Title
The Role of Oxidative Stress in Pancreatic β Cell Dysfunction in Diabetes.

Permalink
https://escholarship.org/uc/item/31k7q3d9

Journal
International journal of molecular sciences, 22(4)

ISSN
1422-0067

Authors
Eguchi, Natsuki
Vaziri, Nosratola D
Dafoe, Donald C
et al.

Publication Date
2021-02-03

DOI
10.3390/ijms22041509

Peer reviewed
Abstract: Diabetes is a chronic metabolic disorder characterized by inappropriately elevated glucose levels as a result of impaired pancreatic β cell function and insulin resistance. Extensive studies have been conducted to elucidate the mechanism involved in the development of β cell failure and death under diabetic conditions such as hyperglycemia, hyperlipidemia, and inflammation. Of the plethora of proposed mechanisms, endoplasmic reticulum (ER) stress, mitochondrial dysfunction, and oxidative stress have been shown to play a central role in promoting β cell dysfunction. It has become more evident in recent years that these 3 factors are closely interrelated and importantly aggravate each other. Oxidative stress in particular is of great interest to β cell health and survival as it has been shown that β cells exhibit lower antioxidative capacity. Therefore, this review will focus on discussing factors that contribute to the development of oxidative stress in pancreatic β cells and explore the downstream effects of oxidative stress on β cell function and health. Furthermore, antioxidative capacity of β cells to counteract these effects will be discussed along with new approaches focused on preserving β cells under oxidative conditions.

Keywords: pancreatic β cells; oxidative stress; anti-oxidants; diabetes

1. Introduction

Diabetes is a chronic metabolic disorder affecting 400 million people worldwide and 30.2 million adults aged 18 years or older in just the US [1]. Type 2 diabetes mellitus (T2DM) is characterized by the inability of the pancreatic β cell to produce enough insulin to maintain glycemic control due to increased insulin demand caused by insulin resistance. β cell dysfunction and dedifferentiation, and reduced β cell mass are also suggested to be a central event in the development of the disease [2]. It is well known that hyperglycemia, hyperlipidemia, and inflammation, some of the most common characteristics of a diabetic condition, contribute to β cell damage and dedifferentiation primarily through promoting ER stress, mitochondrial dysfunction, and oxidative stress. Although ER stress and mitochondrial dysfunction have been implicated in β cell dysfunction and apoptosis independently, more recently their pathological role in aggravating β cell oxidative stress has gained particular interest [3]. Pancreatic β cells are particularly susceptible to oxidative stress due to their high endogenous production of reactive oxygen species (ROS) and their low antioxidant capacity, suggesting that oxidative stress may play an important role in β cell failure [4]. Oxidative stress is known to be involved in the pathogenesis of a wide range of diseases ranging from cardiovascular disease to cancer, and extensive studies have been conducted to investigate the effectiveness of potential pharmacological agents targeting oxidative stress [5]. Thus, understanding the molecular mechanisms involved in oxidative stress induced β cell dysfunction may inform novel approaches to treating T2DM.

This review aims to first briefly discuss ways in which toxic environmental factors lead to mitochondrial dysfunction, ER stress, and oxidative stress, and then explore downstream pathways of oxidative stress implicated in β cell dysfunction and death. Lastly, new
therapeutic approaches to combat the downstream effect of oxidative stress in β cells will be explored.

2. Effect of Environmental Stressors on β Cells

2.1. Endoplasmic Reticulum Stress

Due to the increased demand for insulin synthesis and secretion under diabetic conditions, β cells dysfunction is closely associated with ER stress. Proinsulin accounts for 30–50% of cellular protein synthesis of β cells, and approximately 20% of newly synthesized proinsulin fails to reach its native conformation, suggesting a high incidence of proinsulin misfolding [6]. The increased demand overwhelms the ER folding capacity and leads to ER stress. In response, β cell activates the two responses of unfolded protein response (UPR): Adaptive UPR and apoptotic UPR, which work to promote either insulin biosynthesis and secretion or apoptosis. Human islets of patients with T1 and T2DM show increased expression of ATF3 and C/EBP homologous protein (CHOP), pathways of apoptotic UPR, and Bip, an ER chaperone stimulated in adaptive UPR [7]. Supporting this, incubation of human pancreatic β cells under hyperglycemia, hyperlipidemia, and with proinflammatory cytokines results in activation of both adaptive and apoptotic UPR [8–13]. In contrast however, more recently, Dai C. et al. demonstrated that the adaptive UPR response was not activated in human β cells under chronic hyperglycemia and hyperlipidemia, suggesting that prolonged glucotoxicity and lipotoxicity may cause defective adaptive UPR response to resolve ER Stress [14]. Several pathways have been implicated in the pathogenesis of ER stress. Both hyperlipidemia and inflammatory cytokines induce ER Ca\textsuperscript{2+} depletion, which impairs chaperones from the protein folding machinery and causes accumulation of misfolded protein [8,10,15–18]. Additionally, alteration in miRNA profile under proinflammatory treatment and upregulation of cholesterol synthesis under hyperlipidemia are also suggested to contribute to ER stress in human and rodent β cells [19–23].

2.2. Mitochondrial Dysfunction

Proper mitochondrial function is crucial to nutrient sensing and insulin secretion in β cells. The increased metabolism as a result of higher glycolytic flux after a meal results in increased cytosolic ATP level. This rise in ATP closes ATP gated K+ channels, which result in depolarization of β cells and the subsequent opening of Ca\textsuperscript{2+} channels, which is coupled to the exocytosis of insulin granules [24]. This signaling cascade is significantly altered in T2DM due to defects in mitochondrial metabolism [25]. Compared to control islets, islets of patients with diabetes mellitus (DM) show reduced glucose stimulated insulin secretion (GSIS), which was associated with lower ATP/ADP ratio, decreased mitochondrial membrane potential, and downregulation of expression of genes associated with energy metabolism [25,26]. Furthermore, mitophagy has also been associated with β cell failure in DM [27]. Mitophagy participates in mitochondrial quality control by selectively removing damaged mitochondria, and malfunction of mitophagy is considered to contribute to β cell destruction. Interestingly, mitochondrial rho GTPase 1 [27], PTEN-induced putative kinase 1, NIP3-like protein X, mitofusion 2, and microtubule-associated protein light chain 3, important mitophagy related genes, have been shown to be augmented in islets of prediabetic patients while significantly downregulated in islets of newly diagnosed and long term diabetic patients, indicating mitophagy impairment in DM [28]. Supporting these observations, transcriptomic and proteomic studies on mice and healthy and diabetic human β cells treated in hyperglycemic and hyperlipidemic conditions demonstrated decreased expression of glycolytic, oxidative phosphorylation, and tricarboxylic acid cycle related genes [9,20,26,29–31]. Additionally, both hyperglycemia and hyperlipidemia treatment significantly increased respiration, decreased ATP content, lowered mitochondrial membrane potential, and increased mitochondrial volume, signs that indicate mitochondrial uncoupling and dysfunction [30,32–34]. Another study showed both hyperlipidemia and inflammatory cytokine (IL-1β, TNF-α, IFN-γ) treatment altered mitochondria morphology
and dynamics through inhibiting mitochondrial fusion, a response to mitochondrial stress important in maintaining health and respiratory efficiency [35,36].

In addition to mitochondrial dysfunction, diabetic condition is closely associated with mitochondria mediated apoptosis. Upon proapoptotic stimuli, cytochrome c is released from mitochondria into the cytoplasm, where it participates in the activation of caspase-9 and subsequent activation of apoptosis executioner caspases 3, 6, and 7 that dismantle the cell. Thus, cytochrome c release from mitochondria is a key step in the initiation of apoptosis. It has been demonstrated that ROS generated by mitochondria trigger apoptosis through a process that involves cytochrome c release in INS-1 cells and mouse β cells [37,38]. Another mechanism by which ROS induces apoptosis is by causing mitochondrial fission. Li F et al. demonstrated that ROS generated by nicotinamide adenine dinucleotide phosphate oxidase (NOX) activation under palmitate treatment of β cell activate ROS-sensitive transient receptor potential melastatin-2 (TRPM2) channels, which subsequently causes abnormal mitochondrial fission [39]. Importantly, silencing of the ROS sensitive TRPM2 channel or treatment of cells with the antioxidant N-acetylcysteine (NAC) in human β cells prevents palmitate induced β cell death and mitochondrial fragmentation, thus highlighting the importance of ROS in stimulating mitochondrial dysfunction and apoptosis [39]. Another mechanism possibly involved in oxidative stress induced apoptosis in human β cells is through the downregulation of Bcl-2, a prosurvival protein [40].

