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Review Article

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The molecular basis for the failure of insulin secretion that leads to the onset of type 2 diabetes

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Abstract

Type 2 diabetes is a chronic metabolic condition characterized by hyperglycemia resulting from insulin resistance and impaired insulin secretion. This disease has become a major public health issue worldwide, affecting millions of people. The exact molecular mechanisms underlying the failure of insulin secretion leading to the onset of type 2 diabetes remain to be fully elucidated. However, recent studies have greatly advanced our understanding of this complex process, identifying key molecules and pathways involved in insulin secretion failure. This review will discuss the molecular basis for the failure of insulin secretion, with a focus on the role of key molecules and pathways implicated in this process.

Keywords: Type 2 diabetes, insulin secretion, health issue, molecules and pathways

Introduction

Insulin secretion is a complex process that involves several steps, including glucose metabolism, depolarization of the plasma membrane, calcium influx, and exocytosis of insulin-containing granules from pancreatic β-cells. Glucose-induced insulin secretion is the primary mechanism by which β-cells adjust insulin secretion in response to changes in blood glucose levels. This process involves the metabolism of glucose to generate ATP, which in turn triggers the closure of the ATP-sensitive K+ channels (KATP) in the plasma membrane of β-cells. The resulting depolarization of the plasma membrane leads to the opening of voltage-gated calcium channels (VGCCs), allowing calcium influx into the cell. This triggers the fusion of insulin-containing granules with the plasma membrane, leading to the release of insulin into the bloodstream.

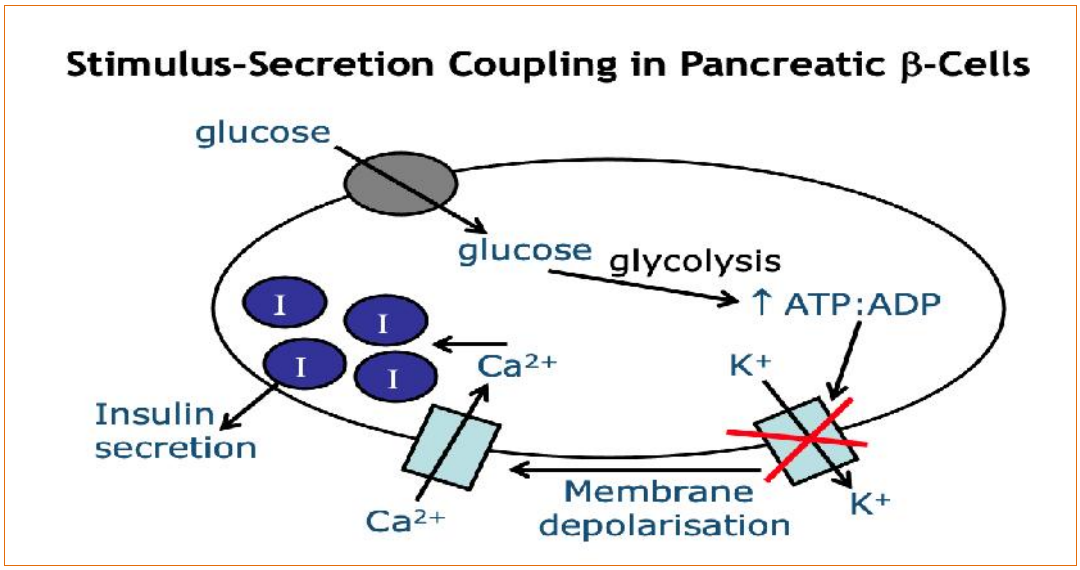

Fig 1 Stimulus – Secretion Coupling in Pancreatic beta cells.

The failure of insulin secretion that leads to the onset of type 2 diabetes is thought to be multifactorial, involving both genetic and environmental factors.

Genetics:

Over the past decade, significant progress has been made in identifying genetic risk factors for type 2 diabetes. Genome-wide association studies (GWAS) have identified more than 100 gene regions that are associated with an increased risk of developing the disease. The most significant genetic risk factor for type 2 diabetes is a variant in the TCF7L2 gene, which accounts for approximately 10% of the genetic risk. Other genes that have been linked to type 2 diabetes include PPARG, KCNJ11, and ABCC8, among others (1).

