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The Impact of B-Cell Replication on Insulin Resistance

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Abstract

Type 2 diabetes is characterized by a reduction in the mass of b-cells, which is linked to the failure of b-cell compensation. Understanding the mechanism responsible for the adaptive increase in b-cell mass in vivo is essential for the development of effective diabetes treatments. Signaling pathways involving insulin and the insulin receptor (IR) have been identified as crucial in promoting compensatory b-cell proliferation in response to chronic insulin resistance. However, there is ongoing debate regarding the necessity of IR for compensatory b-cell proliferation in specific circumstances. It is plausible that IR may serve as a scaffold for the signaling complex, regardless of its ligand. Additionally, the pathway involving forkhead box protein M1/polo-like kinase 1/centromere protein A has been recognized as a key player in adaptive b-cell proliferation under various conditions such as diet-induced obesity, hyperglycemia, pregnancy, aging, and acute insulin resistance.

Recent research has also highlighted the role of interactions between islets and adipose tissue, as well as the liver, through humoral factors in adaptive b-cell proliferation. Notably, this response is particularly evident in cases of acute insulin resistance, irrespective of the IR/insulin signal, and is dependent on the forkhead box protein M1/polo-like kinase 1/centromere protein a pathway. However, a major obstacle in utilizing b-cells for treating human diabetes is the variations between human and rodent islets. This review concentrates on the signaling pathways that govern adaptive b-cell proliferation, taking into account the aforementioned challenges, with the aim of advancing diabetes therapy.

Keywords: Insulin, Diabetes, Beta Cells

Introduction

Recent research suggests that the failure of b-cells, along with insulin resistance, is a significant contributing factor in the progression of type 2 diabetes [1]. As the compensation by b-cells diminishes, individuals transition from having normal glucose tolerance to impaired glucose tolerance, ultimately leading to the development of type 2 diabetes. Consequently, there is a pressing need for therapeutic interventions that can reverse b-cell failure and promote a beneficial increase in b-cell mass and function [2,3].

Previous studies conducted on animal models and potentially on humans have demonstrated the potential to enhance insulin secretion in response to insulin resistance by augmenting b-cell mass and improving b-cell function. However, it remains uncertain whether there is a genuine compensatory increase in b-cell mass in humans [4,5]. Various strategies have been proposed to expand the endogenous b-cell mass, including promoting b-cell proliferation, preventing b-cell death, inducing b-cell neogenesis, and controlling b-cell trans-differentiation. Among these approaches, promoting adaptive b-cell proliferation appears particularly promising for augmenting human b-cell

mass, as research indicates that b-cell proliferation is more prevalent than other mechanisms in the human endocrine pancreas [6,7]. Diabetes mellitus (DM) is widely recognized as a metabolic and hormonal disorder that directly affects the body's processing of carbohydrates, fats, and proteins. Therefore, dietary interventions play a crucial role in the management of diabetes and empower individuals to actively take charge of their health. It is well established that diabetes can arise from either insufficient insulin production or resistance to insulin [8-10]. This review focuses on investigating the signaling pathways involved in regulating adaptive b-cell proliferation for the treatment of diabetes.

Methods and Materials

We conducted a review by searching the Google Scholar, PubMed, and Directory Open access Journal databases for relevant information using keywords such as Diabetes, diabetes disorders, Beta cells, Insulin resistance, insulin, albumin, insulin receptors, type 2 diabetes to identify primary comparative studies the effect of beta cells on the treatment of diabetes . The quality and strength levels of the results were considered and when available meta-analyses and systematic reviews, large epidemiological studies and randomized control trials represented the main source of data.

Insulin and Insulin Receptor Signaling

In the context of chronic insulin resistance, various metabolic tissues such as the liver, adipose tissue, intestine, brain, and endocrine pancreas receive signals related to obesity, nutrition, inflammation, and other factors. Understanding the mechanism by which these metabolic signals are transmitted in beta-cells is crucial for enhancing beta-cell expansion [11-13].

To investigate adaptive beta-cell proliferation in response to chronic insulin resistance, the diet-induced obesity (DIO) mouse model is commonly used. In this model, mice are exposed to a high-fat diet for an extended period of time. Another mouse model, known as b-Cell-specific insulin receptor knockout (bIRKO) mice, exhibits the development of hyperglycemia and increased proinsulin levels as they age, similar to type 2 diabetes in humans. These mice also show reduced beta-cell mass due to impaired beta-cell proliferation under high-fat diet conditions. Insulin receptor substrate-2 (IRS-2) has been identified to play a role in compensatory beta-cell replication in DIO mice, partly through glucokinase-mediated glycolysis [14,15].