2.3. Oxidative Stress

Hyperglycemia, hyperlipidemia, and inflammation are all potent factors contributing to ROS production in β cells. At basal level, ROS in fact plays a crucial role in insulin secretion. It has been demonstrated by Llanos et al. that the ROS generation alongside the moderate Ca^{2+} influx after glucose stimulation is required for RyR channel activation [41]. Once activated, these channels provide the intracellular Ca^{2+} increase required for insulin secretion [41]. Moreover, H_{2}O_{2} treatment of islet cells under basal glucose level resulted in augmented insulin secretion, further supporting the concept that ROS plays a critical role in insulin secretion. However, under pathological conditions, the build-up of ROS results in oxidative stress. The major contributor of ROS production is the mitochondrial electron transport chain (ETC). Under hyperglycemic and hyperlipidemic conditions, the increased nicotinamide adenine dinucleotide and flavin adenine dinucleotide levels result in augmented production of ROS through overloading the ETC and causing electrons to leak from complex I and III [42–44]. The electrons react with molecular oxygen to form O_{2}^{•−}, which is quickly converted to H_{2}O_{2} [20,26,29,30]. Left undetoxified, the accumulated H_{2}O_{2} then could be converted into highly reactive hydroxyl radical and OH^{−} by the Fenton reaction in the presence of higher concentrations of transition metals Cu^{2+} and Fe^{2+} [43]. β cells have several antioxidant defense systems including catalase (CAT), glutathione peroxidase (GPx), thioredoxin (TXN), and periredoxins, which play a significant role in the conversion of H_{2}O_{2} into H_{2}O and O_{2} [45,46]. However, although these defense mechanisms are present, it has been demonstrated that pancreatic β cells exhibit a lower expression of CAT and GPx1, suggesting higher susceptibility to ROS damage [4]. Several other mitochondrial pathways are considered to be involved in ROS production in β cells under hyperglycemia, which include protein kinase C (PKC) activation, increased intracellular advanced glycation end product formation, hexosamine pathway activation, polyol pathway activation, and oxidative phosphorylation [47–49]. Furthermore, hyperlipidemia has also been shown to increase ROS production through activation of NOX, induction of matrix metalloproteinase 2 (MMP2), and stimulation of macrophage infiltration [13,50–53]. In addition to increasing ROS production, hyperglycemia and hyperlipidemia aggravate oxidative stress through reducing antioxidant capability, evidenced by the reduction in reduced glutathione (GSH/GSSG ratio) in hyperglycemia, and reduced superoxide dismutase 1 (SOD1) and SOD2 expression in hyperlipidemia in human and rat β cells [14,54,55]. Interestingly, however, in contradiction with the previous studies, in a more recent study by Dai C. et al., hyperglycemic condition did not change superoxide
level and antioxidant enzymes levels including SOD1, SOD2, and GPX1 in human islets, while hyperlipidemic conditions showed a significant increase in superoxide and reduction in antioxidant enzyme levels, suggesting that hyperlipidemia may be the major driving force for ROS production [14]. Another study reported similar results showing palmitate treatment significantly induced NO production and lipid peroxidation, major contributors of oxidative stress, while hyperglycemia had no effect [54]. Similarly to hyperlipidemia, inflammatory cytokines increased production of H₂O₂ and other ROS products, which modulated activity of NOX and increased expression of genes that recruit macrophage to β cells [4,56,57]. Importantly, it has been proposed that these changes result in chemokine production by β cells, thereby trapping them in an inflammatory environment.

2.4. Link between Mitochondrial Dysfunction, ER Stress, and Oxidative Stress

In addition to oxidative stress directly induced by hyperglycemia, hyperlipidemia, and inflammation, mitochondrial dysfunction and ER stress secondary to these conditions can further aggravate ROS production. For example, mitochondrial dysfunction is generally associated with increased ROS production by the organelle itself, which acts to potentiate oxidative stress [58]. One study demonstrated that inflammation results in mitochondrial ROS production, which subsequently activates nuclear factor kappa B (NF-kB) and nitric oxide synthase (iNOS), contributing to oxidative stress through alteration of redox balance and production of NO [59,60]. Mitochondrial ROS production may also further aggravate oxidative stress through contributing to ER stress, evidenced by the reversal of ER stress upon addition of MitoQ, a mitochondrial targeted antioxidant [61]. ER stress is another potent ROS producer and contributes primarily by increasing its oxidative protein folding of proinsulin through its activation of the adaptive UPR, which increases insulin biosynthesis and secretion [62]. Proinsulin folding requires the production of three disulfides for each molecule of proinsulin it synthesizes (3 million disulfides/min per cell), a process which stoichiometrically produces H₂O₂ as a ROS by-product [63,64]. Additionally, ER stress can promote ROS generation through contributing to mitochondrial dysfunction. The Ca²⁺ leakage from ER as a result of ER stress causes disruption of Ca²⁺ homeostasis in mitochondria leading to increased mitochondrial ROS production [65].

Interestingly the interaction between the pairs among ER stress and mitochondrial dysfunction, and oxidative stress is not unidirectional. H₂O₂ treatment of human islets resulted in the increased mRNA expression of ER stress markers CHOP and P581PK [66]. Furthermore, high oxidative conditions have been shown to play a role in ER Ca²⁺ depletion, which impairs the chaperones of the protein folding machinery and subsequently results in misfolded protein accumulation and ER stress [16]. Oxidative stress also induces mitochondrial dysfunction. In a study using INS-1 cells, H₂O₂ treatment resulted in a 4-fold increase in ROS production with a concomitant decrease in ATP production and mitochondrial membrane potential, both of which were reversed by the addition of antioxidant chlorella [67]. Both decreased ATP production and mitochondrial membrane depolarization is associated with impaired insulin secretion [68].

Toxic environmental factors activate several pathways that interact to generate and promote ROS production in β cells. Therefore, the impact of oxidative stress on β cells is a critical factor determining its fate under diabetic conditions.

3. Impact of Oxidative Stress on β Cells, Its Downstream Pathways

Oxidative stress has been shown to alter major pathways important for β cell function and survival. Oxidative stress causes AMP-activated protein kinase (AMPK) activation, mammalian target of rapamycin (mTOR) inhibition, and c-Jun N-terminal kinase (JNK) activation in pancreatic β cell. The following section will discuss the impact of these pathways in potentiating β cell dysfunction.
3.1. AMPK Activation

AMPK pathway plays essential roles in pancreatic β cells, regulating insulin secretion, metabolic processes, proliferation, and survival. In healthy human and mice β cells, hyperglycemia to glucose stimulation is associated with a clear reduction in phosphorylation of AMPK, indicating reduced activation; however under pathological conditions, this reduction is significantly attenuated [69,70]. This reduced inactivation of AMPK may in part be due to oxidative stress, as oxidative stress has been shown to increase AMPK activation in rodent and human β cell lines [45,71,72]. Short term, this increased activation of AMPK plays both protective and harmful roles in β cells. (Figure 1) First off, Xia G. et al. has demonstrated that ROS mediated AMPK activation in INS-1 cells has been shown to protect β cells through promoting autophagy and reducing oxidative stress [71]. Promotion of autophagy under AMPK activation may be mediated by mTOR inhibition, which is well known to inhibit autophagy, as pAMPK plays a role in mTOR inhibition [73]. Additionally, the reduction in oxidative stress by AMPK activation may be mediated by inhibition of NOX2 which in turn reduces ROS production and JNK1/2 activation [74]. Second, increased AMPK levels may aid in maintaining mature β cell identity, as it has been shown in INS-1 cells that loss of AMPK results in upregulation of disallowed genes, which are often expressed in dedifferentiated β cells or other tissues [75,76]. Third, activated AMPK may also play a protective role by increasing insulin secretion and causing compensatory β cell expansion by the upregulation of miR-184 [77,78]. Furthermore, in another study, pAMPK increased insulin secretion through increased uptake of Ca$^{2+}$ into the cytosol [70]. The increased level of cytosolic Ca$^{2+}$ level under pharmacological AMPK activation may induce insulin exocytosis, and enhance intracellular metabolism, which subsequently increases ATP levels and thus contributes to increasing insulin secretion.

On the other hand, increased pAMPK as a result of oxidative stress may also have harmful effects. Zhang Y et al. showed that ROS mediated upregulation of pAMPK in

![Figure 1](image-url) Downstream effects of upregulation of AMP-activated protein kinase (AMPK) activation via oxidative stress. The upregulation of AMPK has both protective and harmful effects. AMPK exerts its protective effect through inhibiting mTOR, NOX2, and β cell disallowed genes, and increasing expression of miR184 and uptake of Ca$^{2+}$. Taken together, they increase autophagy and insulin secretion, and decrease oxidative stress and β cell dedifferentiation. AMPK also has harmful effects mediated by the activation of ERK and inhibition of mTOR, both of which results in decreased β cell proliferation.
rat β cells resulted in a downstream increase in extracellular-signal-regulated kinase (p-ERK), which is known to impair β cell proliferation and result in reduced β cell mass [72]. Additionally, pAMPK overexpression increased β cell apoptosis and reduced insulin secretion in mice islet cells [79]. Furthermore, pAMPK may have an inhibitory effect on mTOR, which may be a potent cause of β cell mass loss as mTOR plays a crucial role in maintaining and increasing β cell mass through regulating translation, cell growth, autophagy, proliferation, cell size, and apoptosis [80–82]. Lastly, most importantly, although oxidative stress mediated upregulation of pAMPK may contribute to improving β cell function and survival in the short term, long term activation of pAMPK has been shown to have detrimental effects on β cell viability and function. In a study that chronically activated γ2 AMPK, mice β cells showed reduced insulin release, reduced basal β cell activity, and upregulated β cell disallowed gene expression [83]. It is highly probable that oxidative stress although at first may promote β cell survival and function, contributes to pAMPK mediated decline in β cell mass and function as diabetes progresses. Finally, it is important to note that histological studies of islets of patients with T2DM show reduced pAMPK expression [84]. This may suggest that early in DM, the activation of AMPK is upregulated due to several factors including oxidative stress as a protective mechanism, but chronic activation of AMPK results in damage to β cells, and as the disease progresses, eventually to a decline in activated AMPK.