TCF7L2 is a transcription factor that plays a crucial role in Wnt signalling and glucose metabolism. The TCF7L2 gene is located on chromosome 10q25.2, and several variants in this gene have been associated with an increased risk of type 2 diabetes. The rs7903146 variant is the most strongly associated with the disease and has been shown to impair insulin secretion and increase hepatic glucose production. PPARG is a transcription factor that plays a crucial role in adipocyte differentiation and lipid metabolism. The PPAR gamma gene (PPARG) is located on chromosome 3p25 and is associated with the development of obesity and insulin resistance, two major risk factors for type 2 diabetes. Several studies have shown that the rs1801282 variant in the PPARG gene is strongly associated with an increased risk of type 2 diabetes.HNF1A encodes a transcription factor that regulates the expression of several genes involved in glucose metabolism, including insulin secretion and hepatic gluconeogenesis. The risk allele of HNF1A rs1169288 is associated with an increased risk of developing type 2 diabetes and impaired insulin secretion (10). The mechanism by which the risk allele contributes to the development of the disease is thought to impair insulin secretion by reducing beta-cell mass or function (11).

Recent research has also identified several genes involved in β-cell function and the regulation of glucose homeostasis that are associated with T2DM. For example, the gene encoding the glucose transporter type 2 (GLUT2) and glucokinase (GCK) have been shown to play an essential role in the regulation of insulin secretion and glucose metabolism. A genome-wide association study identified a SNP in the intron of GCK that was associated with changes in fasting

plasma glucose levels and an increased risk for T2DM. Another genetic locus associated with the

development of T2DM is the KCNJ11/ABCC8 locus, which codes for the KATP (ATP-sensitive potassium) channels located in pancreatic β-cells. These channels modulate the secretion of insulin by the β-cells by regulating the influx of calcium ions. The minor allele of rs5219 in the KCNJ11 gene has been associated with an increased risk of T2DM.

The CAP10 gene, located on chromosome 13, has been a topic of research interest regarding its involvement in type 2 diabetes (T2D) development. This gene encodes for a cytoskeletal protein that is involved in the formation of podosomes, which are adhesion structures in cells. Research indicates that variants in the CAP10 gene may directly influence insulin secretion and sensitivity. Various studies have demonstrated a relationship between CAP10 gene variants and T2D development. A genome-wide association study (GWAS) conducted in Chinese individuals identified a CAP10 gene polymorphism (rs2237895) that was significantly associated with an increased risk of T2D (1). Similarly, a study in European populations linked CAP10 gene variants with abnormal glucose metabolism and insulin resistance (2). Furthermore, animal models have shown that deleting the CAP10 gene leads to impaired glucose tolerance and insulin resistance (3).One study suggests that CAP10 gene variants may impair insulin secretion by affecting cell adhesion and communication in the pancreas (4). Another theory is that CAP10 gene variants may increase insulin resistance by altering adipocyte function, leading to impaired glucose uptake (5).In addition to its association with T2D, the CAP10 gene has also been linked with the risk of other metabolic disorders, including obesity and dyslipidaemia. A study investigating the relationship between CAP10 gene variants and obesity found that certain polymorphisms were significantly associated with an increased risk of obesity (6).

Obesity and T2D

Obesity is a significant risk factor for the development of T2D, and genetic factors also contribute to the link between obesity and T2D.

Variants in the FTO gene have been associated with an increased risk of obesity and T2D, highlighting a potential genetic link between these two conditions.SLC30A8 gene: The SLC30A8 gene encodes the zinc transporter 8, which is involved in insulin secretion. The rs13266634 variant of SLC30A8 has been associated with an increased risk of type 2 diabetes in different populations. A study conducted in the Chinese population found that the rs13266634 risk allele is associated with a higher risk of type 2 diabetes (4).Beta-cells are responsible for the production and secretion of insulin in the pancreas. Several genetic variants implicated in T2D, such as TCF7L2, CDKAL1, and HHEX, affect beta-cell function. These variants affect insulin secretion, and their presence increases the risk of developing T2D.

Glucolipotoxicity and Beta cell function

Glucolipotoxicity refers to the harmful effects of elevated glucose and lipid levels on pancreatic beta-cell function and survival. The chronic exposure of beta-cells to high levels of glucose and fatty acids induces oxidative stress, endoplasmic reticulum (ER) stress, inflammation, and apoptosis. These processes contribute to beta-cell dysfunction and impaired insulin secretion, leading to hyperglycemia and the progression of type 2 diabetes.

