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Molecular mechanism of action on Beta cell dysfunction in Diabetes

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ABSTRACT: The pancreas is a glandular organ that impacts the functioning of the entire whole body. Beta cells are special and unique cells in the pancreas that produce, store and release the hormone insulin. Islet cells that produce and secrete hormones directly into the bloodstream. The β-cell performs a special and unique role in human physiology being the only cell capable of elaborating a hormone (insulin) which can decrease blood glucose with the aid of promoting the uptake and metabolism of sugar in peripheral tissues. The main function of a beta cell is to produce and secrete insulin – the hormone responsible for regulating levels of glucose in the blood. The pancreas play an important key role in the regulation of macronutrient digestion and hence metabolism/energy homeostasis by releasing various digestive enzymes and pancreatic hormones. It is positioned behind the stomach within the left upper abdominal cavity and is partitioned into head, body and tail. Pancreatic islet dysfunction, which includes impaired insulin secretion in β cells, is the chief pathology of diabetes. In β cells, oxidative stress, evoked by chronic hyperglycemia, used to be inducing dysfunction of a critical transcription factor, PDX1, caused by its nucleocytoplasmic translocation via interactions with the insulin and JNK signaling pathways and some other transcription factor, FOXO1. These studies clarified the molecular mechanisms of action of beta cells.

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INTRODUCTION:

The pancreas is a glandular organ that impacts the functioning of the entire whole body. Beta cells are unique and special cells in the pancreas that produce, store and release the hormone called insulin. Islet cells that produce and secrete hormones directly into the bloodstream. The β-cell plays an important and unique role in human physiology being the only cell capable of elaborating a hormone (insulin) which can decrease blood glucose level by promoting the uptake and metabolism of sugar in peripheral tissues [1]. Pancreas is an organ located in the abdomen. It plays an essential role in converting the food we eat into fuel for the body's cells. The pancreas has two foremost functions: an

exocrine function characteristic that helps in digestion and an endocrine feature that regulates blood sugar. The pancreas is located behind the stomach in the upper left abdomen. It is surrounded by means of different other organs including the small intestine, liver, and spleen. It is spongy, about six to ten inches long, and is shaped like a flat pear or a fish extended horizontally across the abdomen. The pancreas is a 6 inch-long flattened gland that lies deep within the abdomen, between the stomach and the spine. It is connected to the duodenum, which is part of the small intestine. Only about 5 % of the pancreas comprises endocrine cells. These cells are clustered in groups inside the pancreas and look like little islands of cells when examined under a microscope. These organizations of pancreatic endocrine cells are recognized as pancreatic islets or greater specifically, islets of Langerhans (named after the scientist who discovered them) [2]. Pancreatic beta cells do not produce enough insulin or our body can't use the insulin after that pancreas produces, can develop diabetes. Diabetes can cause gastroparesis, a reduction in the motor function of the digestive system. Diabetes also affects what happens after digestion. If we don't have enough insulin and when we eat a meal high in carbohydrates, sugar levels can go up and cause symptoms like hunger and weight loss. Over the long term, it can lead to heart related problems and kidney disease among other problems [3]. The pancreatic beta cell function and mass are reduced from the clinical onset of both types of diabetes mellitus (DM) and this is accompanied with the aid of a corresponding deterioration of glycaemic control [4]. The emerging pancreatic insufficiency is the inability of the pancreas to biosynthesize and/or secretes digestive enzymes in quantity enough to digest and absorb food components in the intestines. Insufficiency generally happens as an end result of injury to the pancreas, which can be prompted through a range of medical conditions, e.g., recurrent acute pancreatitis, chronic pancreatitis, diabetes, autoimmune diseases, after pancreatectomy surgery [5]. Type 1 diabetes is an autoimmune disease. It takes place when the immune system attacks and destroys the beta cells in the pancreas so that they can no longer produce insulin. The actual purpose remains unknown; however it may additionally be due to genetic and environmental factors, including viruses. In type 1 diabetes (T1DM), the phenomenon is more severe and is mainly due to the autoimmune attack of auto reactive T cells against islet beta cells. It is assumed that about 70 to 90 % of the beta cell mass is misplaced at the time of clinical presentation, which is typically abrupt, with acute metabolic decompensation [6] Type 2 diabetes starts when the body's muscle, fat, and liver cells emerge as unable depended on supply to process glucose. The pancreas reacts by means of producing extra insulin, but in time, it cannot produce sufficient insulin. The body can no longer control blood glucose levels. In type 2 diabetes (T2DM), the pathogenesis is complex, and in most cases, the reduction of beta cell function and mass is related with different degrees of insulin resistance. The clinical presentation of patients with T2DM varies widely; from very asymptomatic to symptoms of ketoacidosis and accordingly, blood glucose concentration at diagnosis may additionally vary from mildly increased to severe hyperglycemia [7]. The focus of this paper is to present the main factors and mechanisms associated with reduction of beta cell function.

