Pancreatic β-cell apoptosis in type 2 diabetes is related to post-translational modifications of p53 (Review)

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Abstract. Pancreatic β-cells are the only cells that synthesize insulin to regulate blood glucose levels. Various conditions can affect the mass of pancreatic β-cells and decrease insulin levels. Diabetes mellitus is a disease characterized by insulin resistance and chronic hyperglycemia, mainly due to the loss of pancreatic β-cells caused by an increase in the rate of apoptosis. Additionally, hyperglycemia has a toxic effect on β-cells. Although the precise mechanism of glucotoxicity is not fully understood, several mechanisms have been proposed. The most prominent changes are increases in reactive oxygen species, the loss of mitochondrial membrane potential and the activation of the intrinsic pathway of apoptosis due to p53. The present review analyzed the location of p53 in the cytoplasm, mitochondria and nucleus in terms of post-translational modifications, including phosphorylation, O-GlcNAcylation and poly-ADP-ribosylation, under hyperglycemic conditions. These modifications protect p53 from degradation by the proteasome and, in turn, enable it to regulate the intrinsic pathway of apoptosis through the regulation of anti-apoptotic and pro-apoptotic elements. Degradation of p53 occurs in the proteasome and depends on its ubiquitination by Mdm2. Understanding the mechanisms that activate the death of pancreatic β-cells will allow the proposal of treatment alternatives to prevent the decrease in pancreatic β-cells.

Contents

1. Introduction

The highly specialized pancreatic β-cells are located in the pancreas in structures called islets of Langerhans (1). They play a unique and important role in the physiology of organisms, as they synthesize the hormone insulin (2). This protein travels through the bloodstream to reach target peripheral tissues to promote the uptake, utilization and storage of nutrients, mainly glucose (3). Therefore, β-cells are responsible for producing and secreting insulin under tight regulation, which helps maintain circulating glucose concentrations in the physiological range (1).

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Insulin release is carefully regulated through a feedback system that involves both insulin-sensitive tissues and β-cells. The demand for insulin depends on physiological and pathological conditions, such as aging, pregnancy and obesity. Therefore, β-cells must adapt to these conditions by activating different mechanisms, such as hyperplasia and hypertrophy, as well as increasing insulin synthesis and secretion (2). In situations of metabolic stress, the demand for insulin increases, and β-cells initially release more insulin to respond to this demand. However, β-cell functions tend to decline in response to this stress, resulting in decreased glucose tolerance (3). Since insulin plays a fundamental role in regulating glucose metabolism, any alteration in its secretion, action, or both can generate a series of metabolic imbalances characterized by chronic hyperglycemia known as diabetes mellitus (DM) (2,3).

DM represents a serious public health problem worldwide (4). In recent decades, the health and economic burdens of DM have increased worldwide, significantly impacting low- and middle-income countries (5). The 10th edition of the IDF Diabetes Atlas reports a continued global increase in the prevalence of diabetes; by 2021, 537 million adults (20-79 years) were living with diabetes, and this number is projected to increase to 643 million by 2030 and 783 million by 2045 (6). It has also been reported that by 2021, diabetes was responsible for 6.7 million deaths and that there were also 541 million adults with glucose intolerance, which places them at high risk of suffering from diabetes (Fig. 1).

Diabetes can be divided into two main categories: i) Type 1 diabetes (T1D) and ii) type 2 diabetes (T2D) (7). T1D involves an autoimmune process that gradually and selectively destroys the β-cells of the pancreas, leading to total insulin deficiency (7). While T2D encompasses ~90% of all DM cases, with most presenting with a prediabetic state (7). Tissue sensitivity to the actions of insulin is reduced, mainly in muscle, liver and adipose tissue (8). This leads to failure in the internalization of glucose in response to normal concentrations of this hormone, which is known as insulin resistance (IR) (8). The clinical manifestations of the disease occur when β-cells are unable to produce sufficient compensatory insulin to counteract the resistance of the body to insulin (9-12). Increased blood glucose can lead to autoxidation or cross-linking with proteins present in the serum (protein glycosylation) to give rise to a series of highly reactive structures termed Amadori compounds (13). Prior to the clinical manifestations of T2D, the β-cell mass decreases by up to 60% due to the increased rate of apoptosis (11,12). In this sense, it should be noted that apoptosis is a form of cell death that occurs in both physiological and pathological situations in multicellular organisms and constitutes a common mechanism of cell replacement, tissue remodeling and renewal of damaged cells (14). Although it is a complex process, it is characterized by cell shrinkage, chromatin condensation, DNA fragmentation and the formation of apoptotic bodies (Fig. 2) (14). Apoptotic cells are rapidly phagocytosed by neighboring cells or macrophages, thus preventing an inflammatory reaction (14,15).

Various potential mechanisms have been identified to explain the increase in β-cell apoptosis during T2D, among which chronic hyperglycemia is a key factor (12). The process of cell death by apoptosis involves the participation of a series of regulatory factors. One of the most crucial and widely studied factors in this process is p53, which functions as the 'guardian of the genome' since it plays a fundamental role in the supervision of cellular stress and in inducing apoptosis in tissues where stressors cause severe and irreversible damage (16).

Therefore, the present review focuses on the role of p53 in reducing pancreatic β-cells in the context of hyperglycemia. It was previously shown that an increase in glucose promotes the mobilization of p53 toward the mitochondria, increasing the production of reactive oxygen species (ROS) by modifying the mitochondrial membrane potential (17). Therefore, a series of experimental evidence corresponding to the post-translational modifications of p53 induced by hyperglycemia has been obtained (Table I). These effects are closely related to the regulation of apoptosis in the pancreatic β-cell line RINm5F by high glucose. In addition, the regulation that this protein undergoes through its ubiquitination by murine protein double minute 2 (Mdm2) will be analyzed (10,11,18).

For the present narrative literature review, PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Web of Science (https://clarivate.com/products/scientific-and-academic-research/research-discovery-and-workflow-solutions/webofscience-platform/) were searched using the keywords 'apoptosis', 'pancreatic β-cell apoptosis and hyperglycemia', 'p53 and pancreatic β-cell apoptosis', 'p53 and hyperglycemia', 'post-translational modifications of p53', and 'p53 and ROS'. The most relevant articles in English were selected and reviewed, and articles that analyzed the role of p53 in the death of pancreatic β-cells due to high glucose levels were identified. Also included is the description of death by apoptosis, as well as other mechanisms involved in the damage of β-cells due to high glucose levels.

2. Apoptotic pathways are the crossroads where signals and regulatory mechanisms converge

Apoptosis constitutes an essential mechanism for the selective elimination of cells and is integrally involved in various biological events (19). This process involves the activation of caspases, a family of proteases with a cysteine residue in their active site that is key in the transduction and execution of apoptotic signals in response to various stimuli (14). They exist as zymogens (proenzymes) in the cytoplasm, endoplasmic reticulum, mitochondria and nuclear matrix of most cells (20). The apoptosis process can be triggered by two fundamental pathways, the extrinsic pathway and the intrinsic pathway, with both pathways including the activation of caspases (14,20).

The extrinsic pathway of apoptosis is induced by death receptors belonging to the superfamily of tumor necrosis factor (TNF) receptors. Two of the most characterized receptors are the Fas receptor, also termed CD95 or apoptosis-1 protein, and the TNF receptor (TNFR). These receptors share a homologous sequence called the death domain (DD), which can initiate a cascade of events that lead to apoptosis upon receiving extracellular signals (Fig. 3) (19). The ligands that bind to these receptors belong to the TNF family and include the Fas ligand and TNF. The activated Fas receptor recruits adapter molecules such as the Fas-associated DD (FADD), which also contains a DD that binds to the Fas receptor analog