Several studies have suggested that glucolipotoxicity plays a crucial role in the development and progression of type 2 diabetes. A high-fat diet and excess glucose consumption contribute to the accumulation of lipid droplets in beta-cells, impairing insulin secretion and promoting beta-cell dysfunction. Long-term exposure to high glucose and lipid levels also induces ER stress responses in beta-cells, leading

to the activation of pro-inflammatory pathways and the release of cytokines. This state of chronic inflammation contributes to the development of insulin resistance and the progression of type 2 diabetes. Several interventions have been proposed to target glucolipotoxicity and improve the outcomes of type 2 diabetes. Lifestyle modifications, such as dietary changes and

exercise, have been shown to improve glucose and lipid metabolism and reduce insulin resistance. Pharmacological interventions, including glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter-2 (SGLT2) inhibitors, have been shown to promote beta-cell health and improve glucose control in patients with type 2 diabetes.

Inflammation

Inflammation is a key factor in the development of T2D, as chronic inflammation impairs insulin sensitivity and disrupts glucose homeostasis. This paper will discuss the role of inflammation in T2D and how it contributes to disease progression.

Chronic inflammation is involved in the development of insulin resistance and beta-cell dysfunction, which are key features of T2D. Various immune cells, such as macrophages, T-cells, and B-cells, play a significant role in the pathogenesis of T2D. Inflammation develops in multiple organs and tissues, involving several cytokines and adipokines.

The adipose tissue is a significant contributor to chronic inflammation in T2D. Adipose tissue has a crucial role in energy homeostasis, and it is the largest endocrine organ in the body. Adipose tissue inflammation is characterized by the infiltration of macrophages and other immune cells that secrete pro-inflammatory cytokines like TNF-α, IL-6, and IL-1β. Elevated levels of these cytokines impair insulin signaling and glucose uptake in adipocytes, leading to insulin resistance.

Metabolic inflammation in T2D also involves the liver, muscle, and pancreas. The liver plays a critical role in glucose production and lipid metabolism. Inflammation in the liver leads to steatosis and insulin resistance, which increase the risk of T2D. In muscle, pro-inflammatory cytokines like TNF-α impair insulin sensitivity, reducing glucose uptake and increasing inflammation. The pancreas is also affected by chronic inflammation in T2D. Inflammation impairs pancreatic beta-cell function, reduces

insulin secretion, and contributes to the progression of T2D.Cytokine inhibitors are a relatively new class of medications that can inhibit the activity of pro-inflammatory cytokines such as IL-1β and TNF-α. These medications have been used to treat other inflammatory diseases such as rheumatoid arthritis, and have shown promise in improving glycemic control in patients with type 2 diabetes.

Two cytokine inhibitors, canakinumab and gevokizumab, have been tested in clinical trials for the treatment of type 2 diabetes. Canakinumab, a monoclonal antibody that inhibits IL-1β, was shown to improve insulin sensitivity and reduce markers of inflammation in patients with type 2 diabetes. Gevokizumab, a monoclonal antibody that inhibits TNF-α, was also shown to improve insulin sensitivity and reduce markers of inflammation in patients with type 2 diabetes. However, both medications are expensive and may have adverse effects such as infections and allergic reactions. In conclusion, T2DM is a complex metabolic disorder that is characterized by hyperglycemia due to defects in insulin secretion and/or insulin sensitivity. The regulation of insulin secretion involves complex interactions between beta-cells of the pancreatic islets, glucose metabolism, and various signalling pathways. Dysregulation of these pathways can lead to the failure of insulin secretion and the development of T2DM.

Conclusion

The failure of insulin secretion leading to type 2 diabetes is a multifactorial process influenced by both genetic and environmental factors. Key molecules and pathways, such as TCF7L2, PPARG, and HNF1A, play critical roles in β-cell function and glucose homeostasis. TCF7L2, a transcription factor involved in Wntsignaling and glucose metabolism, has variants associated with impaired insulin secretion. PPARG, another transcription factor, contributes to insulin resistance and obesity, both risk factors for type 2 diabetes. HNF1A, which regulates glucose metabolism, is linked to impaired insulin secretion. Recent research also highlights other genes involved in β-cell function. Understanding these mechanisms is essential for developing targeted therapies to improve insulin secretion and manage type 2 diabetes effectively.

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