ROLE OF BETA CELLS:

The predominant feature of a beta cell is to produce and secrete insulin – the hormone responsible for regulating levels of glucose in the blood. When blood glucose levels begin to rise (e.g. during digestion), beta cells rapidly respond through secreting some of their stored insulin while at the identical time growing production of the hormone. In people with diabetes, however, these cells are both attacked and destroyed by means of the immune system (type 1 diabetes), or are unable to produce adequate quantities of insulin needed for blood sugar control (type 2 diabetes) [5].

Amylin and C-peptide

In addition to insulin, beta cells additionally secrete the hormone Amylin and called C-peptide, a byproduct of insulin production. Amylin slows the rate of glucose entering the bloodstream, making it a greater short-term regulator of blood glucose levels. C-peptide is a molecule that helps to prevent neuropathy and other vascular complications by assisting in the repair of the muscular layers of the arteries. It is secreted into the bloodstream in equal quantities (or moles) to insulin [6,7].

Beta cells in type 1 diabetes:

In type 1 diabetes, beta cells die from a misguided attack with the aid of the body's immune system. How and why that happens is not clear, but the results of a study published in early 2011 suggest that these pancreatic cells become stressed at the earliest stages of the disease process. In mice, beta cells respond to this stress by

triggering a cell death pathway that results in the loss of beta cell function, and subsequently the loss of beta cell mass. The study authors from the Indiana University School of Medicine said the 'exciting' findings raise the possibility that beta cell stress could be part of the trigger for the autoimmune process that leads to type 1 diabetes [8,9].

Beta cells in type 2 diabetes:

In type 2 diabetes, the body will become resistant to its insulin and tries to compensate through producing a greater extent of insulin. Research has proven that chronically elevated blood glucose levels (chronic hyperglycemia) over a long period of time can lead to beta cells wearing out, referred to as beta cell turnover or beta burnout. Scientists are yet to totally recognize the exact cause of the failure of beta cells in type 2 diabetes. They hypothesise that glucotoxicity may additionally be one aspect amongst other potential factors including the effects of lipoproteins, leptin and also cytokines, which are active proteins of the body's immune system.

Pancreatic Endocrine Tissue Comprises 1 %, or Less, of the Pancreas and Is Organized as Clusters of Cells Dispersed throughout the Exocrine Pancreas.

These cell clusters, the islets of Langerhans, are heterogeneous and composed of three most important cell types that secrete distinct hormones. The majorities of islet cells contain insulin secreting β cells and act as glucose sensors, releasing insulin in response to increased circulating glucose. The mechanism controlling regulated insulin secretion from β cells is proven in the right panel.

It's convenient to say we are what we eat, however this simple statement belies the complexity of metabolic signalling that goes into balancing food intake consumption with energy expenditure. One hormone in particular insulin is a critically important regulator of whole total body energy metabolism. It is secreted from the pancreas when blood glucose levels are high, and it acts to maintain glucose homeostasis via promoting glucose uptake and storage in muscle, fat, and liver. When insulin secretion is absent or reduced, or when peripheral tissues fail to respond to insulin, the result is hyperglycemia leading subsequently to diabetes. Diabetes impacts greater than 170 million people worldwide and is associated with several long-term complications including nerve damage, kidney failure, microcirculatory impairment, and a greater risk for heart disease and stroke [7-9].