Interestingly, the expression of proteins involved in the insulin receptor (IR) signaling cascade, such as IR, IRS-2, and protein kinase B, is decreased in human islets from individuals with type 2 diabetes compared to non-diabetic controls. This suggests that pathways promoting beta-cell multiplication independent of insulin signaling could be potential therapeutic targets for restoring beta-cell mass in patients with type 2 diabetes. Recent research has discovered a molecule called inceptor, also known as the insulin inhibitory receptor, which can reduce IR signaling through clathrin-mediated endocytosis, leading to decreased beta-cell proliferation [16-18]. This finding supports the idea that IR in beta-cells plays a role in regulating beta-cell proliferation. However, the exact function of insulin secreted by beta-cells in regulating beta-cell proliferation remains uncertain. The manner in which high concentrations of insulin secreted by b-cells affect the b-cells themselves, whether through autocrine or paracrine mechanisms, is still unclear. Two hypotheses, namely the "ligand-receptor interaction" hypothesis and the "signaling scaffold" hypothesis, have been proposed to elucidate the role of the insulin receptor (IR) in b-cell proliferation [19].

The ligand-receptor interaction hypothesis, specifically the insulin-dependent signal known as the ligand-dependent receptor activation signal, lacks clarity regarding the phosphorylation state of the insulin receptor (IR) in b-cells. On the other hand, the signaling scaffold provided by IR facilitates the formation of signaling complexes at the plasma membrane, allowing for the transmission of intracellular signals through adaptor proteins such as IRS-2. Furthermore, the nuclear translocation of IR has been identified as a transcriptional regulator. Therefore, a comprehensive investigation into the phosphorylation state and intracellular localization of IR in b-cells is imperative for comprehending b-cell adaptation to insulin resistance [20,21].

The Pathway Involving Forkhead Box Protein M1 (FOXM1), Polo-Like Kinase 1 (PLK1), and Centromere Protein a (CENP-A) Plays a Crucial Role in Promoting the Proliferation of B-Cells by Controlling the Progression of the M Phase in the Cell Cycle

To gain a deeper comprehension of the regulation of the cell cycle in b-cells, it is crucial to recognize that mature pancreatic b-cells are predominantly in a state of dormancy known as the G0 phase. The transition of these cells from G0 to the G1 phase of the cell cycle is influenced by glucose or IR/insulin signaling. Nevertheless, the precise mechanisms that govern the subsequent stages of the cell cycle, such as the G2/M checkpoint and M phase, have remained ambiguous in b-cells. Notably, bIRKO b-cells lacking IR not only experienced G0 cell cycle arrest but also M-phase arrest, indicating a potential link between IR signaling pathways and the G2/M cell cycle checkpoint in b-cells. Analysis of gene expression in bIRKO b-cells unveiled the downregulation of specific genes related to the M phase of the cell cycle, including centromere protein A (CENP-A) and polo-like kinase 1 (PLK1), which are crucial for chromosome segregation [22,23].

Hence, the Forkhead Box Protein M1/ Polo-like Kinase 1/ Centromere Protein A pathway may have a role in governing b-cell proliferation by regulating the M phase of the cell cycle. CENP-A, a variant of histone H3 specific to centromeres, is indispensable for the recruitment and assembly of kinetochore proteins, as well as for the advancement of mitosis and the separation of chromosomes in mammalian cells. PLK1, a kinase involved in mitosis, serves diverse functions, particularly in the control of mitotic initiation and completion [24,25]. The transcription factor FoxM1, belonging to the forkhead box protein M1 family, has been identified as a direct regulator of CENP-A and PLK1 expression in b-cells. Knocking out CENP-A specifically in b-cells of mice resulted in reduced adaptive proliferation of b-cells in models of aging, pregnancy, diet-induced obesity (DIO) through high-fat diet (HFD), hyperglycemia caused by high glucose levels, and acute insulin resistance induced by the administration of the insulin receptor antagonist S96124. This pathway involving FoxM1, PLK1, and CENP-A is also necessary for b-cell replication through sympathetic nerve relay27. Notably, the expression of CENP-A was significantly decreased in b-cells from individuals with type 2 diabetes compared to non-diabetic control participants [26,27]. Therefore, the FoxM1/PLK1/CENP-A pathway plays a central role in the adaptive proliferation of b-cells in mice and likely also in humans (Figure 1,2).

