Programmed cell death in metabolic syndrome: From molecular mechanisms to therapeutic strategies (Review)

JIALIN ZHONG[1,2*], MAOFU ZHANG[1,2*], YAFANG ZHENG[1,2], CUICUI GONG[1,2], YASHENG DENG[1,2], LISHA SUN[1,2], DONGQI ZHOU[1,2], QIAN ZHOU[1,2] and QIU CHEN[1]

[1]Department of Endocrinology, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan 610072, P.R. China; [2]School of Clinical Medicine, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan 610075, P.R. China

Received May 25, 2026; Accepted August 19, 2026

DOI: 10.3892/ijmm.2026.5977

Abstract. Metabolic syndrome (MetS) is a clinical syndrome primarily characterized by insulin resistance, integrating central obesity, hyperglycemia, hypertension and dyslipidemia. It is associated with increased risks of type 2 diabetes mellitus, non-alcoholic fatty liver disease and atherosclerosis. Due to its high prevalence, complex pathogenesis and lack of effective treatments, MetS has become a notable global health issue. Current therapeutic approaches mainly emphasize weight reduction through caloric restriction and increased physical activity, or pharmacological interventions to improve lipid profiles, blood pressure and blood glucose; however, their efficacy remains suboptimal. Growing evidence indicates that programmed cell death (PCD), as a key driver of inflammation, serves a crucial role in the development and progression of MetS. The present review provides a comprehensive overview of recent advances in the understanding of how established and emerging forms of PCD contribute to MetS pathogenesis, including apoptosis, pyroptosis, autophagy, ferroptosis, necroptosis, PANoptosis and disulfidptosis. Particular emphasis is placed on their molecular mechanisms, tissue-specific functions, regulatory crosstalk and therapeutic potential. Additionally, the present review discusses novel regulatory approaches and potential therapeutic strategies based on PCD network intervention, offering theoretical foundations and directions for developing innovative therapies to prevent and treat MetS and its complications.

Correspondence to: Professor Qiu Chen, Department of Endocrinology, Hospital of Chengdu University of Traditional Chinese Medicine, 39 Shierqiao Road, Jinniu, Chengdu, Sichuan 610072, P.R. China
E-mail: chenqiu1005@cdutcm.edu.cn

*Contributed equally

Abbreviations: MetS, metabolic syndrome; IR, insulin resistance; T2DM, type 2 diabetes mellitus; PCD, programmed cell death; NAFLD, non-alcoholic fatty liver disease; RIPK, receptor-interacting protein kinase; NASH, non-alcoholic steatohepatitis; IRS, insulin receptor substrates; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; MAPK, mitogen-activated protein kinase; FFA, free fatty acid; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; VAT, visceral adipose tissue; LPS, lipopolysaccharides; SCFAs, short-chain fatty acids; TRADD, TNFR-associated death domain; FADD, Fas-associated death domain; Bcl-2, B-cell lymphoma-2; Bax, Bcl-2-associated X protein; ERS, endoplasmic reticulum stress; UPR, unfolded protein response; ROS, reactive oxygen species; VSMCs, vascular smooth muscle cells; VECs, vascular endothelial cells; ox-LDL, oxidized low-density lipoprotein; cIAP, cellular inhibitor of apoptosis protein; DAMPs, damage-associated molecular patterns; IAPP, islet amyloid polypeptide; LDL, low-density lipoprotein; CCs, cholesterol crystals; PAMPs, pathogen-associated molecular patterns; GSDMD, gasdermin D; AGEs, advanced glycation end products; AMPK, adenosine monophosphate-activated protein kinase; mTOR, mammalian target of rapamycin; IGF, insulin-like growth factor; Atg, autophagy-related gene; LIP, labile iron pool; PUFAs, polyunsaturated fatty acids; LOXs, lipoxygenases; GPX4, glutathione peroxidase 4; GSH, glutathione; TG, triglyceride; MAFLD, metabolic-associated fatty liver disease

Key words: metabolic syndrome, programmed cell death, inflammasome, insulin resistance, molecular mechanisms, therapeutic targets