Types of Pancreatic secretion:

The secretion of pancreas is both exocrine and endocrine. In endocrine secretion, the secreted molecules end up in the blood and they reach their target cells throughout the body via the blood circulation. By contrast, exocrine secretion does not involve the circulation and the products are released directly into the outside. Most of the pancreas serves the exocrine features of secreting digestive enzymes into the gut. Less than 1 % of the pancreatic tissue is devoted to an endocrine function. The endocrine tissue of the pancreas is organized as cell clusters, called the islets of Langerhans, which are dispersed at some stage in the pancreatic exocrine tissue and receive a rich vascular (blood vessel) supply (Fig 1). A pancreatic islet involves three most important cell types. Pancreatic α cells (15 %) occupy the islet periphery and secrete glucagon in response to low blood glucose. Glucagon opposes the actions of insulin, thereby increasing circulating glucose levels. Pancreatic δ cells, the least abundant cell type (5 %), are dispersed throughout the islet and secrete somatostatin, which has important paracrine effects that suppress insulin and glucagon secretion. The insulin-secreting β cells are the most abundant cell type (80 %) and comprise the islet core [9,10].

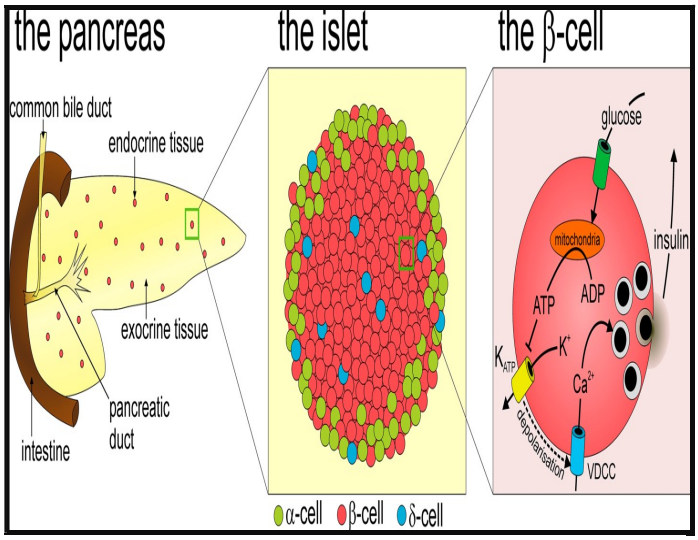

Fig 1. The pancreatic endocrine tissues.

The pancreas has key roles in the regulation of macronutrient digestion and consequently metabolism/energy homeostasis by means of releasing a number of digestive enzymes and pancreatic hormones. It is located behind the stomach within the left upper abdominal cavity and is partitioned into head, body and tail. The majority of this secretory organ consists of acinar or exocrine cells that secrete the pancreatic juice

containing digestive enzymes, such as amylase, pancreatic lipase and trypsinogen, into the ducts, that is, the main and the foremost pancreatic and the accessory pancreatic duct. In contrast, pancreatic hormones are released in an endocrine manner, that is, direct secretion into the bloodstream. The endocrine cells are clustered together, thereby forming the so-called islets of Langerhans, which are small, island-like structures within the exocrine pancreatic tissue that account for only 1 to 2 % of the entire organ (Fig 2). There are five different cell types releasing various hormones from the endocrine system: glucagon-producing α-cells,2 [8] which represent 15 to 20 % of the total islet cells; amylin-, C-peptide- and insulin-producing β-cells, which account for 65 to 80 % of the total cells; pancreatic polypeptide (PP)-producing γ-cells, [9] which comprise 3 to 5 % of the total islet cells; somatostatin-producing δ-cells, which constitute 3 to 10 % of the total cells; and ghrelin-producing ε-cells [10], which comprise <1 % of the total islet cells. Each of the hormones has distinct functions. Glucagon will increase blood glucose levels, whereas insulin decreases them [11]. Somatostatin inhibits both glucagon and insulin release [12], whereas PP regulates the exocrine and endocrine secretion activity of the pancreas [13]. Altogether, these hormones regulate glucose homeostasis in vertebrates, as described in more detail below. Although the islets have a similar cellular composition among different species, that is, human, rat and mouse, their cytoarchitecture differs greatly. Although islets in rodents are primarily composed of β-cells located in the center with other cell types in the periphery, human islets exhibit interconnected α- and β-cells [14].

