Pink1 gene: a key player in the pathophysiology of type 2 diabetes mellitus

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Type 2 diabetes mellitus (T2DM) is a complicated metabolic condition with insulin resistance and poor glucose metabolism. Emerging evidence indicates the significance of (PTEN-induced putative kinase 1 (Pink1) in the progression of diseases. Pink1 encodes a protein kinase, which regulates and maintains mitochondrial activity, this mostly affects mitophagy and energy generation. Mutations in the Pink1 gene have been associated to oxidative stress, mitochondrial malfunction, and impaired cellular energy output. The presence of insulin resistance and T2DM may be caused by each of these characteristics. To understand Pink1 potential function in the development of diabetes, this review paper investigates the molecular mechanisms through which it influences glucose metabolism and insulin signaling. Based on preclinical investigations, there is potential for developing innovative therapeutic strategies that specifically target Pink1. These strategies could aim to regulate insulin resistance, improve glucose metabolism, and preserve beta-cell function among individuals diagnosed with diabetes. The following areas of research include figuring out how precisely Pink1 functions in diabetes, translating preclinical findings into clinical settings, exploring precision medicine approaches that specifically target Pink1, and identifying possible therapeutic targets within the Pink1 pathway. This review aims to enhance our understanding of Pink1 impact on T2DM and develop personalized treatments for metabolic disorders. Furthermore, it underscores the significance of persisting with this type of investigation to enhance diabetes treatment strategies.

Keywords:
glucose homoeostasis, insulin resistance, metabolic disorder, pink1 gene, type 2 diabetes mellitus

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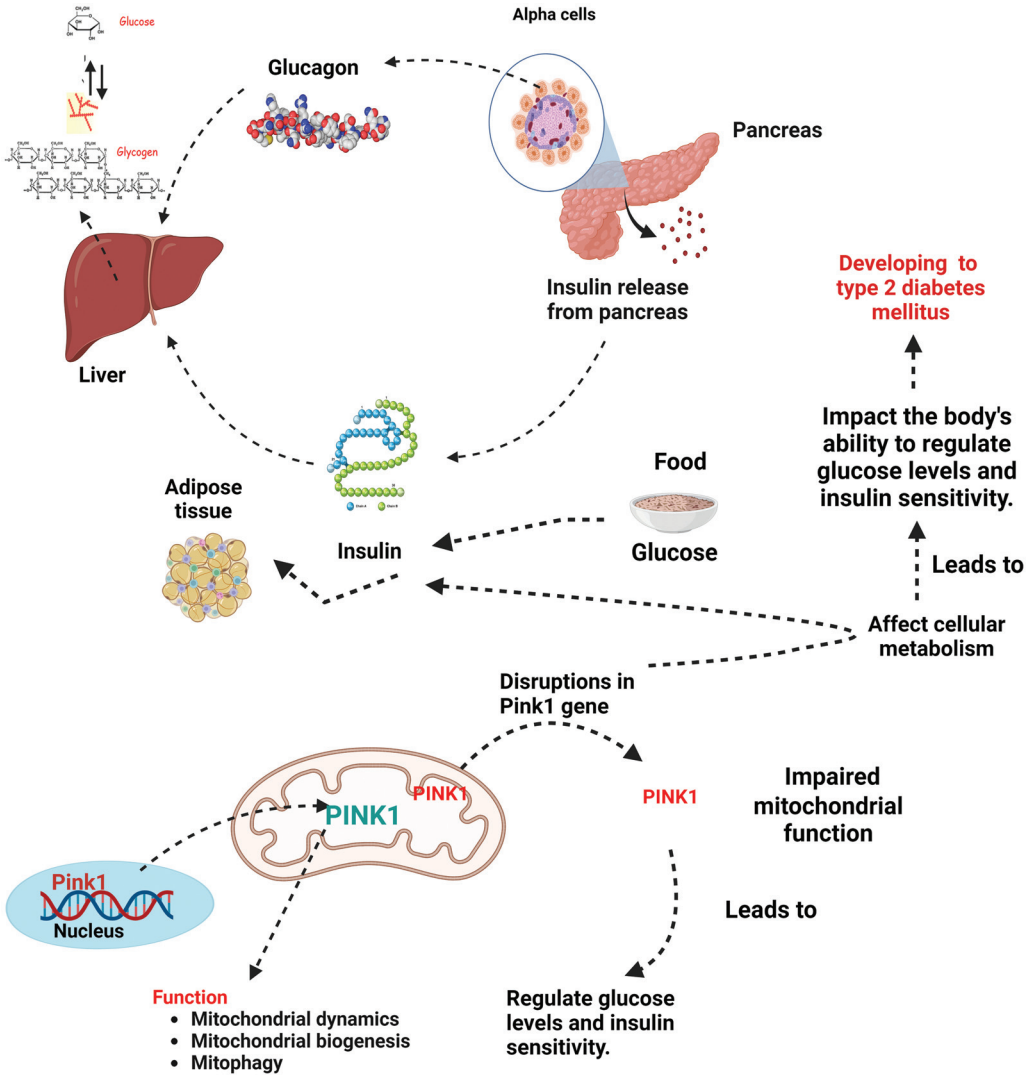
Introduction