Contents

1. Introduction

Metabolic syndrome (MetS) is a complex cluster of metabolic disorders primarily comprising central obesity, insulin resistance (IR), hypertension, hyperglycemia and dyslipidemia. These factors markedly increase the risk of severe

complications, including type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD) and atherosclerotic cardiovascular disease (1). Currently, the global prevalence of MetS is rising sharply. According to the 2011-2018 National Health and Nutrition Examination Survey (2), ~39.8% of U.S. adults met the criteria for MetS, with prevalence reaching up to 56.4% among adults aged 60 years and older. In China, the estimated prevalence of MetS has reached 24.2% and increases with age (3). Notably, global mortalities attributable to MetS continue to rise, posing a major public health challenge (4). Research indicates that MetS is closely linked to multiple factors, including genetic predisposition, lifestyle and environmental influences, which collectively contribute to IR and chronic low-grade inflammation, ultimately progressing to MetS (5). However, current treatments for MetS remain primarily focused on lifestyle modifications, including a balanced diet, increased physical activity, weight management and symptomatic control of blood pressure and blood glucose. A comprehensive, systematic treatment protocol has not yet been established. Therefore, an improved understanding of the underlying pathophysiological mechanisms of MetS is crucial for developing effective prevention and treatment strategies.

In recent years, the pathogenic role of programmed cell death (PCD) in MetS has attracted considerable attention (6). PCD refers to a highly regulated, genetically controlled process of cell self-elimination, including multiple forms such as apoptosis, necroptosis, pyroptosis, autophagy and ferroptosis. It serves a crucial role in various biological processes, including cell renewal, development, tissue homeostasis and immunity (7). Historically, apoptosis was considered the primary mode of cell death in MetS, involved in processes such as pancreatic β-cell depletion and atherosclerotic plaque formation (8). Recently, other PCD pathways with strong pro-inflammatory characteristics have been identified. Pyroptosis, a lytic cell death mediated by inflammasomes, induces metabolic stress and systemic inflammation by releasing large amounts of pro-inflammatory factors (9). Necroptosis is typically triggered by metabolic stress, with receptor-interacting protein kinases [receptor-interacting serine/threonine-protein kinase (RIPK) 1 and RIPK3] recognized as key mediators in fatty liver disease and IR development. Ferroptosis, characterized by iron-dependent lipid peroxidation, contributes notably to hepatocyte loss and endothelial dysfunction in non-alcoholic steatohepatitis (NASH). Autophagy typically exerts protective cellular quality-control functions in insulin-sensitive tissues, but its dysfunction markedly accelerates metabolic deterioration. Similarly, novel inflammatory death pathways such as PANoptosis and disulfidptosis have been increasingly identified in MetS-associated organ damage (10). Although current research has preliminarily elucidated individual roles of PCD pathways in MetS, systematic discussions on their core interactive mechanisms and therapeutic targeting remain inadequate. Therefore, the present review aimed to comprehensively discuss the mechanisms of apoptosis, necroptosis, pyroptosis, autophagy, ferroptosis, PANoptosis and disulfidptosis in MetS. Furthermore, it explores therapeutic strategies targeting PCD to provide theoretical foundations and directions for developing novel interventions against MetS and its complications.

2. Methods

Literature search strategy. The present review followed the reporting principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (11). A comprehensive literature search was performed using three electronic databases: PubMed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://www.webofscience.com/), ScienceDirect (https://www.sciencedirect.com/) and Google Scholar (https://scholar.google.com/). The search period covered from database inception to December 2025. A search strategy combining subject headings and free-text terms was adopted. The main keywords included 'metabolic syndrome', 'obesity', 'insulin resistance', 'type 2 diabetes mellitus', 'metabolic dysfunction-associated steatotic liver disease', 'atherosclerosis', 'programmed cell death', 'apoptosis', 'pyroptosis', 'autophagy', 'ferroptosis', 'necroptosis', 'PANoptosis', 'disulfidptosis' and 'therapeutic strategies'. Duplicate records were removed before subsequent screening. Two independent reviewers screened the retrieved records and assessed the eligibility of full-text articles according to predefined criteria. The PRISMA flow diagram of the literature retrieval process is presented in Fig. 1.