3.2. mTOR Inhibition

mTOR is an evolutionarily conserved, nutrient-responsive serine-threonine kinase that has two functionally and structurally distinct complexes: mTORC1 and mTORC2. Downstream targets of mTORC1 primarily work to stimulate anabolic growth while those of mTORC2 increase proliferation and survival. In general, as discussed earlier, in healthy β cells, mTOR pathway plays an essential role in maintaining β cell mass through regulating cell cycle, autophagy, proliferation, and apoptosis [80]. Although no studies have been conducted in β cell, mTORC1 is ordinarily inhibited under oxidative stress, potentially through the activation of AMPK [82]. The inactivation of mTORC1 may have several detrimental effects (Figure 2), the first of which is the increased expression of Thioredoxin-interacting protein (TXNIP) and shuffling of it into the mitochondria under oxidative stress conditions [85–87]. TXNIP is a ubiquitously expressed protein that influences cellular redox balance through negatively regulating the TXN antioxidant systems [88]. In addition to inhibiting reduced TXN, once in the mitochondria, TXNIP can bind to TXN2, thereby releasing apoptosis signal regulating kinase 1 (ASK1) from its inhibition and initiating mitochondria mediated β cell apoptosis [86]. Supporting the implication of mTORC1 in this pathway, Maedler K. et al. reported that mouse islet and β cell lines with MTORC1 knockout (KO) showed mitochondrial dysfunction and oxidative stress with an associated increase in TXNIP and carbohydrate-response element-binding protein (ChREBP) [89]. Another mediator implicated in TXNIP induced apoptosis under oxidative stress is NLR family pyrin domain containing 3 (NLRP3) inflammasome. It has been demonstrated that TXNIP induced NLRP3 inflammasome assembly leads to the activation of procaspase 1, which then induces cell death through the formation of micro pores in the plasma membrane and through interleukin(IL-1β) activation [90–93]. The importance of the TXNIP/TXN2/ASK1 pathway in mitochondria mediated apoptosis in β cell is supported by the study that showed that TXNIP deficient INS-1 cells are able to prevent mitochondrial death pathway under glucotoxic conditions [94]. Furthermore, TXNIP has an inhibitory effect on TXN, thereby reducing the TXN-dependent enzymatic antioxidant defense against H2O2 in β cells and potentiating the toxicity of cytosolic ROS [95]. Importantly, ChREBP, as well as TXNIP, have been found to be upregulated in pancreatic autopsy section from patients with T2DM, suggesting that activation of this pathway may be one of the major contributors of β cell pathogenesis in diabetes [85].
Figure 2. Downstream effects of downregulation of mTOR via oxidative stress. The downregulation of mTOR primarily harms β cells through initiating mitochondrial mediated apoptosis through the upregulation of Thioredoxin-interacting protein (TXNIP), inducing mitochondrial dysfunction, increasing β cell dedifferentiation, and decreasing insulin secretion and β cell proliferation.

Current knowledge of other effects of mTOR inhibition by oxidative stress is very limited. However, studies in mTORKO mice and rapamycin as mTOR inhibitor in β cells allows us to create an idea of the potential effects of mTOR downregulation. For example, it has been demonstrated that β-cell-specific loss of mTORC1 causes DM and β-cell failure due to defects in proliferation, autophagy, apoptosis, and insulin secretion in mice [96]. Furthermore, β cell specific mTOR KO mice as well as mTOR deficient β cell line has revealed compromised mitochondrial membrane potential and respiration, which lead to impaired ATP production, lower intracellular Ca\(^{2+}\) levels, impaired insulin secretion, and ROS production [87]. mTOR has also been shown to be important to maintain β cell mature identity and to suppress α cell enriched genes including MAF BZIP transcription factor B (MafB), suggesting a potential role of oxidative stress in β cell dedifferentiation [97].

It is clear that downregulation of mTOR in β cells could potentially have a major detrimental impact on its function and viability. Interestingly, however, mTORC1 has been suggested to be increased under glucotoxic conditions and to cause β cell dysfunction as well [98–100]. The effect of hyperlipidemic conditions on mTOR level is less clear. Some studies demonstrate decreased mTOR level with increasing palmitate concentration, while other studies demonstrate increased mTOR level; however, no results reached statistical significance [73,101,102]. Moreover, strangely enough, palmitate treatment partially reversed the mTOR activation in a glucotoxic environment [101]. Thus, combined with the recent study suggesting that only hyperlipidemic conditions resulted in oxidative stress, it is possible that oxidative stress plays a part in the downregulation of mTOR observed under glucolipotoxic treatment; however, more studies directly studying the relation of oxidative stress and mTOR are required to make such argument.

Lastly, it has been shown that human islets of patients with T2D show upregulation of mTORC1 and downregulation of mTORC2 [100]. Thus, it is possible that initial downregu-
ulation of mTORC1 in response to oxidative stress may partly play a role in counterbalancing the elevated mTORC1 levels under glucotoxic conditions. Then, later in the disease, possibly through the downregulation of AMPK activation which is evident in patients with DM, mTORC1 is elevated.

3.3. Mitogen Activated Protein Kinase (MAPK) Activation (JNK/p38 Activation)

Another important pathway activated by oxidative stress in β cells is the JNK pathway. JNK is a MAPK activated under extracellular stress stimuli. In human and rodent β cells, it has been demonstrated by several studies that treatment of β cells with ROS products leads to JNK activation [103–106]. Furthermore, exposure of human β cells to glucose and leptin activates JNK and induces apoptosis; therefore, the impact of activation of JNK in β cells is of great interest [107]. JNK activation has several downstream effects on β cells that ultimately lead to impaired insulin signaling and apoptosis (Figure 3).

![Figure 3. Downstream effects of upregulation of c-Jun N-terminal kinase (JNK) via oxidative stress. The upregulation of JNK have both protective and harmful effects. The upregulation of JNK results in inhibition of the IRS1/2/P13K pathway, resulting in the inhibition of mTOR and nuclear translocation of forkhead box protein O1 (FOXO1). In turn, FOXO1 nuclear translocation results in Pdx1 nuclear exclusion. Overall, these effects result in decreased β cell mass, insulin secretion, and increased β cell dedifferentiation. The upregulation of FOXO1 also has protective effects through its ability to increase expression of β cell mature identity genes including MafA and NeuroD. First, JNK impairs insulin signaling through serine phosphorylation and subsequent inactivation of insulin receptor substrate 1/2 (IRS1/2), which results in hindered downstream activation of phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway in
human β cells [105,108,109]. Inactivation of PI3K/AKT pathway has two major detrimental effects on β cells: Reduced activation of mTOR and nuclear translocation of forkhead box protein O1 (FOXO1). As discussed in the previous section, the downregulation of mTOR contributes to loss of β cell mass. Nuclear translocation of FOXO1 exerts harmful effects under oxidative stress through nuclear exclusion of pancreatic duodenal homeobox1 (PDX-1) and by competing for PDX-1 promoter, both of which results in a decreased level of PDX-1 [110,111]. This reduction in PDX-1 stunts β cell proliferation and growth in rodent and human β cells [112]. PDX-1 also plays a crucial role in glucose stimulated insulin secretion by regulating insulin gene expression and associated genes, and preservation of β cell mature identity, suggesting that FOXO1 nuclear translocation contributes to both impaired insulin secretion and dedifferentiation of β cell under oxidative stress [113–115]. However, FOXO1 nuclear translocation is not solely harmful to β cells. FOXO1 also plays a protective role under oxidative stress through binding with promyelocytic leukemia protein and Sirtuin 1, leading to upregulation of MafA and NeuroD, important transcription factors that maintain β cell maturity [116].

Secondly, JNK activation may induce human β cell apoptosis. H2O2 treatment of human pancreatic islets induced β cell apoptosis which was reversed by treatment with exendin-4, glucagon like receptor agonist, through the downregulation of JNK and glucogen synthase kinase-3 beta (GSK3β) activity, suggesting the potential role of JNK in β cell apoptosis [105]. Additionally, another study demonstrated that ROS derived from NOX2 induced β cell apoptosis through JNK, p38MAPK, and p53 pathways [117]. p38 is another MAPK that is activated by oxidative stress and implicated in β cell apoptosis [118]. In another study, however, transgenic mice with JNK overexpression showed that JNK suffices to inhibit insulin signaling in β cells, but is not sufficient to elicit β cell death, suggesting that oxidative stress may induce other factors that concomitantly works with JNK activation to induce apoptosis rather than JNK working alone [119].

It is also important to highlight JunD as a downstream target of JNK that has been shown to be dysregulated in rodent and human β cells under metabolic stress [120,121]. Furthermore, transcriptomics analysis showed that JunD regulates proinflammatory and proapoptotic factors commonly dysregulated in β cell [121]. However, importantly, JNK upregulated JunD only in hyperglycemic and hyperlipidemic conditions, but not under H2O2 treatment. This shows that the downstream effect of JNK is dependent on the stimuli; further studies directly investigating the downstream effect of JNK activation induced by oxidative stress on β cell are therefore needed to better understand the importance of JNK pathway activation under oxidative stress.

Lastly, it is important to note that although a plethora of studies have demonstrated that NF-κB plays a major role in β cell dysfunction, studies directly investigating the role of oxidative stress in NF-κB activation are limited [122]. One important study by Li X. et al., showed that H2O2 treatment induced apoptosis in mice β cells, which was reversed by the inhibition of NF-κB inducing kinase (NIK), suggesting the potential role of NF-κB in oxidative stress induced apoptosis [123]. One possible mechanism is through the induction of inflamasome NLRP3 by TXNIP under oxidative stress. NLRP3 deletion in mice β cells showed reduced IL-6, a central downstream effect of IL-1β, suggesting that IL-1β may be a downstream target of NLRP3, which is induced under oxidative stress [92]. The upregulation of IL-1β can in turn activate NF-κB, evidenced by a study that treated human EndoC-βH1 β cells with IL-1β and showed upregulation of NF-κB [4]. This highlights the exhaustiveness of the impact of oxidative stress in β cell dysfunction. Although not directly activating NF-κB, through one of its downstream pathways, oxidative stress is able to activate another major pathway involved in β cell failure.