The PTEN-induced putative kinase 1 (Pink1) gene plays a significant role in the pathogenesis of type 2 diabetes mellitus (T2DM), a complex metabolic disease characterized by impaired glucose metabolism and insulin resistance [1,2]. T2DM is a complex condition that arises from a combination of genetic, environmental, and behavioral factors. T2DM is distinguished by compromised glucose metabolism and insulin resistance, resulting in heightened levels of blood glucose [3]. If not effectively controlled, this condition can give rise to severe consequences. The Pink1 gene has been linked in recent research as having a substantial impact on the development of T2DM. The Pink1 gene, plays a part in the functioning of mitochondria and has been associated with diverse facets of cellular metabolism [4]. Mitochondrial dysfunction, oxidative stress, and poor glucose metabolism have been linked to mutations or dysregulation of the Pink1 gene, all of which play crucial roles in the pathogenesis of T2DM [5]. The specific methods via which the Pink1 gene contributes to the development of T2DM are now under investigation. However, it is widely accepted that its participation in mitochondrial function and cellular metabolism is of paramount importance Fig. 1. Mitochondria serve as the primary energy generators within cells, facilitating the production of Adenosine Triphosphate (ATP) by the process of oxidative phosphorylation [8]. Mitochondrial dysfunction can result in an alteration of cellular energy metabolism, hence contributing to the development of insulin and compromised glucose consumption [9]. Moreover, the

Figure 1



Interplay of Insulin, Glucagon, and PINK1 Gene in Type 2 Diabetes Mellitus: The image illustrates the relationship between insulin, glucagon, and type 2 diabetes, with a focus on the role of the PINK1 gene in cellular function and mitochondrial health. Insulin stimulates the uptake of glucose from food, while glucagon promotes the breakdown of glycogen. Glycogen, stored in the liver, is stimulated by glucose to form glycogen. Tissue cells play a crucial role in this process, highlighting the interplay between insulin, glucagon, glycogen, and glucose in regulating blood sugar levels and energy metabolism within the body. The potential relationship between the Pink1 gene and type 2 diabetes mellitus have explained by considering how disruptions in Pink1 gene function may impact cellular metabolism and insulin sensitivity, potentially contributing to the development of type 2 diabetes mellitus. The figure was created *via* BioRender.com [6,7].

Pink1 gene has been associated with the modulation of oxidative stress, a process that is recognized to contribute to the emergence of insulin resistance and impaired functioning of pancreatic beta cells, both of which are fundamental to the pathogenesis of T2DM [10]. To comprehend the intricate association between the activity of the Pink1 gene and the development of T2DM, it is imperative to gain insight into the underlying molecular pathways and explore potential targets for treatment. The Pink1 gene encodes a protein kinase that plays a crucial role in the regulation and function of mitochondria, essential organelles responsible for oxidative phosphorylation and energy production [11,12]. Through the modulation of processes such as mitophagy, and the deliberate removal of damaged mitochondria to ensure cellular energy generation and prevent oxidative stress, Pink1 contributes to the preservation of mitochondrial health [13,14]. According to studies, oxidative stress, aberrant mitochondrial activity, and reduced cellular energy generation may all result from dysfunction or mutations in the Pink1 gene [15,16]. Insulin signaling pathways and glucose metabolism are two key biological processes involved in the development of T2DM, and these disturbances may affect these processes [17,18]. Insulin resistance, which raises blood glucose levels in people with T2DM, brought on by ineffective cell response to insulin [19,20]. Dysregulation of glucose uptake and metabolism in insulin-sensitive tissues, such as muscle and adipose

tissue, is often linked to insulin resistance [21,22]. Insulin resistance and T2DM may arise as a result of interactions between the activity of the Pink1 gene, insulin signaling pathways, and glucose metabolism [23,24]. A fundamental aspect of comprehending the molecular mechanisms of T2DM is the function of the Pink1 gene in its pathogenesis. Future treatments for T2DM and metabolic diseases may result from research into the intricate connections between insulin resistance, glucose metabolism, and Pink1 gene activity. To understand T2DM's molecular pathways, Pink1 gene function must be understood.

