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REVIEW

Focus on Cell Apoptosis, Pyroptosis and Ferroptosis to Explore Strategic Breakthrough for GDM

Jiahui Li, Limei Fan, Yu Nan, Min Wang, Shuli Yang

Department of Gynecology and Obstetrics, The Second Hospital of Jilin University, Changchun, Jilin, 130000, People's Republic of China

Correspondence: Shuli Yang, The Second Hospital of Jilin University, No. 4026, Yatai Street, Nanguan District, Changchun, Jilin, People's Republic of China, Tel +8613500883873, Email yangsl@jlu.edu.cn

Abstract: As an inevitable end of an organism, cell death plays a crucial role in human metabolism. In recent years, inappropriate cell death, such as cellular apoptosis, pyroptosis and ferroptosis, has been shown to be involved in a variety of metabolic diseases. The placenta is an extremely important endocrine organ during pregnancy, which significantly influences fetal health by providing material exchange. Cell death has been found to be associated with several placenta-associated diseases, including gestational diabetes mellitus, preeclampsia and others. Inflammation is closely linked to the direct involvement of pyroptosis and the indirect involvement of apoptosis, and the inflammatory response in the placenta is thought to be an important factor contributing to insulin resistance in patients with gestational diabetes mellitus. Furthermore, the iron requirements of this particular group of pregnant women are bound to be undiminished, yet a range of adverse outcomes can occur with iron overload. This review aims to elucidate the effects of three common and important forms of cell death, including apoptosis, pyroptosis and ferroptosis, in various physiological and pathological contexts. This will enable a better understanding of their potential relevance to gestational diabetes mellitus, which will in turn facilitate further cytomolecular studies and clinical applications.

Keywords: cell death, ferroptosis, pyroptosis, apoptosis, GDM

Introduction

Gestational diabetes mellitus (GDM) is one of the most prevalent pregnancy complications. It is defined as the first occurrence of diabetes during pregnancy due to abnormal glucose metabolism.[1,2] The International Diabetes Federation (IDF) reported that the global prevalence of diabetes in 2019 was 9.3% or 463 million people. It is estimated that the global prevalence of diabetes will increase to 10.2% or 578 million people by 2030 and 10.9% or 700 million people by 2045.[3] In general, GDM is strongly associated with adverse pregnancy outcomes.[1] These include an increased risk of gestational infections, amniotic fluid overload, preterm labor, birth injuries and postnatal infections. Additionally, GDM contributes to fetal hypoxia, neonatal hypoglycemia and macrosomia.[4,5]

Pregnancy is a specific state of metabolic change in which the mother's physiological systems undergo adaptations to facilitate normal fetal development. GDM is a heterogeneous disease whose etiology and pathogenesis are not fully understood.[6] There is no consensus on the underlying pathophysiological events that produce these changes. It has been suggested that the development of GDM is influenced by factors such as genetics, metabolism, IR, levels of inflammatory factors, and oxidative stress.[7–13] The inflammatory response in the placenta is considered to be a key factor contributing to IR in GDM,[14] and both this response and the immune response are considered to be important pathological factors.[15] Two principal approaches are available for the management of GDM: pharmacological treatment and lifestyle modification,[16] with the latter including medical nutrition therapy and physical activity. In the event that adequate glycemic control is not achieved, the addition of insulin or metformin is recommended.[17] The mechanism of action of

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hypoglycemic agents has been the subject of extensive research, yet further standardization is required in determining the appropriate patient population and the applicability of these agents to GDM patients of diverse racial backgrounds.

The Occurrence of GDM

Insulin Resistance

The regulation of blood glucose levels during pregnancy depends on the secretion of insulin by pancreatic β-cells, the clearance of insulin required to maintain hormonal balance during pregnancy, and the action of insulin in the liver, muscle and other tissues. Any disruption to these factors can result in insulin resistance (IR) and elevated serum glucose levels during pregnancy.[18] During normal pregnancy, the increased demand for glucose for fetal growth and elevated insulin demand in the mother results in a physiological form of IR. This is accompanied by increased insulin secretion from the β-cells of the pancreas to compensate and maintain normal blood glucose levels. This phenomenon is most pronounced in the third trimester of pregnancy.[19,20] However, this is influenced by food intake and placental hormone secretion.[21,22] GDM has a complex pathology characterized by increased IR, reduced insulin sensitivity[19] and pancreatic β-cell dysfunction resulting in a relative insufficient insulin secretion, which is also similar to the occurrence of type 2 diabetes mellitus (T2DM).[23] Beyond the inherent physiological IR that accompanies pregnancy, which, if exacerbated, can lead to GDM, the development of IR is further influenced by numerous cytokines and altered hormone levels.[24]

Inflammatory Factors

Once pregnancy is established, the body progressively enters a state of low-grade systemic inflammation.[25] A number of studies have demonstrated that inflammation plays a pivotal role in IR and pancreatic β-cell failure,[26,27] with inflammatory factors acting as initiating factors in the development of IR. The placenta plays a significant endocrine role, synthesizing and secreting a range of inflammatory cytokines that contribute to the chronic inflammatory response and the extent of maternal IR.[28] For instance, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) are the principal inflammatory cytokines that are elevated in IR and GDM. Given that they inhibit insulin signaling pathways and interfere with the anti-inflammatory effects of insulin, they are considered potential mediators of IR.[6] Up to date, the effects of TNF-α, IL-6, and C-reactive protein on the development of IR have been extensively studied. Kirwan et al demonstrated that TNF-α is a marker of IR in pregnancy and that an increase in IR is characteristic of pregnancy, which is closely associated with an increase in TNF-α concentration.[29] The ratio of lipocalin/TNF-α is significantly lower in GDM patients compared to normal pregnancies. This ratio can be used as an important biomarker for assessing pregnant women at high risk of IR and dyslipidaemia, as well as a target for diagnostic and therapeutic monitoring of GDM.[30]

Vascular Endothelial Injury and Cytokines

Vascular disease represents the most significant complication of diabetes mellitus, and endothelial dysfunction is the underlying cause of vascular complications in diabetes mellitus.[31,32] Vascular endothelial cells (VECs) represent the primary target cells for insulin secretion in vivo. GDM-induced elevated blood glucose levels, oxidative stress, and abnormal adhesion of the vascular endothelium result in vascular endothelium damage,[33] leading to increased serum Endothelin-1 (ET-1) secretion, decreased serum NO release, and reduced flow mediated dilation (FMD). Research has demonstrated that endothelial dysfunction in patients with GDM is associated with fasting blood glucose and blood glucose levels 1 or 2 hours after OGTT.[34] These markers may serve as indicators of the extent of GDM and endothelial cell damage, thus helping to predict and prevent long-term complications associated with GDM. It is hoped that in the future, animal models of GDM or large clinical trials will be used to investigate the underlying mechanisms in more detail.

Strategic Breakthroughs – Cell Death in GDM

In recent years, cell death has become a new area of research as different pathogenic mechanisms of GDM have been investigated. Cell death represents a fundamental physiological process in all living organisms. These processes play various roles in diverse biological phenomena, including embryonic development, organ maintenance, ageing,

inflammatory responses and the coordination of immune responses and autoimmunity. The primary function of cell death is to maintain tissue homeostasis by removing nonfunctional, damaged, and harmful cells.[35] Over the years, several types of cell death have been described, including apoptosis, necrosis, autophagic cell death, and lysosomal cell death, which are classified as programmed cell death. And others are classified as inflammatory cell death, including pyroptosis, necroptosis, and NETosis. In recent years, several novel forms of cell death have been discovered, including mitoptosis, paraptosis, immunogenic cell death, entosis, methuosis, parthanatos, ferroptosis, autosis, alkaliptosis, oxeiptosis, cuproptosis, and erebosis.[36] These discoveries have advanced our understanding of cell death and its complexity. In the following discussion, we explore the specific mechanisms by which common cell death processes (apoptosis, pyroptosis and ferroptosis) are involved in the development of GDM, with a view to discovering therapeutic breakthroughs in GDM.