All in all, oxidative stress can harm β cells through various pathways; therefore, the antioxidative capacity of β cells to counteract these effects is a crucial factor in determining its overall health.
4. Antioxidant Properties of β Cells

Gene expression profiling of antioxidative enzymes in different cell types of human pancreatic islets demonstrated a profound deficiency of antioxidant capacity of β cells compared to other cells. First off, superoxide inactivating enzymes SOD1 and SOD2, which were the highest expressed antioxidative enzymes, were 1.4-fold higher in non β cells than in β cells. Even more surprising however, H$_2$O$_2$ inactivating enzymes GPx and CAT showed 15-fold lower and 3-fold lower expression, respectively, in β cells [4]. Supporting this is another study that investigated the antioxidant capacity of human β cells from patients with T1DM and T2DM, which showed catalase and GPx expression much lower in β cells compared to α cells. Furthermore, they showed that diabetic islet showed significantly lower β/α cell ratio compared to healthy islets and demonstrated that upon exposure to oxidative stress, β cells showed significantly lower survival and viability with increased DNA damage compared to α cells [124]. Interestingly, however, more recently Stancill J. et al. demonstrated that when human EndoC-βH1 cells are exposed to physiologically relevant H$_2$O$_2$ levels (50 µM) in a continuous manner, β cells are able to detoxify it through peroxiredoxin and thioredoxin antioxidant system [45,95,125]. In contrast, when treated with an H$_2$O$_2$ bolus (100 µM), β cells are unable to remove it and it results in DNA damage and reduced viability [45]. Furthermore, in comparison to the low expression of GPx and CAT, peroxiredoxin, thioredoxin, and thioredoxin reductase genes are readily expressed in mice and rat β cells [45]. However, a limitation of this study is that it only recorded the effect of physiological H$_2$O$_2$ levels on β cells for 4 h, thus it will be interesting to see whether prolonged exposure to the physiological H$_2$O$_2$ level will exhibit similar effects as the bolus or if β cells will be able to continuously neutralize it.

When ROS production exceeds the antioxidant capacity of β cells, Kelch-like ECH Associated protein 1 (KEAP1)/Nuclear factor erythroid 2-related factor 1 (Nrf2)/antioxidant pathway is activated. In a study by Wang J. et al. hyperglycemic rats fed a high fat diet (HFD), and db/db mice showed substantial Nrf2 expression in β cells, while hyperglycemic rats fed HFD and ebselen, an antioxidant, and mice with GPx1 overexpression in β cells prevented Nrf2 expression [126]. Nrf2-keap1 signaling pathway plays a significant role in protecting the cells against various stressors including endogenous and exogenous oxidants. A study investigating the effect of Nrf2 activation by dh404 on human pancreatic islets found upregulation of common antioxidant enzymes including NAD(P)H: Quinone oxidoreductase, Heme oxygenase 1 (HO-1), glucose 6 phosphate dehydrogenase (G6Pd), sulfiredoxin-1, and thioredoxin reductase1 (TXNRD1) [127]. Furthermore, Nrf2 activation decreased the expression of inflammatory mediators and protected human β cells against oxidative stress [127]. Interestingly, a study that evaluated tumor necrosis factor-alpha (TNF-α), Nrf2, and HO-1 levels in normal glucose tolerance, patients with pre-DM, and T2DM found that TNF-α increased Nrf2 and HO-1 decreased as patients became more diabetic, suggesting that, along with aggravation of oxidative stress and inflammatory response, Nrf2 activation and HO-1 expression were both inhibited [128]. One possible explanation of the decline in Nrf2 and HO-1 activity is through the downregulation of PI3K/AKT pathway under conditions of oxidative stress. PI3K/AKT activation is thought to induce Nrf2, and thus its downregulation would continually decrease Nrf2 activation [129].

5. New Therapeutic Methods

The complicated nature of downstream pathways of oxidative stress in pancreatic β cells makes it a difficult intervention point. As discussed, oxidative stress increases AMPK activation and mTOR inhibition, and there is a possibility that inhibiting these effects would confer protection against oxidative stress in β cells. However, both decreased AMPK and elevated mTOR activity also display their own associated detrimental effects on β cell function. Thus, we focus on new therapeutic methods regulating mitochondrial function, JNK activation, and antioxidant pathways to improve β cell function. A mitochondria targeted antioxidant MitoQ has been shown to reduce ROS production, O2 consumption,
ER stress markers, and accordingly increase insulin secretion [61]. Anti-diabetic medication such as thiazolidinediones, peroxisome proliferator-activated receptor (PPAR) agonists, have been shown to improve mitochondrial health and increase its biogenesis [130]. In addition to protecting mitochondrial function, PPAR-γ activation with rosiglitazone, anti-diabetic drug in thiazolidinediones class, increased insulin secretion, induced FOXO1 nuclear exclusion, and decreased β cell apoptosis in rats [131]. Similarly, incubation of islets of T2D patients with metformin, one of the most commonly used thiazolidinediones, increased β cell insulin content and glucose induced insulin secretion with concomitant decrease in apoptosis and oxidative stress markers [132]. It has also been demonstrated that PPAR-γ activation inhibited cytokine induced JNK activation, which could protect islets from JNK induced dysfunction [133]. Pharmacological JNK inhibitor has also been associated with improved islet survival and function. Ficus Carica leaves extract and cell permeable peptides successfully reduced the expression levels of pJNK with a concomitant reduction in apoptosis-related proteins [134,135]. Lastly, more recently, pharmacological approaches focused on activating Nrf2 pathway have gained momentum. Pharmacological activation of Nrf2 pathway by dimethyl fumarate (DMF), oltipraz, dh404, curcumin, and sulforaphane in human and/or rodent β cells have been shown to protect β cells under different stressors by preserving β cell function and mass [127,136–138]. Furthermore, 9 months of curcumin treatment successfully reduced the number of prediabetic patients who advanced to T2DM [139]. Curcumin is considered to impede the progression of diabetes through its antioxidative properties as well as modulation of insulin secretion pathway. An in vitro study that tested the effect of curcumin on human islets reported enhanced expression of common antioxidants including HO-1 and NADPH at both the mRNA and protein level, with a concomitant reduction in β cell apoptosis [140]. Furthermore, Rouse et al. demonstrated that curcumin increased insulin secretion through inhibition of phosodiesterases, thereby increasing the level of cAMP, a crucial component of insulin secretion pathway [141]. In other studies, stimulation of IL-6 protects human β cells from stress induced apoptosis by upregulating autophagy and coupling it with an antioxidant response, an effect mediated by the activation of the Nrf2 pathway [142,143]. Furthermore, more recently, estrogen therapy has been discussed as a potential therapeutic target. Stimulation of estrogen receptors favor islet survival, lipid homeostasis, glucose stimulated insulin biosynthesis and secretion, and proliferation [144]. Silibin preserves β cell mass and function through upregulation of estrogen receptor and subsequent activation of the Nrf2 pathway [145]. Thus, continuing studies on pharmacological Nrf2 pathway activation in β cells hold tremendous preventative and therapeutic potential.

6. Conclusions

Oxidative stress plays a critical role in inducing β cell dysfunction and death through the alteration of several important pathways that regulate β cell function and health. Moreover, the ability of oxidative stress to influence apoptotic UPR in ER and mitochondrial apoptosis highlights its destructive role of tying together various pathogenic pathways to further augment the devastative state of β cells. Thus, pharmacological intervention focused on enhancing antioxidative capacity of β cell will play an important role in the preservation of β cells under diabetic conditions.

Author Contributions: N.E. and H.I. conceived and designed the study; N.E. drafted the manuscript; N.E., N.D.V., D.C.D., and H.I. edited and revised the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data is contained within the article.

Conflicts of Interest: The authors declare no conflict of interest.
Abbreviations

T2DM Type 2 Diabetes Mellitus
ER Endoplasmic Reticulum
ROS Reactive Oxygen Species
UPR Unfolded Protein Response
CHOP C/EBP homologous protein
GSIS Glucose Stimulated Insulin Secretion
ETC Electron Transport Chain
CAT Catalase
GPx Glutathione peroxidase
PKC Protein Kinase C
NOX Nicotinamide adenine dinucleotide phosphate oxidase
MMP2 Matrix metalloproteinase 2
GSH Reduced Glutathione
GSSG Oxidized Glutathione
SOD Superoxide dismutase
UCP2 Mitochondrial uncoupling protein 2
NF-κB Nuclear factor kappa B
iNOS Nitric oxide synthase
AMPK AMP-activated protein kinase
mTOR Mammalian target of rapamycin
JNK c-Jun N-terminal kinase
p-ERK Extracellular-signal-regulated kinase
TXNIP Thioredoxin-interacting protein
TXN Thioredoxin
ASK1 Apoptosis signal regulating kinase 1
KO Knockout
ChREBP Carbohydrate-response element-binding protein
NLRP3 NLR family pyrin domain containing 3
IL Interleukin
MafB MAF BZIP transcription factor B
MAPK Mitogen activated protein kinase
IRS1/2 Insulin receptor substrate 1/2
PI3K/AKT Phosphoinositide 3-kinase/Protein kinase B
FOXO1 Forkhead box protein O1
PDX1 Pancreatic duodenal homeobox1
S6K3 Glycogen synthase kinase-3 beta
TRPM2 ROS-sensitive transient receptor potential melastatin-2
NAC N-acetylcysteine
IKK NF-κB inducing kinase
KEAP1 Kelch-like ECH Associated protein 1
Nrf2 Nuclear factor erythroid 2-related factor 1
HFD High fat diet
HO-1 Heme oxygenase 1
G6PD Glucose 6 phosphate dehydrogenase
TXNRD1 Thioredoxin reductase1
TNF-α Tumor necrosis factor-alpha
PPAR Peroxisome proliferator-activated receptor
DMF Dimethyl fumarate

References

1. Saklayen, M.G. The Global Epidemic of the Metabolic Syndrome. Curr. Hypertens Rep. 2018, 20, 12. [CrossRef] [PubMed]
2. Hudish, L.I.; Reusch, J.E.; Sussel, L. beta Cell dysfunction during progression of metabolic syndrome to type 2 diabetes. J. Clin. Investig. 2019, 129, 4001–4008. [CrossRef] [PubMed]
3. Hasnain, S.Z.; Prins, J.B.; McGuckin, M.A. Oxidative and endoplasmic reticulum stress in beta-cell dysfunction in diabetes. J. Mol. Endocrinol. 2016, 56, R33–R54. [CrossRef] [PubMed]
21. Kong, F.J.; Wu, J.H.; Sun, S.Y.; Zhou, J.Q. The endoplasmic reticulum stress/autophagy pathway is involved in cholesterol-induced pancreatic beta-cell injury. Diabetes Metab. 2015, 41, 105–118. [CrossRef]