Discovering the exact links between insulin resistance, glucose metabolism, and Pink1 gene activity may lead to new T2DM and metabolic disease treatments. Ongoing research into the complex relationships between insulin resistance and potential pharmaceutical interventions holds hope for the development of future treatments for metabolic diseases and T2DM. It is imperative to comprehend the mechanisms that underlie insulin resistance, including aberrant glucose metabolism and impaired insulin signaling pathways, in order to develop targeted therapies [25]. The primary objective of the research is to discover new drug targets that can improve glucose uptake, insulin sensitivity, and metabolic function [26]. Furthermore, the objective of developments in personalized medicine is to customize treatments according to unique attributes, such as lifestyle choices and genetic predispositions. Emerging therapeutic approaches may encompass novel pharmaceuticals that regulate critical metabolic pathways, including analogs of insulin, SGLT-2 inhibitors, and incretion-based drugs [27]. In addition, dietary and physical activity modifications continue to be essential elements of comprehensive management strategies for T2DM and metabolic disorders. Advances in the creation of personalized and efficacious remedies for these widespread health conditions remain propelled by the collaborative endeavors of pharmaceutical companies, clinicians, and researchers. The Pink1 gene, is involved in many molecular pathways that contribute to glucose homeostasis. The preservation of steady blood glucose levels within a certain range is known as 'glucose homeostasis,' and it is a process necessary for both regular cellular activity and general health.

Molecular mechanisms of the Pink1 gene in glucose homoeostasis

To ensure stable blood sugar levels and support optimal physiological function, the human body must regulate glucose homeostasis. This intricate system regulates the absorption, retention, and distribution of glucose by precisely coordinating the functions of several hormones, organs, and metabolic routes [28]. The pancreas secretes glucagon and insulin, the primary hormones responsible for regulating glucose levels in the body. Insulin is released when blood glucose levels rise, typically after consuming a meal high in carbohydrates. Its main function in muscle and adipose tissue is to aid in the absorption of glucose into cells, allowing for its storage or transformation into energy. Insulin aids in glycogenesis, the metabolic conversion of glucose to glycogen in the body and muscles, leading to a decrease in blood sugar levels [29]. On the other hand, when blood glucose levels fall, usually as a result of fasting or physical activity, the pancreas releases glucagon. Glucagon functions differently from insulin because it converts glycogen stored in the liver into glucose through a process called glycogenolysis [30]. The hormone glucagon is responsible for initiating the process of gluconeogenesis, which is the production of glucose from noncarbohydrate sources such as amino acids and glycerol that are not carbohydrates. These actions increase blood sugar levels, ensuring that tissues that require energy have an adequate supply of glucose [31]. In addition to glucagon and insulin, several hormones play a role in glucose homeostasis. Cortisol, a stress hormone produced by the adrenal glands, can boost blood sugar levels by increasing gluconeogenesis and inhibiting glucose uptake by tissues [29]. In response to acute stress or danger, the adrenal medulla produces another stress hormone called adrenaline, which accelerates glycogen breakdown and rapidly boosts blood sugar levels [32].

The Pink1 gene is involved in various molecular pathways in the regulation of glucose metabolism [33–35]. The role of Microtubule (MT) signaling via melatonin assessment in diabetes mellitus (DM) was highlighted by a genome-wide association study that found links between melatonin and DM [36]. Regarding the etiology of DM, the role of MT signaling is unclear. Furthermore, the relationship between high glucose and the mortality of neuronal cells as well as the impact of melatonin on the activity of mitophagy regulators in neuronal cells were studied. Another study revealed that whereas excessive hyperglycemia increased Pink1gene and LC-3B expressions, it drastically decreased Mitotracker fluorescence intensity and cytochrome c oxidase subunit 4 expression [33,37]. Silencing Pink1 resulted in elevated cleaved caspase expression, an augmentation in annexin V-positive cells, accumulation of reactive oxygen species (ROS), and

perturbation of the mitochondrial membrane potential. It was investigated that the ROS scavenger N-acetyl cysteine pretreatment reduced the elevated levels of Pink1 and glucose-simulated melatonin receptor 1B (MTNR1B) mRNA. Pretreatment with the MT2 receptor-specific inhibitor 4-P-PDOT suppresses the upregulation of Pink1 expression in neuronal cells. An investigation has been carried out to ascertain the manner in which melatonin exerts its impact on the phosphorylation of Akt, nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB), and the translocation of the nucleus. The elimination of Pink1 expression resulted in the eradication of the ROS in the mitochondria, which is regulated by melatonin, as well as the levels of caspase-3 and caspase-9, and the number of cells positive for annexin V. Additionally, it has been demonstrated that melatonin enhances the expression of Pink1 through the MT2/Akt/NF-κB signaling pathway. This stimulation plays a crucial role in the prevention of neural cell death in the presence pf excessive glucose (high glucose level in body) [33].