Cellular Apoptosis

In 1972, Kerr, Wyllie, and Currie first employed the term apoptosis to describe a morphologically distinct form of cell death in a seminal paper[37] that provided a comprehensive account of the morphological changes associated with apoptosis, including membrane blistering, reduction in cell size, nuclear fragmentation, chromatin condensation, phosphatidylserine (PtdSer) exposure at the cell surface, and apoptotic body formation. The study of the mechanisms involved in the process of apoptosis in mammalian cells has led to the investigation of programmed cell death that occurs during the development of the nematode Cryptobacterium hidradii.[38] Subsequently, apoptosis has been identified as a discrete and pivotal mode of "programmed" cell death, which is genetically determined and involves the elimination of cells. Given that apoptotic vesicles are efficiently cleared in vivo, apoptosis is typically not associated with the release of damage-associated molecular patterns (DAMPs), which may recruit inflammatory cells and cause damage to surrounding tissues. Apoptosis is an evolutionarily conserved mode of cell death regulation, generally regarded as a homeostatic, non-inflammatory process.[39] However, it is also indirectly involved in inflammatory responses, such as in GSDME-expressing cells, where chemotherapeutic agents or inflammatory factors that normally trigger apoptosis-mediated cell death further result in the activation of cellular pyroptosis.[40] A hallmark of apoptosis is the clearance of damaged, infected and senescent cells without the need for immune system activation.[41] These apoptotic pathways initiate an apoptotic cysteine asparaginase cascade reaction that leads to the cleavage of hundreds of apoptotic substrates, resulting in typical apoptotic features.[41,42] Apoptosis is also an essential mechanism employed by the immune system to combat infections and eliminate cells with irreparable DNA damage.[43] The process of apoptosis and related mechanisms are depicted in Figure 1. Appropriate apoptosis is essential for the maintenance of pregnancy, but hyperglycemia aberrates the apoptotic process in placental trophoblast cells, which involves alterations at several cellular-molecular and other levels as described below.

Apoptosis and GDM – Variation at Different Molecular Levels

Characteristic Changes in the Placenta and Hematology of GDM

The placenta is typically larger and heavier in women with GDM compared to women with normal pregnancies, suggesting altered trophoblast cell proliferation, differentiation, and death.[45] Both apoptosis and autophagy are involved in the development of the human placenta. In molecular genomics experiments on human placentas, increased apoptosis has been observed in studies of previous pregnancy complications, such as preeclampsia (PE) and fetal growth restriction (FGR). p53 plays a pivotal and complex role in regulating trophoblast cell turnover in response to hypoxic stress.[46,47] However, the role of apoptosis in the placenta of GDM patients remains unclear. The application of KEGG data analysis revealed the presence of nine pathways affected by GDM-induced damage in the GDM placenta. Among these, the death receptor, mitochondrial pathways, and TNFα signaling pathways have been identified as the most closely associated with placental growth in a hyperglycemic environment. In contrast to the findings observed in conventional pregnancies, GDM placentas have been shown to exhibit a decrease in apoptosis,[48,49] whereas other studies have not yielded the same results.[50] A few studies have investigated autophagy changes in GDM placentas, but the results have been inconsistent.[51,52] The results of an experimental study conducted in Taiwan, China, showed that the placentas of normal and GDM pregnant women showed different degrees of apoptotic changes, and Bcl-2 family proteins may be involved in

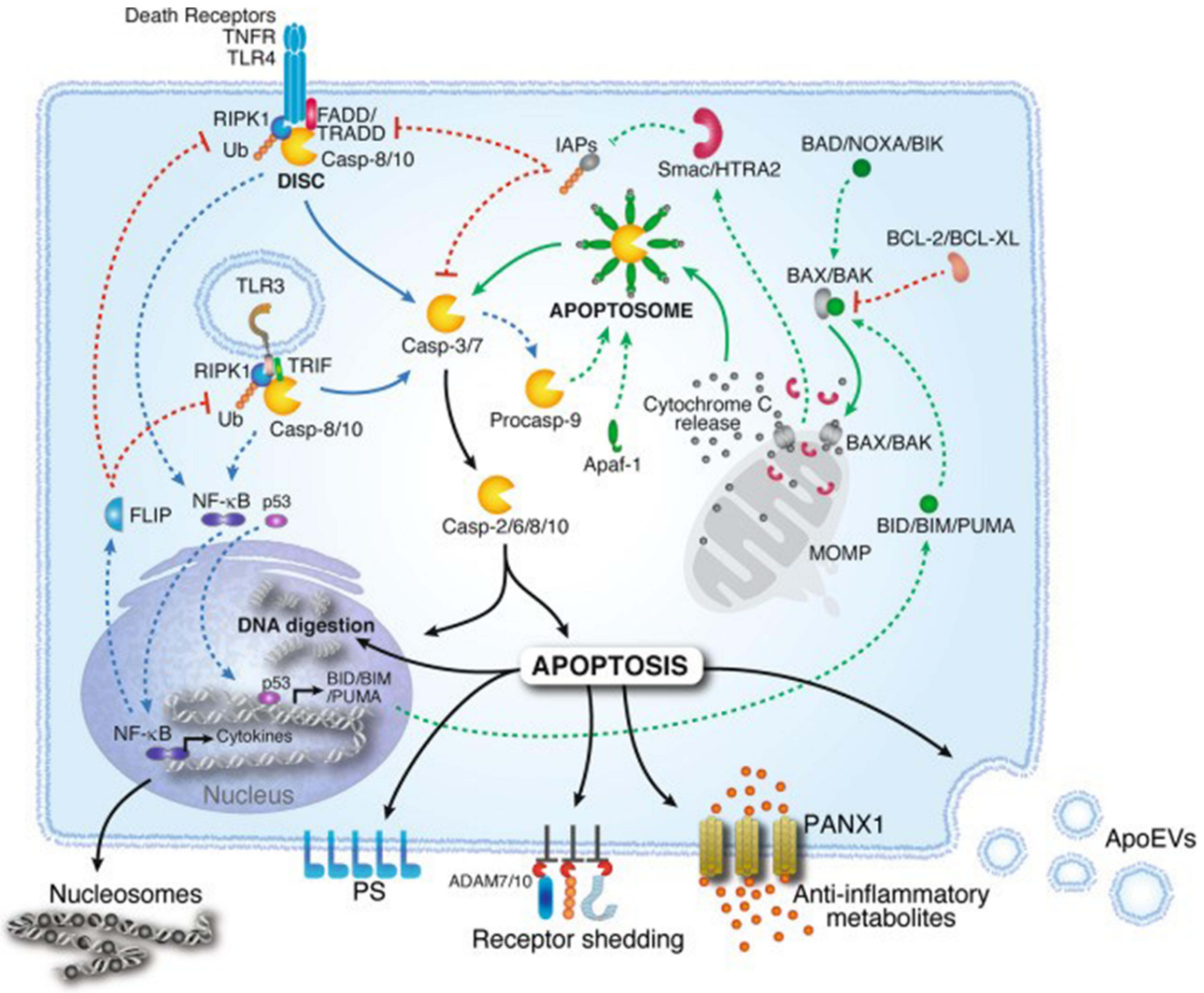

Figure 1 The process of apoptosis and related mechanisms.
Notes: Two main pathways are involved in apoptosis: the intrinsic pathway, which is initiated by the oligomerization of the B-cell lymphoma 2 (BCL-2) family proteins BAK and BAX, and the exogenous pathway, which is triggered by the involvement of membrane receptors such as tumor necrosis factor (TNF) receptor 1 (TNFR1), death receptors, or Toll-like receptors (TLR). Apoptotic cells release messengers in the form of nucleosome structures, which include shedding receptors, anti-inflammatory metabolites, and molecules packaged in apoptotic extracellular vesicles (ApoEV). Phosphatidylserine (PS) molecules exposed on the outer surface of the plasma membrane act as "eat me" signals for phagocytes. Copyright © 2021. Reproduced from Bertheloot D, Latz E, Franklin BS. Necroptosis, pyroptosis and apoptosis: an intricate game of cell death. *Cell Mol Immunol*. 2021;18(5):1106–1121.[44]

the regulation of these changes. Additionally, hyperglycemia was observed to result in elevated levels of Bcl-xL and reduced levels of Bak and Bad compared to standard culture conditions.[53]

IL-34 is a recently discovered pro-inflammatory cytokine consisting of 242 amino acids,[54] which plays a crucial role in the development of several diseases. A cross-sectional study conducted in China found elevated concentrations of IL-34 in maternal and cord blood samples from patients with GDM. The levels were found to be positively correlated with maternal and cord blood homeostatic model assessment for insulin resistance (HOMA-IR). IL-34 has been shown to enhance apoptosis through the colony-stimulating factor 1 receptor (CSF-1R), while inhibiting cell viability and pancreatic β-cell function. The findings of this study indicate that IL-34 may serve as a potential biomarker in patients with GDM.[54]