26. Segerstolpe, A.; Palasantza, A.; Eliasson, P.; Andersson, E.M.; Andreasson, A.C.; Sun, X.; Picelli, S.; Sabirsh, A.; Clausen, M.; et al. Functional and morphological alterations of mitochondria in pancreatic beta cells from type 2 diabetic patients. Diabetologia 2005, 48, 452–461. [CrossRef]

29. Cnop, M.; Abdulkarim, B.; Bottu, G.; Cunha, D.A.; Igoillo-Esteve, M.; Masini, M.; Turatsinze, J.V.; Griebel, T.; Villate, O.; Santin, I.; et al. RNA sequencing identifies dysregulation of the human pancreatic islet transcriptome by the saturated fatty acid palmitate. Diabetes 2014, 63, 1978–1993. [CrossRef]

30. Cunha, D.A.; Hekerman, P.; Ladriere, L.; Bazarra-Castro, A.; Ortis, F.; Wakeham, M.C.; Moore, F.; Rasschaert, J.; Cardozo, A.K.; et al. Proinsulin misfolding and endoplasmic reticulum stress during the development and progression of diabetes. Mol. Med. 2015, 21, 2135–2138. [CrossRef]

38. Cardozo, A.K.; Ortiz, F.; Storning, J.; Feng, Y.M.; Rasschaert, J.; Tonnesen, M.; Van Eylen, F.; Mandrup-Poulsen, T.; Herchuelz, A.; Eizirik, D.L. Cytokines downregulate the sarcoendoplasmic reticulum pump Ca²⁺ ATPase 2b and deplete endoplasmic reticulum Ca²⁺, leading to induction of endoplasmic reticulum stress in pancreatic beta-cells. Diabetes 2005, 54, 452–461. [CrossRef]

81. Bellomo, E.; et al. Ion channels and transporters are involved in mitochondrial calcium dysregulation during long-term exposure to high glucose in human pancreatic beta-cells. J. Mol. Endocrinol. 2007, 38, R1–R26. [CrossRef]

86. Dieters, M.; Tackenberg, A.; Palasjuk, K.; Szeliga, M.; et al. Impact of palmitate on the proteomic landscape of deteriorating pancreatic islets in type 2 diabetic rats. Mol. Cell Proteom. 2017, 16, 353–365. [CrossRef] [PubMed]

87. Bjursell, M.K.; et al. Single-Cell Transcriptome Profiling of Human Pancreatic Islets in Health and Type 2 Diabetes. Cell Metab. 2016, 24, 593–607. [CrossRef] [PubMed]

94. Chen, L.; Liu, C.; Gao, J.; Xie, Z.; Chan, L.W.C.; Keating, D.J.; Yang, Y.; Sun, J.; Zhou, F.; Wei, Y.; et al. Inhibition of Miro1 disturbs mitophagy and pancreatic beta-cell function interfering insulin release via IRS-Akt-Foxo1 in diabetes. Oncotarget 2017, 8, 90693–90705. [CrossRef]
28. Bhansali, S.; Bhansali, A.; Walia, R.; Saikia, U.N.; Dhawan, V. Alterations in Mitochondrial Oxidative Stress and Mitophagy in Subjects with Prediabetes and Type 2 Diabetes Mellitus. *Front. Endocrinol. (Lausanne)* 2017, 8, 347. [CrossRef]

29. Chen, X.; Cui, Z.; Wei, S.; Hou, J.; Xie, Z.; Peng, X.; Li, J.; Cai, T.; Hang, H.; Yang, F. Chronic high glucose induced INS-1 beta cell mitochondrial dysfunction: A comparative mitochondrial proteome with SILAC. *Proteomics* 2013, 13, 3030–3039. [CrossRef]

30. Haythorne, E.; Rohm, M.; van de Bunt, M.; Breteron, M.F.; Tarasov, A.I.; Blacker, T.S.; Sachse, G.; Silva Dos Santos, M.; Terron Exposito, R.; Davis, S.; et al. Diabetes causes marked inhibition of mitochondrial metabolism in pancreatic beta-cells. *Nat. Commun.* 2019, 10, 2474. [CrossRef]

31. Jeffrey, K.D.; Alejandro, E.U.; Luciani, D.S.; Kalynyak, T.B.; Hu, X.; Li, H.; Lin, Y.; Townsend, R.R.; Polonsky, K.S.; Johnson, J.D. Carboxypeptidase E mediates palmitate-induced beta-cell ER stress and apoptosis. *Proc. Natl. Acad. Sci. USA* 2008, 105, 8452–8457. [CrossRef] [PubMed]  

32. Carlsson, C.; Borg, L.A.; Welsh, N. Sodium palmitate induces partial mitochondrial uncoupling and reactive oxygen species in rat pancreatic islets in vitro. *Endocrinology* 1999, 140, 3422–3428. [CrossRef] [PubMed]

33. Doliba, N.M.; Liu, Q.; Li, C.; Chen, J.; Chen, P.; Liu, C.; Frederick, D.W.; Baur, J.A.; Bennett, M.J.; Naji, A.; et al. Accumulation of 3-hydroxytetradecenoic acid: Cause or corollary of glucolitotoxic impairment of pancreatic beta-cell bioenergetics? *Mol. Metab.* 2015, 4, 926–939. [CrossRef] [PubMed]

34. Guo, T.; Liu, T.; Sun, Y.; Liu, X.; Yang, R.; Li, H.; Li, Z.; Zhang, Z.; Tian, Z.; Tian, Y. Sonodynamic therapy inhibits palmitate-induced beta cell dysfunction via PINK1/Parkin-dependent mitophagy. *Cell Death Dis.* 2019, 10, 457. [CrossRef] [PubMed]

35. Baltrusch, S. Mitochondrial network regulation and its potential interference with inflammatory signals in pancreatic beta cells. *Diabetologia* 2016, 59, 683–687. [CrossRef]

36. Molina, A.J.; Wikstrom, J.D.; Stiles, L.; Las, G.; Mohamed, H.; Elorza, A.; Walzer, G.; Twigg, G.; Katz, S.; Corkey, B.E.; et al. Mitochondrial networking protects beta-cells from nutrient-induced apoptosis. *Diabetes* 2009, 58, 2303–2315. [CrossRef]

37. Selezniev, K.; Zhao, C.; Zhang, X.H.; Song, K.; Ma, Z.A. Calcium-independent phospholipase A2 localizes in and protects mitochondria during apoptotic induction by staurosporine. *J. Biol. Chem.* 2006, 281, 22275–22288. [CrossRef]

38. Zhao, Z.; Zhang, X.; Zhao, C.; Choi, J.; Shi, J.; Song, K.; Turk, J.; Ma, Z.A. Protection of pancreatic beta-cells by group VIA phospholipase A2(2)-mediated repair of mitochondrial membrane peroxidation. *Endocrinology* 2010, 151, 3038–3048. [CrossRef]

39. Llanos, P.; Contreras-Ferrat, A.; Barrientos, G.; Valencia, M.; Mears, D.; Hidalgo, C. Glucose-Dependent Insulin Secretion in Pancreatic Islets from Male Rats Requires Ca2+ Release via ROS-Stimulated Ryanodine Receptors. *PLoS ONE* 2015, 10, e0129238. [CrossRef] [PubMed]

40. El-Azzouny, M.; Evans, C.R.; Treutelaar, M.K.; Kennedy, R.T.; Burant, C.F. Increased glucose metabolism and glycerolipid fission and pancreatic beta-cell death in rodents. *Cell Death Differ.* 2017, 24, 1999–2012. [CrossRef]

41. Back, S.H.; Kang, S.W.; Kim, J.; Chung, H.T. Endoplasmic reticulum stress in the beta-cell pathogenesis of type 2 diabetes. *Diabetologia* 2017, 60, 1445–1451. [CrossRef] [PubMed]

42. Panigrahy, S.K.; Bhatt, R.; Kumar, A. Reactive oxygen species: Sources, consequences and targeted therapy in type 2 diabetes. *J. Drug Target.* 2017, 25, 93–101. [CrossRef]

43. Robertson, R.P. Chronic oxidative stress as a central mechanism for glucose toxicity in pancreatic islet beta cells in diabetes. *J. Biol. Chem.* 2004, 279, 42351–42354. [CrossRef]

44. Eguchi, K.; Manabe, I.; Oishi-Tanaka, Y.; Ohsgu, M.; Kono, N.; Ogata, F.; Yagi, N.; Ohno, U.; Kimoto, M.; Miyake, K.; et al. Saturated fatty acid and TLR signaling link beta cell dysfunction and islet inflammation. *Cell Metab.* 2010, 15, 518–533. [CrossRef]

45. Liu, C.; Wan, X.; Ye, T.; Fang, F.; Chen, X.; Chen, Y.; Dong, Y. Matrix metalloproteinase 2 contributes to pancreatic Beta cell injury induced by oxidative stress. *PLoS ONE* 2014, 9, e110227. [CrossRef] [PubMed]

46. Sato, Y.; Fujimoto, S.; Mukai, E.; Sato, H.; Tahara, Y.; Ogura, K.; Yamago, M.; Ogura, M.; Nagashima, K.; Inagaki, N. Palmitate induces reactive oxygen species production and beta-cell dysfunction by activating nicotinamide adenine dinucleotide phosphate oxidase through Src signaling. *J. Diabetes Investig* 2014, 5, 19–26. [CrossRef] [PubMed]
53. Zou, R.; Xue, J.; Huang, Q.; Dai, Z.; Xu, Y. Involvement of receptor-interacting protein 140 in palmitate-stimulated macrophage infiltration of pancreatic beta cells. *Exp. Med. 2017*, 14, 483–494. [CrossRef] [PubMed]

