtpn. By doing so, miR-124 can change the rate by which insulin is secreted. The action of miR-124 will not affect the total amount of insulin released [12]. Hence, “how” GSIS occurs is altered. Unlike the regulation of miR-124, miR-204 affects the total insulin available for release. miR-204 inhibits Foxa2, an insulin transcription factor. When Foxa2 is inhibited, the total insulin available in vesicles is reduced [16]. Note that the rate of insulin secretion is not affected. The responsiveness of the β cell to serum glucose levels may not change. Some miRs do not change how GSIS occurs, but rather they affect “when” it occurred. MiR-133 suppresses GSIS in the presence of glucose, forming glucotoxicity. MiR-133 inhibits poly(pyrimidine tract binding protein expression (PTB)). This inhibits insulin synthesis, decreasing insulin available for exocytosis. Another miR, miR-146a, also inhibits GSIS in response to IL-1β. Hence, it may form the basis by which IL-1β and inflammation inhibit insulin secretion [32].

Finally, the example of miR-29 illustrates how delicately a miR can change a biochemical cascade. In the presence of miR-29, GSIS is inhibited. Though GSIS is inhibited, increased glucose concentrations can still increase insulin secretion. miR-29 does not completely inhibit insulin secretion.

*Corresponding author: LuGuang Luo, Center for Stem Cell Research, Department of Medicine/Research, Prior Building Floor 2, 525 Chalkstone Avenue, Providence, Rhode Island, 02908, USA, Tel: +1 401 456 5344; Fax: +1 401 456 5759; E-mail: Lluo@rwmc.org

Received December 04, 2015; Accepted December 07, 2015; Published December 11, 2015


Copyright: © 2015 Kim JW, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
miRs affect apoptosis in response to a stimulus

Apoptosis is programmed cell death (a chronic cell loss process) differing from necrosis (an acute cell loss process). Initiating apoptosis usually requires a special trigger or stimulus. Unlike GSIS, apoptosis cannot be subtly altered but rather its direct response to a stimulus is. A group of miRs initiates β cell apoptosis through β cell detection of a cytotoxic agent. These include either lipids or cytokines. miR-24 is responsible for the mechanism of lipotoxicity in β cell. miR-24 is over-expressed in response to palmitate, a lipid [29]. Then it reduces bcl-2 levels, which induces apoptosis [41,42]. In another instance, the stimuli for the miR are adjacent cells. miR-146a inhibits apoptosis in response to the presence of bone marrow stem cells. miR-146a inhibits FAS, which is crucial to the canonical FAS-mediated apoptotic pathway. This improves β cell longevity and increases β cell mass [43].

miRs regulate β cell replication as a compensatory mechanism for diabetes mellitus type 2 or insulin resistance

When β cells undergo replication, the β cell mass increases, increasing the total insulin secreted from the pancreas. miR-7 regulates replication in response to insulin resistance. miR-7 inhibits the mTOR pathway to increase β cell replication through mTORC1. miR-7 is lowered during insulin resistance, demonstrated in cadaveric studies. [10,21]. As a result, insulin secretion increases in response to insulin resistance. Another miR, miR-184, increases β cell replication in response to diabetes mellitus type 2 through argonaute2. During states of insulin resistance, miR-184 is decreased. miR-184 no longer inhibits argonaute2. Once argonaute2 levels rise, cell proliferation increases [22]. This increases total insulin secretion in the setting of increased diabetes mellitus. In an abstract by Wu, bone marrow stem cells influence adjacent human pancreatic islets via miR-24-2. miR-24-2 inhibits P16INK4a, which inhibits PDX1. The net effect is increased β cell replication. This partly explains the observation that bone marrow co-cultured with human pancreatic islets improves the longevity of the islets and miR-24-2 may play a critical role in human β cell replication [43].

miR-7 affects β Cell development through PDX-1 and ISL-1

miR-7 is involved in development by “fine tuning” the timing of this developmental process. The number of studies looking at miRs during human pancreatic β cell development is limited and less definitive [44]. But several studies suggest the role for miR-7 during development. First, knockout studies have demonstrated that miRs are necessary for β cell development [45]. Second, the expression of miR-7 correlates with β cell development in human fetal pancreatic tissue [35]. Third, expression of miR-7 is associated with human embryonic stem cells that convert into insulin producing cells (IPCs) [34]. It is possible that miR-7 is involved in converting human embryonic stem cells into insulin producing cells (IPCs). Finally, miR-7 is associated with PDX-1 and ISL-1. PDX-1 is found in differentiated β cells. ISL-1 is a marker for differentiated endocrine cells [46]. Another study suggests that miR-7 also controls the timing of β cell differentiation. Starting week 9 until to 14~18 weeks of gestation, miR-7 is expressed at a higher level, which coincides with β cell development process [32,33]. Thus, miR-7 may play a role in fine-tuning the timing of the necessary β cell developmental biochemical cascades.

miR Pathways can be Inhibited or Stimulated

Exposing pancreatic β cells to oligonucleotides with the same sequences as a miR could activate that pathway [47]. Alternatively, oligonucleotides with the complementary sequence could bind and inhibit these miRs [48]. A number of the studies looking at the effect of a miR on a biochemical cascade used oligonucleotides that either mimicked a target miR or had the complementary sequence [28,48,49]. However, in vivo, miRs are vulnerable to degradation by serum ribonucleases [6]. The naked miR requires a vector to deliver it to the pancreatic β cells. Previous studies have looked at different vectors to protect and deliver miRs to the target cells. These include exosomes [50,51], micro-vesicles [52], and modified viruses [53].

Conclusion

The studies examining miRs in the human pancreatic islet model are limited. But they offer a new potential therapeutic strategy for diabetes mellitus. miRs fine tune existing biochemical pathways in human pancreatic islets. By inhibiting or stimulating these miR pathways with oligonucleotides, a patient’s β cells and glycemic status can clinically be fine-tuned.

Acknowledgement

This work was funded by grants from the US National Institutes of Health (NIH) 1R01DK097380-01A1 (L.L.) and National Center for Research Resources (COBRE, 5P20RR018757-10), Juvenile Diabetes Research Foundation International (JDRF) foundation 1-2007-180 (L.L.) and Roger Williams Hospital Research fund (L.L.).

References