The Role of Related Members of the Galactose Lectin Family

Galactose lectins are involved in the regulation of maternal-fetal immune tolerance and the promotion of angiogenesis in

placenta formation, thus playing an important role in placenta formation and pregnancy maintenance.[55,56] Galactose lectin-3 (Gal-3) is a member of the β-galactoside-binding lectin family that broadly regulates intercellular and extracellular interactions in biological organisms.[57] A number of studies have demonstrated that Gal-3 plays a role in both physiological and pathological processes associated with pregnancy-related disorders, including GDM.[58,59] Mechanistically, galectin-3 impedes pivotal stages of the insulin signaling pathway, including the phosphorylation of the insulin receptor, phosphatidylinositol-dependent protein kinase 1(PDK1), and Akt.[60] The plasma Gal-3 levels were found to be elevated in GDM patients compared to normoglycemic patients during the early and mid-pregnancy periods. However, there was no significant difference in plasma Gal-3 levels between the two groups in maternal and cord blood samples. This may be related to satisfactory glycemic control in both groups during late pregnancy.[61] A significant increase in galectin-3 expression was observed in trophoblast cells exposed to high glucose concentrations (25 mM).[61,62]

Foxc1 is a transcription factor that plays an important role in a variety of cellular activities, including apoptosis.[63] Silencing of Foxc1 has been shown to significantly induce apoptosis, while overexpression of Foxc1 has been demonstrated to significantly reduce apoptosis.[61,63] The finding that the Gal-3/foxc1 pathway protects HTR-8/SVneo cells from high glucose-induced apoptosis may be related to the important function of galactoglucan lectin-3 in the maintenance of fetal development,[59,61] and this finding addresses a gap in the literature. The findings indicate that Gal-3 acts to antagonize high glucose-induced apoptosis in trophoblast cells, a result that is consistent with previous studies.[61,64] Furthermore, previous studies have observed a notable decline in Gal-13 expression in placental tissue and a further pronounced reduction in serum Gal-13 levels in pregnant women diagnosed with GDM. This leads to the conclusion that lower levels of Gal-13 may result in an imbalance between pro- and anti-inflammatory processes in the placenta, thereby favoring the development of GDM.[65]

CircCHD2 Regulated Apoptosis

Circular RNA (circRNA) is a recently discovered endogenous non-coding RNA that regulates gene expression and is involved in the pathogenesis of various diseases, including diabetes mellitus.[66] CircRNA is involved in the development and progression of IR, pancreatic β-cell dysfunction, inflammation, autophagy, apoptosis, and endothelial dysfunction in GDM.[67–70] A study of 30 patients with GDM and 30 normal pregnancies found that 227 circRNAs were significantly upregulated and 255 circRNAs were significantly downregulated in placental villi of GDM patients. Further bioinformatics studies identified a large number of miRNA binding sites on these differentially expressed circRNAs, which are associated with the pathogenesis of GDM. This suggests that aberrant expression of circRNAs in placental villi may be associated with the pathogenesis of GDM.[67] Previous studies have demonstrated that circCHD2 is overexpressed in the placenta of patients with GDM. Additionally, the circCHD2/miR-33b/ULK1 axis may be associated with autophagy in the placenta of patients with GDM.[71] The preceding study examined the impact of diminished circCHD2 expression on HG-induced autophagy and apoptosis in HTR-8/SVneo cells. The results demonstrate that downregulated circCHD2 expression significantly alleviates HG-induced autophagy and apoptosis in HTR-8/SVneo cells and suppresses the expression of autophagy- and apoptosis-related signaling proteins, such as cleaved-caspase3. Moreover, the impact of circCHD2 downregulation on HG-treated HTR-8/SVneo cells was significantly blocked by the autophagy agonist Rapamycin.[66]

The Role of MUC1 in the Pathology of GDM

MUC1, a membrane-bound mucin, is a highly glycosylated protein found in human trophoblasts. Elevated MUC1 protein expression in patients with GDM has been linked to impaired placental glucose uptake and apoptosis.[72] The Wnt/β-catenin pathway has been demonstrated to play a role in trophoblast differentiation and placental development in pregnant women.[73] Aberrant signaling expression of this pathway may also be involved in the pathogenesis of GDM.[74] MUC1 has been demonstrated to stimulate the Wnt/β-catenin pathway and its downstream genes (eg, TCF4, CyclinD1, c-Myc, etc).[75] It is evident that β-catenin, a pivotal element in the Wnt/β-catenin signaling pathway, possesses a distinct binding site for MUC1. Elevated MUC1 interacts with β-catenin to activate the Wnt/β-catenin pathway, which contributes to the expression of its target genes c-Myc and CyclinD1 and induces trophoblast cell dysfunction in the GDM placenta (see Figure 2). Conversely, reduced MUC1 has been shown to promote trophoblast proliferation and migration while inhibiting apoptosis.[72]

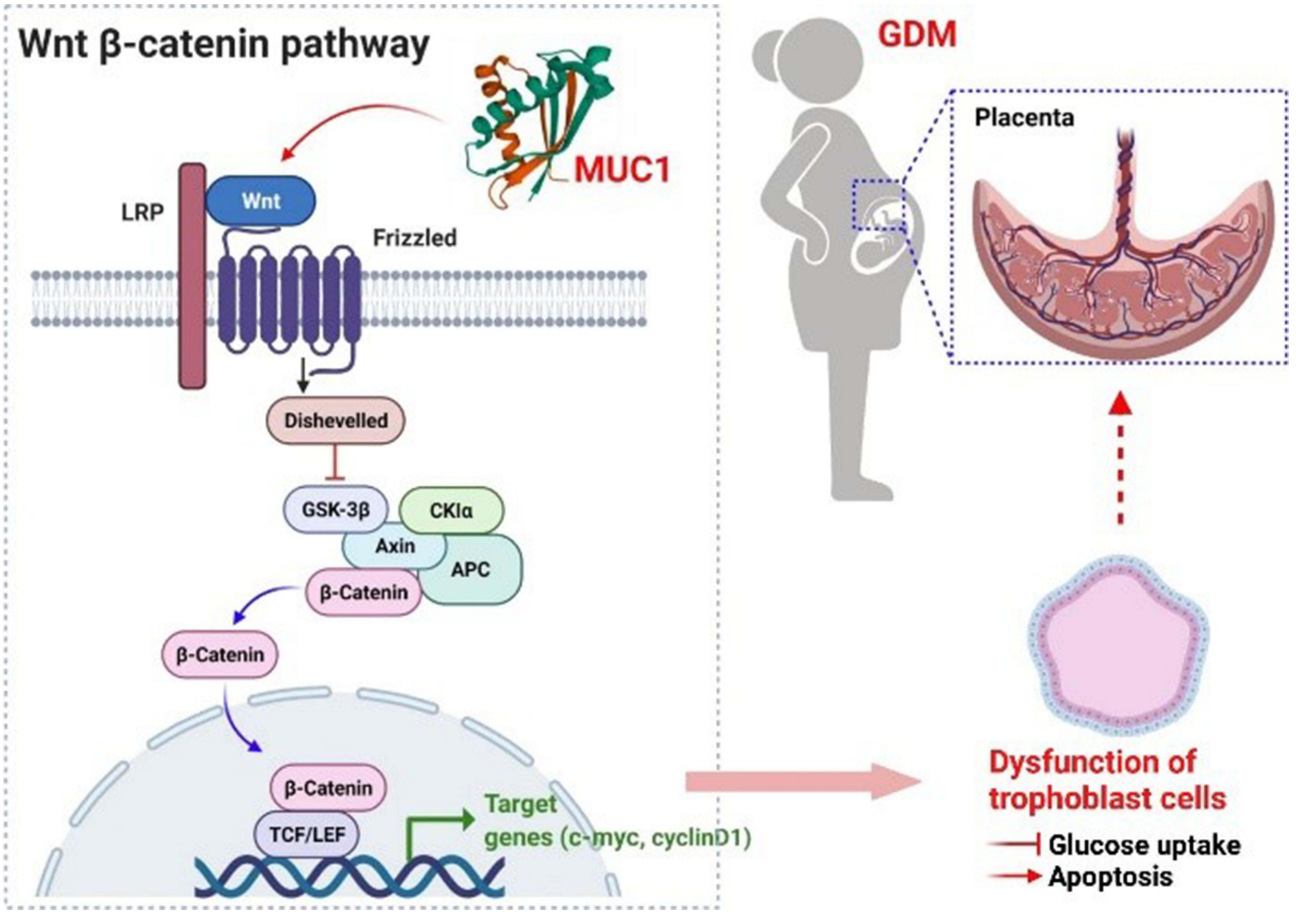

Figure 2 A proposed model that showed the potential mechanisms underlying the role of MUC1 in the pathology of GDM.
Notes: The proposed mechanism by which MUC1 is involved in the pathology of GDM via the Wnt/β-catenin signaling pathway in trophoblast dysfunction. Copyright © 2023. Reproduced from Cui SS, Zhang P, Sun L et al. Mucin1 induced trophoblast dysfunction in gestational diabetes mellitus via Wnt/β-catenin pathway. *Biological Research*. 2023. 56(1):48.[72]

Therapeutic Effects of Galactooligosaccharide on GDM

Galactooligosaccharide (GOS) is essential for consumer as food supplementation. GOS has been demonstrated to impede proteins associated with the apoptosis pathway, thereby suggesting a potential therapeutic effect on GDM by modulating intestinal flora, as well as lipid and glucose metabolism. In experimental studies conducted on rats, the administration of GOS has been observed to reverse the expression of glucose transporter type 4 (GLUT4) in the GDM group.[76] In the metabolic response, PI3K transfers PIP2 into PIP3, which, in turn, activates the AKT by phosphorylation, thus promoting the balance of blood glucose and lipid.[77] Furthermore, the findings of this study demonstrate that the administration of GOS was able to reverse the protein expression ratios of p-PI3K/PI3K, p-Akt/Akt, Bax and Bcl2 in the GDM group.[76] The above results suggest that GOS may regulate glucose metabolism in GDM rats. However, the applicability of the results in human experiments needs to be further investigated.