54. Alnahdi, A.; John, A.; Raza, H. N-acetyl cysteine attenuates oxidative stress and glutathione-dependent redox imbalance caused by high glucose/high palmitic acid treatment in pancreatic Rin-5F cells. *PLoS ONE 2019*, 14, e0226696. [CrossRef] [PubMed]

55. Chen, Y.; Zhang, J.; Lin, Y.; Lei, Q.; Guan, K.L.; Zhao, S.; Xiong, Y. Tumour suppressor SIRT3 deacetylates and activates manganese superoxide dismutase to scaveng e ROS. *EMBO Rep.* 2011, 12, 534–541. [CrossRef] [PubMed]

56. Morgan, D.; Oliveira-Emilio, H.R.; Keane, D.; Hirata, A.E.; Santos da Rocha, M.; Bordin, S.; Curi, R.; Newsholme, P.; Carpinelli, A.R. Glucose, palmitate and pro-inflammatory cytokines modulate production and activity of a phagocyte-like NADPH oxidase in rat pancreatic islets and a clonal beta cell line. *Diabetologia 2007*, 50, 359–369. [CrossRef] [PubMed]

57. Eizirik, D.L.; Sammeth, M.; Bouckenrooge, T.; Bottu, G.; Sisino, G.; Igoillo-Esteve, M.; Orlis, F.; Santin, L.; Colli, M.L.; Barthson, J.; et al. The human pancreatic islet transcriptome: Expression of candidate genes for type 1 diabetes and the impact of pro-inflammatory cytokines. *Plos Genet.* 2012, 8, e1002552. [CrossRef]

58. Murphy, M.P. Mitochondrial dysfunction indirectly elevates ROS production by the endoplasmic reticulum. *Cell Metab 2013*, 18, 145–146. [CrossRef]

59. Azevedo-Martins, A.K.; Lortz, S.; Lenzen, S.; Curi, R.; Eizirik, D.L.; Tiedge, M. Improvement of the mitochondrial antioxidant defense status prevents cytokine-induced nuclear factor-kappaB activation in insulin-producing cells. *Diabetes 2003*, 52, 93–101. [CrossRef]

60. Broniowska, K.A.; Oleson, B.J.; McGraw, J.; Naatz, A.; Mathews, C.E.; Corbett, J.A. How the location of superoxide generation influences the beta-cell response to nitric oxide. *J. Biol. Chem.* 2015, 290, 7952–7960. [CrossRef]

61. Escribano-Lopez, I.; Banuls, C.; Diaz-Morales, N.; Iannantuoni, F.; Rovira-Llopis, S.; Gomis, R.; Rocha, M.; Hernandez-Mijares, A.; Murphy, M.P.; Victor, VM. The Mitochondria-Targeted Antioxidant MitoQ Modulates Mitochondrial Function and Endoplasmic Reticulum Stress in Pancreatic beta Cells Exposed to Hyperglycaemia. *Cell Physiol. Biochem.* 2019, 52, 186–197. [CrossRef] [PubMed]

62. Haynes, C.M.; Titus, E.A.; Cooper, A.A. Degradation of misfolded proteins prevents ER-derived oxidative stress and cell death. *EMBO J.* 2014, 33, 957–967. [CrossRef] [PubMed]

63. Papa, F.R. Endoplasmic reticulum stress, pancreatic beta-cell degeneration, and diabetes. *Cold Spring Harb. Perspect. Med.* 2012, 2, a007666. [CrossRef] [PubMed]

64. Broniowska, K.A.; Oleson, B.J.; McGraw, J.; Naatz, A.; Mathews, C.E.; Corbett, J.A. How the location of superoxide generation influences the beta-cell response to nitric oxide. *J. Biol. Chem.* 2015, 290, 7952–7960. [CrossRef]

65. Kaufman, R.J.; Back, S.H.; Kaufman, R.J. Endoplasmic reticulum stress, pancreatic beta-cell degeneration, and diabetes. *Cold Spring Harb. Perspect. Med.* 2012, 2, a007666. [CrossRef] [PubMed]

66. Haynes, C.M.; Titus, E.A.; Cooper, A.A. Degradation of misfolded proteins prevents ER-derived oxidative stress and cell death. *Cell Metab. 2013*, 18, 145–146. [CrossRef]

67. Back, S.H.; Kaufman, R.J. Endoplasmic reticulum stress and type 2 diabetes. *Annu. Rev. Biochem.* 2012, 81, 767–793. [CrossRef] [PubMed]

68. Papa, F.R. Endoplasmic reticulum stress, pancreatic beta-cell degeneration, and diabetes. *Cold Spring Harb. Perspect. Med.* 2012, 2, a007666. [CrossRef] [PubMed]

69. Blaudez, D.; De Wilde, R.; De Brabander, K.; De Vos, P.; Leteurtre, E.; Vandevelde, L.; Le Maux, J.P.; Conard, M.; Deruez, J.; et al. The human pancreatic islet transcriptome: Expression of candidate genes for type 1 diabetes and the impact of pro-inflammatory cytokines. *PLoS ONE 2012*, 8, e1002552. [CrossRef]

70. Eizirik, D.L.; Sammeth, M.; Bouckenrooge, T.; Bottu, G.; Sisino, G.; Igoillo-Esteve, M.; Orlis, F.; Santin, L.; Colli, M.L.; Barthson, J.; et al. The human pancreatic islet transcriptome: Expression of candidate genes for type 1 diabetes and the impact of pro-inflammatory cytokines. *Plos Genet.* 2012, 8, e1002552. [CrossRef]

71. Murphy, M.P. Mitochondrial dysfunction indirectly elevates ROS production by the endoplasmic reticulum. *Cell Metab 2013*, 18, 145–146. [CrossRef]

72. Kaufman, R.J.; Back, S.H.; Song, B.; Han, J.; Hassler, J. The unfolded protein response is required to maintain the integrity of the endoplasmic reticulum, prevent oxidative stress and preserve differentiation in beta-cells. *Diabetes Obes. Metab.* 2010, 12 (Suppl. 2), 99–107. [CrossRef]

73. Papa, F.R. Endoplasmic reticulum stress, pancreatic beta-cell degeneration, and diabetes. *Cold Spring Harb. Perspect. Med.* 2012, 2, a007666. [CrossRef] [PubMed]

74. Haynes, C.M.; Titus, E.A.; Cooper, A.A. Degradation of misfolded proteins prevents ER-derived oxidative stress and cell death. *Cell Metab. 2013*, 18, 145–146. [CrossRef]

75. Back, S.H.; Kaufman, R.J. Endoplasmic reticulum stress and type 2 diabetes. *Annu. Rev. Biochem.* 2012, 81, 767–793. [CrossRef] [PubMed]

76. Blaudez, D.; De Wilde, R.; De Brabander, K.; De Vos, P.; Leteurtre, E.; Vandevelde, L.; Le Maux, J.P.; Conard, M.; Deruez, J.; et al. The human pancreatic islet transcriptome: Expression of candidate genes for type 1 diabetes and the impact of pro-inflammatory cytokines. *PLoS ONE 2012*, 8, e1002552. [CrossRef] [PubMed]
77. Martinez-Sanchez, A.; Nguyen-Tu, M.S.; Cebola, I.; Yavari, A.; Marchetti, P.; Piemonti, L.; de Koning, E.; Shapiro, A.M.J.; Johnson, P.; Sakamoto, K.; et al. miR-184 expression is regulated by AMPK in pancreatic islets. *FASEB J.* 2018, 32, 2587–2600. [CrossRef]

78. Tattikota, S.G.; Rathjen, T.; Haussler, J.; Khedar, A.; Kabra, U.D.; Pandey, V.; Sury, M.; Wessels, H.H.; Mollet, I.G.; Eliasson, L.; et al. miR-184 Regulates Pancreatic Beta-Cell Function According to Glucose Metabolism. *J. Biol. Chem.* 2015, 290, 20284–20294. [CrossRef]

79. Richards, S.K.; Parton, L.E.; Leclerc, I.; Rutter, G.A.; Smith, R.M. Over-expression of AMP-activated protein kinase impairs pancreatic (beta)-cell function in vivo. *J. Endocrinol.* 2005, 187, 225–235. [CrossRef]

80. Blandino-Rosano, M.; Chen, A.Y.; Schey, J.O.; Alejandro, E.U.; Gould, A.P.; Taranukha, T.; Elghazi, L.; Cras-Meneur, C.; Bernal-Mizrachi, E. mTORC1 Signaling and Regulation of Pancreatic Beta-Cell Mass. *Cell Cycle* 2011, 11, 1892–1902. [CrossRef]

81. Riboulet-Chavey, A.; Diraizon, P.; Seow, L.K.; Wong, F.S.; Rutter, G.A. Inhibition of AMP-activated protein kinase protects pancreatic beta-cells from cytokine-mediated apoptosis and CD8+ T-cell-induced cytotoxicity. *Diabetes* 2008, 57, 415–423. [CrossRef] [PubMed]

82. Wang, J.; Yang, X.; Zhang, J. Bridges between mitochondrial oxidative stress, ER stress and mTOR signaling in pancreatic beta cells. *Cell Signal.* 2016, 28, 1099–1104. [CrossRef] [PubMed]

83. Alhawiti, N.M.; Al Mahri, S.; Aziz, M.A.; Malik, S.S.; Mohammad, S. TXNIP in Metabolic Regulation: Physiological Role and Therapeutic Outlook. *Curr. Drug Targets* 2017, 18, 1095–1103. [CrossRef]

84. Ardestani, A.; Lupse, B.; Kido, Y.; Leibowitz, G.; Maedler, K. mTORC1 Signaling: A Double-Edged Sword in Diabetic Beta Cells. *Cell Metab.* 2018, 27, 314–331. [CrossRef]

85. Del Guerra, S.; Lupi, R.; Marselli, L.; Masini, M.; Bugliani, M.; Sbrana, S.; Torri, S.; Pollera, M.; Boggi, U.; Mosca, F.; et al. Functional and molecular defects of pancreatic islets in human type 2 diabetes. *Diabetes* 2005, 54, 727–735. [CrossRef]