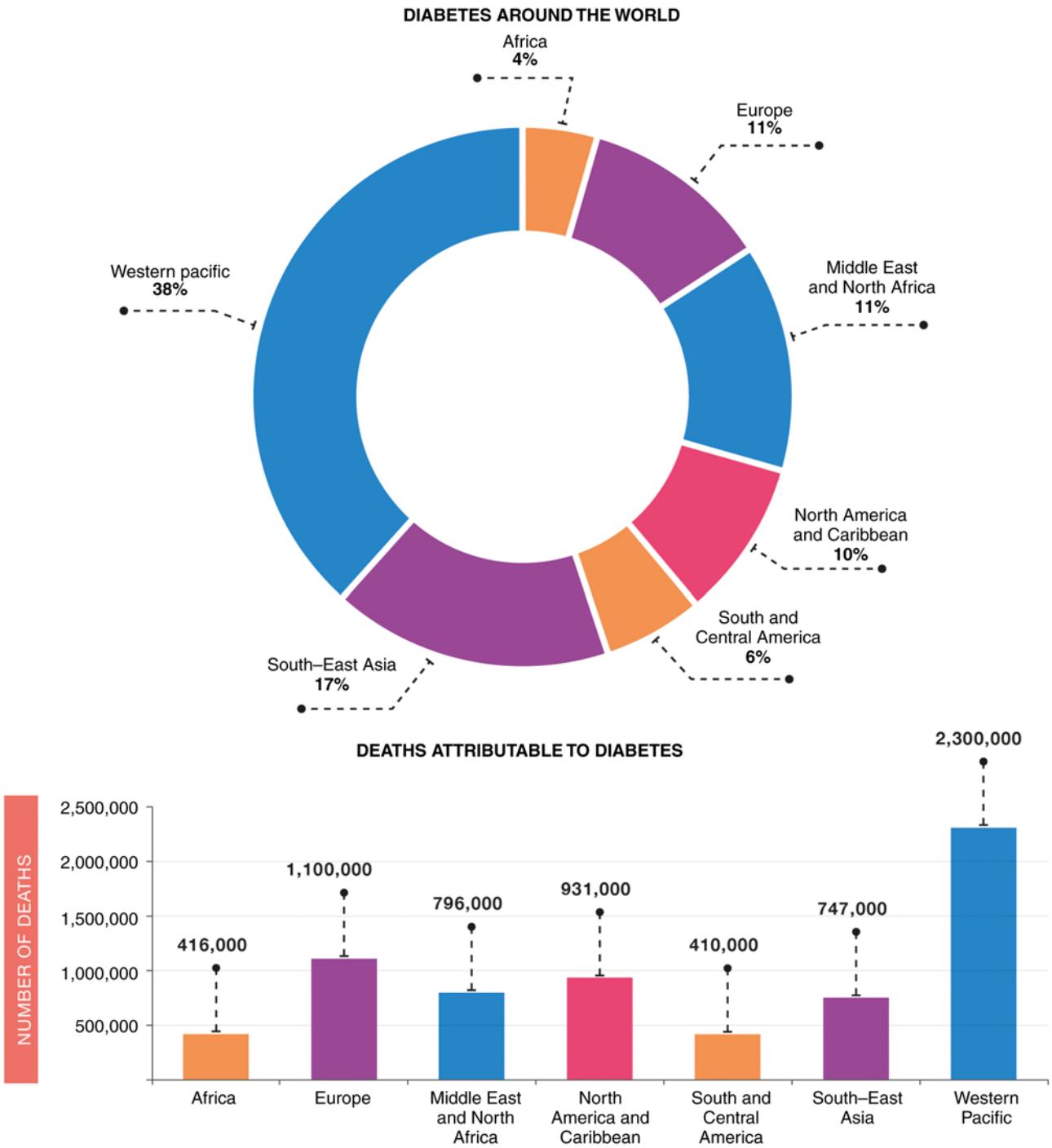

Figure 1. Diabetes and diabetes-related deaths are common globally. The figure shows the percentage of people affected by diabetes in different regions around the world, based on a total of 537 million cases in 2021. In addition, the graph provides insight into the number of deaths attributed to diabetes in various regions worldwide, based on a total of 6.7 million reported deaths up to 2021. The informative visual imagery was created using data sourced from the tenth edition of the IDF Diabetes Atlas (6).

domain, and a death effector domain (DED) that binds to a Fas receptor analog domain of procaspase-8 (14,19). This enzyme, also termed FADD-like IL-1β-converting enzyme (FLICE), undergoes autocatalytic activation by binding to FADD, becoming active caspase-8 (21). The complex formed by Fas, FADD and FLICE is called the death-inducing signaling complex. Caspase-8 activates effector caspases 3, 6 and 7, which in turn release various cellular proteins involved in proteolysis and DNA degradation. In the case of TNF receptors (TNFR-I and TNFR-II), they recruit the adapter molecule TRADD (TNFR-associated death domain) (21). Thus, the complex formed by these components activates both initiator caspases (8 and 10) and effector caspases (3, 6 and 7), similar to what is observed with the Fas receptor (22,23).

The intrinsic pathway of apoptosis is triggered by internal signals that focus on mitochondria (23). In the context of the intrinsic pathway, there are contact zones between the mitochondrial membranes, termed ‘dense zones’, whose protein components interact to form the mitochondrial permeability transition pore (PTP), which includes proteins of different

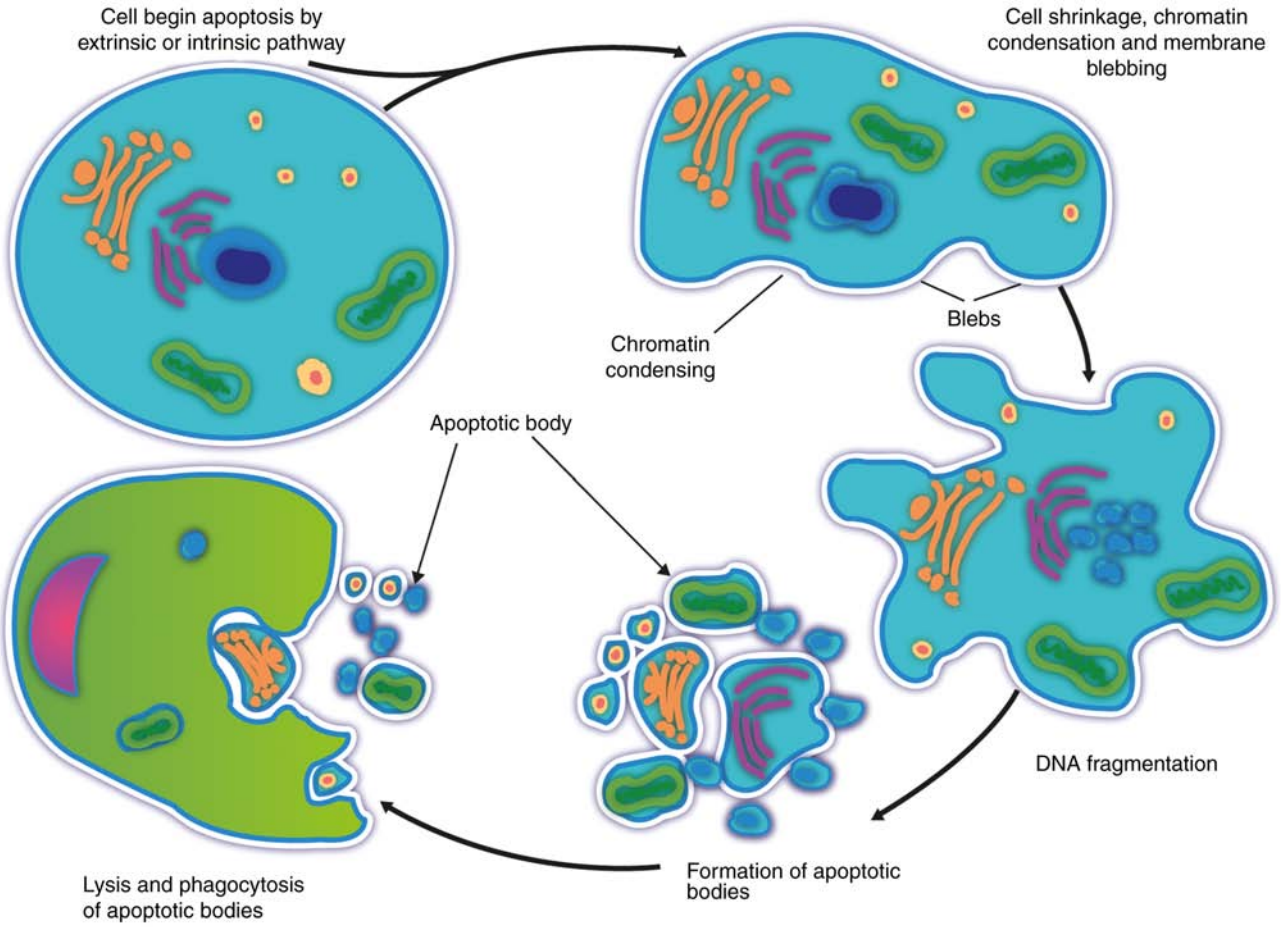

Figure 2. Cell death by apoptosis. Apoptosis is a physiological mechanism of programmed cell death that begins with early chromatin condensation, leading to the formation of perinuclear chromatin masses and decreased nuclear size, cytoplasm compaction and cytoskeletal alterations, leading to cellular shrinkage. In the same way, intranuclear DNA fragmentation occurs, which leads to fragmentation of the cell, forming small vesicles called apoptotic bodies still surrounded by a membrane, which changes its composition, resulting in the translocation of phosphatidylserine to its surface, which serves as a recognition signal for macrophages; thus, the bodies are quickly phagocytosed.