The Pink1 gene encodes a mitochondrial kinase that functions as a safeguard against oxidative stress-induced apoptosis. [38]. It is encoded through the PARK6 gene, which is associated with Parkinson's disease (PD). The association between T2DM and PD (Parkinson's Disease) may be attributed to the interplay of glucose metabolism, insulin generation in beta cells, and mitochondrial activity, indicating a clear relationship between these factors. An investigation was conducted to assess the response of beta-cells without Pink1 to glucose stimulation, with the aim of determining the effect of Pink1 deletion on their functioning. In addition, it was revealed that the absence of Pink1 resulted in a significant reduction in glucose uptake in primary intact islets and mouse pancreatic beta-cells (MIN6 cells). Concurrently, there was an increase in the concentration of calcium inside the cells, resulting in a higher rate of insulin secretion under low-glucose conditions [39].

Tacrolimus, an immunosuppressive drug, is prescribed for the management of newly diagnosed diabetes post-transplantation (NODAT). Previous studies have focused primarily on investigating the impact of TAC on islet β cells concerning its potential diabetogenic characteristics. It has been recently determined that hepatic insulin resistance is likely the primary mechanism by which TAC induces NODAT. When TAC injections were administered daily to rodents, a disruption in glucose metabolism was observed. As phosphorylation levels of insulin receptor substrate 2 (IRS2), protein kinase B beta (pAKT2), glucose transporter type 2 (GLUT2), and IRS2 (mRNA and protein levels) were all reduced in response to TAC, these results collectively indicate that hepatic insulin signaling was dysregulated. Moreover, it was established that the primary mechanism by which TAC disrupted hepatic glucose homeostasis was through the Pink1/Parkin pathway. By employing human liver cell lines for mechanistic analyses, it was determined that TAC increased the expression of Pink1/Parkin [40].

Developing and advancing atherosclerosis are consequences of endothelial cell dysfunction in individuals with diabetes. Liraglutide was previously shown to reduce NO production and eNOS phosphorylation when used to treat human umbilical vein endothelial cells (HUVECs). It also decreased oxidative stress and apoptosis in response to high glucose exposure [41]. It is hypothesized that Liraglutide exerts its protective effects through the inhibition of Pink1/Parkin-mediated mitophagy. Significant reductions in high glucose-induced ROS in mitochondria, Pink1 expression, and Parkin accumulation in mitochondria were seen after treatment with liraglutide, but Sirtuin (SIRT1) expression was restored. Through the use of RNA silencing to inhibit Parkin, HUVECs treated with high glucose showed an elevation in apoptotic responses that could not be prevented by Liraglutide. Additionally, there was a decrease in the levels of ROS in both the mitochondria and cytosol, as well as a reduction in mitochondrial mass and membrane potential. Liraglutide efficiently prevents the malfunctioning of cells caused by high glucose levels by inhibiting Pink1/Parkin-dependent mitophagy. It does this by acting upstream of the Pink1/Parkin pathway. Thus, to mitigate the risk of atherosclerosis, its utilization as a supplementary treatment for T2DM is justified [42].

The pink1 gene effect on insulin signaling pathways

The transcription of the insulin gene into the nucleus of the pancreatic beta cell is the first step in the intricate process by which the human body produces insulin. The messenger RNA (mRNA) that has been transcribed is processed to create a fully developed mRNA molecule that contains the instructions needed to generate insulin [35,43]. The mRNA is translated by ribosomes located in the cytoplasm for the creation of the preproinsulin polypeptide chain. The chain's signal sequence is broken down to form proinsulin, which is then transported to the endoplasmic reticulum (ER) [44]. Fully mature

insulin is synthesized after additional alterations and processing in the endoplasmic reticulum. This is followed by proinsulin being housed in secretory vesicles found in the Golgi apparatus. There, it undergoes proteolytic cleavage that results in the creation of fully mature insulin and removes the C-peptide [45]. When blood glucose levels are increased, vesicles release serum insulin in response. This organ's primary job is to regulate how much glucose is absorbed and stored in particular tissues. As a result, it plays a crucial role in maintaining both blood glucose levels that are within normal ranges and metabolic homeostasis [46].