Molecular mechanism(s) regulating human β-cell proliferation:

The nuclear factor kappa-B (NFκB) is retained in the cytosol and its function is repressed with the aid of inhibitors of nuclear tissue kappa-B kinase subunit epsilon (IKK-ε). WS6 blocks IKK-ε inhibition on NFκB, which can translocate into the nucleus and promote cell growth. TGF-β pathway influences β-cell proliferation with the aid of activation of SMAD3. SB431542, a TGF-βR inhibitor, promotes cell growth by preventing SMAD3 activation. Insulin receptor (IR)/insulin-like growth factor (IGF1R) and glucagon-like peptide 1 receptor (GLP-1R) signaling pathways trigger β-cell regeneration via modulating PI3K-AKT axis, resulting in the inhibition of glycogen synthase kinase-3β (GSK3β) activity. In addition, inactivation of GSK3β is also additionally obtained by treatments with GNF7156 and GNF4877, GSK3β inhibitors, or osteoprotegerin (OPG) or denosumab. In particular, OPG and denosumab act as mimics of receptor activator of nuclear aspects kappa-B ligand (RANKL), preventing its interaction with receptor activator of nuclear factor kappa-B (RANK) and avoiding the activation of the extrinsic apoptotic pathways. Moreover, the hepatokine SerpinB1 and the elastase inhibitor sivelestat stimulate human β-cell proliferation growing the phosphorylation level ranges of mitogen-activated protein kinase 3 (MAPK3), protein kinase cAMP-dependent type II regulatory subunit beta (PRKAR2B) and GSK3β, likely following inhibition of proteases as elastase, cathepsin G, or proteinase 3. These consequences might involve the protease-activated receptor (PARs) signaling; however such a hypothesis requires further additional investigations. The dual-specificity tyrosine-regulated kinase-1a (DYRK1A) represses β-cell proliferation through phosphorylating and retaining into the cytosol the nuclear factor of activated T cells (NFAT). The inhibition of DYRK1A, using small molecules as harmine or 5-iodotubercidin (5-IT), results in the decrease of the phosphorylation state of NFAT, which translocate into the nucleus and activate the mitogenic pathways in human β-cells [13-15].