cellular parts: The cytoplasm (hexokinase), outer membrane [voltage-gated anion channel (VDAC)], inner membrane [adenine nucleotide translocase (ANT)] and mitochondrial matrix [cyclophilin D (CpD)] (24). Under physiological conditions, the different components of the PTP are scattered (25). Thus, VDAC contributes to the permeabilization of the outer membrane, ANT specifically controls the passage of the different phosphorylated and unphosphorylated forms of adenine nucleotides through the inner membrane, and CpD is a peptidyl-propyl isomerase that is crucial for protein folding (26). When an apoptotic stimulus reaches the mitochondria, these protein components can assemble, forming a pore with a radius of 1.0-1.3 nm, allowing the nonselective passage of molecules <1.5 kDa (25). Its opening leads to the permeabilization of mitochondrial membranes, which contributes to mitochondrial dysregulation and the loss of transmembrane potential ($\Delta\psi m$) due to an increase in matrix osmolarity (24). In addition, the entry of water causes swelling of mitochondria and rupture of the outer membrane, releasing molecules from the intermembrane space into the cytoplasm (25). A total of 79 peptide components that are released during the opening of the PTP have been characterized (25,26). These components include molecules with known pro-apoptotic activity, such as cytochrome c (cyt c), Smac/DIABLO, apoptotic protease activating factor 1 (Apaf-1) and apoptosis-inducing factor (AIF), and some members of the caspase family, such as caspase-2 and caspase-9 (27,28). Once released into the cytoplasm, these agents can activate different apoptotic pathways. AIF triggers chromatin condensation and DNA fragmentation independent of caspase activation (29). The pro-apoptotic proteins Bax and Bak have been shown to accelerate the opening of VDAC channels and allow cytochrome c egress, while the anti-apoptotic proteins Bcl-2 and Bcl-XL close these channels by directly binding to Bax and Bak (30,31). Cytochrome c released into the cytosol favors the activation of Apaf-1, which can oligomerize in the presence of cytochrome c and deoxyadenosine triphosphate (dATP) (23). The oligomers recruit procaspase-9 using the recruitment domain of Apaf-1, thus forming the apoptosome (23). Mature caspase-9 is released from the complex and activates effector caspases 3, 6 and 7, leading to the initiation of the proteolytic cascade essential for apoptosis (15,27,32).

3. Glucolipotoxicity and p53 activation

Among the mechanisms involved in the induction of damage to pancreatic β-cells, those related to the combination of hyperglycemia and hyperlipidemia are the most studied. This

Table I. Characteristics of the main articles reviewed.

First author/s, year	Methodology	Results	(Refs.)
Ortega-Camarillo *et al*, 2006	- Apoptosis index: FC (PS exposure) and DNA fragmentation - p53 localization: WB/IF - ROS production: FC (DCDHF-DA) - ψm: JC-1 confocal microscopy - NADPH-oxidase inhibitors	- High glucose increased apoptosis and translocation of p53 protein to the mitochondria of RINm5F cells - Alterations in ψm and an increase in NADPH-oxidase and mitochondrial ROS were also observed. - Increased glucose stimulated p53 mobilization to mitochondria, ROS production and pancreatic β-cell death	(17)
Flores-López *et al*, 2013	- P-p53, p-p38MAPK: WB mitochondria/cytosol - Apoptosis - Caspase-3; Bcl-2/Bax ratio and cyt c: WB mitochondria/cytosol - DNA fragmentation - P38 MAPK inhibitor	- Localization of p53 and its phosphorylation in mitochondria was repressed in RINm5F cells cultured at high glucose and with the p38 MAPK inhibitor. - Deletion of p38 MAPK also prevented mitochondrial cytochrome c egress and decreased apoptosis of RINm5F cells	(11)
Flores-López *et al*, 2012	- Phosphorylation - O-N-Acetylglucosaminylation and Poly-ADP-ribosylation of P53: IP; WB	- The localization and phosphorylation of p53 at Ser 15 and Ser 392 in mito chondria were associated with an increase in ROS, decrease in the Bcl-2/Bax ratio and increase in apoptosis. - High glucose increased PARP concentration and Poly-ADP-ribosylation of p53 in the nuclear fraction. - N-acetylglucosaminylation of p53 increases first in the cytosol and at 24 h in the mitochondria, together with p53 mobilization to this organelle. - High glucose induces apoptosis in RINm5F cells in a time-dependent manner without any changes of mRNA p53 expression, although alterations occur in intracellular distribution and phosphorylation.	(18)
Barzalobre-Gerónimo *et al*, 2015	- p53-Mdm2 complex: IP; WB; IF - Ub-p53: WB - pAkt: WB	- High glucose reduced Mdm2 (mRNA and protein) but increased Mdm2 and Akt phosphorylation. - It observed p53-Mdm2 complex formation, but p53 ubiquitination was suppressed. Phosphorylation of p53 Ser15 and ATM was increased by high glucose. Therefore, the reduction of pancreatic β-cells mass is favored by stabilization of p53 due to reduced expression of Mdm2 and low p53 ubiquitination.	(10)

Table I. Continued.

First author/s, year	Methodology	Results	(Refs.)
Barzalobre-Geronimo *et al*, 2023	- Animals drinking water containing either 40% sucrose or 40% fructose. - Glucose tolerance test was performed at week 15. - After 4 months was measured: - Apoptosis: TUNEL. - Bax and p53: WB, IF and qPCR. - Insulin, triacylglycerol, serum glucose and fatty acids in pancreatic tissue were measured	- Carbohydrate in drinking water promotes apoptosis and mobilization of p53 from the cytosol to the mitochondria of rat pancreas β-cells before blood glucose rises. An increase in p53, miR-34a and Bax mRNA ($P<0.001$) was detected in the sucrose group. In addition to hypertriglyceridemia, hyperinsulinemia, glucose intolerance, insulin resistance, accumulation of visceral fat and increased pancreatic fatty acids in the sucrose group. Carbohydrate consumption increases p53 and its mobilization into β-cell mitochondria and increases the rate of apoptosis, which occurs before serum glucose levels increase.	(9)

WB, western blotting; IF, immunofluorescence; FC, flow cytometry; PS, phosphatidylserine; ROS, reactive oxygen species; P-p53, phosphorylated p53; HG, high glucose; Ub-p53, p53 ubiquitination; qPCR, quantitative polymerase chain reaction; DCDHF-DA, dichlorodihydrofluorescein-diacetate; JC-1, 5,5',6,6'-tetrachloro-1,1',3,3'-tetraethylbenzimidazolylcarbocyanine iodide; ψm, mitochondrial membrane potential; TUNEL, TdT-mediated dUTP-nick end-labeling.

is justified by the exacerbated increase in the number of obese people, including infants, worldwide. An increase in free fatty acids (FFAs) in the circulation combined with IR and hyperglycemia, which are frequently observed in individuals with obesity, constitutes a state known as glucolipotoxicity and is involved in the pathogenesis of T2D (33).

Excessive and chronic accumulation of fatty acids inhibits insulin secretion in response to glucose and increases the intracellular production of lipid intermediates, which are toxic to β-cells and activate apoptosis (34). In these circumstances, the activity of carnitine palmitoyl transferase 1 decreases due to the increase in malonyl-CoA, resulting in the subsequent esterification of FFAs and the generation of complex lipids such as sphingolipids and ceramides, which accumulate in pancreatic β-cells and trigger cell death (33).

An increase in FFAs promotes p53 activity. It has been shown that in pancreatic β-cells (NIT-1 cells), palmitic acid inhibits cell proliferation by increasing the expression of p53 (34) and activates apoptosis via the p38 MAPK/p53 and NFκB pathway (35). The apoptosis of β-cells induced by exposure to FFAs has also been related to the expression of miR-34 (36), which inhibits Akt and Mdm2 activation and p53 degradation (10,37). Glucolipotoxicity also promotes the inflammatory response in β-cells, which is manifested by the increased activity of proinflammatory cytokines such as IFN-γ and TNF-α, which contribute to the dysfunction and death of β-cells (38). Alterations in the expression of the transcription factors Mafa and PDX-1 and of the insulin gene have also been observed after exposure to FFAs and glucose (35,37).

4. Endoplasmic reticulum stress

Alterations in protein folding and the accumulation of poorly folded proteins in the endoplasmic reticulum generate a state known as endoplasmic reticulum stress. This response begins with the activation of protein kinase RNA-like ER kinase (PERK), activating transcription factor-6 and inositol-requiring enzyme-1, whose activation decreases the translation of proteins and increases the folding capacity of the endoplasmic reticulum and the degradation of poorly folded proteins (38). If this process is not successful, then the apoptosis process begins (38).