86. Bozadjieva, N.; Blandino-Rosano, M.; Chase, J.; Dai, X.Q.; Cummings, K.; Gimeno, J.; Dean, D.; Powers, A.C.; Gittes, G.K.; Ruegg, J.; et al. Nutrient Metabolism, Subcellular Redox State, and Oxidative Stress in Pancreatic Islets and Beta-Cells. *J. Biol. Chem.* 2005, 280, 216–224. [CrossRef]

87. Bartolome, A.; Kimura-Koyanagi, M.; Asahara, S.; Guillen, C.; Inoue, H.; Teruyama, K.; Shimizu, S.; Kanno, A.; Garcia-Aguilar, J.; et al. mTORC1 Signaling and Regulatory Complexes in Pancreatic Islets from Humans with Type 2 Diabetes. *Diabetes* 2013, 62, 1883–1892. [CrossRef]

88. Shalev, A.; Saxena, G.; Chen, J.; Fontes, G.; Poitout, V.; Shalev, A. Lack of TXNIP protects against mitochondria-mediated apoptosis but not against fatty acid-induced ER stress-mediated beta-cell death. *Diabetes* 2009, 58, 2454–2464. [CrossRef]

89. Saxena, G.; Chen, J.; Shalev, A. Intracellular shuttling and mitochondrial function of thioredoxin-interacting protein. *J. Biol. Chem.* 2010, 285, 3997–4005. [CrossRef]

90. Oslowski, C.M.; Hara, T.; O'Sullivan-Murphy, B.; Kanekura, K.; Lu, S.; Hara, M.; Ishigaki, S.; Zhu, L.J.; Hayashi, E.; Hui, S.T.; et al. Loss of mTORC1 signaling alters pancreatic alpha cell mass and impairs glucagon secretion. *Cell Metab.* 2015, 22, 322–334. [CrossRef]

91. Rojas, J.; Bermudez, V.; Palmar, J.; Martinez, M.S.; Olivar, L.C.; Nava, M.; Tomey, D.; Rojas, M.; Salazar, J.; Garicano, C.; et al. TXNIP in Metabolic Regulation: Physiological Role and Therapeutic Outlook. *Nat. Commun.* 2017, 8, 15094. [CrossRef] [PubMed]

92. Yavari, A.; Stocker, C.J.; Ghaffari, S.; Wargent, E.T.; Steeples, V.; Czibik, G.; Pinter, K.; Bellahcene, M.; Woods, A.; Martinez de Morentin, P.B.; et al. Chronic Activation of gamma2 AMPK Induces Obesity and Reduces beta Cell Function. *Cell Metab.* 2016, 23, 821–836. [CrossRef] [PubMed]

93. Zhou, R.; Tardivel, A.; Fontes, G.; Saxena, G.; Poitout, V.; Shalev, A. Thioredoxin-interacting protein mediates ER stress-induced beta cell death through initiation of the inflammasome. *Cell Metab.* 2012, 16, 265–273. [CrossRef]

94. Alhawiti, N.M.; Al Mahri, S.; Aziz, M.A.; Malik, S.S.; Mohammad, S. TXNIP in Metabolic Regulation: Physiological Role and Therapeutic Outlook. *Curr. Drug Targets* 2017, 18, 1095–1103. [CrossRef]

95. Osłowski, C.M.; Hará, T.; O'Sullivan-Murphy, B.; Kanekura, K.; Lu, S.; Hara, M.; Ishigaki, S.; Zhu, L.J.; Hayashi, E.; Hui, S.T.; et al. mTORC1 Signaling and Regulatory Complexes in Pancreatic Islets from Humans with Type 2 Diabetes. *Diabetes* 2013, 62, 1883–1892. [CrossRef]

96. Bozadjieva, N.; Blandino-Rosano, M.; Chase, J.; Dai, X.Q.; Cummings, K.; Gimeno, J.; Dean, D.; Powers, A.C.; Gittes, G.K.; Ruegg, J.; et al. Nutrient Metabolism, Subcellular Redox State, and Oxidative Stress in Pancreatic Islets and Beta-Cells. *J. Biol. Chem.* 2005, 280, 216–224. [CrossRef]

97. Yin, Q.; Ni, Q.; Wang, Y.; Zhang, H.; Li, W.; Nie, A.; Wang, Q.; Ning, G. Raptor determines beta-cell identity and plasticity independent of hyperglycemia in mice. *Nat. Commun.* 2020, 11, 2538. [CrossRef]

98. Bartolome, A.; Kimura-Koyanagi, M.; Asahara, S.; Guillen, C.; Inoue, H.; Teruyama, K.; Shimizu, S.; Kanno, A.; Garcia-Aguilar, J.; et al. mTORC1 Signaling and Regulatory Complexes in Pancreatic Islets from Humans with Type 2 Diabetes. *Diabetes* 2013, 62, 1883–1892. [CrossRef]

99. Yuan, T.; Rafizadeh, S.; Gorrepati, K.D.; Lupse, B.; Oberholzer, J.; Maedler, K.; Ardestani, A. Reciprocal regulation of mTOR complexes in pancreatic islets from humans with type 2 diabetes. *Diabetologia* 2017, 60, 668–678. [CrossRef]

100. Yuan, T.; Rafizadeh, S.; Gorrepati, K.D.; Lupse, B.; Oberholzer, J.; Maedler, K.; Ardestani, A. Reciprocal regulation of mTOR complexes in pancreatic islets from humans with type 2 diabetes. *Diabetologia* 2017, 60, 668–678. [CrossRef] [PubMed]
102. Marafie, S.K.; Al-Shawaf, E.M.; Abubaker, J.; Arefianian, H. Palmitic acid-induced lipotoxicity promotes a novel interplay between Akt-mTOR, IRS-1, and FFAR1 signaling in pancreatic beta-cells. *BioI. Res.* 2019, 52, 44. [CrossRef] [PubMed]

103. Jiao, J.; Dou, L.; Li, M.; Lu, Y.; Guo, H.B.; Man, Y.; Wang, S.; Li, J. NADPH oxidase 2 plays a critical role in dysfunction and apoptosis of pancreatic beta-cells induced by very low-density lipoprotein. *Mol. Cell Biochem.* 2012, 370, 103–113. [CrossRef] [PubMed]

104. Kaneto, H.; Xu, G.; Fujii, N.; Kim, S.; Bonner-Weir, S.; Weir, G.C. Involvement of c-Jun N-terminal kinase in oxidative stress-mediated suppression of insulin gene expression. *J. Biol. Chem.* 2002, 277, 30010–30018. [CrossRef] [PubMed]

105. Kim, J.Y.; Lim, D.M.; Moon, C.I.; Jo, K.J.; Lee, S.K.; Baik, H.W.; Lee, K.H.; Lee, K.W.; Park, K.Y.; Kim, B.J. Exendin-4 protects oxidative stress-induced beta-cell apoptosis through reduced JNK and GSK3beta activity. *J. Korean Med. Sci.* 2010, 25, 1626–1632. [CrossRef] [PubMed]

106. Zhao, Y.; Sun, H.; Li, X.; Zha, Y.; Hou, W. Hydroxysafflor yellow A attenuates high glucose-induced pancreatic beta-cells oxidative damage via inhibiting JNK/c-jun signaling pathway. *Biochem. Biophys. Res. Commun.* 2018, 505, 353–359. [CrossRef]

107. Maedler, K.; Schütz, F.T.; Bielman, C.; Berney, T.; Bonny, C.; Rentkii, M.; Donath, M.Y.; Roduit, R. Glucose and leptin induce apoptosis in human beta-cells and impair glucose-stimulated insulin secretion through activation of c-Jun N-terminal kinases. *FASEB J.* 2008, 22, 1905–1913. [CrossRef]

108. White, M.F. IRS proteins and the common path to diabetes. *Am. J. Physiol. Endocrinol. Metab.* 2002, 283, E413–E422. [CrossRef]

109. Yung, J.H.M.; Giacca, A. Role of c-Jun N-terminal Kinase (JNK) in Obesity and Type 2 Diabetes. *Cells* 2020, 9, 706. [CrossRef]

110. Kaneto, H.; Matsuoka, T.A.; Nakatani, Y.; Kawamori, D.; Miyatsuka, T.; Matsuhisa, M.; Yamasaki, Y. Oxidative stress, ER stress, and the JNK pathway in type 2 diabetes. *J. Mol. Med. (Berl)* 2005, 83, 429–439. [CrossRef]

111. Wang, J.; Wang, H. Oxidative Stress in Pancreatic Beta Cell Regeneration. *Oxid. Med. Cell Longev.* 2017, 2017, 1930261. [CrossRef] [PubMed]

112. Haynes, H.L.; Moss, L.G.; Schisler, J.C.; Haldeman, J.M.; Zhang, Z.; Rosenberg, P.B.; Newgard, C.B.; Hohmeier, H.E. Pdx-1 activates islet alpha- and beta-cell proliferation via a mechanism regulated by transient receptor potential cation channels 3 and 6 and extracellular signal-regulated kinases 1 and 2. *Mol. Cell Biol.* 2013, 33, 4017–4029. [CrossRef] [PubMed]

113. Brissova, M.; Shiota, M.; Nicholson, W.E.; Gannon, M.; Knobel, S.M.; Piston, D.W.; Wright, C.V.; Powers, A.C. Reduction in pancreatic transcription factor PDX-1 impairs glucose-stimulated insulin secretion. *J. Biol. Chem.* 2002, 277, 11225–11232. [CrossRef]

114. Gao, T.; McKenna, B.; Li, C.; Reichert, M.; Nguyen, J.; Singh, T.; Yang, C.; Pannikar, A.; Doliba, N.; Zhang, T.; et al. Pdx1 maintains beta cell identity and function by repressing an alpha cell program. *Cell Metab.* 2014, 19, 259–271. [CrossRef] [PubMed]