In conclusion, apoptosis is involved in GDM at multiple levels, which updates our understanding, and the relevant mechanisms we mentioned are shown in Figure 3.

Cellular Pyroptosis

Pyroptosis is a lytic form of programmed cell death.[78] It is defined as cell death that is induced by gasdermin pores in the plasma membrane.[35] This process is characterized by pore formation, membrane rupture, cell swelling, and the release of cellular contents,[79] which ultimately leads to DNA fragmentation, cellular blistering, and the formation of pyroptotic vesicles.[80] The initiating event of cellular pyroptosis is the activation of inflammasomes, which are multiprotein

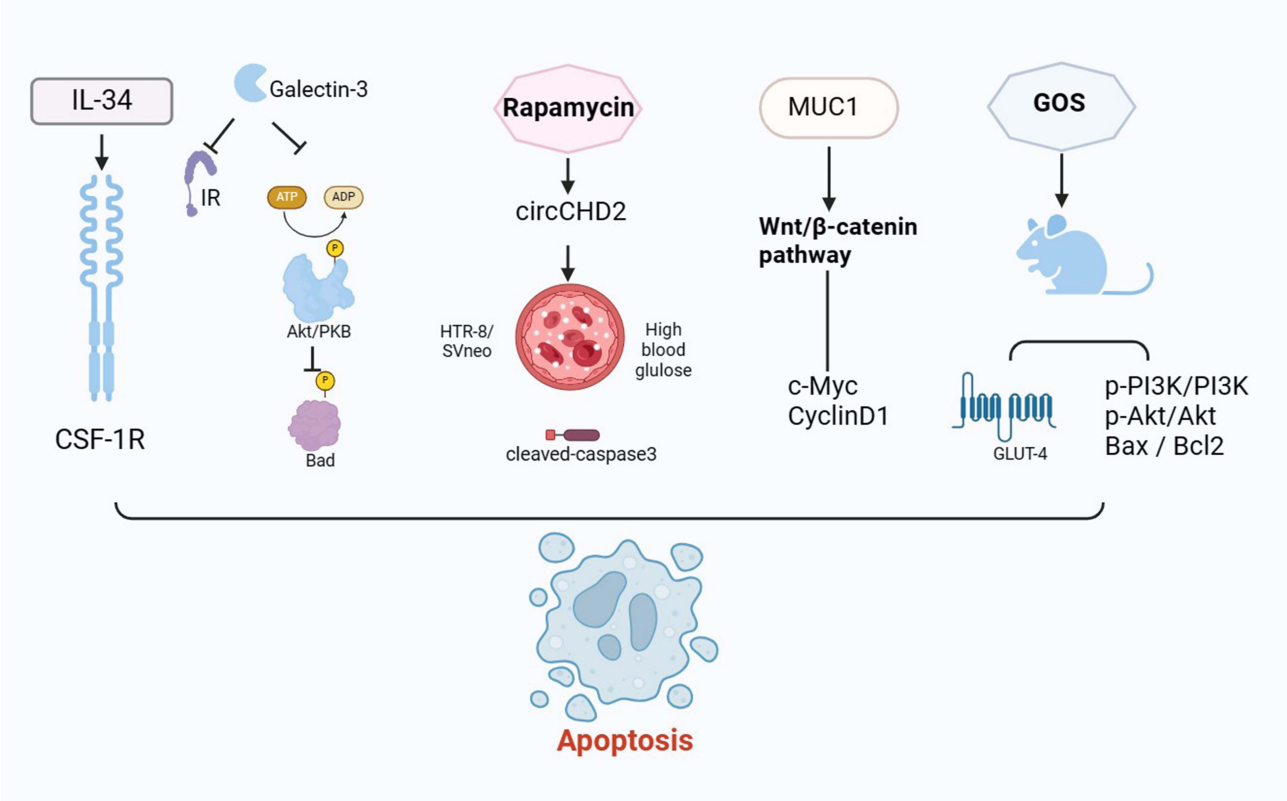

Figure 3 Apoptosis involved in the pathogenesis of GDM.
Notes: Created in BioRender. Li, (J) (2025) https://BioRender.com/xqagtm9. As detailed above, IL-34, Gal-3, MUC1, GOS are shown to antagonize or induce the occurrence of apoptosis at different levels.

complexes that activate caspase-1.[81] The processes that initiate the development of complex pyroptosis include the classical inflammasome pathway (activated by cysteine-1), the non-classical inflammasome pathway (activated by caspase-4, 5 in humans and caspase-11 in mice),[82–84] as well as other pathways that have been the subject of recent investigation (including apoptotic caspases-mediated pathway and granzymes-mediated pathway).[79] The involvement of various cysteine aspartic enzymes has led to the recent definition of cellular pyroptosis as "gasdermin-mediated programmed necrotic cell death". This definition is based on the observation that gasdermin activation and pore formation in the cell membrane are features shared by both.[85] In the atypical pathway, caspase-4/5 (human) and caspase-11 (mouse) are directly activated by their lipopolysaccharide (LPS) ligands.[86] Upon oligomerization of the LPS-cysteine complex, caspase-4/5/11 acts as effector proteins, cleaving full-length gasdermin D (GSDMD) and triggering focal death.[87] Upon activation, caspase-4/5/11 cleaves the junction region of GSDMD to release its N-terminal pore-forming structural domain (GSDMD-NT). Pore-formation and release of cytokines and tissue factor lead to cell lysis, inflammation, coagulation, and tissue damage.[88] The process of cellular pyroptosis and related pathways are depicted in Figure 4. Activation of the inflammasome and release of inflammatory factors trigger IR, and cellular pyroptosis in the placenta as an important pro-inflammatory pathway in the development of GDM deserves further investigation.

Cellular Pyroptosis and GDM – A Novel Target for GDM

Inflammatory Response in GDM to the Involvement of Pyroptosis

Pyroptosis is a highly inflammatory form of cell death.[89] In a mouse model, Carlos et al demonstrated that NLRP3-induced pyroptosis contributes to the onset and progression of type 1 diabetes mellitus (T1DM) (although GDM is mostly T2DM). The study found that non-obese diabetic (NOD) mice showed increased expression of NLRP3 and pro-IL-1β in their pancreatic lymph nodes (PLNs). Furthermore, multiple low doses of streptozotocin (STZ) increased the expression of the sensor protein NLRP3, the adaptor molecule apoptosis associated speck like protein (ASC), and the pro-