Excessive weight gain can lead to a state of insulin resistance, during which insulin-dependent tissues are unable to internalize glucose molecules (3). In these circumstances, the demand for insulin increases, and β-cells must synthesize and secrete more insulin. This demand also falls on the endoplasmic reticulum, which must process more insulin molecules (8). Exposure to saturated FFAs such as palmitate affects the response capacity of the endoplasmic reticulum and increases the levels of poorly folded proteins, resulting in stress in the endoplasmic reticulum (38). If the demand for continuous insulin and ER stress are not resolved, then apoptosis is activated due to the PERK-dependent increase in the transcription factor CHOP, increased expression of the pro-apoptotic proteins Puma and DP5, and inhibition of the anti-apoptotic protein MCL-1 (39). One study has reported that endoplasmic reticulum stress markers are also increased in patients with T2D (38). The participation of p53 in stress-induced apoptosis of the endoplasmic reticulum

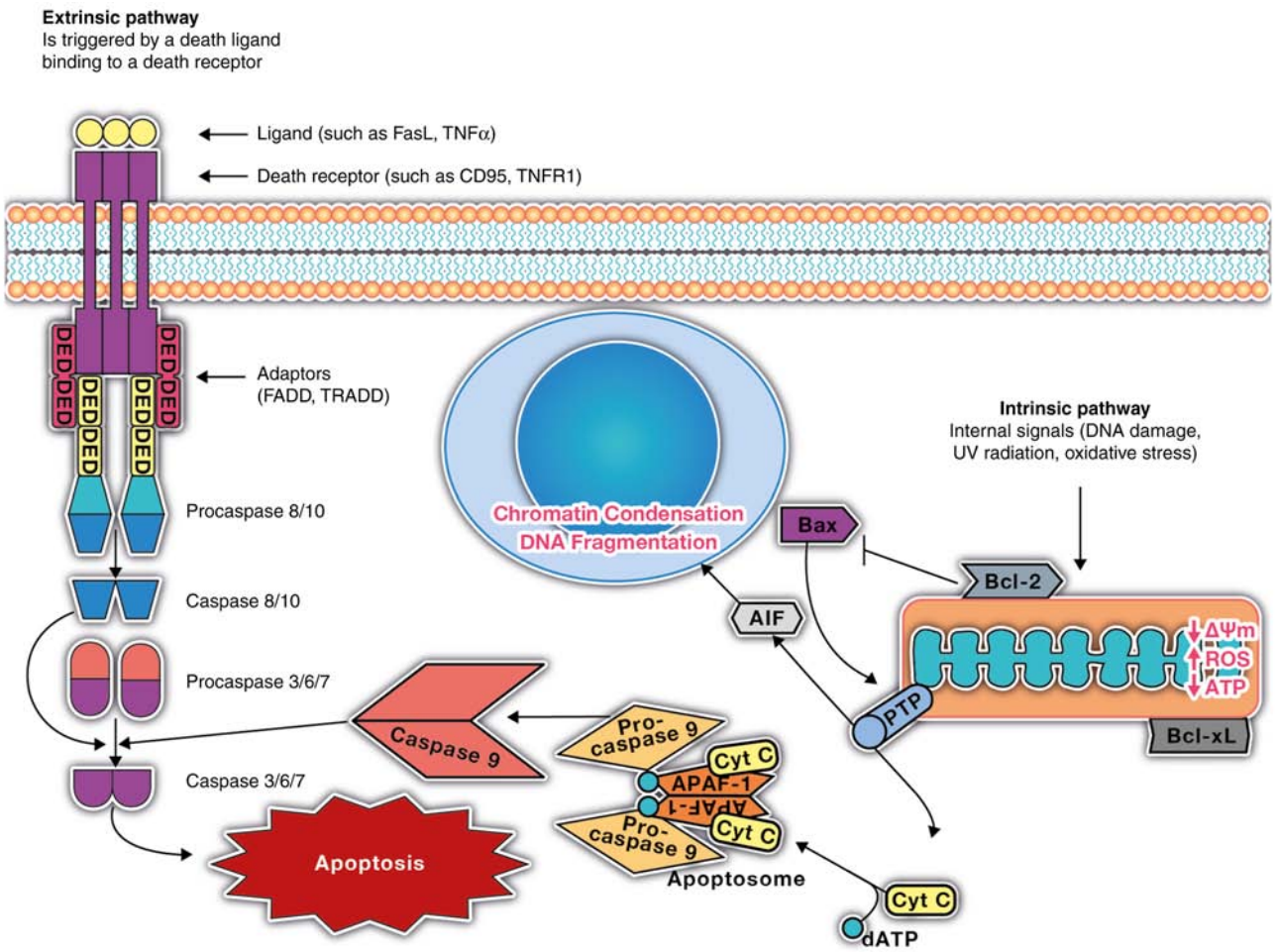

Figure 3. Pathways of apoptosis. There are two main signaling pathways by which a cell becomes apoptotic. The extrinsic pathway begins by binding specific ligands to death receptors on the cell surface, and this interaction leads to the activation of caspases 8 and 10. The intrinsic pathway begins at the mitochondrial level and leads to the formation of the apoptosome, a protein complex that leads to the activation of caspase-9. Caspases 8, 10 and 9 are known as regulatory caspases, and when active, they begin an activation cascade of other molecules, including caspases 3, 6 and 7, which are known as effector caspases that initiate the proteolytic cascade that leads to death by apoptosis. TNFR1, tumor necrosis factor receptor 1; FADD, Fas-associated DD; TRADD, TNFR-associated death domain; APAF-1, apoptotic protease activating factor 1; Cyt c, cytochrome c; dATP, deoxyadenosine triphosphate; ROS, reactive oxygen species; DED, death effector domain; PTP, permeability transition pore; Δψm, transmembrane potential.

has been related to the regulation of the expression of pro-apoptotic and anti-apoptotic proteins.

5. Implication of cytokines and inflammation in pancreatic β-cell dysfunction

Obesity constitutes a chronic low-intensity inflammatory state that activates the innate immune system, which in turn can alter glucose tolerance, contribute to the development of insulin resistance, and progress to diabetes and cardiovascular disease (40,41). An increase in the plasma concentration of C-reactive protein in the acute phase predicts the presence of coronary heart disease, metabolic syndrome and T2D (40).

In addition, Hotamisligil (41) was one of the first researchers to establish that adipocytes express TNF-α and that this expression is related to obesity and resistance to systemic insulin. Other proinflammatory molecules, such as resistin, IL-6, serum amyloid A3, acid glycoprotein A1 and monocyte chemotactic protein-1, are also expressed in adipose tissue and potentially induce themselves in response to obesity and diabetes. These proinflammatory molecules contribute to alterations in pancreatic β-cells (42). Diabetes is characterized by the infiltration of inflammatory cells into the pancreas, which favors the progressive destruction of β-cells (7). T cells and infiltrated macrophages produce and secrete inflammatory cytokines such as IL-1β, IFN-γ and TNF-α, which contribute to the loss of β-cells due to apoptosis activation (43,44). This process highlights the participation of the NF-κB nuclear factor, which regulates the expression of genes involved in the response to stress, growth, survival and cellular apoptosis (45). Previous studies have shown that IκB transgenic mice-/- (NF-κB inhibitor protein), which are specific to β-cells, do not develop streptozotocin-induced diabetes (45).

In adipose tissue, in addition to storing energy, hormones such as adiponectin, leptin, resistin, and visfatin and other mediators such as interleukins that regulate lipid and glucose metabolism are produced, which also affect the function of β-cells (46). Therefore, there is a close association between the levels of adipokines secreted by adipose tissue and the proper functioning of pancreatic β-cells. The inhibitory effects of leptin on insulin synthesis, either directly in the pancreas or indirectly mediated by the autonomic nervous

system, have been previously reported (47). Adiponectin is an anti-inflammatory and anti-apoptotic cytokine. A decrease in adiponectin plasma levels in obese individuals has been associated with insulin resistance, metabolic syndrome and T2D (47). Adiponectin exerts its effects through its interaction with its receptors (adipoR1 and adipoR2). In addition to having anti-inflammatory properties, it contributes to the activation of AMP-activated protein kinase in the muscle and liver and increases the use of glucose and the oxidation of fatty acids (40,47).

6. Apoptosis and oxidative stress

Increased apoptosis in β-cells plays a precise role in the initiation and progression of T2D (48). Among the possible mechanisms that explain the increase in apoptosis in these cells, the production of ROS of mitochondrial origin stands out (49). In T2D, IR is primarily compensated for by enhanced insulin secretion by β-cells. However, over time, this mechanism can fail and lead to a loss of metabolic regulation, resulting in chronic exposure of β-cells to elevated levels of glucose (33). Notably, the increase in intracellular levels of Ca^{2+} necessary for the exocytosis of insulin also contributes to the formation of ROS. Overproduction of free radicals decreases the activity of the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH), resulting in increased concentrations of glycolytic metabolites, such as glyceraldehyde-3-phosphate or fructose-6-phosphate (35-38,48,49). Finally, GAPDH inhibition increases the levels of metabolites of the glycolytic pathway. Consequently, the substrate for the polyol pathway increases, and the enzyme aldose reductase consumes available NADPH and decreases the antioxidant mechanisms of β-cells (50). Furthermore, pancreatic β-cells have a low capacity to respond to oxidative stress as the expression of antioxidant enzymes is also low (51). In addition, the reaction of ROS with biomolecules causes an autocatalytic chain reaction with subsequent cellular damage and activates mechanisms that emphasize the death of β-cells and decreased cell mass (48).

It was previously showed that by culturing RINm5F pancreatic β-cells in the presence of a high concentration of glucose (30 mM), the percentage of viable cells significantly decreased after 48 h compared with that of the control (low glucose, LG). These findings were consistent with the substantial increase in the percentage of apoptotic cells (44%) at 72 h compared with that in the control group (Fig. 4A) (11). Oxidative stress has been identified as another critical mediator in the cell death process with the ability to trigger or modulate apoptosis, and it has been found that the pro-apoptotic role of ROS is manifested through alterations in mitochondrial function, causing the release of cytochrome c (32,52).