Compensatory Proliferation of Beta-Cells in Models of Acute and Chronic Insulin Resistance is Observed

In both chronic and acute models of insulin resistance, compensatory proliferation of beta-cells is observed to increase beta-cell mass in rodents [28,29]. The chronic model of insulin resistance is represented by the diet-induced obesity (DIO) model through high-fat diet (HFD) feeding and genetic causes of insulin resistance. In mice with

severe obesity and insulin resistance, such as db/db and ob/ob mice, increased beta-cell proliferation is observed, although glucotoxicity and lipotoxicity also affect beta-cells. Impaired beta-cell proliferation in DIO models is observed in beta-cell-specific IRS-2 knockout mice (bIRKO mice) and in beta-cell-specific glucokinase knockout mice, indicating the crucial role of insulin receptor (IR)/IRS-2-mediated signaling in adaptive beta-cell replication in response to chronic insulin resistance. The adaptive increase in beta-cell proliferation observed in liver-specific IR knockout (LIRKO) mice disappears in IR-deficient beta-cells (bIRKO/LIRKO mouse) [30].

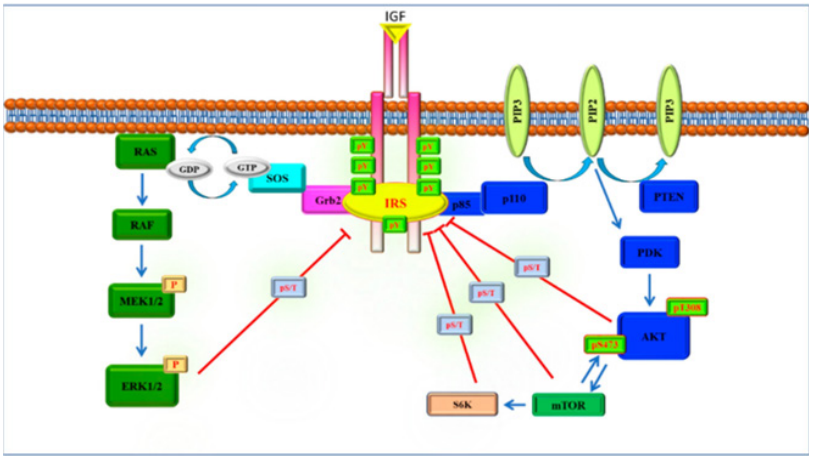

Figure 1: The role of insulin receptors in B cells.

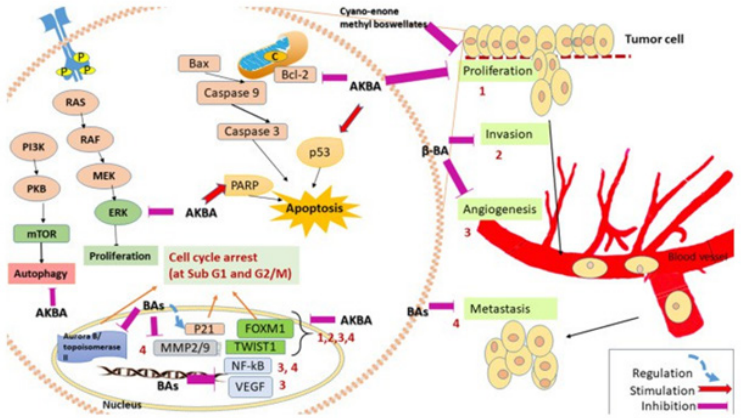

Figure 2: The foxM1/PLK1/CENP-A patgway plays a central role in adaptive B cells proliferation.

In DIO mice, the process of beta-cell proliferation is regulated by various signaling pathways depending on the type of insulin resistance model. In acute models such as pregnancy, glucose infusion, partial pancreatectomy, and administration of insulin receptor antagonists, insulin signaling-mediated FoxO1 nuclear export and subsequent Cyclin D2 expression play a role in promoting beta-cell proliferation. Additionally, serotonin receptor 2B stimulation on beta-cells with serotonin, produced by the beta-cells themselves through prolactin, contributes to adaptive beta-cell proliferation during pregnancy through autocrine and paracrine signaling. Glucose infusion enhances beta-cell proliferation mediated by IRS-2, while beta-cell proliferation after partial pancreatectomy occurs through an IRS-2-independent pathway. Pharmacological inhibition of the insulin receptor with S961 or OSI-906 can also facilitate potent beta-cell proliferation [31-33].

Interestingly, the activation of the insulin receptor is not necessary for b-cell replication in response to acute insulin resistance, as demonstrated by the lack of suppression of S961-induced b-cells in knockout mice of the insulin receptor and IRS-2. Furthermore, the FoxO1-mediated insulin signal is dispensable for b-cell compensation induced by S961. In OSI-906-treated mice, b-cell proliferation persists even after normalization of blood glucose levels, indicating that glucose/glucokinase-mediated insulin signaling is also unnecessary [34-36]. The b-cell proliferation induced by acute models is mediated by M phase-related cell cycle genes and the FoxM1/PLK1/CENP-A pathway, but not IRS-2 or cyclin D2, which are induced in the chronic DIO model. Therefore, there are distinct signaling pathways that regulate adaptive b-cell proliferation between acute and chronic insulin resistance models [37].