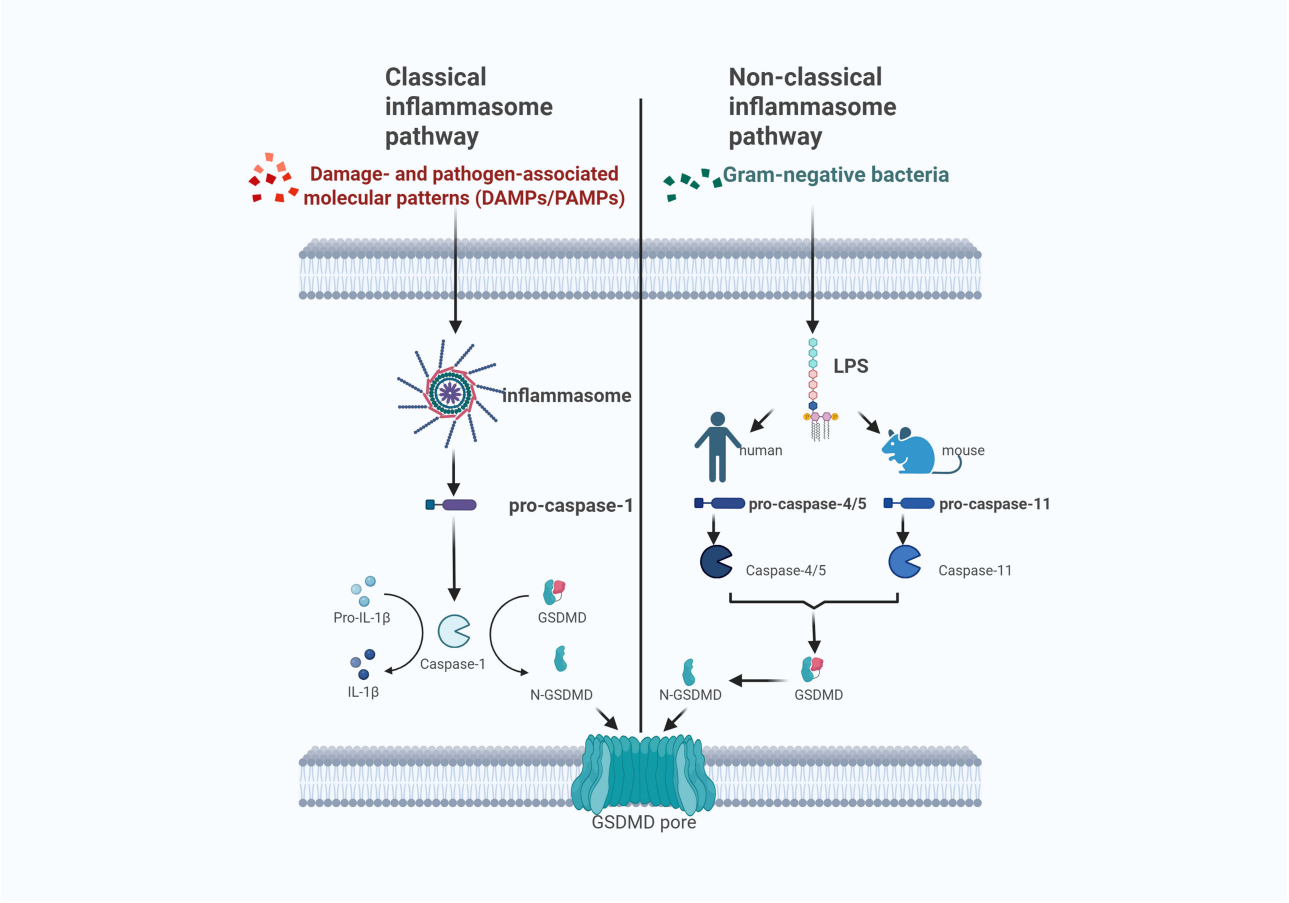

Figure 4 Illustration of pyroptosis pathways.
Notes: Created in BioRender. Li, (J) (2025) https://BioRender.com/c7asaar. This mainly includes canonical and non-canonical models of NLRP3 inflammasome activation. Pyroptosis exhibits unique features including caspase-1-mediated cell membrane perforation, NLRP3 inflammasome promotion, along with subsequent discharge of DAMPs and proinflammatory cytokines.

inflammatory cytokine pro-IL-1β in C57BL/6 mice. Additionally, diabetic mice exhibited an increase in mitochondrial DNA (mtDNA), which induced remarkable IL-1β production and caspase-1 activation by wild-type (WT) macrophages.[90] The question of whether this feature also applies to human GDM patients, based on these results, remains to be investigated further. However, it has fueled attempts to explore alternative therapies in human T1DM using drugs that cause extracellular mtDNA degradation.

Genetic Characteristics

However, it has been demonstrated that GDM is associated with dysfunctions in glucose and lipid metabolism involving multiple genes. In our previously published review,[91] it was mentioned that the TP53-induced glycolysis-regulated phosphatase gene (TIGAR) plays a role in inflammation and oxidative stress in the placenta of patients with GDM through a series of molecular effects.[92,93] In addition, it has been posited that the induction of SPEN paralog and direct homolog C-terminal domain containing 1 (SPOCD1) expression by chorionic mesenchymal stem cells (VMSCs) results in the activation of β-catenin pathways, which subsequently induce cellular death.[94]

Involvement of Sterol Regulatory Element Binding Protein 1

It has been demonstrated that pregnant women with GDM exhibit elevated serum levels of nucleotide-binding domain, leucine-rich repeat, NLRP3, caspase-1, IL-1, and IL-18 in comparison to those with uncomplicated pregnancies. This finding suggests that pyrogenic factors may play a role in the pathogenesis of GDM by promoting chronic inflammation.[95] Sterol regulatory element binding protein 1 (SREBP1) is a transcription factor belonging to the basic

Helix-Loop-Helix leucine zipper family (bHLH-Zip).[96] Previous studies[97–99] have demonstrated that activation of SREBP1 triggers endoplasmic reticulum stress, which subsequently leads to cell death through the activation of NLRP3 inflammatory vesicles and subsequent release of cellular IL-1β, ultimately resulting in cell death. It has been observed that serum SREBP1 expression is positively correlated with Caspase-1, IL-18, and IL-1β, but not with NLRP3.[95] Silent information regulator 1 (SIRT1) is a highly conserved NAD+-dependent deacetylase that plays a pivotal role in numerous biological processes. These processes include regulation of energy metabolism, anti-inflammatory responses, IR, and glucolipid metabolism, as well as numerous other diverse biological processes.[100] SIRT1 was found to be negatively correlated with the expression of SREBP1, IL-1β, and IL-18. However, no correlation was observed between NLRP3 and Caspase-1. In contrast, serum levels of SREBP1 were significantly elevated in patients with GDM, with significantly higher expression of cellular focal NLRP3, Caspase-1, IL-1β, and IL-18.[95] The observed variations in results may be attributable to variations in gestational age or the different sampling periods.

Mechanisms of Metformin Involvement in Pyroptosis in GDM

SIRT1 is an essential regulator of inflammation by altering NF-κB.[101] The applicability of metformin for the treatment of GDM is highly controversial, but metformin treatment has been shown to stimulate AMPK/SIRT1/NF-κB signaling, thereby inducing caspase3/GSDME-mediated cell pyroptosis. Moreover, metformin-induced mitochondrial dysfunction has been observed to promote the AMPK/SIRT1 pathway, leading to pyroptosis. Metformin was found to cleave GSDME to produce more GSDME-N by activating caspase3 in GSDME-expressing cells, suggesting that metformin activates caspase3/GSDME to induce pyroptosis.[102]

The involvement of cellular pyroptosis in the development of GDM (see Figure 5) is summarized below.

Cellular Ferroptosis

Ferroptosis is not a form of cellular suicide, but rather a form of cellular self-injury that ultimately results in death.[103] In conceptual terms, ferroptosis can be regarded as a byproduct of cellular metabolism. Oxygen and iron are essential drivers of metabolism, leading to the production of reactive oxygen species (ROS) as an inevitable byproduct. If a specific class of ROS, phospholipid peroxides (PLOOH), cannot be neutralized efficiently and thus accumulates to disrupt plasma membrane integrity. Furthermore, the process of cellular lipid peroxidation is not restricted in pathological states,[104–107] and a ferroptosis ensues.[108] Iron is an essential element for fetal growth and development. The placenta serves as an intermediary, facilitating the exchange of substances between the mother and the fetus. This enables the fetus to obtain iron from the maternal circulation.[109] As pregnancy progresses, there is an increase in maternal erythrocyte mass and acceleration in placental and fetal growth, resulting in an elevated physiological demand for iron in late pregnancy.[110] In the context of pathology, excessive and protracted oxidative stress has been demonstrated to result in sustained iron death, which in turn engenders pathological outcomes such as shallow trophoblastic infiltration and vascular lumen narrowing.[111]

Unlike other forms of regulated cell death, ferroptosis does not involve the participation of cysteinyl asparaginase, mixed lineage kinase domain-like protein (MLKL), or GSDMD. Instead, its hallmark is the peroxidation of cell membranes,[112] which is characterized by mitochondrial atrophy, increased membrane density, disruption of membrane integrity, and intracellular NADH depletion.[113] Iron-containing cells exhibit distinct cellular morphologies, including reduced density and rupture of the outer mitochondrial membrane, as well as reduced or absent inner mitochondrial cristae.[35] Ferroptosis occurs when free intracellular iron atoms react with hydrogen peroxide (H2O2), which promotes the over-oxidation of polyunsaturated fatty acids (PUFA). This event leads to further oxidation of lipids, which produces toxic byproducts.[103] The synthesis of PUFA-PL, iron metabolism, and mitochondrial metabolism can cause lipid peroxidation-induced ferroptosis. Conversely, the GPX4-GSH system, FSP1-CoQH system, and DHODH-CoQH2 system can inhibit lipid formation and thus ferroptosis.[114] In addition to these factors, the apoptosis-inducing factor mitochondrial 2 (AIFM2), which has been appropriately renamed ferroptosis inhibitory protein 1 (FSP1), has been demonstrated to exert a pivotal glutathione-independent influence on the inhibition of ferroptosis.[115,116] FSP1 is particularly responsible for preserving coenzyme Q10 (CoQ) in a reduced state, thereby trapping lipid free radicals at