ROS and oxidative stress in pancreatic β-cells exposed to high concentrations of glucose are characterized by an alteration in the potential of the mitochondrial membrane and a modification of its permeability (17). This alteration allows the release of pro-apoptotic proteins such as cytochrome c into the cytosol after 24 h of culture with high glucose. In addition, the activation of caspase-3 is promoted (11,17). The balance between pro- (Bax) and anti-apoptotic (Bcl-2) proteins, among others, plays an important role in the permeability of mitochondrial membranes and the release of other pro-apoptotic proteins (53,54). In this sense, it was shown that the Bcl-2/Bax ratio in the mitochondria decreases significantly after 24 h of culture with high glucose, which indicates the cytotoxicity induced by the high concentration of glucose in β-cells (11,17). These results are in accordance with previous reports that hyperglycemia induces apoptosis in β-cells, causing a decrease in Bcl-2 expression and an increase in Bax expression, aspects associated with cytochrome c release and caspase-3 activation (18,55). High glucose decreased ERK 1/2 phosphorylation. This observation is related to an increase in apoptosis and a decrease in the rate of cell proliferation (18). ERK 1/2 phosphorylation has been shown to modulate genes related to proliferation, differentiation, migration and death depending on the duration, magnitude and cellular location (56). In β-cells, activation of ERK 1/2 favors the synthesis and secretion of insulin in response to glucose and inhibits apoptosis (57); therefore, its inactivation impacts cellular functions and the β-cell mass.

During the process of apoptosis, protein translocation between the nucleus, cytoplasm and mitochondria occurs, which promotes the regulation of this process of cell death (17). The p53 protein is part of this group of proteins and is known to be a regulator of apoptosis when the cell presents irreparable damage to its structure (58,59).

7. Dual role of the p53 protein: The guardian of the genome and mediator of apoptosis in pancreatic β-cells

The p53 protein is known as the 'guardian of the genome', and its activation leads to a series of crucial biological consequences, ranging from the regulation of the cell cycle and DNA recombination to chromosome segregation, cell aging and the induction of apoptosis (60,61). In response to different extracellular and intracellular stimuli, such as DNA damage, p53 is activated, triggering various biological responses such as cell cycle arrest or cell death. After cell damage, the levels of p53 in cells rapidly increase. This increase is mainly attributed to post-translational modifications that alter the half-life of the protein and to the increase in the translation of its mRNA, which results in the regulation of its target genes (60,61).

The *p53* gene on chromosome 17 (17p13.1) is composed of 11 exons, of which exon 1 contains a noncoding sequence. In exon 2, there are two putative transcription start sites, and exon 11 contains a stop codon and a large noncoding sequence. The p53 protein has 393 amino acids divided into functional domains (Fig. 5) (60). The transactivation domain (TAD) is located at its N-terminal end and is essential for interactions with coactivators and transcriptional corepressors (60,61). TADs are composed of two homologous subdomains, TAD1 (residues 1-40) and TAD2 (residues 41-61), which share conserved Φ-XX-Φ-Φ sequence motifs (where Φ represents hydrophobic amino acids and X represents any amino acid), which are common to numerous transcriptional regulatory proteins (62). The TAD is a proline-rich region (PRD; residues 63-97) followed by a highly conserved DNA-binding domain (DBD; residues 102-292), characterized by specific binding to DNA sequences (63). Following the DBD, a binding region harboring an integrated nuclear localization signal (NLS; residues 301-323) is presented, followed by the tetramerization domain (TET; residues 323-356), which includes a nuclear

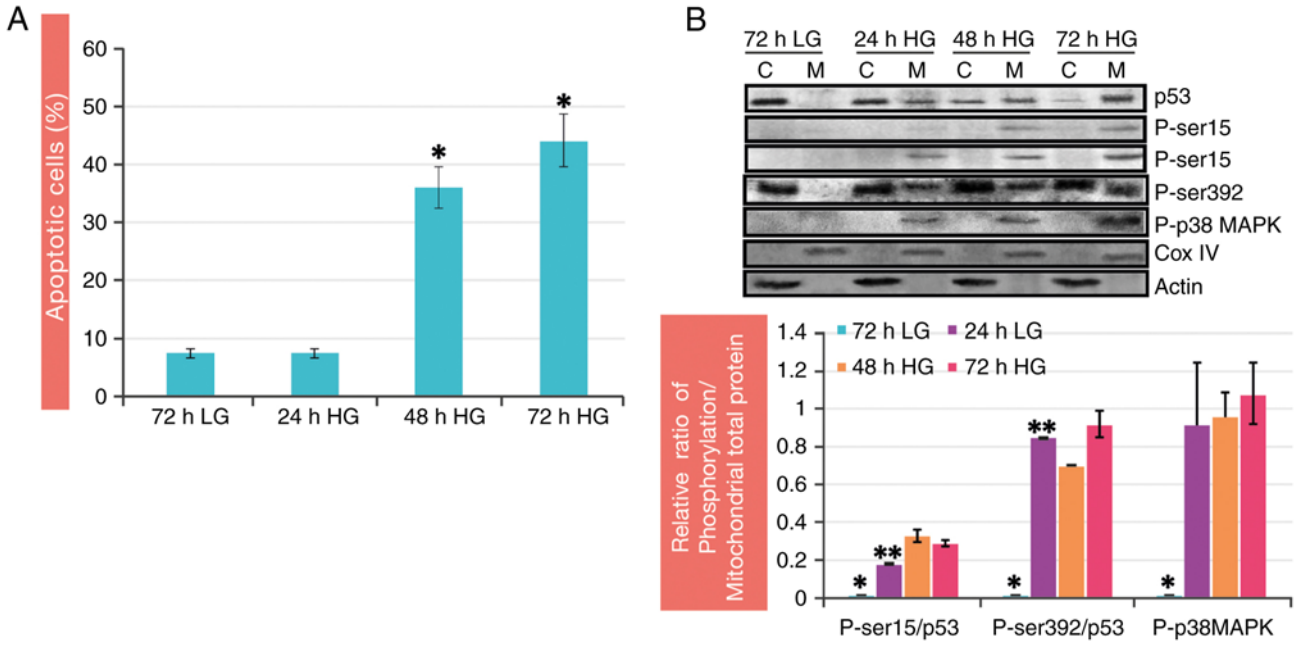

Figure 4. Increased glucose induces p53 and p38 MAPK phosphorylation and apoptosis in pancreatic β-cells. RINm5F pancreatic cells were cultured with 30 mM glucose for 24, 48 or 72 h. (A) Percentage of apoptotic cells, *P<0.001 vs. 72 h LG and 24 h HG. (B) Phosphorylation of p53 at Ser15 and Ser392 and p38 MAPK in mitochondria. *P<0.001 and **P<0.005 vs. the control. Reproduced/Adapted from (11), original figures 1C and 3A with permission from the Springer Nature license number: 5756580343582). P-, phosphorylated; LG, low glucose; HG, high glucose; C, cytosol; M, mitochondria.

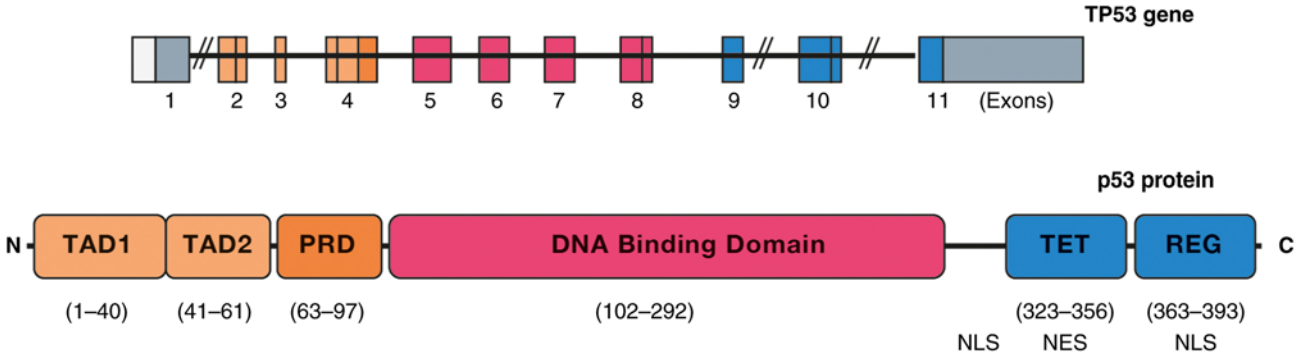

Figure 5. Structures of the TP53 gene and p53 protein. A schematic representation of the 11 exons of the TP53 gene is shown, of which one is not encoded. TP53 encodes a protein of 393 amino acids that has five domains: TAD, PRD, DNA-binding domain, TET and REG. TAD, transactivation domain; PRD, proline-rich region; TET, tetramerization domain; REG, regulatory domain; NLS, nuclear localization signal; NES, leucine-rich nuclear export signal.

export signal. Finally, there is a mostly disordered C-terminal regulatory domain (residues 363-393) (60). This last domain is characterized by its basic nature; it contains two additional NLSs, and it is a zone of important protein-protein interactions that regulate the activity of p53, which binds to DNA in tetrameric form (60,61). The formation of this quaternary structure depends on the correct activation of p53 and post-translational modifications of the TET (63). The C-terminal region is essential for the formation of tetramers (64).