Protein activity and regulation of mitochondrial organelles are governed by the Pink1 gene. Existing research has examined the possibility that the Pink1 gene, which is primarily responsible for regulating mitochondrial health, could also influence insulin signaling pathways [47]. The gene Pink1 is linked to familial PD and functions as a serine/threonine kinase that specifically targets mitochondria [38,48]. As a consequence, Pink1 has protective effects against mitochondrial damage caused by neurotoxins. However, when Pink1's activity is suppressed by RNA interference or when disease-associated Pink1 mutations are used, it leads to mitochondrial damage mediated by ROS [24]. Remarkably, individuals with T2DM exhibited decreased levels of Pink1 compared with those without diabetes. The deficiency of Pink1 leads to malfunctioning of mitochondria and hampers the ability of β cells to take up glucose [39]. Metabolic complications may arise as a consequence of impaired Pink1 expression and dysfunction in individuals with diabetes [49]. Recently it has been investigated that Pink1 enhanced insulin resistance in liver cells treated with palmitic acid (PA) via the activation of the Jun N-terminal Kinase (JNK) and Extracellular Signal-Regulated Kinase (ERK) signaling pathways. This suggests that Pink1 might be a potential new target for the treatment of diabetes [50]. In addition, the Pink1/Parkin signaling pathway plays a vital role in the alteration of glucose homeostasis in the liver produced by TAC [40].

Pink1/Parkin signaling pathway involvement in high glucose-mediated cell death is suggested by the fact that its activation promotes mitophagy and protects cells from apoptosis and death, whereas Pink1/Parkin pathway regulation of cell mitophagy and mitochondrial damage is critical [51]. Prior research has demonstrated that cadmium-induced ROS stimulates autophagy and mitophagy in mice via regulation of the Pink1/Parkin pathway [52,53]. Furthermore, over 75 mM glucose-induced regulation of retinal pigment epithelium autophagy and apoptosis is significantly influenced by the Pink1/Parkin signaling pathway [54]. Furthermore, it has been investigated that high glucose levels stimulate apoptosis in the retinal pigment epithelium and impede cell proliferation and mitophagy via regulation of the ROS-mediated inactivation of the pathways ROS/Pink1/Parkin [55]. Mutations in the PARK6 gene, which codes for Pink1, are responsible for recessive early-onset Parkinsonism. The impact of changes in signaling pathways on the reduction of dopamine neurons in recessive Parkinsonism is unclear, even though Pink1 and Parkin aid in the breakdown of depolarized mitochondria in cultured cells. Accumulating data suggests that impaired Akt cell survival signaling is associated with both sporadic and familial PD. Both insulin and IGF-1 have neuroprotective effects in various situations, and the signaling pathway involving IGF-1 and Akt protects the loss of dopamine neurons in several animal models of PD. The efficient transmission of IGF-1 and insulin-dependent Akt signals requires Pink1. This finding implies that Pink1-related Parkinsonism could potentially be influenced by impaired IGF-1/Akt signaling, which renders dopaminergic neurons more vulnerable to stress-induced cell death [56]. DM is a major factor in the low survival rates that are seen in patients who have had lung transplantation. It is well known that diabetic pulmonary ischemia-reperfusion (IR) damage is mostly caused by mitochondrial dysfunction. Adiponectin reduced the negative effects of oxidative stress, inflammation, apoptosis, and mitochondrial dysfunction caused by reperfusion in diabetic lung ischemia-reperfusion damage. This was achieved by activating the SIRT1-PINK1 signaling pathway, which in turn promoted mitophagy [57].

Presently, scientists are in the process of elucidating the specific mechanisms through which Pink1 modulates insulin signaling pathways. Conversely, there is speculation that Pink1 might exert an influence on insulin sensitivity through its roles in protein interactions, autophagy, and mitochondrial activity. Further investigation is necessary to gain a comprehensive understanding of the implications of Pink1 in insulin signaling and its potential relevance to metabolic disorders such as diabetes.

Regulation of GLUT4 expression via Pink1 gene

An area of research with great potential is the study of the relationship between mitochondrial activity and glucose metabolism. This may be done by