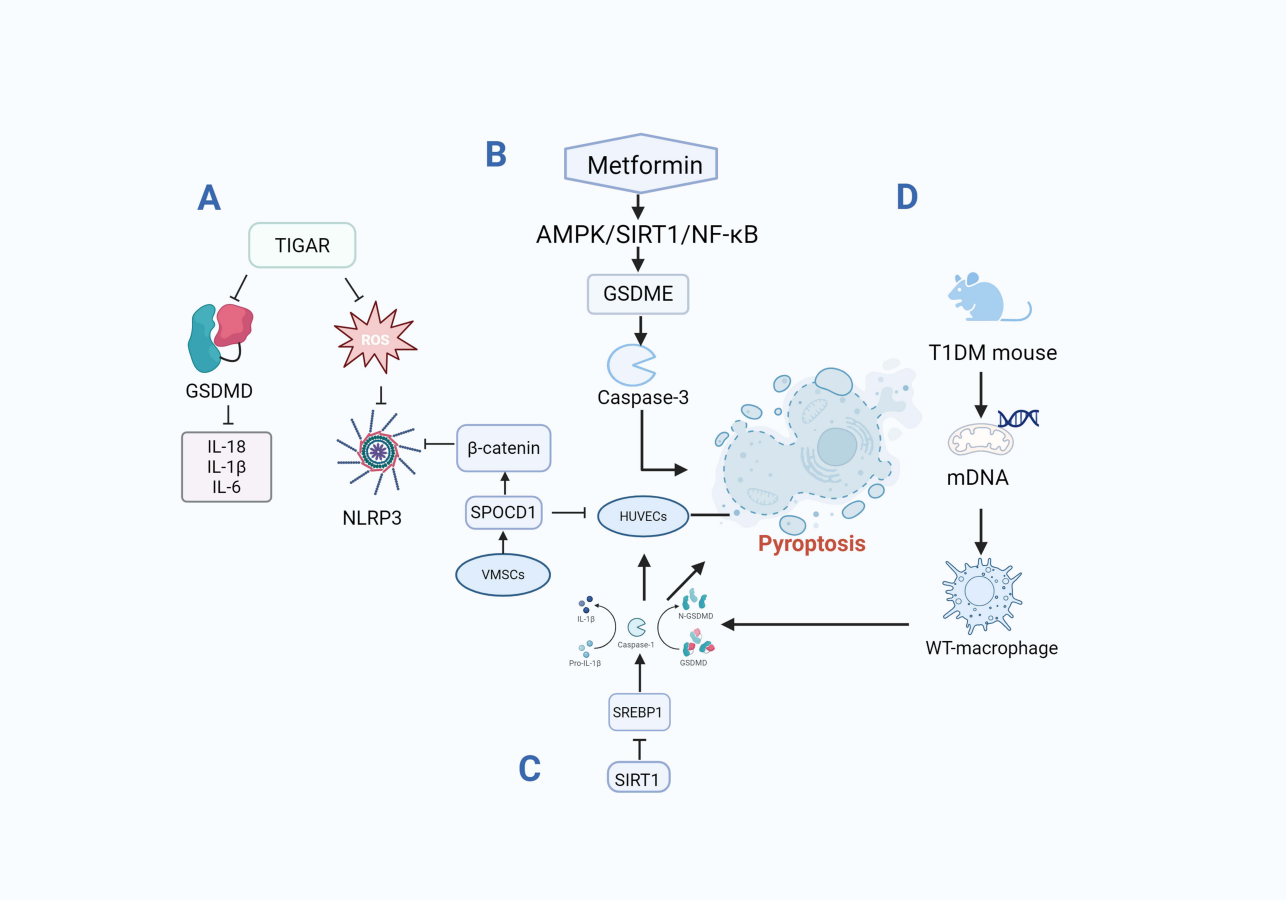

Figure 5 Cellular pyroptosis in the development of GDM.
Notes: Created in BioRender. Li, (J) (2025) https://BioRender.com/ztjvrvl. The activation of inflammatory factors plays a key role in pyroptosis: TIGAR inhibits the activation of GSDMD, inhibits ROS production, and then inhibits the activation of NLRP3; Metformin promotes the activation of NLRP3 by promoting the activation of GSDME; SIRT-1 inhibits pyroptosis caused by caspase-1; In the T1DM model of mice, mtDNA was increased in diabetic mice, which induced large amounts of IL-1β and caspase-1 activation in WT macrophages.

the plasma membrane and preventing lipid peroxidation. The signaling pathways associated with ferroptosis are illustrated in Figure 6.

Ferroptosis and GDM, a Revolutionary Discovery

Iron Has Important Roles During Pregnancy

The average daily iron requirement during pregnancy increases to approximately 1000–1200 mg, in order to meet the needs of the mother and the fetus for erythropoiesis, growth, and development.[110] In both developed and developing populations, the body's need for iron has increased dramatically, rendering pregnancy a life stage that is particularly vulnerable to iron deficiency.[118] Pregnant women frequently supplement their diets with iron to treat any insidious anemia, assuming that if the anemia is not present, there will be no negative consequences. However, in women who are already iron-enriched, this can lead to iron overload and an increased risk of certain pregnancy complications, including GDM.[118] However, there is a lack of consensus in the literature regarding the timing of iron supplementation during pregnancy and its potential to increase the risk of GDM. Recent high-quality systematic evaluations and meta-analyses have demonstrated a significant positive association between iron supplementation during pregnancy and the risk of GDM.[118] At the same time, this finding provides a foundation for future studies to further explore the optimal timing and dosage of iron supplementation during pregnancy.

The accumulation of iron in cells results in the formation of a novel type of iron-dependent lipid peroxidation-mediated cell death, which has been designated as "ferroptosis". Ferroptosis plays a pivotal role in the pathogenesis of

