

Beta Cell Death Mechanism in Type 2 Diabetes: An Overview

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ABSTRACT

Beta cell failure is central to the development and progression of type 2 diabetes (T2D). This article examines the mechanism of beta cell death in T2D. Chronic hyperglycemia and hyperlipidemia are toxic to beta cells and progressively lead to apoptosis. It is triggered by metabolic alterations such as glucotoxicity, lipotoxicity, inflammation, endoplasmic reticulum (ER) stress, mitochondrial dysfunction and oxidative stress. Our review focuses on the apoptosis of beta cell induced by hyperglycemia, hyperlipidemia, beta cell fatigue, and inflammation. This review may suggest areas for future research on the therapeutic options for protecting beta cell function/mass by targeting various underlying factors and mechanisms with a role in disease progression.

Keywords: beta cell death; type 2 diabetes; glucotoxicity; lipotoxicity; beta cell fatigue; inflammation

INTRODUCTION

Diabetes mellitus (DM) is a global pandemic that threatens human health and global economy [1]. According to the data released by International Diabetes Federation, the global prevalence of DM in 2021 was 10,5% (536,6 million people) and is estimated to increase to 12,2% (783,2 million people) in 2045. Approximately 90 – 95% of patients with DM suffer from T2D [2]. T2D is mostly experienced by female [3,4] and elderly patients [5,6]. T2D occurs due to the loss of beta cell function with previous condition of insulin resistance [7]. The dysfunction of beta cell lead to decrease the glucose tolerance [8]. Prior to the diagnosis of DM, the patients had decreased the structure and function of beta cell. When the beta cell intrinsically (defense mechanism) is weaker than the external stress (offense mechanism), it can lead to beta cell failure [9]. In addition to hyperglycemia, the increase in free fatty acids (FFA) also affects the failure of beta cell [10]. Beta cell failure greatly affects the patient's clinical outcome. However, the significance of beta cell failure in patients with T2D is still often overlooked [11]. In addition to the neglect of beta cell failure, the mechanism by which cell mass decreases is still under investigation. However, the available evidence suggests that hyperglycemia induces apoptotic cell death, which may be the key pathological mechanism of diabetes. The focus of this paper is to present the main factors and mechanisms associated with reduction of beta cell mass such as glucotoxicity, lipotoxicity, beta cell fatigue, and inflammation.

DISCUSSION

Insulin Resistance and Beta Cell Death

Blood glucose levels are the primary physiological factor controlling insulin production by pancreatic beta cells [12].

Despite the beta cells already releasing insulin, insulin resistance raises blood glucose levels. Additionally, excess calories and insulin resistance increase the amount of FFA in the blood that can not be converted into lipids [13]. This causes beta cells to secrete more insulin. Early in the process of hyperglycemia, beta cell mass and function often rise [14]. This happens as a coping mechanism to counteract insulin resistance and preserve normal blood glucose levels [15]. Beta cells, however, are unable to adjust to the long-term demands of peripheral insulin resistance when T2D develops, and the hyperinsulinemia state transforms into a condition of relative insulin insufficiency. As a result, hyperglycemia happens following the consumption of many carbs [16].

Some of the mechanisms involved in beta cell dysfunction and death in T2D are as follows:

A. Glucotoxicity

Glucotoxicity is a non-physiological situation and cell damage brought on by prolonged exposure to high glucose concentrations as well as decreased insulin synthesis and secretion in pancreatic islets. Beta cell death is accelerated by glucotoxicity effects brought on by insulin resistance and visceral obesity [17]. The inflammatory pathway of monocyte nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) activated by glucose on a high-calorie diet can induce nitric oxide (NO) synthase which is an important signal in cytokine-induced beta cell death, because inhibition of NO synthase has been shown to prevent cell death [18].

Because the pancreatic islets produce very low levels of antioxidants, long-term hyperglycemia and a rise in the development of advanced glycation end products (AGEs) can cause chronic oxidative stress [19]. Oxidative stress indicators including 8-hydroxy-2'-deoxyguanosine and nitrotyrosine were considerably greater in T2D patients than in controls [20]. Reactive oxygen species (ROS), particularly hydroxyl radicals, obstruct the processing of pancreatic duodenal homeobox-1 (PDX-1) mRNA, a transcription factor necessary to control cell viability, gene expression, and insulin release. As a result, beta cell damage might result from ROS and oxidative stress [21].

B. Lipotoxicity

Diabetes is associated with dyslipidemia characterized by increased circulating FFA and changes in lipoprotein profile. Increased levels of FFA can induce apoptosis in beta cells. FFA induces NO synthase expression resulting an increase in NO production. In addition, the action of the anti-apoptotic factor Bcl-2 is strongly suppressed by FFA [22]. The accumulation of triglycerides in the pancreatic islets of Zucker Diabetic Fatty (ZDF) rats as a T2D model is toxic. Increased glucose metabolism due to hyperglycemia leads to the formation of malonyl-CoA, which inhibits FFA oxidation and leads to the formation of potentially toxic long-chain acyl-CoA esters. Another lipid to watch out for is ceramides. These biologically active sphingolipids can be produced by cleavage of plasma membrane lipids or can be formed de novo from saturated fatty acids and have been shown to cause oxidative stress, mitochondrial dysfunction, and apoptosis [23].

C. Beta cell fatigue

Beta cell has high sensitivity to glucose fluctuations. The beta cells promptly release insulin when fluctuations in glucose levels are brief, such as those that occur after a meal. It will cause a proapoptotic signal if the time is longer and the glucose levels are higher [24]. The increased need for proinsulin and insulin production is the reason of this. Beta cell ER stress results from an increase in protein flow through the ER, which is caused by increased proinsulin production [25].

D. Inflammation

Increased levels of inflammatory mediators in T2D can impact pancreatic cells in addition to insulin-sensitive tissues and blood vessel walls. Numerous experimental studies in humans and in diabetes models have shown that inflammatory mediators like Tumor Necrosis Factor (TNF), Macrophage Inflammatory Protein-1 (MIP-1), C-Reactive Protein (CRP), Interleukin 1 (IL-1), and Interleukin 6 (IL-6) play a role in the pathogenesis of increased Beta cell apoptosis [26]. Due to its structural similarity to other cytokines and receptor-induced signaling cascades, leptin is now also regarded as a proinflammatory cytokine. Adipocytes are the major cells that express leptin. Chronic exposure to leptin promotes beta cell death [27]. The oxidation of fat cells, proteins, and nucleic acids will result in fragmentation or cross-linking if there is an excessive production of free radicals or an insufficient supply of bodily antioxidants. This condition will result in the loss of pancreatic beta cells [28].

CONCLUSIONS

T2D is a chronic metabolic disorder that is an epidemic problem. Its pathophysiology revolves around a unique phenomenon of programmed β cell death such as glucotoxicity, lipotoxicity, beta cell fatigue, and inflammation. For the optimal T2D prevention, strategies aimed at maintaining beta-cell mass and function are required.

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