investigating how the Pink1 gene influences the expression of GLUT4, which regulates glucose transport. The glucose transporter protein GLUT4 plays a crucial role in facilitating the uptake of glucose in muscle and adipose tissue, particularly when insulin is produced [58]. Subsequently, insulin resistance develops due to the diminished sensitivity to insulin caused by the elevated levels of lactate dehydrogenase (LDH) [59]. Triglyceride accumulation causes an increase in ROS, which in turn impairs the functioning of mitochondria. The reduction in mitochondrial oxidative capacity and ATP/Adenosine Diphosphate (ADP) ratio in the liver, muscles, and adipose tissue leads to the development of class 1 GLUT transporter, which in turn causes insulin resistance [60]. Pink1 is translocated into mitochondria, where it undergoes division and degradation, in accordance with typical physiological conditions [61,62]. A depolarized membrane potential induces impaired import of Pink1 from damaged mitochondria. Phosphate groups are appended to ubiquitin molecules at serine 65, whereas Pink1 maintains its position stable on the outer mitochondrial membrane. By means of this procedure, the E3 ubiquitin ligase Parkin is partially recruited and activated [63,64]. Additionally, neurodegenerative diseases often incorporate deficiencies in mitochondrial quality control. Transporting Pink1 mRNA to the mitochondrial surface via tethering is necessary for the stabilization of Pink1-based damage detection. The relationship between insulin resistance and mitochondrial dysfunction has been proposed to be mediated by a metabolic switch that regulates the localization of *Pink1* mRNA and the activity of Pink1 in neurons via insulin and AMPK signaling [64]. Podocytes are the only cells in the glomerulus that are responsive to insulin. In response to insulin, they have the ability to enhance glucose absorption by causing the movement of glucose transporters GLUT1 and GLUT4 to the cell membrane [65]. In addition to regulating glucose transport, insulin also modifies the actin cytoskeleton, which is crucial for maintaining the correct structure and function of podocyte foot processes [66]. Podocytes are renal cells found in the glomerulus of the nephron. The foot processes of podocytes are specialized projections or extensions of these cells. When it comes to setting up and maintaining the glomerular filtration barrier inside the renal system, the foot processes are crucial. By interdigitating with nearby foot processes, filtration slits are created, improving the glomerular filtration barrier's capacity for selective permeability. This permeability protects the preservation of essential proteins and cells and makes it easier to filter blood and produce urine. Dysfunction or damage to podocyte foot processes can result in proteinuria and many renal disorders [67]. Pink1 is essential for efficient insulin signaling and the maintenance of podocyte permeability. Therefore, Pink1 could potentially be utilized as a therapeutic target to prevent or manage diabetic nephropathy [68].

The presence of Alzheimer's disease (AD) is increasingly supported by evidence indicating an aberrant cerebral glucose metabolism. A reduction in the brain's metabolism has a direct impact on brain function, as glucose is the primary energy source utilized by the brain. Constructively evaluating the aberrant glucose metabolism linked to the accumulation of phosphorylated tau and amyloid beta in the brain of AD patients has been investigated. IRS/PI3K/Akt/AMPK signaling and GLUTs were implicated in the progression of AD, as demonstrated by the interrelation between insulin signaling and the disease. AGEs accumulation, polyol activation, mitochondrial permeability, Pink1/parkin defects, lysosome-mitochondrial crosstalk, and autophagy/mitophagy were among the additional contributing factors that were evaluated in relation to the mitochondrial dysfunction in the defective glucose metabolism. In summary, the poor use of glucose in the brain in AD is influenced by the growing involvement of changes in glucose metabolism, the effect of insulin signaling, and malfunction in mitochondria [69].

Pink1 gene contribution to the function of beta-cells and insulin secretion

The regulation of mitochondrial movement and morphology plays a critical role in the development of T2DM and its associated vascular problems. Indeed, mitochondria play a crucial role in controlling the release of insulin, and mutations in mtDNA have been associated with the onset of T2DM. Recently, a new mutation called m.8561C greater than G in MT-ATP6/8, which are subunits of mitochondrial ATP synthase, has been identified as the cause of DM and hypergonadotropic hypogonadism [70]. Pink1 is a serine/threonine kinase that is exclusively directed to mitochondria and works to inhibit stress-induced cell death. Research has shown that the absence of Pink1 function and the presence of homozygous mutations in the Pink1 gene (also known as PARK6) are important variables that contribute to the development of early onset autosomal recessive PD [71]. Previous study has shown that the lack or malfunction of Pink1 in neurons leads to a series of mitochondrial disorders. The

variables listed above lead to a reduction in the ability to regulate calcium levels, an increase in the formation of ROS via NADPH oxidase, a decrease in the electrical potential across the mitochondrial membrane, inhibition of the sodium calcium exchanger, and poor transport of glucose into the cell [72,73]. The Pink1 gene mutations have been widely shown to be the cause of early-onset autosomal recessive PD [71,74]. Pink1 is a protein found in mitochondria, and there is now substantial evidence indicating that malfunctioning mitochondria play a crucial role in PD [75,76]. Although the primary manifestation of Pink1 mutations in patients is the death of dopaminergic neurons in the substantia nigra of the brain, recent studies have suggested that dysfunction or dysregulation of the Pink1 gene may also be a potential risk factor for the metabolic disorder T2DM [24,77]. A deficit in Pink1 hinders the proper functioning of β-cells in the pancreas, leading to increased levels of basal insulin secretion in laboratory settings and a tendency for raised basal plasma insulin in living organisms. In light of the reported correlation between PD and T2DM and the relationship between glucose metabolism, insulin secretion in β-cells, and the response of β-cells deficient in Pink1 to glucose stimulation, it was examined whether the absence of Pink1 impacted their functionality. The absence of Pink1 activity seems to interfere with the ability to detect glucose levels, resulting in increased insulin secretion that is not dependent on glucose absorption. This indicates that Pink1 plays a crucial role in the functioning of β-cells [39].