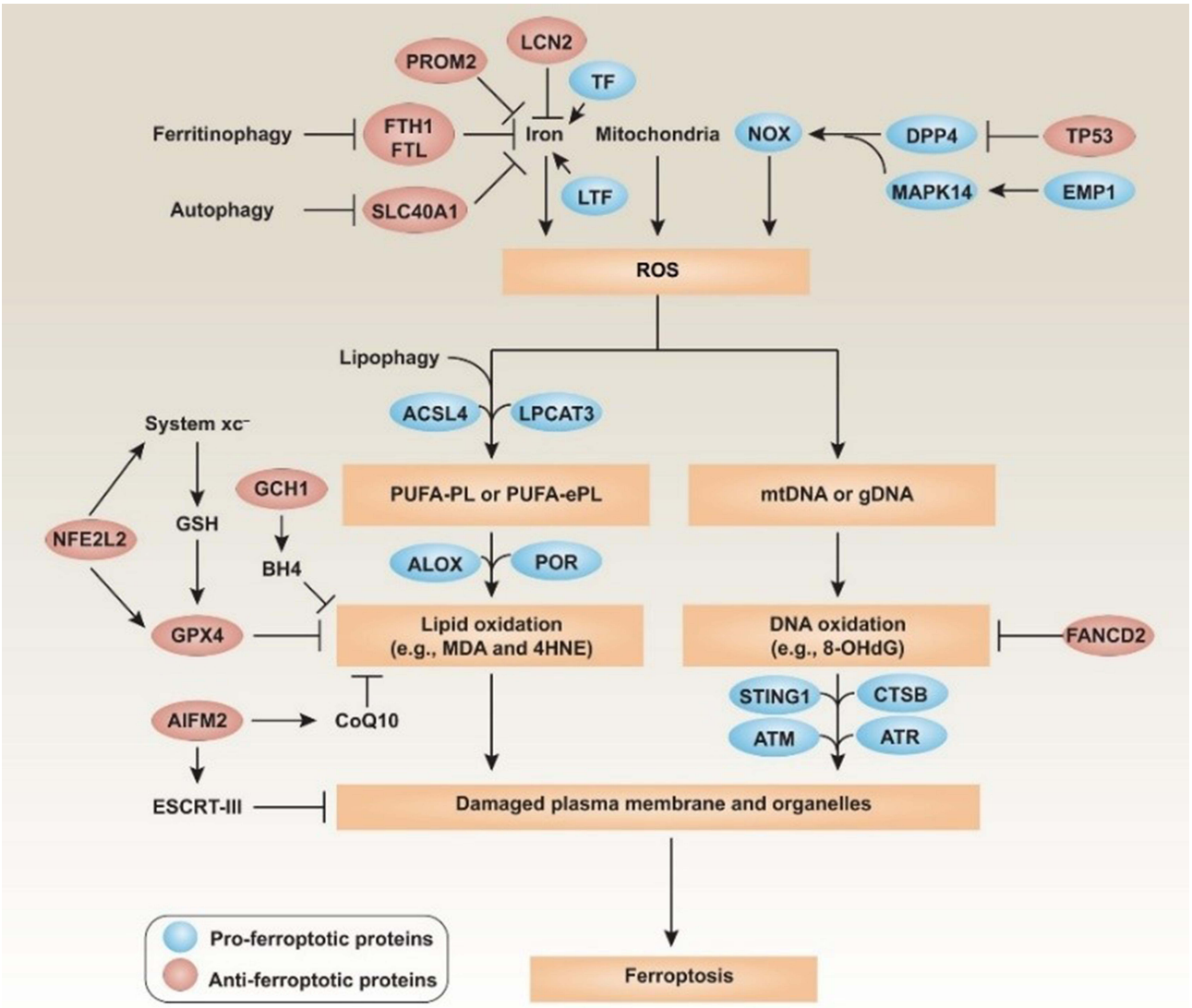

Figure 6 Signaling pathways in ferroptosis.[117]
Notes: Copyright © 2021. John Wiley and Sons. Reproduced from Liu J, Kang R, Tang D. Signaling pathways and defense mechanisms of ferroptosis. *FEBS* J. 2022;289(22):7038–7050. © 2021 Federation of European Biochemical Societies. Ferroptosis is an oxidative form of cell death that can be regulated at multiple levels. Antioxidants, including glutathione, Coenzyme Q10, and tetrahydrobiopterin, can limit lipid peroxidation through various upstream and downstream pathways. Oxidative DNA damage also contributes to ferroptosis. Inhibitors of this process include FANCD2. Erythroid 2-like 2-dependent gene transcription and the endosomal sorting complex required for transport-III-dependent membrane repair can prevent ferroptosis. Conversely, selective autophagy can promote this process by degrading ferritin or lipid droplets.

numerous diseases, including acute kidney injury, ischemia-reperfusion injury, Parkinson's disease, and diabetes mellitus.[119–121] It is noteworthy that pancreatic β-cells exhibit a relatively high iron content and depend on mitochondrial respiration for insulin secretion. Oxidative stress has long been a topic of considerable research interest related to pancreatic β-cell dysfunction.[122] Pancreatic β-cells, which are responsible for the production and secretion of insulin, are highly dependent on iron for both processes. Due to their low antioxidant capacity, β-cells appear to be particularly susceptible to damage from ROS and have a specific sensitivity to iron overload This characteristic contributes to the over-accumulation of iron under hyperglycemic conditions.[123] Iron overload, particularly in women with elevated iron levels, can exacerbate reactive oxygen species accumulation and oxidative damage, ultimately leading to apoptosis of pancreatic β-cells and resulting in decreased insulin secretion.[124] Recently, there is growing evidence to suggest that ferroptosis may play a role in the development of GDM and that ferroptosis-related genes may influence the molecular mechanisms underlying GDM.[125]

Connection Role of SLC7A11/GPX4

From a physiological standpoint, ferroptosis is tightly regulated by a glutathione-mediated detoxification pathway driven by the SLC7A11/GPX4 axis.[126] Furthermore, ferroptosis plays a role in the pathogenesis of GDM, as it is promoted by SIRT3-regulated activation of the AMPK-mTOR axis and inhibition of glutathione peroxidase 4 (GPX4) in GDM.[127] These findings have been identified as significant factors in the identification of key targets that regulate ferroptosis. Zheng et al also demonstrated that correcting the imbalance of fatty acid oxidation/peroxidation-induced ferroptosis ameliorated placental injury in GDM.[128] A recent bioinformatics study identified CCNB2 and CDK1 as potential biomarkers for ferroptosis in GDM. Both of these proteins have been shown to be effective indicators for the diagnosis of GDM.[129]

CircHIPK3-An Efficient Molecular Target for the Treatment of GDM

The findings of the experimental studies provide a broad direction for the treatment of GDM. An experimental study by Jiang et al[130] demonstrated that circHIPK3 knockdown was found to accelerate cell viability and reduce apoptosis, ROS, and iron levels, suggesting a role in ferroptosis promotion. The circHIPK3/miR-1278/DNA methyltransferase 1 (DNMT1) axis regulates AMPK-mTOR ferroptosis following GPX4 methylation in HG-cultured HTR-8/SVneo cells. Consequently, circHIPK3 may be a highly efficacious molecular therapeutic target for the treatment of GDM.

Adiponectin Enhanced IR

Adiponectin (ADPN) is a protein produced in large quantities by adipose tissue that enhances insulin sensitivity, exerts anti-inflammatory effects, and reduces plasma glucose levels.[131] The mechanism of this has been demonstrated in cellular experiments. ADPN inhibits the expression of carnitine acyl transferase I (CPT-1) and GLUT4 in placental tissues of GDM mice, a process that can be achieved by regulating CPT-1. ADPN corrects fatty acid oxidation/peroxidation by restoring CPT-1 activity to correct ferroptosis induced by fatty acid oxidation/peroxide imbalance, thereby ameliorating placental injury in GDM.[128]

The relationship between iron death and GDM is summarized as depicted in Figure 7.

Comparative Analysis of Cell Death Types in GDM

In multicellular organisms, cells are continuously generated during development, tissue homeostasis, and host defense. Therefore, the cell death pathway is essential for the removal of senescent and damaged cells in order to maintain healthy homeostasis.[81] Researches have demonstrated that the involvement of three cell death types is also closely associated with the development of GDM, at the genetic, metabolic, cellular, and molecular levels. For instance, hyperglycemia has been demonstrated to disrupt the apoptotic process in placental trophoblast cells; the pro-inflammatory effects of cellular pyroptosis have been implicated in IR; and pancreatic β-cells, which possess a low antioxidant capacity and are vulnerable to damage by ROS, exhibit heightened sensitivity to iron overload. The multifaceted role of cell death in the development of GDM is exemplified by the following: For instance, β-catenin itself has been shown to inhibit NLRP3 inflammatory vesicle-induced macrophage pyroptosis, and it was found that the over-expression of SPOCD1 activated the β-catenin pathway, which inhibited high levels of apoptosis and pyroptosis in glucose-induced HUVECs. Furthermore, the reduction of MUC1 has been demonstrated to reduce the activation of the Wnt/β-catenin pathway, which could promote trophoblastic cell death. The activation of this pathway has been shown to promote the proliferation and migration of trophoblast cells, while concurrently inhibiting apoptosis. It is important to note that not all patterns of cell death modes are singularly involved in the development of GDM. By synthesizing the various factors implicated in cell death, the underlying pathophysiology of GDM becomes more comprehensible, thus facilitating the identification of future therapeutic interventions.

Summary and Perspective

The management of GDM is a matter that necessitates meticulous deliberation, given its potential repercussions for the fetus in uterus. The present study proposes a novel association between cell death and GDM, and identifies recently explored therapeutic avenues for further research.