Interorgan Networks for the Regulation of Adaptive B-Cell Proliferation

The islets' function, encompassing insulin secretion and b-cell proliferation, is not solely under their own regulation. Instead, it is a product of reciprocal regulation with other organs or cells through various means like metabolites, hormones, exosomes, or neurons in vivo. While metabolic organs such as the liver, adipose tissue, and skeletal muscle are key players in this regulation, other systems and organs like the gastrointestinal system, bone, placenta, kidney, thyroid, endothelial cells, reproductive organs, adrenal and pituitary glands, gut microbiota, and immune cells are also thought to contribute to b-cell biology [38]. This interorgan communication is vital for adaptive b-cell proliferation as peripheral tissues must detect and convey the status of insulin resistance to b-cells to uphold precise glucose homeostasis. Previous research has pinpointed circulating factors that influence

b-cell proliferation in different models. For example, LIRKO mice display significantly increased adaptive b-cell proliferation, partly due to a circulating factor originating from the liver [39-45].

LIRKO mice demonstrate a notable rise in adaptive b-cell proliferation, partly due to the presence of serpin B1, a liver-derived circulating factor that inhibits leukocyte-neutrophil elastase. The liver-derived protease inhibitor-induced b-cell proliferation is impeded by insulin receptor (IR) deficiency in b-cells, indicating a potential role of IR signaling in mediating the effects of serpin B1 on b-cell replication in the context of chronic liver insulin resistance. Conversely, serum factors from adipocytes are likely to stimulate b-cell replication during acute insulin resistance induced by S961, through the activation of the E2F1 and FoxM1/PLK1/CENP-A pathway, independently of IR. These results suggest that different tissues may influence adaptive b-cell proliferation under chronic or acute conditions [46].

Moreover, while glucagon-like peptide-1 alone does not boost human b-cell proliferation, the combination of a glucagon-like peptide-1 receptor agonist with a DRYK1A inhibitor can enhance cell replication in human islet b-cells. This implies that a variety of humoral factors secreted by different tissues may be required to regulate b-cell functions in vivo [47,48]. Given the intricate regulation of b-cell proliferation by various organs through multiple factors, an in vitro coculture system may not fully replicate the in vivo environment for evaluating b-cell proliferation. Therefore, the establishment of an in vivo coculture system, where multiple organs are transplanted and cocultured simultaneously, could be a valuable approach for investigating compensatory b-cell proliferation [49].

The disparity between mouse and human islets poses a significant challenge in advancing research on adaptive B-cell proliferation. In recent years, there has been a growing utilization of human islets in studies, particularly in Asian countries. However, it is important to note that human islets exhibit considerable variability in experimental outcomes, especially in terms of cell proliferative capacity among different donors. This variability makes it difficult to fully comprehend the underlying mechanisms solely through studies using human islets. Therefore, the integration of animal models with human islets in research becomes necessary [50].

An autopsy analysis of human pancreas samples has shed light on the differences in B-cell mass between obese and lean individuals in the USA and Japanese populations. In the USA population, obese individuals were found to have a 1.5-fold increase in B-cell mass compared to lean individuals. However, this increase was not observed in the Japanese population. It is worth noting that Asian individuals, in general, tend to have a leaner physique compared to white individuals and may have a lower tolerance for obesity due to genetic and epigenetic factors. As a result, Asian diabetes patients may have a limited ability to increase B-cell mass in response to obesity compared to their European or American counterparts.

To fully understand the mechanisms of adaptive B-cell proliferation in Asian diabetes patients, it is crucial to consider studies using human islets from Asian donors. These studies should take into account the ethnic, genetic, and epigenetic differences that exist among different populations. By doing so, researchers can unravel the intricate mechanisms underlying adaptive B-cell proliferation and gain valuable insights into the management and treatment of diabetes in Asian populations [51-53].

Conclusion

The mechanism of adaptive b-cell proliferation is diverse and involves interorgan communication. Additionally, the b-cell mass can be influenced by genetic background, racial/ethnic disparities, environmental factors, diet, exercise, aging, comorbidities, medications, and lifestyle choices. As a result, the development of diabetes due to the failure of compensatory b-cell responses can stem from a wide range of causes. Therefore, comprehensive reverse translational research incorporating integrated analysis of adaptive b-cell responses is necessary to bridge the gap between preclinical and clinical studies.

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