Pink1 gene dysfunction and insulin resistance

It is hypothesized that Pink1, is a mitochondrial localized kinase that provides protection to the mitochondria from oxidative stress (OS). Pink1 and Parkin work in tandem to initiate a series of phosphorylation reactions that result in the activation of Parkin. A series of reactions are initiated in response to Pink1/Parkin system activation, which regulates mitophagy and mitochondrial regeneration [78]. Pyrotechrome c, which is liberated from impaired mitochondria, functions as the stimulus molecule for the intrinsic pathway of apoptosis. There are dysregulated molecular processes that are shared between persons with IR and PD, which are also often seen in people with T2DM and PD. PD is a prevalent condition characterized by motor and neuronal impairments [79]. PD leads to impairment and its global incidence is on the rise [80]. Familial PD has been linked to the occurrence of several mutations in the Parkin and Pink1 proteins [81]. Animal model studies indicate that the Parkin/Pink1 pathway is involved in regulating the quality of mitochondria. Typically, the Parkin and Pink1 proteins collaborate to remove malfunctioning mitochondria [82]. Furthermore, Parkin facilitates the ubiquitination of the PARIS protein, leading to its proteasomal destruction. The degradation process stimulates the activation of PGC-1α, a transcriptional coactivator of peroxisome proliferator-activated receptor gamma coactivator 1. This protein is important for encoding genes associated with the synthesis and operation of mitochondria [81].

Pink1 plays a critical role in inhibiting cellular apoptosis through two distinct mechanisms. Firstly, it enhances the rate at which damaged mitochondria undergo mitophagy, thereby reducing the loss of free electrons. Secondly, it impedes the release of cytochrome c from the mitochondria [72,83]. Mutations in the Pink1 gene have been closely associated with neurological diseases such as Parkinson's disease (PD). However, there is also evidence suggesting a potential connection between Pink1 and glucose metabolism. Research has revealed that obese individuals exhibit a higher overall body mass (OBM) compared with lean individuals, leading to a compensatory increase in antioxidants, as indicated by a rise in total antioxidant status (TAS). In obese patients with T2DM, a decrease in PINK1 expression was observed in comparison to lean T2DM patients. This decreased expression of PINK1 in the obese population is believed to hinder its capacity to protect the mitochondria from oxidative stress, ultimately leading to a decrease in mitochondrial DNA content [84]. Specifically, studies have demonstrated changes in the expression of Pink1 in individuals who are inactive, obese, or have T2DM. Moreover, the absence of Pink1 leads to calcium accumulation in the mitochondria, resulting in calcium excess. This excess calcium activates NADPH oxidase, leading to the generation of ROS. Hyperoxide-induced cellular injury is accompanied by insulin resistance, which may result from increased ROS production inhibiting the glucose transporter. This evidence underscores the intricate relationship between Pink1, cellular apoptosis, mitochondrial function, and glucose metabolism, shedding light on the potential implications for conditions such as obesity and T2DM [2,85,86]. The reduced expression of PINK1 in the obese group may be unable to adequately protect the mitochondria against the elevated oxidative stress, potentially leading to decreased mitochondrial DNA (mtDNA) content.

Additionally, the role of decreased PINK1 in contributing to beta-cell dysfunction or insulin resistance in obese patients with T2DM needs to be further explored, given PINK1's involvement in oxidative stress-induced apoptosis.

The absence of Pink1 alters glucose metabolism, which is probably responsible for meeting the increased energy needs reported in Pink1-deficient proliferating cells, such as fibroblasts. Furthermore, it has been shown that the stabilization of HIF1α *via* ROS-mediated processes is the molecular mechanism accountable for this metabolic adaptability. Investigations using mitochondrial-tagged antioxidant enzymes have shown that mitochondrial-derived ROS are very likely to have a crucial impact on the stability of HIF1α. Nevertheless, the potential contribution of cytosolic ROS to this phenomenon cannot be ruled out. Indeed, the reduction of catalase and peroxiredoxin has been associated with the absence of Pink1 in other species, such as zebrafish [72,87]. Subcellular autophagy and oxidative phosphorylation are both compromised in the absence of Pink1. In vivo and in cultured Pink1−/− mouse embryonic fibroblasts and primary cortical neurons, hypoxia-inducible factor-1α (HIF1α) stabilization is induced by Pink1 deficiency. Pyruvate dehydrogenase kinase-1, a target of HIF1, was upregulated in response to this effect, which was mediated by ROS within the mitochondria. PDH activity is inhibited. Moreover, in the absence of Pink1, HIF1α stimulation of glycolysis occurs, and cell proliferation in Pink1−/− mice is dependent on the stabilization of intracellular glucose metabolism by HIF1α. HIF1α is maintained when Pink1 is absent, as it alters glucose metabolism [87].