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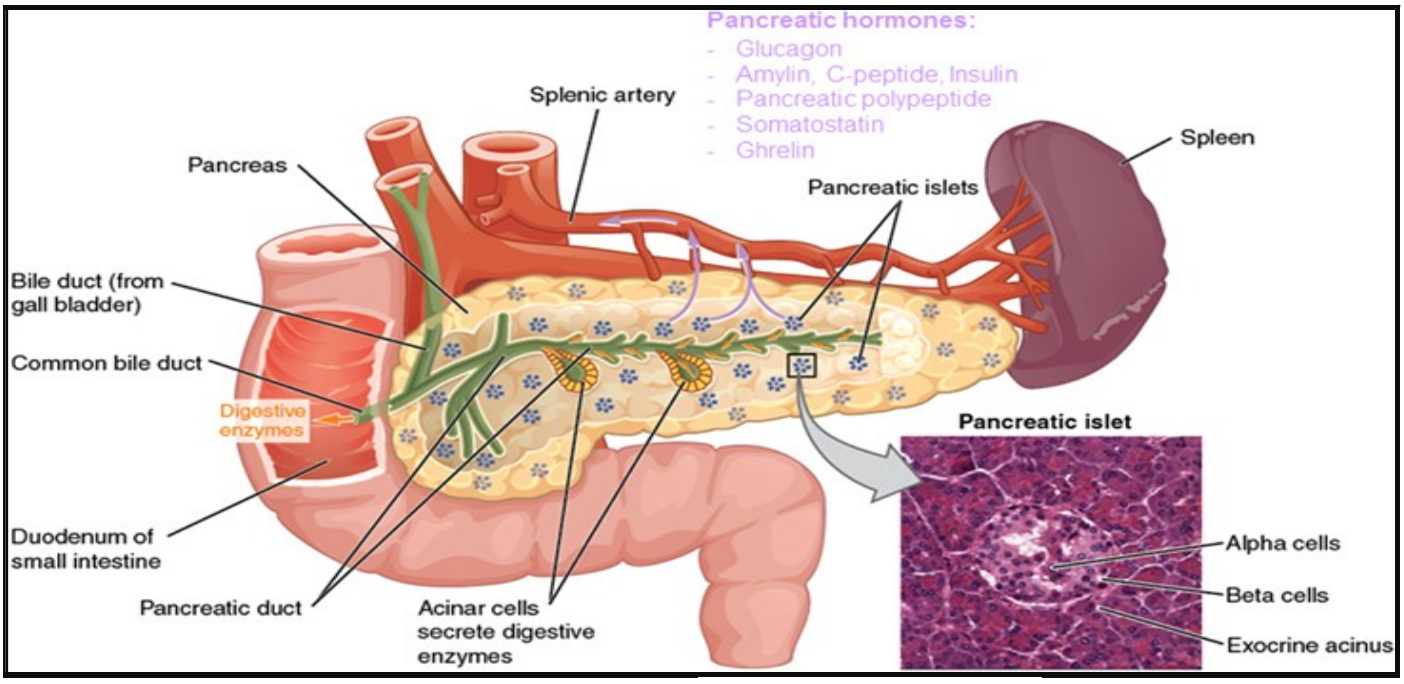

Fig 2. The clusters of islets of langerhans present in the endocrine cells of pancreas.