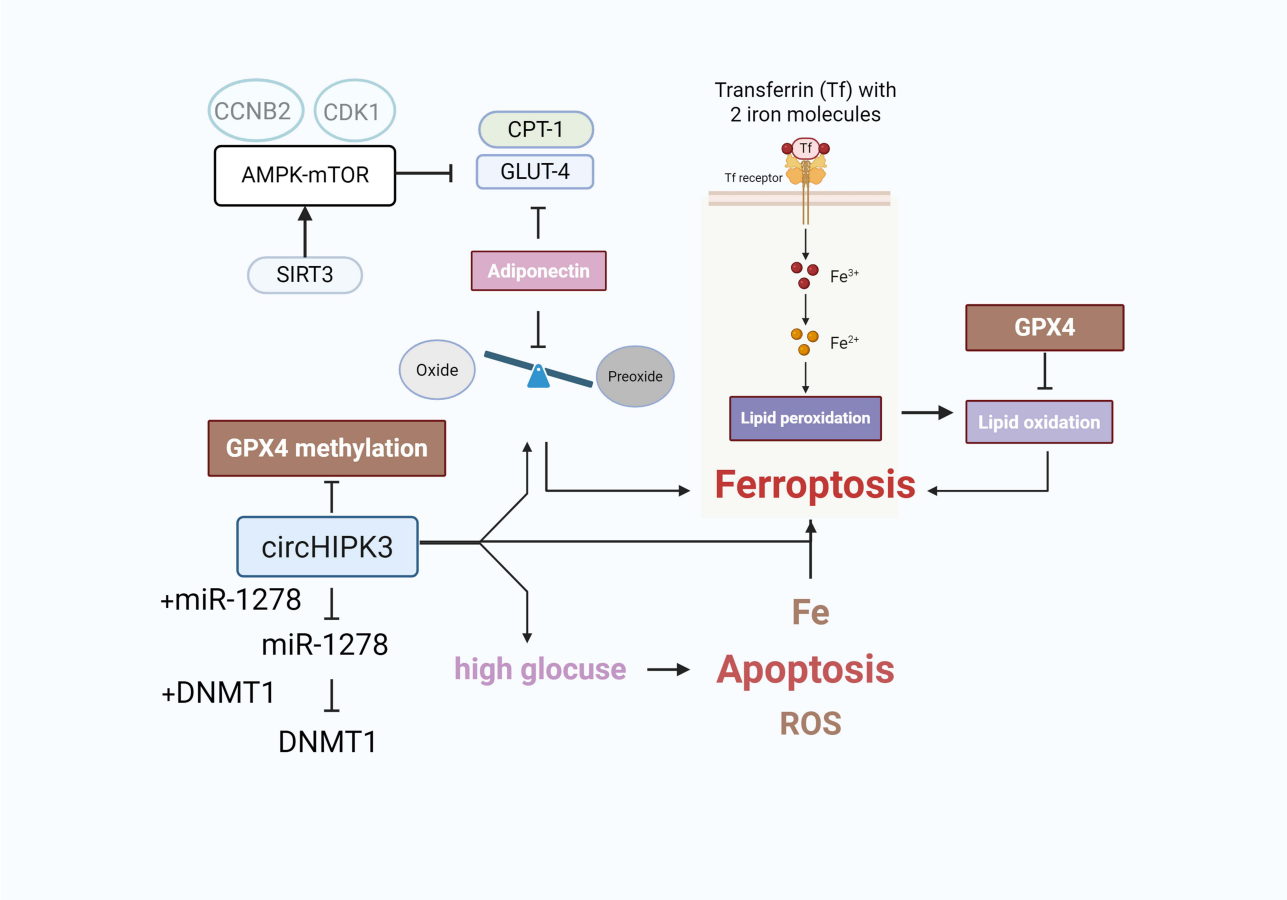

Figure 7 Ferroptosis and GDM.
Notes: Created in BioRender. Li, (J) (2025) https://BioRender.com/pm3ef0w. circHIPK3 may promote ferroptosis by regulating GPX4 DNA methylation through the miR-1278/DNMT1 axis in HTR-8/SVneo cells cultured in high glucose. The circHIPK3/miR-1278/DNMT1 axis controls ferroptosis by regulating GPX4 methylation in these cells.[130]

(a) The targeting of apoptosis: The autophagy agonist rapamycin significantly blocked the down-regulation of circCHD2 in HG cells and improved the expression of apoptotic proteins. And, Glucose metabolism in GDM rats was improved by GOS administration.

(b) For cellular pyroptosis, due to the characteristic increase in mtDNA in diabetic mice, WT macrophages were induced to produce significant amounts of IL-1β and activate Caspase-1. This has led to the exploration of alternative therapies for human T1DM by using drugs that can lead to the degradation of extracellular mtDNA. Metformin, a widely used pharmaceutical agent that enhances insulin sensitivity, is employed in non-pregnant women. However, concerns regarding its safety during pregnancy have led to inconsistent clinical standards for its use internationally. In combination with previous studies, we found that metformin activates caspase3/GSDME and induces apoptosis, which adds evidence for its use in the clinic. Furthermore, HG has been observed to induce cellular pyroptosis and the subsequent release of inflammatory factors, such as IL-1β and IL-18. This process has been shown to result in both local and systemic inflammation, as well as the triggering of IR. Therefore, effective inhibition of maternal-fetal cellular pyroptosis and its resultant release of inflammasome and inflammatory factors is expected to be a new target for the treatment of GDM.

(c) With regard to cellular ferroptosis, pregnant women have a special need for iron, and we can "control" iron death clinically by detecting a decrease in serum iron levels. In addition, genetic studies have shown that circHIPK3 knock-down improves cell viability and reduces cellular ROS and iron content, and that ADPN corrects fatty acid oxidation/peroxidation by restoring the activity of CPT-1, thereby ameliorating placental damage in GDM.

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The process of cell death has been demonstrated to be a highly intricate phenomenon, with a multitude of central players capable of disrupting the delicate equilibrium of the cellular environment, from the initiation of life to the cessation of life and from pro-inflammatory to anti-inflammatory signaling. Due to space limitations, only three common forms of cell death are analyzed in this review. It is hoped that in the future, clinical studies on the association between cell death and GDM will benefit more patients. Although not exhaustive, these findings collectively suggest that the three forms of cell death are intricately linked to the development of GDM. A more profound comprehension of the fundamental mechanisms has enabled the identification of prospective targets for the inhibition of cell death and the suppression of GDM development. This, in turn, will result in a marked enhancement in pregnancy outcomes. For instance, by modulating maternal and fetal immune tolerance to inhibit high glucose-induced apoptosis in trophoblast cells, developing drugs that lead to extracellular mtDNA degradation to inhibit the activation of inflammatory vesicles for the treatment of hyperglycemia in humans, and modulating of iron oxidation to ameliorate placental damage in GDM. Cell death is a fundamental process for the survival and adaptation of multicellular organisms. However, it must be tightly regulated to prevent disease. A comprehensive understanding of cell death signaling mechanisms reveals opportunities to combat aberrant cell death in disease.[132] In the context of pregnancy, the investigation of cellular molecular processes is particularly beneficial for the advancement of human development. It is anticipated that further high-quality and large-scale studies will be conducted in this direction.

Abbreviations

GDM, gestational diabetes mellitus, IDF, The International Diabetes Federation, IR, insulin resistance, T2DM, type 2 diabetes mellitus, TNF-α, tumor necrosis factor-α, IL, interleukin, RF, The Random Forest Model, SVM, Support Vector Machine Model, GLM, Generalized Linear Model, VECs, Vascular endothelial cells, ET-1, endothelin-1, FMD, flow mediated dilation, PtdSer, phosphatidylserine, DAMPs, damage-associated molecular patterns, BCL-2, B-cell lymphoma 2, TNF, tumor necrosis factor, TNFR1, tumor necrosis factor receptor 1, TLR, toll-like receptors, ApoEV, apoptotic extracellular vesicles, PS, phosphatidylserine, PE, preeclampsia, FGR, fetal growth restriction, HOMA-IR, homeostatic model assessment for insulin resistance, CSF-1R, colony-stimulating factor 1 receptor, Gal-3, galactose lectin-3, PDK1, phosphatidylinositol-dependent protein kinase 1, circRNA, Circular RNA, GOS, galactooligosaccharide, GLUT4, glucose transporter type 4, LPS, lipopolysaccharide, GSDMD, gasdermin D, GSDMD-NT, N-terminal pore-forming structural domain, T1DM, type 1 diabetes mellitus, NOD, non-obese diabetic, PLNs, pancreatic lymph nodes, STZ, streptozotocin, ASC, apoptosis associated speck like protein, mtDNA, mitochondrial DNA, WT, wild-type, TIGAR, TP53-induced glycolysis-regulated phosphatase gene, SPOCD1, SPEN paralog and direct homolog C-terminal domain containing 1, VMSCs, mesenchymal stem cells, SREBP1, sterol regulatory element binding protein 1, bHLH-Zip, basic Helix-Loop-Helix leucine zipper family, SIRT1, silent information regulator 1, ROS, reactive oxygen species, PLOOH, phospholipid peroxides, MLKL, mixed lineage kinase domain-like protein, H2O2, hydrogen peroxide, PUFA, polyunsaturated fatty acids, AIFM2, apoptosis-inducing factor mitochondrial 2, FSP1, ferroptosis inhibitory protein 1, CoQ, coenzyme Q10, GPX4, glutathione peroxidase 4, ADPN, adiponectin, DNMT1, DNA methyltransferase 1, CPT-1, carnitine acyl transferase I.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the paper has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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