Inclusion criteria. Studies were included according to the following criteria: i) Studies investigating the involvement of PCD pathways in metabolic syndrome or its related metabolic disorders, including obesity, IR, T2DM, metabolic dysfunction-associated steatotic liver disease (MASLD), cardiovascular complications and related metabolic abnormalities; ii) studies focusing on classical or emerging PCD pathways, including apoptosis, pyroptosis, autophagy, ferroptosis, necroptosis, PANoptosis and disulfidptosis; iii) clinical studies, animal models and *in vitro* studies exploring the molecular mechanisms, pathological roles, biomarkers or therapeutic potential of PCD in metabolic disorders; iv) studies evaluating pharmacological agents, natural compounds, lifestyle interventions or molecular targets that modulate PCD pathways for metabolic disease treatment; v) full-text articles published in English.

Exclusion criteria. The following types of publications were excluded: i) Reviews, meta-analyses, editorials, letters, conference abstracts and other secondary literature; ii) duplicate publications or studies with insufficient experimental information; iii) studies unrelated to MetS, metabolic disorders or PCD mechanisms; iv) studies lacking detailed information regarding molecular mechanisms, pathological effects, therapeutic interventions or clinical relevance; v) articles without available full text or published in languages other than English.

Data extraction and literature selection. After duplicate removal, two-stage screening was performed based on titles/abstracts and full-text assessment. Eligible studies were systematically reviewed, and relevant information was extracted, including publication characteristics, study model (clinical population, animal model or cellular model), metabolic disease phenotype, PCD pathway involved, molecular mechanisms, regulatory targets and therapeutic interventions. The included studies were categorized according to different PCD modalities and their roles in MetS-associated

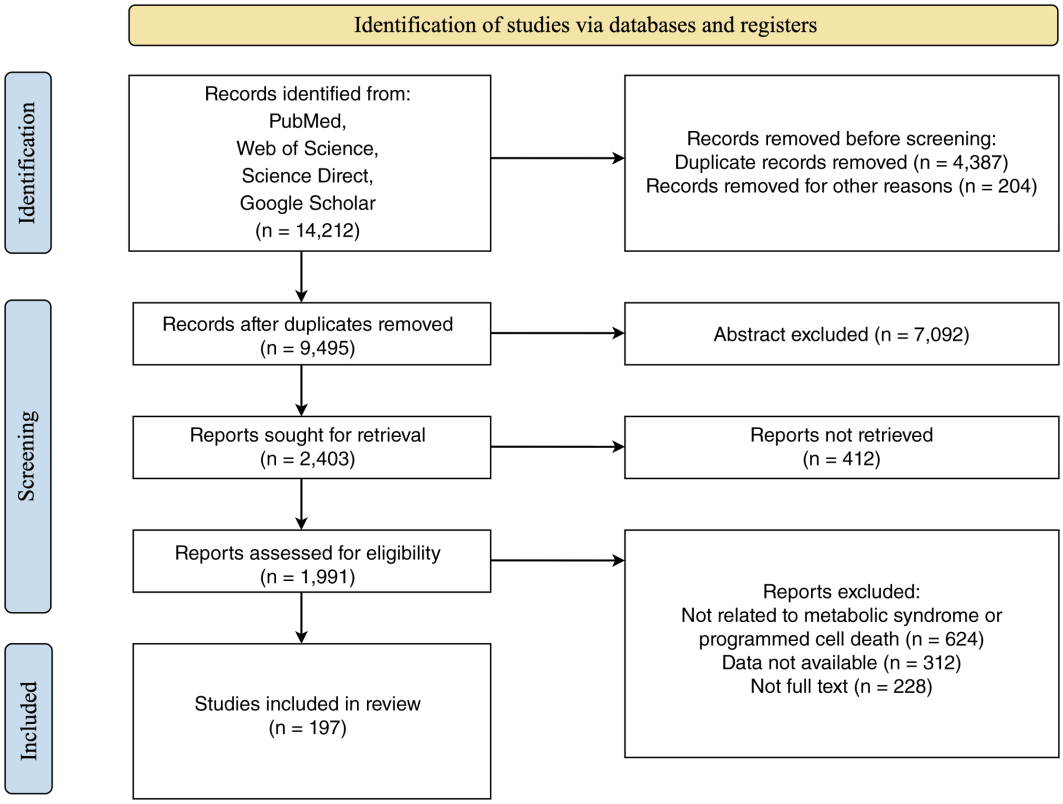

Figure 1. Flow diagram of the literature search and study selection process. The flow diagram illustrates the process of literature identification, screening, eligibility assessment and inclusion of studies according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A total of 14,212 records were initially identified from PubMed, Web of Science, ScienceDirect and Google Scholar. After removal of duplicates and irrelevant records, the remaining articles were screened based on titles, abstracts and full texts. Studies were excluded according to predefined criteria, including lack of relevance to metabolic syndrome or programmed cell death, unavailable data and absence of full-text access. Finally, 197 studies were included in the present review. The figure was created using Figdraw (www.figdraw.com).