One of the essential functions of p53 is to monitor cell stress and prevent the proliferation of damaged cells by inducing apoptosis (58). As a nuclear transcription factor, p53 can activate the transcription of pro-apoptotic genes such as bax and puma (65,66). Moreover, p53 can repress the expression of anti-apoptotic genes such as bcl-2 and bcl-XL (30). In addition, p53 also regulates the expression of death receptors. An example is the death receptor Fas, which mediates apoptosis through its interaction with the FasL ligand and, in turn, is under the regulation of p53 (60).

Another prominent function of p53 is its role in regulating apoptosis through transcription-independent mechanisms (67,68). In response to multiple apoptotic stimuli, a fraction of p53 translocates into mitochondria, where it establishes physical interactions capable of inhibiting the anti-apoptotic proteins Bcl-2 and Bcl-XL (69). Likewise, it contributes to the activation of the pro-apoptotic Bax and Bak proteins that induce permeabilization of the outer mitochondrial membrane by acting on VDAC, allowing the release of apoptotic activators into the cytoplasm (27,70). During the characterization of p53, the possibility of its involvement in the regulation of cell organelle functions was raised, which has been supported by the observation of the mobilization of p53 toward the outer mitochondrial membrane during apoptosis in response to stress from γ radiation (62,71,72).

Exposure to high concentrations of glucose has been linked to the apoptotic death of β-cells, a phenomenon that has been associated with the translocation of the p53 protein into mitochondria (17). The excessive consumption of carbohydrates induces metabolic alterations, negatively impacting the cellular functions of β-cells and triggering their death (9). The role of p53 in the death of pancreatic β-cells has recently been analyzed using a model in which Sprague Dawley rats were subjected to carbohydrate supplementation. For four months, the animals received drinking water containing either 40% sucrose or 40% fructose. Carbohydrate ingestion induced both apoptosis and the mobilization of p53 from the cytosol to the mitochondria of rat pancreatic β-cells, even before blood glucose levels rose (9). In addition, the ability of p53 knockout mice to regenerate the β-cell population and rescue the diabetic phenotype has been demonstrated (73,74). This finding emphasizes the critical importance of this protein in the progression of diabetes. However, there is at least one report that contradicts the participation of p53 in β-cell death (75).

The p53 protein is a transcription factor that is responsible for monitoring DNA damage (60). Depending on the severity of the damage, p53 induces apoptosis or arrests the cell cycle until DNA repair mechanisms are activated. Activation of p53 occurs in response to various types of stress, leading to its stabilization and accumulation (63). p53 is also known to be involved in the induction of apoptosis by acting directly on mitochondria, where it forms complexes with the Bcl-2 and Bcl-XL proteins through its DBD and precedes the release of cytochrome c and the activation of caspase-3 (76).

The apoptosis of β-cells exposed to high glucose concentrations has been demonstrated to occur due to the exit of cyt c into the cytosol and a decrease in the Bcl-2/Bax ratio in mitochondria (11,17). These events are related to the mobilization of p53 to mitochondria, increased ROS and decreased mitochondrial membrane potential (11). Thus, it was concluded that high glucose conditions regulate the intracellular distribution of p53 and favor its mitochondrial localization (11,17). In addition, it promotes post-translational modifications of p53 that prevent its degradation and increase its biological activity (9-11,17,18).

8. Post-translational modifications can regulate p53 in β-cells under hyperglycemic conditions

Under physiological conditions, the p53 protein remains in a latent state, reaching expression levels in some cell types that are undetectable by immunohistochemical or Western blot techniques (60). This protein, with a half-life close to 15 min in some cell types, is found in an inactive conformation that is diffusely located in the cell, frequently being cytoplasmic (77). Although the p53 protein is found at low concentrations in non-stressed cells, it is rapidly stabilized and activated in response to various stimuli (59). These stimuli, which are associated with cellular stress, such as direct damage to DNA by UV or ionizing radiation, redox changes, hypoxia or thermal shock, increase the levels of the p53 protein in the cell (78). This increase results from both greater protein stability and biochemical activation through post-translational modifications.

The functions of p53 are regulated by at least 10 different types of post-translational modifications, the most frequent being phosphorylation, ubiquitination, poly-ADP-ribosylation, acetylation, sumoylation, methylation, glycosylation and O-GlcNAcylation at serine (Ser)149 of p53 (79-82). Various enzymes catalyze these modifications and contribute to p53 activation through a wide variety of mechanisms (83,84). A number of these modifications are related to an increase in their ability to arrest the cell cycle or induce apoptosis (58,59). The permanence and functions of p53 in β-cells under hyperglycemic conditions are controlled by different post-translational modifications, including phosphorylation, O-GlcNAcylation and poly-ADP-ribosylation, depending on the intracellular environment (17,18).

p53 protein can be regulated by phosphorylation in response to hyperglycemia: Implications for cell stability and functions. It has been argued that the levels of the p53 protein are intrinsically linked to the balance between its synthesis and degradation, and it is evident that any effect on these events will have different consequences in the cell (59,60). A previous study has confirmed that high glucose concentrations do not modify p53 transcription (10).

By contrast, it has been suggested that its mobilization and increase in mitochondria result from protein stabilization, which depends on post-translational modifications such as phosphorylation (11). The p53 protein contains multiple phosphorylation-prone sites on (Ser)/threonine (Thr) residues distributed throughout the protein, with enrichment at the N-terminus (57). Most of these sites can become phosphorylated under cellular stress conditions, thus regulating the functions of p53 (60). Phosphorylation of p53 at the N-terminus, which occurs in the cytosol, has been related to an increase in the transcription of the pro-apoptotic protein Bax (85-87). On the other hand, phosphorylation at the C-terminal end of Ser 392 (or Ser 389 in mice) is related to the formation of p53 tetramers, DNA binding and the induction of apoptosis, in addition to contributing to the suppression of tumors (88).

It has been previously reported that p53 is phosphorylated at Ser15 and Ser392 in the mitochondria of pancreatic β-cells cultured under high-glucose conditions (11). Phosphorylation at these residues likely contributes to protein stability and is an essential requirement for the interaction of p53 with pro- and/or anti-apoptotic proteins (11). In studies in which RBL-2H3 cells (mast cells) were treated with eugenol (anti-allergenic), it was reported that p53 phosphorylation at the Ser15 residue in mitochondria facilitates the interaction of p53 with Bcl-2 and Bcl-xL, which in turn induces changes in the $\Delta\psi m$ and the release of cytochrome c (88). It is relevant to mention that the observation of p53 phosphorylation at residue Ser 392 in mitochondria in response to hyperglycemia seems to be the only one thus far. However, there are at least two studies linking the phosphorylation of this serine by p38 MAPK kinase with Bax activation and apoptosis in myocytes cultured with high glucose (89-91). Notably, p38 MAPK plays an important role in regulating insulin secretion (92). Since p53 has multiple phosphorylation sites, multiple kinases, including those activated by oxidative stress, such as p38 MAPK, regulate this process (93,94). Under high glucose conditions, the subcellular redistribution of p38 MAPK (from the cytosol to mitochondria) is stimulated, but its activation is only observed in the mitochondrial fraction (Fig. 4B). The localization and phosphorylation

of p53 coincide with the phosphorylation of p38 MAPK in mitochondria during high glucose treatment (11). These findings were confirmed by colocalization studies of the phosphorylated proteins by confocal microscopy, where a high colocalization coefficient was observed for both p53 and p38 MAPK in mitochondria (11). To verify the participation of p38 MAPK in p53 phosphorylation, a specific inhibitor of p38 MAPK (SB203580) was added to cultured RINm5F cells exposed to high glucose. The results demonstrated that the inhibitor prevented p53 phosphorylation at the Ser 392 and Ser 15 residues at all time points tested. Similarly, a decrease in the release of cytochrome c and the rate of apoptosis were observed (11). These data corroborate that p38 MAPK activation under these conditions is responsible for p53 phosphorylation at the Ser 392 and Ser 15 residues in mitochondria. Previous studies in other cell types have revealed that under conditions of hyperglycemia, oxidative stress and UV radiation, p38 MAPK regulates apoptosis by phosphorylating p53 at Ser 392 (85,94,95) and Ser 15 (96). In addition, p38 MAPK inhibition affects p53 mobilization to mitochondria (11). Phosphorylation likely has a protective effect on p53, preventing its interaction and recognition by Mdm2, which in turn preserves its stability and degradation, allowing its mobilization to mitochondria. This would trigger the activation of apoptosis, as well as its association with anti-apoptotic proteins (10,11).

The interaction between p53 and Bcl-2 in the mitochondrial fraction of cells treated with 30 mM glucose was observed after 24 h. Inhibition of p53 phosphorylation at Ser392 and Ser15 by a p38 MAPK inhibitor affected the association of p53 with Bcl-2. These results indicate that this phosphorylation is very important for promoting the association of p53 with Bcl-2 and for p53 to remain in the mitochondria (11).