115. Kawamori, D.; Kaneto, H.; Nakatani, Y.; Matsuoka, T.A.; Matsuhashi, M.; Hori, M.; Yamashita, Y. Oxidative stress, ER stress, and the JNK pathway in type 2 diabetes. *J. Mol. Med. (Berl)* 2005, 83, 429–439. [CrossRef]

116. Wang, J.; Wang, H. Oxidative Stress in Pancreatic Beta Cell Regeneration. *Oxid. Med. Cell Longev.* 2017, 2017, 1930261. [CrossRef] [PubMed]

117. Yuan, H.; Zhang, X.; Huang, X.; Lu, Y.; Tang, W.; Man, Y.; Wang, S.; Xi, J.; Li, J. NADPH oxidase 2-devoid reactive oxygen species mediate FFAs-induced dysfunction and apoptosis of beta-cells via JNK, p38 MAPK and p53 pathways. *PLoS ONE* 2010, 5, e15726. [CrossRef] [PubMed]

118. Zhang, H.; Zhou, C.; Sun, Z.; Yan, X.; Wang, H.; Xu, H.; Ma, J.; Zhang, Y. Linderane protects pancreatic beta cells from streptozotocin (STZ)-induced oxidative damage. *Life Sci.* 2019, 233, 116732. [CrossRef]

119. Lanuza-Masdeu, J.; Arevalo, M.I.; Vila, C.; Barbera, A.; Comis, R.; Caéles, C. In vivo JNK activation in pancreatic beta-cells leads to glucose intolerance caused by insulin resistance in pancreas. *Diabetes* 2013, 62, 2308–2317. [CrossRef]

120. Eckhoff, D.E.; Smyth, C.A.; Eckstein, C.; Bilbao, G.; Young, C.J.; Thompson, J.A.; Contreras, J.L. Suppression of the c-Jun N-terminal kinase pathway by 17beta-estradiol can preserve human islet functional mass from proinflammatory cytokine-induced destruction. *Surgery* 2003, 134, 169–179. [CrossRef]

121. Good, A.L.; Cannon, C.E.; Haemmerle, M.W.; Yang, J.; Stanescu, D.E.; Doliba, N.M.; Birnbaum, M.J.; Stoffers, D.A. JUND regulates pancreatic beta cell survival during metabolic stress. *Mol. Metab.* 2019, 25, 95–106. [CrossRef] [PubMed]

122. Meyerovich, K.; Ortis, F.; Cardozo, A.K. The non-canonical NF-kappaB pathway and its contribution to beta-cell failure in diabetes. *J. Mol. Endocrinol.* 2018, 61, F1–F6. [CrossRef] [PubMed]

123. Li, X.; Wu, Y.; Song, Y.; Ding, N.; Lu, M.; Jia, L.; Zhao, Y.; Liu, M.; Chen, Z. Activation of NF-kappaB-Inducing Kinase in Islet beta Cells Causes beta Cell Failure and Diabetes. *Mol. Ther.* 2020, 28, 2430–2441. [CrossRef] [PubMed]

124. Miki, A.; Ricordi, C.; Sakuma, Y.; Yamamoto, T.; Misawa, R.; Mita, A.; Molano, R.D.; Vaziri, N.D.; Pileggi, A.; Ichii, H. Divergent antioxidant capacity of human islet cell subsets: A potential cause of beta-cell vulnerability in diabetes and islet transplantation. *PLoS ONE* 2013, 8, e0196570. [CrossRef] [PubMed]

125. Stancill, J.S.; Happ, J.T.; Broniowska, K.A.; Hogg, N.; Corbett, J.A. Peroxiredoxin 1 plays a primary role in protecting pancreatic beta-cells from hydrogen peroxide and peroxynitrite. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 2020, 318, R1004–R1013. [CrossRef] [PubMed]
127. Masuda, Y.; Vaziri, N.D.; Li, S.; Le, A.; Hajighasemi-Ossareh, M.; Robles, L.; Foster, C.E.; Stamos, M.J.; Al-Abodullah, I.; Ricordi, C.; et al. The effect of Nrf2 pathway activation on human pancreatic islet cells. PLoS ONE 2015, 10, e0131012. [CrossRef]

128. Liu, Y.; Zeng, Y.; Miao, Y.; Cheng, X.; Deng, S.; Hao, X.; Jiang, Y.; Wan, Q. Relationships among pancreatic beta cell function, the Nrf2 pathway, and IRS2: A cross-sectional study. Postgrad. Med. 2020, 132, 720–726. [CrossRef]

129. Zhu, Y.; Ren, C.; Zhang, M.; Zhong, Y. Perilipin 5 Reduces Oxidative Damage Associated With Lipotoxicity by Activating the PI3K/ERK-Mediated Nrf2-ARE Signaling Pathway in INS-1 Pancreatic beta-Cells. Front. Endocrinol. (Lausanne) 2020, 11, 166. [CrossRef]

130. Montgomery, M.K. Mitochondrial Dysfunction and Diabetes: Is Mitochondrial Transfer a Friend or Foe? Biology 2019, 8, 33. [CrossRef]

131. Kim, H.S.; Hwang, Y.C.; Koo, S.H.; Park, K.S.; Lee, M.S.; Kim, K.W.; Lee, M.K. PPAR-gamma activation increases insulin secretion through the up-regulation of the free fatty acid receptor GPR40 in pancreatic beta-cells. PLoS ONE 2013, 8, e50128. [CrossRef]

132. Marchetti, P.; Del Guerra, S.; Marselli, L.; Lupi, R.; Masini, M.; Pollera, M.; Bugliani, M.; Boggi, U.; Vistoli, F.; Mosca, F.; et al. Pancreatic islets from type 2 diabetic patients have functional defects and increased apoptosis that are ameliorated by metformin. J. Clin. Endocrinol. Metab. 2004, 89, 5535–5541. [CrossRef] [PubMed]

133. Diaz-Delfin, J.; Morales, M.; Caelles, C. Hypoglycemic action of thiazolidinediones/peroxisome proliferator-activated receptor gamma by inhibition of the c-Jun NH2-terminal kinase pathway. Diabetes 2007, 56, 1865–1871. [CrossRef] [PubMed]

134. Bonny, C.; Oberson, A.; Negri, S.; Sauser, C.; Schorderet, D.F. Cell-permeable peptide inhibitors of JNK: Novel blockers of beta-cell death. Diabetes 2001, 50, 77–82. [CrossRef]

135. Zhang, Y.; Li, Y.; Ma, P.; Chen, J.; Xie, W. Ficus carica leaves extract inhibited pancreatic beta-cell apoptosis by inhibiting AMPK/JNK/caspase-3 signaling pathway and antioxidation. Biomed. Pharm. 2020, 122, 109689. [CrossRef]

136. Den Hartogh, D.J.; Gabriel, A.; Tsiani, E. Antidiabetic Properties of Curcumin I: Evidence from In Vitro Studies. Nutrients 2020, 12, 118. [CrossRef]

137. Schultheis, J.; Beckmann, D.; Mulac, D.; Muller, L.; Esselen, M.; Dufer, M. Nrf2 Activation Protects Mouse Beta Cells from Glucolipotoxicity by Restoring Mitochondrial Function and Physiological Redox Balance. Oxid. Med. Cell Longev. 2019, 2019, 7518510. [CrossRef]

138. Song, M.Y.; Kim, E.K.; Moon, W.S.; Park, J.W.; Kim, H.J.; So, H.S.; Park, R.; Kwon, K.B.; Park, B.H. Sulforaphane protects against cytokine- and streptozotocin-induced beta-cell damage by suppressing the NF-kappaB pathway. Toxicol. Appl. Pharm. 2009, 235, 57–67. [CrossRef]

139. Chuengsamarn, S.; Rattanamongkolgul, S.; Luechapudiporn, R.; Phisalaphong, C.; Jirawatnotai, S. Curcumin extract for prevention of type 2 diabetes. Diabetes Care 2012, 35, 2121–2127. [CrossRef] [PubMed]

140. Balamurugan, A.N.; Akhov, L.; Selvaraj, G.; Pugazhenth, S. Induction of antioxidant enzymes by curcumin and its analogues in human islets: Implications in transplantation. Pancreas 2009, 38, 454–460. [CrossRef]

141. Rouse, M.; Younes, A.; Egan, J.M. Resveratrol and curcumin enhance pancreatic beta-cell function by inhibiting phosphodiesterase activity. J. Endocrinol. 2014, 234, 107–117. [CrossRef] [PubMed]

142. Linnemann, A.K.; Blumer, J.; Marasco, M.R.; Battiola, T.J.; Umhoefer, H.M.; Han, J.Y.; Lamming, D.W.; Davis, D.B. Interleukin 6 protects pancreatic beta cells from apoptosis by stimulation of autophagy. FASEB J. 2017, 31, 4140–4152. [CrossRef] [PubMed]

143. Marasco, M.R.; Conteh, A.M.; Reissaus, C.A.; Cupit, J.E.; Appleman, E.M.; Mirmira, R.G.; Linnemann, A.K. Interleukin-6 Reduces beta-Cell Oxidative Stress by Linking Autophagy With the Antioxidant Response. Diabetes 2018, 67, 1576–1588. [CrossRef] [PubMed]

144. Mauvais-Jarvis, F.; Le May, C.; Tiano, J.P.; Liu, S.; Kilic-Berkmen, G.; Kim, J.H. The Role of Estrogens in Pancreatic Islet Physiopathology. Adv. Exp. Med. Biol. 2017, 1043, 385–399. [CrossRef] [PubMed]

145. Chu, C.; Gao, X.; Li, X.; Zhang, X.; Ma, R.; Jia, Y.; Li, D.; Wang, D.; Xu, F. Involvement of Estrogen Receptor-alpha in the Activation of Nrf2-Antioxidative Signaling Pathways by Silibinin in Pancreatic beta-Cells. Biol. Ther. 2020, 28, 163–171. [CrossRef] [PubMed]