pathological processes. Particular attention was given to the molecular interactions among different cell death pathways, their contribution to metabolic inflammation, mitochondrial dysfunction, oxidative stress and tissue injury, as well as their potential therapeutic implications.

Evidence quality assessment and grading. To evaluate the strength and translational relevance of evidence supporting the involvement of each PCD pathway in MetS, included studies were assessed according to predefined criteria, including study design, methodological rigor, mechanistic validation, reproducibility and relevance to human metabolic diseases. Studies were categorized according to a modified evidence hierarchy adapted for preclinical and clinical research. Level A (strong evidence): Findings supported by human clinical studies, including prospective cohort studies, large-scale case-control studies or clinical investigations with mechanistic validation, together with consistent evidence from experimental models. Level B (moderate evidence): Findings derived from *ex vivo* human tissue studies (such as adipose tissue, liver biopsies or pancreatic islets) with mechanistic analyses, or from well-designed animal studies (including genetic knockout/knock-in models) showing reproducible effects. Level C (preliminary evidence): Findings mainly obtained from cellular models or single animal studies without independent replication, particularly studies relying primarily on pharmacological intervention without genetic validation. Level D (emerging evidence): Findings from recently identified PCD pathways (suhch as PANoptosis and disulfidptosis) with limited direct evidence in MetS, mainly supported by metabolic stress-related models or extrapolation from other disease contexts.

3. Pathophysiological mechanisms of MetS

MetS represents a self-sustaining cycle of central obesity and IR, triggering downstream consequences such as chronic low-grade inflammation, lipotoxicity and oxidative stress. These factors collectively establish the foundation for developing cardiovascular disease and T2DM (Fig. 2) (4). During the compensatory stage, pancreatic β-cells secrete insulin in excess to maintain glucose homeostasis, resulting in hyperinsulinemia (12). Defective signaling downstream of insulin receptors impairs the tyrosine phosphorylation of insulin receptor substrates (IRS), thereby weakening the essential phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway responsible for insulin's metabolic effects (13). Conversely, the mitogen-activated protein kinase (MAPK) signaling pathway, associated with cell proliferation and inflammation, becomes relatively hyperactivated. In obesity, increased lipolysis in adipose tissue leads to excessive free fatty acid (FFA) release. Elevated FFAs enter the liver and muscle tissues, inhibit glucose oxidation through the Randle cycle, and activate multiple kinases, including protein