Furthermore, p53 phosphorylation was detected at Ser15 in the nuclear fraction. Previous studies have confirmed that this phosphorylation at Ser15 caused by UV radiation or hydrogen peroxide is due to ataxia telangiectasia mutated kinase (ATM) activation. It should be noted that phosphorylation of this residue when the protein is in the cell nucleus helps to stabilize and activate the transcriptional functions of p53, which are related to the regulation of apoptosis (97). The results of the present study showed an increase in ATM phosphorylation in the cytosol and nucleus in response to high glucose exposure, probably because of the oxidative stress that prevails under these conditions (17,98). In this context, ATM-deficient mice exhibit oxidative stress and damage to DNA, proteins and lipids via ROS (98). In addition, the administration of antioxidants such as N-acetyl cysteine has been shown to be effective in reducing oxidative damage, reversing neurological deficits and preventing premature aging in these animal models (99). ATM plays a crucial role by phosphorylating numerous substrates needed for DNA repair, cell cycle regulation and apoptosis, including the p53 protein (97). In addition, p53 phosphorylation at Ser15 in the nuclear fraction appears to be related to ATM activation (98). Furthermore, streptozotocin-induced p53 activation by ATM is a critical event in DNA damage in β-cells *in vitro* (100). However, ATM activation is likely also associated with the phosphorylation of other proteins and indirectly regulates p53. ATM can phosphorylate p53 through Chk2 activation (101,102) or phosphorylate Mdm2 at Ser395, thus preventing p53 ubiquitination and degradation; thus, ATM could be an adjacent mechanism for p53 stabilization (84,101). Additionally, the relevance of ATM activation in glucose metabolism has been noted, although the precise underlying mechanisms have not yet been determined. ATM inhibition affects the incorporation of glucose into muscle and adipose tissue through the mobilization of GLUT4, which is why it has been linked to the development of insulin resistance and T2D (100).

O-GlcNAcylation. O-GlcNAcylation is a regulatory mechanism of p53 stability and function in response to glucose. It is a noncanonical glycosylation process involving the attachment of single O-linked N-acetylglucosamine (O-GlcNAc) moieties to Ser and Thr residues of cytoplasmic, nuclear and mitochondrial proteins (102,103). O-GlcNAcylation is another post-translational modification of p53 and depends on glucose availability. In this mechanism, two enzymes participate: OGT (O-linked N-acetylglucosamine transferase), which adds N-acetylglucosamine residues to several proteins at the hydroxyl group of Ser and Thr, and O-GlcNAcase (N-acetylglucosaminidase), which eliminates the N-acetylglucosamine residues from the proteins (104). Physiologically, disruption of O-GlcNAc homeostasis has been implicated in the pathogenesis of a plethora of human diseases, including cancer, diabetes and neurodegeneration (105). O-GlcNAcylation has been linked to T2D since the expression of OGT RNA in the pancreas and brain is increased (2 Studies have reported that the protein level of p53 is elevated in the liver of patients with T2DM, partly because hepatic p53 is stabilized by O-GlcNAcylation and plays an essential role in the physiological regulation of glucose homeostasis (79,80). O-GlcNAcylation has been shown to stabilize p53 and prevent its degradation (81).

In a high-glucose environment, p53 O-GlcNAcylation is related to its stability and stops its degradation. O-GlcNAcylation does not interfere with phosphorylation, but it stimulates p53 apoptotic function (105-107). In the studies presented in the present review, it was observed that O-GlcNAcylation precedes apoptosis and increases as apoptosis signals appear in RINm5F cells under hyperglycemic conditions (Fig. 6). In addition, the O-GlcNAcylation of p53 promotes its mobilization to mitochondria, which can contribute to the release of pro-apoptotic factors (18). O-GlcNAcylation of p53 at Ser149 increases its stability upon interference with Thr155 phosphorylation and weakens the interaction of p53 with Mdm2, along with the ubiquitination and thus proteolysis of p53, which translates into greater stability of p53. Thus, it is hypothesized that O-GlcNAcylation stabilizes p53 and may create a signal for its mobilization to the mitochondria.

Interaction between PARP and p53: Modulation of DNA repair and apoptosis in response to cell damage and high glucose conditions. When DNA damage occurs in cells, poly (ADP-ribose) polymerase (PARP), a nuclear protein of 116 kDa with two zinc finger motifs that bind to DNA and specifically detect nicks or breaks, is activated (108,109).

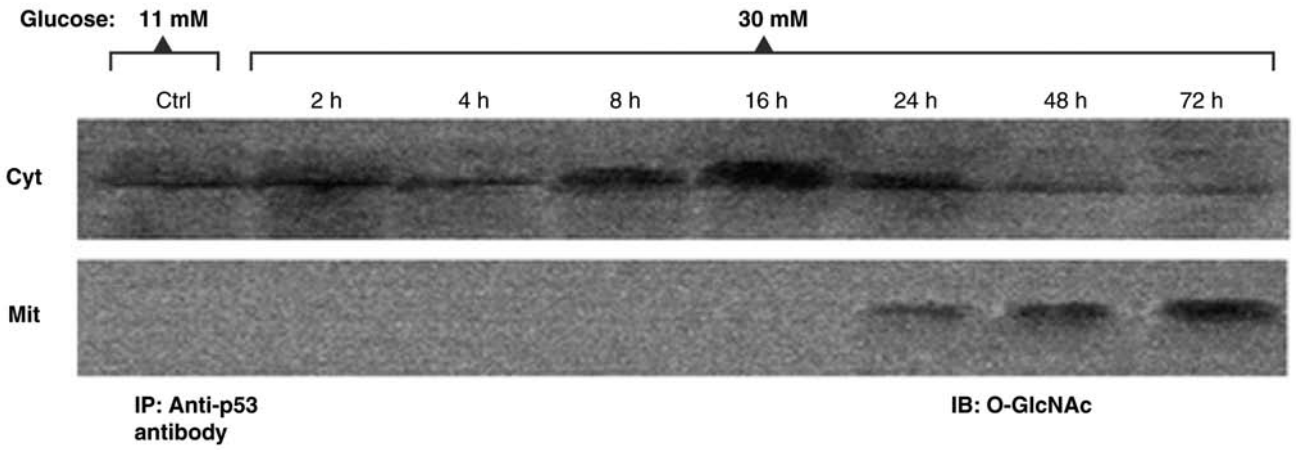

Figure 6. Effect of hyperglycemia on p53 O-GlcNAcylation. Immunoprecipitation of p53 and development with an anti-O-linked-N-acetylglucosamine antibody in the cytosolic and mitochondrial fractions of RINm5F cells. p53 O-GlcNAcylation was detected at low concentrations even in the Ctrl fraction, and it increased in the cytosolic fraction after 8 h in cells treated with 30 mM glucose, possibly as a mechanism by which p53 protects against degradation by proteolysis. In the Mit, p53 O-GlcNAcylation begins to be detected after 24 h, coinciding with its mobilization toward this organelle (18). Image and data obtained by L. A. Flores-Lopez (first author). Cyt, cytoplasm; Mit, mitochondria; O-GlcNAc, O-linked-N-acetylglucosaminylation; Ctrl, control.

PARP catalyzes the transfer of ADP-ribose units from NAD^+, an essential cofactor in ATP synthesis and redox potential balance, to glutamic acid and aspartic acid residues of several nuclear proteins (108). This post-translational modification is important for the activation of a series of cellular processes, including DNA repair and replication, gene transcription, the inflammatory response and cell death, and occurs mainly in response to DNA damage generated by genotoxic agents, as well as different stimuli to DNA damage, such as infection and stress (109-111). *In vivo* immunoprecipitation of PARP and p53 has shown that both proteins interact, and that this PARP-p53 interaction may affect the function of the p53 protein, as it is ADP-ribosylated by PARP in response to DNA damage or cellular aging (112).

The amino-terminal region of the PARP protein contains a target sequence of caspases 3 and 7 that is responsible for PARP proteolysis into two fragments of 89 and 24 kDa. This proteolytic breakdown is currently considered a marker of caspase-dependent apoptosis (112). Fragments generated by the action of caspases 3 and 7 contribute to the inactivation of the intact enzyme (113). PARP fragmentation coincides with the induction of apoptosis in β-cells by hyperglycemia (10). These results agree with previous reports showing that hyperglycemia induces the apoptosis of β-cells and pancreatic cell lines, such as RINm5F (11,17). Short-term treatment of RINm5F cells with high glucose (2-16 h) induces an increase in PARP protein (18). Immunoprecipitation assays revealed an association between PARP and p53, as well as poly-ADP-ribosylation of p53 in the nuclear fraction, which promotes the function of p53 in DNA repair mechanisms in the early stages of cell damage (10,18). Poly-ADP-ribosylation of p53 under high-glucose conditions also likely contributes to its stability and mobilization in mitochondria (18). After 24 h, PARP degrades and becomes inactivated, which leads to a decrease in poly-ADP-ribosylation of p53. PARP fragmentation and inactivation coincided with increased Bax in mitochondria, cytochrome c release, and increased apoptosis of RINm5F cells due to high glucose conditions (18).