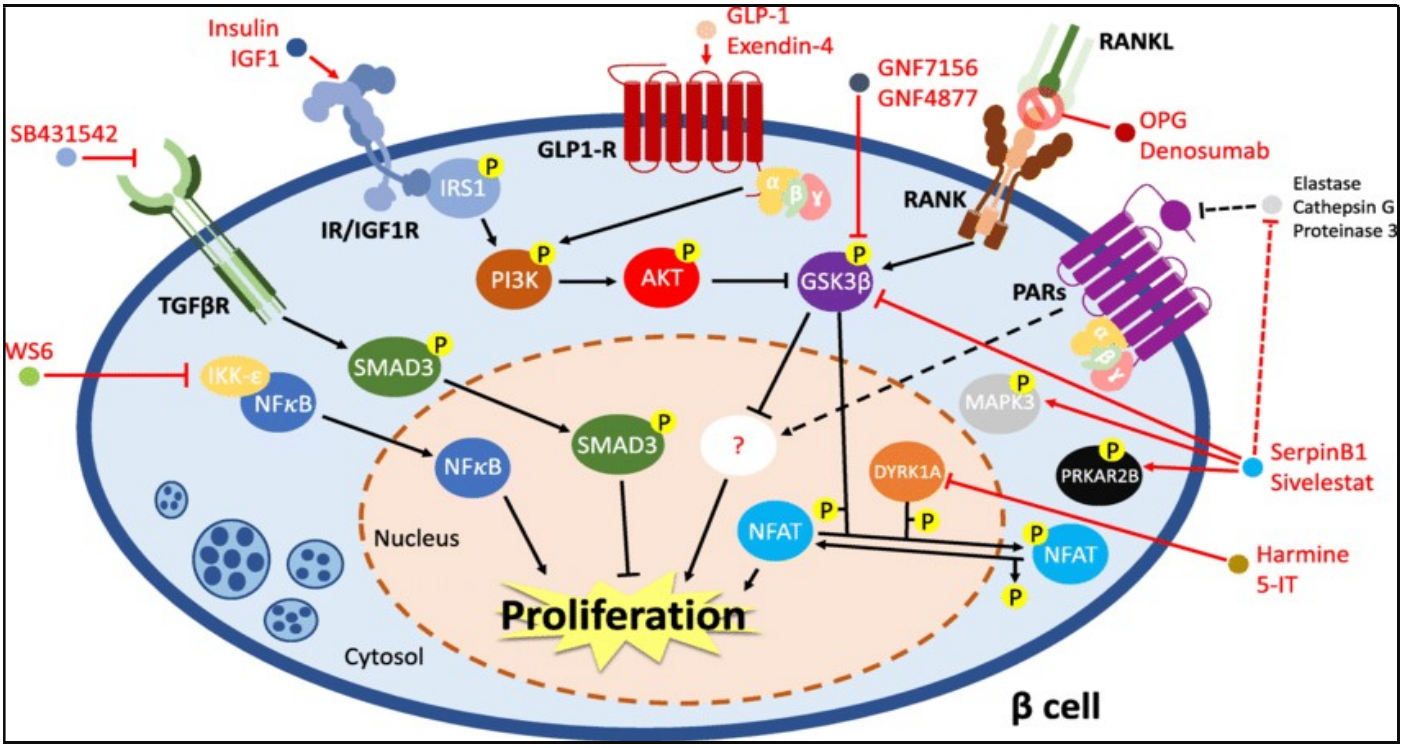

Fig 3. The molecular mechanism(s) regulating human β-cell proliferation.

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NFAT, which translocate into the nucleus and activate the mitogenic pathways in human β-cells [13-15].

First, we targeted the possible mechanisms underlying the pancreatic β-cell dysfunction in diabetes. In β cells, under the chronic hyperglycemic condition associated with diabetes, both insulin secretion and biosynthesis are impaired [16]. In addition, the decrease in β-cell mass due to increased apoptosis, impaired proliferation, and possibly dedifferentiation also plays an important essential part in the pathophysiology. As a common frequent factor involved in both these dysfunctions, we focused on a β-cell specific transcription factor, PDX1 (pancreatic and duodenal homeobox 1), which is essential important in the pancreas and β-cell development and differentiation, together with the controlling functions of mature β cells, including the expression of insulin [17]. On the other hand, oxidative stress that is induced with the aid of the excessive glucose has been revealed to be implicated in the progression of β-cell dysfunction in type 2 diabetes [18]. Under diabetic conditions, the ranges levels of reactive oxygen species (ROS) increase in many tissues and organs, including β cells, through the activation of the mitochondrial electron transport chain [19] or the acceleration of glycation reactions [20], which causes various forms of tissue damage in patients with diabetes [21]. Interestingly, while oxidative stress has been shown to induce PDX1 dysfunction [22], antioxidant treatment in animal models for type 2 diabetes has been observed to retrieve PDX1 expression in β cells [23].

Therefore, we further explored the molecular mechanism of the oxidative stress-induced deterioration of PDX1 function characteristics by targeting its intracellular localization [24]. Immunocytochemistry of endogenous PDX1 and exogenously introduced green fluorescent protein (GFP)-tagged PDX1 showed that PDX1 translocated from the nuclei into the cytoplasm of the β-cell line, HIT-T15, in response to the oxidative stress. In contrast, a dominant negative form of a stress-signaling kinase, c-Jun N-terminal kinase (JNK), inhibited the oxidative stress-induced PDX1 translocation, suggesting an essential fundamental role for this stress-transmitting pathway. Through deletion research studies of GFP-tagged PDX1 fragments, we recognized a classical leucine-rich nuclear export signal (NES) in the mouse PDX1 protein. These findings revealed a novel mechanism that negatively regulates PDX1 features through oxidative stress, leading to greater understanding of β-cell dysfunction in diabetes.