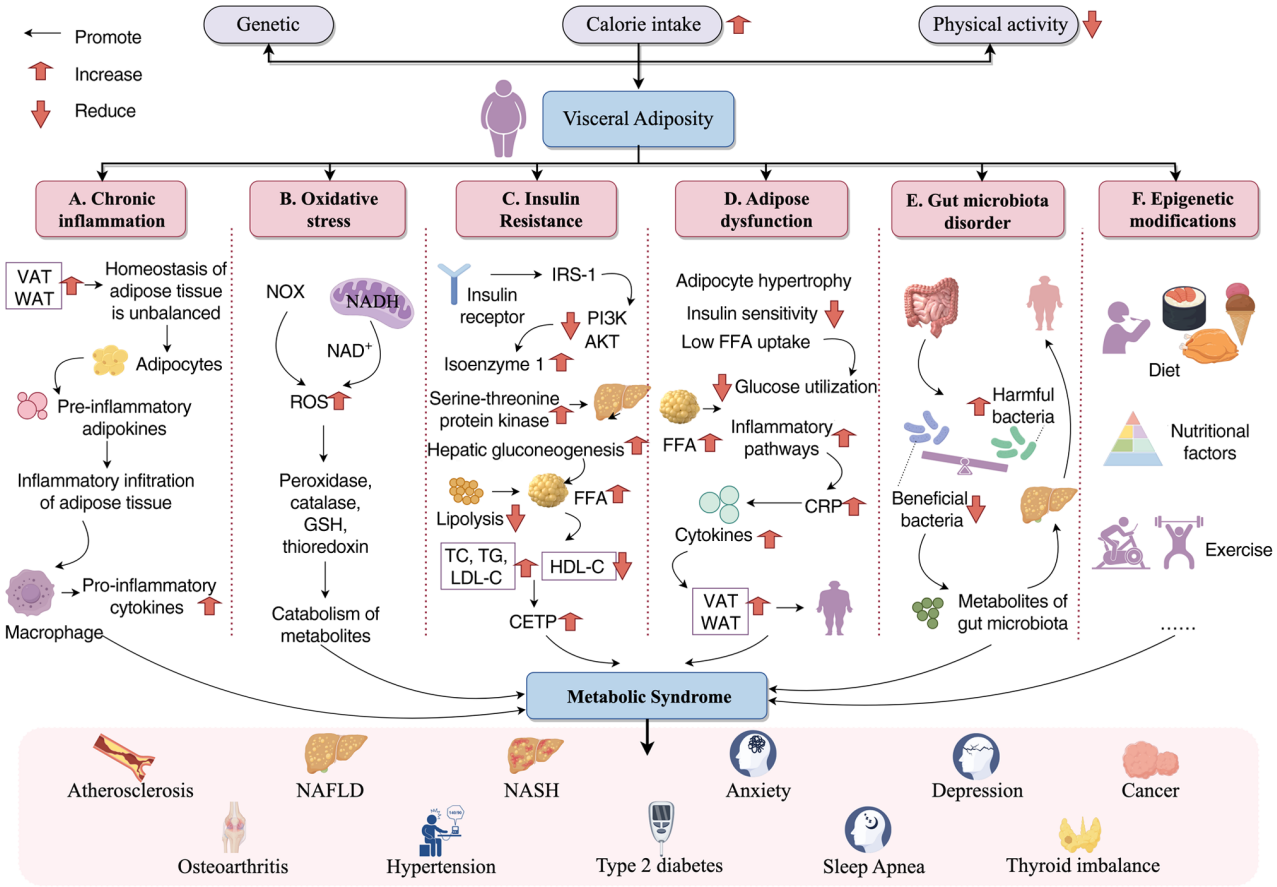

Figure 2. Schematic diagram of the pathophysiological mechanisms of MetS. (A) Chronic inflammation: Imbalance between VAT and WAT homeostasis leads to adipocyte release of pro-inflammatory adipokines, attracting macrophage infiltration and secretion of pro-inflammatory cytokines. This triggers chronic inflammation in adipose tissue, ultimately driving diseases such as atherosclerosis. (B) Oxidative stress: Visceral fat accumulation causes excessive reactive ROS production via NADH-mediated NOX enzymes; simultaneously, insufficient antioxidants such as peroxidase and GSH fail to neutralize ROS, leading to abnormal metabolite degradation and exacerbated oxidative damage. (C) Insulin resistance: Inhibition of insulin receptor signaling pathways (IRS-1, PI3K, AKT) leads to enhanced hepatic gluconeogenesis and lipolysis, elevated FFA, TC, TG and LDL-C, along with reduced HDL-C. This ultimately induces type 2 diabetes, hypertension and other conditions. (D) Adipose tissue dysfunction: Adipocytes undergo excessive hypertrophy, leading to reduced insulin sensitivity and diminished FFA uptake/glucose utilization. Massive FFA release activates inflammatory pathways, elevating CRP and cytokines. This further exacerbates visceral fat accumulation, creating a vicious cycle. (E) Gut microbiota dysbiosis: Visceral fat accumulation disrupts gut microbiota balance, increasing harmful bacteria while reducing beneficial ones. Abnormal microbial metabolites further exacerbate inflammation and metabolic disorders, acting as a contributing factor to MetS. (F) Epigenetic modifications: Environmental factors such as diet, nutrition and exercise influence gene expression through epigenetic modifications, indirectly regulating visceral fat accumulation and subsequent metabolic abnormalities. The figure was created using Figdraw (www.figdraw.com). MetS, metabolic syndrome; VAT, visceral adipose tissue; WAT, white adipose tissue; ROS, reactive oxygen species; NOX, NADPH oxidase; GSH, glutathione; IRS-1, insulin receptor substrate 1; FFA, free fatty acid; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CRP, C reactive protein; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis AKT, protein kinase B; PI3K, phosphoinositide 3-kinase.