9. Dual regulation of p53: Interaction between Mdm2 and ubiquitination activity in the context of hyperglycemia and cellular stress

Cell survival largely depends on the p53 concentration. Mdm2 is one of the regulatory mechanisms of p53. Mdm2 is an E3 ubiquitin ligase that binds to p53 and adds ubiquitin residues to it for proteasomal degradation. However, the fate of p53 depends on Mdm2 activation and the addition of ubiquitins, after which mono- or polyubiquitylation is regulated by Mdm2 (114). As previously cited, the formation of the p53-Mdm2 complex is determined by the post-translational modifications of both proteins. The ubiquitylation, SUMOylation and phosphorylation of Mdm2 disrupts the formation of the p53-Mdm2 dimer and stabilizes p53. Phosphorylation of Mdm2 at Ser395 by ATM activation has been shown to decrease the ability of Mdm2 to drive p53 degradation.

Furthermore, it was previously reported that Mdm2 phosphorylation by Akt is involved in the regulation of p53, as it reduces transactivation and increases p53 ubiquitination (115,116). Akt is a critical regulator of cell proliferation and survival (115). Phosphorylation of Mdm2 at Ser166 and Ser186 by Akt increases its E3 ligase activity, and can protect cells against p53-induced apoptosis caused by hyperglycemia (10). Notably, other kinases, such as ERK 1/2, can phosphorylate Mdm2 at Ser166. However, with increased glucose, ERK 1/2 decreases and apoptosis increases (11).

Increased glucose decreases Mdm2 mRNA and protein levels in the nucleus and cytosol, Mdm2 expression is regulated by p53 (10). Previous studies have shown that in cells cultured with high concentrations of glucose, p53 is not found entirely in the nucleus but is mobilized to other organelles, such as mitochondria (11,17). Therefore, it cannot stimulate the expression of Mdm2. Furthermore, DNA fragmentation due to hyperglycemia can also affect Mdm2 mRNA expression (10).

The E3 ubiquitin ligase activity of Mdm2 is situated within the RING-finger domain in the carboxyl-terminal region, where the lysine acceptor is also found, whose main function is to mark p53 for degradation (117). The central

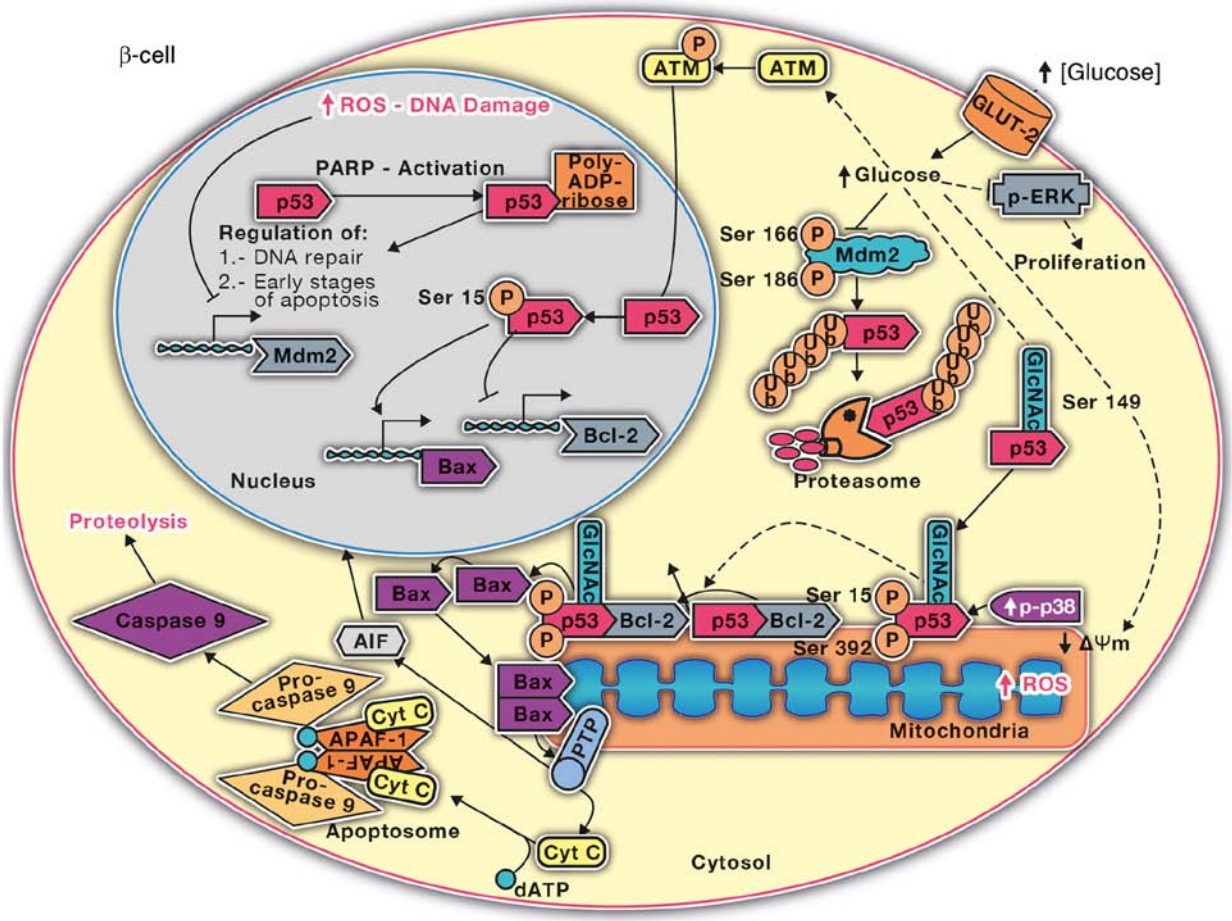

Figure 7. Regulation of p53 due to high glucose in pancreatic β-cells. Poly-ADP-ribosylation occurs in the early stages of RINm5F cell culture with high glucose, which allows p53 to regulate DNA damage repair and the early stages of apoptosis. p53 O-GlcNAcylation is increased in the cytosol and stabilizes p53, enabling its migration to the mitochondria, where it is phosphorylated via p38 MAPK. The phosphorylation of p53 likely promotes its interaction with anti-apoptotic proteins (Bcl-2) and the release of pro-apoptotic elements such as cytochrome c. These events lead to the activation of caspases. High glucose conditions also inhibit the phosphorylation and activation of Mdm2 and the ubiquitination of p53, as well as its degradation by the proteasome. ROS, reactive oxygen species; PARP, poly (ADP-ribose) polymerase; Mdm2, murine protein double minute 2; ATM, ataxia telangiectasia mutated kinase; p, phosphorylated; GlcNAc N-Acetylglucosamine, dATP, deoxyadenosine triphosphate; Δψm, transmembrane potential; cyt c, cytochrome c; Ub, ubiquitin; AIF, apoptosis-inducing factor; APAF-1, apoptotic protease activating factor 1; PTP, permeability transition pore.

Mdm2 acidic domain binds to the RING-finger domain and stimulates its catalytic activation and ubiquitin release by the E2 enzyme (117). The interaction between the acidic domain and the RING-finger domain is modulated by phosphorylated ATM (10). In this model, an increase in ATM phosphorylation due to hyperglycemia was also observed, so it cannot be ruled out that stress and the phosphorylation cascade induced by high glucose may phosphorylate some residues present in or near the RING-finger domain and the acidic core domain of Mdm2 and suppress p53 polyubiquitination and degradation.

By contrast, ubiquitination of p53 depends on the energy supply. Hyperglycemia increases ROS and mitochondrial uncoupling, leading to decreased ATP levels. Therefore, if ATP decreases, ubiquitins cannot condense the glycine residues of their carboxyl-terminal region with the lysine residues of p53, and p53 degradation is inhibited (114,115).

10. Conclusions

The mechanisms involved in pancreatic β-cell loss due to hyperglycemia are not yet fully known. Hyperglycemia is characterized by exacerbated ROS production, which stimulates the activation of phosphorylation cascades that may suppress Mdm2 E3 ubiquitin ligase activity and inhibit the p53-Mdm2 complex. Thus, it prevents p53 degradation and promotes p53 recruitment to mitochondria and β-cell death. Other changes initiated by hyperglycemia, such as poly-(ADP-ribosylation) and O-GlcNAcylation, also influence p53 stabilization and activation (Fig. 7). The studies described in the present review aimed to elucidate the biochemical events related to the loss of β-cells in patients with T2D. These findings offer a reference point for the search for new therapeutic targets, possibly for post-translational modifications of p53.

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Availability of data and materials

Not applicable.

Authors' contributions

LAFL, AAR and COC conceptualized the study; LAFL, COC, AAR, ACR, IDlMDlM and SEF performed the investigation; LAFL, COC, IDlMDlM, SEF, IGT, RVR, AAR and GLV wrote, reviewed and edited the manuscript; LAFL visualized the study; LAFL and COC performed study supervision and analyzed the information. Data authentication is not appliable. All the authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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