Since oxidative stress and the activation of the JNK pathway induce nucleocytoplasmic translocation of PDX1, we sought to explore the missing link that mediates the phenomenon between the JNK pathway and PDX1. We mainly targeted another important transcription factor, FOXO1 (forkhead box O1), which is reported to counterlocalize PDX1 [25], and found that FOXO1 mediates between the JNK pathway and PDX1 [26]. FOXO1 was found to change its intracellular localization from the cytoplasm to the nucleus in HIT-T15 cells under an oxidative stress load. Oxidative stress impaired insulin signaling activity, represented with the aid of phosphorylation of Akt, which in turn critically controlled the intracellular localization of FOXO1 by direct phosphorylation. The overexpression of JNK also induced the nuclear localization of FOXO1, while the suppression of JNK reduced the oxidative stress-induced nuclear localization of FOXO1.

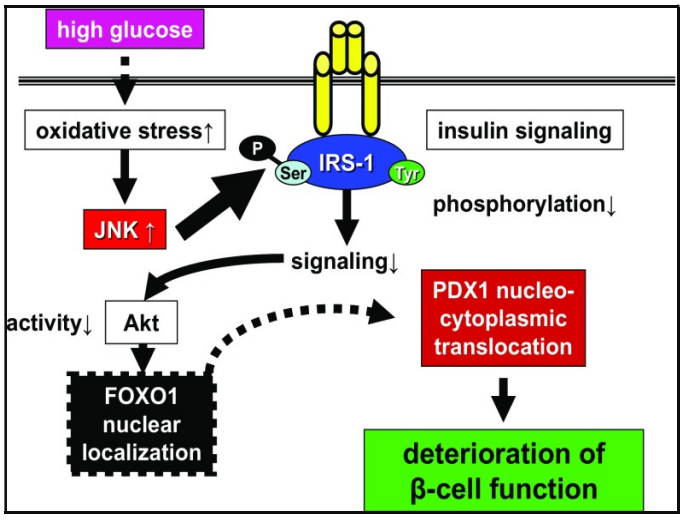

Fig 4. The molecular mechanisms involved in β-cell dysfunction in diabetes.

Furthermore, adenovirus-mediated FOXO1 overexpression reduced the nuclear expression of PDX1, whereas siRNA-mediated knockdown of FOXO1 retained the nuclear PDX1 under oxidative stress. Based on these findings, we clarified that the JNK-Akt-FOXO1-PDX1 axis was pertinent to the impairment of PDX1 function, and that this pathway may additionally explain, at least in part, the molecular mechanisms involved in β-cell dysfunction in diabetes (Fig 4). These data also highlight the pathophysiological significance of the JNK pathway in diabetes and necessitate further studies targeting the signaling [26,27].

Molecular model underlying impaired PDX1 function characteristics in β cells under diabetes. Oxidative stress triggered via chronic hyperglycemia up regulates JNK

signaling in β cells. JNK impairs insulin signaling through the increase in IRS-1 serine phosphorylation and minimizes in-functioning tyrosine phosphorylation. Impaired Akt activity fails to phosphorylate FOXO1, leading to its nuclear localization. Nuclear-localized FOXO1 induces the nucleocytoplasmic translocation of PDX1, which subsequently results in the deterioration of PDX1 features and β-cell function. IRS insulin receptor substrate.

CONCLUSION:

Taken together, the work summarized in this review. Overall review of the pancreas function, role of beta cells. Through basic fundamental molecular studies that explored the underlying mechanisms of pancreatic endocrine islet dysfunction, we recognized deterioration in insulin signaling induced with the aid of chronic high glucose followed by the up regulation of oxidative stress in β cells. In β cells, oxidative stress induces the dysfunction of PDX1 through its nucleocytoplasmic translocation with the aid of interactions with the insulin and JNK signaling pathways and FOXO1. These studies explain the molecular mechanisms underlying β-cell dysfunction in diabetes, and provide important guidance towards a future therapeutic approach to the disease.

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