Potential benefits of pink1 targeting for the treatment of T2DM

T2DM is characterized by impaired mitochondrial activity, elevated generation of ROS, and reduced ATP levels. Mitochondrial fusion is regulated by many proteins, such as mitofusin-1 (MFN1), mitofusin-2 (MFN2), and optic atrophy (OPA-1), whereas mitochondrial fission is governed by mitochondrial fission 1 (FIS1), dynamin-related protein 1 (DRP1), and mitochondrial fission factor (MFF). Parkin and Pink1 are involved in mitophagy, a process that requires mitochondrial fission [88]. The $\Delta\Psi m$ of β-cells undergoes alterations that are associated with oxidative stress and T2DM. The modification in β-cells may be strongly linked to changes in mitochondrial dynamics, resulting in reduced insulin production in response to glucose stimulation, as shown by prior research [88,89]. In T2DM, the fusion and fission processes in β-cells are constantly changing. Studies have shown that high blood sugar levels and increased levels of palmitate reduce fusion and hinder the absorption of oxygen by mitochondria [90,91]. In addition, recent research has shown that Pink1 reduces palmitate-induced insulin resistance in liver cells by inhibiting ROS-mediated MAPK pathways [50,92].

There is a possibility that the treatment of T2DM might include the use of precision medicine approaches that precisely target Pink1. An investigation that was conducted revealed that it could also play a part in regulating the glucose balance and metabolism, which offers new insights into the process of diabetes development. This complex metabolic disease causes insulin resistance, poor glucose metabolism, and pancreatic β-cells destruction. Individuals with T2DM share these traits. This is an issue of international scope, impacting individuals across the globe [40]. Given the crucial function that mitochondria perform in producing cellular energy and preserving metabolic equilibrium, there is significant therapeutic potential in exploring the impact of Pink1 on cellular metabolism, insulin signaling pathways, and mitochondrial function. An understanding of the possible impacts of directly modifying Pink1 expression or activity on cellular energy generation, mitochondrial function, and insulin sensitivity is essential for the development of individualized treatment strategies for T2DM. This understanding is necessary to produce tailored treatment plans. In pursuit of novel strategies to enhance insulin sensitivity, glucose tolerance, and beta-cell function in individuals with diabetes, investigators are presently examining the therapeutic ramifications of modifying Pink1 to discover additional methods to improve these attributes.

Future perspective and conclusion

Pink1 has a crucial function in regulating insulin signaling pathways and glucose metabolism via several molecular mechanisms, it needs further investigation to fully understand these processes. The intricate interplay among Pink1, insulin sensitivity, and mitochondrial activity holds promise for developing personalized treatments for diabetes. Translating discoveries from preclinical research into practical clinical applications by targeting Pink1 in type T2DM is crucial. This approach allows for the exploration of personalized treatment alternatives that specifically target the molecular processes associated with the disorders targeting Pink1 and its

associated pathways using precision medicine approaches has the potential to significantly transform diabetic care. Through comprehending the influence of Pink1 on glucose control and insulin sensitivity, it is possible to lay the groundwork for personalized diabetes management. Exploring novel therapeutic targets within the Pink1 pathway for addressing insulin resistance, glucose metabolism, and beta-cell function is vital. Identifying targets within the Pink1 signaling cascade may unveil innovative treatments for diabetes.

To conclude, Pink1 gene exerts a substantial influence on metabolic diseases and is a pivotal factor in the development of T2DM. The intricate relationship between Pink1 activity, mitochondrial function, insulin signaling pathways, and glucose metabolism suggests its pivotal role in diabetes. Understanding the molecular processes behind Pink1 might enhance the development of precise therapies for diabetes by offering valuable knowledge on insulin signaling, glucose regulation, and beta-cell function. Targeting Pink1 could aid in addressing insulin resistance, boosting glucose metabolism, and preserving beta-cell function, underscoring the need for further investigation. To deepen our comprehension of metabolic disorders and improve T2DM treatment, it is essential to explore Pink1's role in diabetes, translate research findings into clinical applications, and advance precision medicine approaches.

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