kinase Cθ (PKCθ), JNK and inhibitor of NF-κB kinase subunit β (IKKβ). These kinases subsequently phosphorylate IRS-1, further impairing insulin signaling (14). Additionally, adipose-derived inflammatory cytokines, particularly tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), activate JNK and the IKKβ/NF-κB pathways, exacerbating disruptions in insulin signaling (15).

Compared with subcutaneous adipose tissue, visceral adipose tissue (VAT) demonstrates greater metabolic activity but has limited capacity for lipid storage. Secretion of adiponectin, a beneficial adipokine promoting insulin sensitivity and fatty acid oxidation, is substantially reduced. By contrast, multiple pro-inflammatory adipokines, including leptin, resistin, TNF-α and IL-6, exhibit increased secretion, thereby leading to adipose tissue dysfunction (16). When the adipocyte lipid storage capacity is exceeded, fat deposition occurs ectopically. Enlarged, hypoxic adipocytes recruit pro-inflammatory M1 macrophages, forming characteristic 'crown-like structures' (17). Activated immune cells, together with adipocytes, release extensive inflammatory cytokines and chemokines into systemic circulation, disrupting insulin signaling and promoting atherogenesis.

Recently, the gut microbiota has emerged as a pivotal environmental factor influencing MetS (18). Specific microbial communities enhance energy extraction from food, contributing to obesity. Increased intestinal permeability facilitates entry of lipopolysaccharides (LPS) into the portal circulation, inducing metabolic endotoxemia and systemic inflammatory responses. Additionally, certain microbial metabolites such as short-chain fatty acids (SCFAs) and trimethylamine N-oxide markedly influence host metabolism. While SCFAs generally confer health benefits, bacterial cell wall components such

as LPS and peptidoglycan trigger host immune responses, elevating cardiovascular disease risk (19). Epigenetic modifications, influenced indirectly by lifestyle factors such as diet and exercise, have recently been identified as notable regulators of visceral fat accumulation and associated metabolic disorders.

4. PCD in MetS

Multiple forms of PCD contribute to the pathogenesis of MetS, but their roles differ substantially in terms of biological functions, tissue distribution and the strength of available evidence. Established pathways, including apoptosis, pyroptosis, autophagy and ferroptosis, have been extensively investigated and represent major mechanisms linking metabolic stress to organ dysfunction. By contrast, emerging pathways such as necroptosis, PANoptosis and disulfidptosis remain under investigation and require further validation in metabolic disorders.

Apoptosis

Mechanisms of apoptosis. Apoptosis is characterized by cell shrinkage, chromatin condensation, DNA fragmentation and apoptotic body formation via membrane blebbing. These apoptotic bodies are subsequently cleared by macrophages or neighboring cells without eliciting inflammation (20). The apoptosis cascade primarily involves two pathways: Extrinsic and intrinsic. In the extrinsic pathway, extracellular ligands such as TNF-α, Fas ligand and TRAIL bind to corresponding receptors (DR4, DR5 and Fas), transmitting death signals into the cell (21). Following this binding, proteins including TNFR-associated death domain (TRADD), Fas-associated death domain (FADD) and caspase-8 form complexes, thereby activating caspase-8. Activated caspase-8 initiates apoptosis by cleaving downstream effectors caspase-3, caspase-6 and caspase-7 (22). By contrast, the intrinsic mitochondrial pathway activates BH3-only proteins under cellular stress conditions. BH3-only proteins inhibit anti-apoptotic B-cell lymphoma-2 (Bcl-2) family proteins, activating pro-apoptotic molecules such as Bcl-2-associated X protein (Bax) and Bcl-2 homologous antagonist/killer. This process induces mitochondrial outer membrane permeabilization, causing cytochrome *c* and other pro-apoptotic factors to be released into the cytoplasm. Subsequently, cytochrome C binds to apoptotic protease activating factor-1, forming apoptosomes that activate caspase-9, ultimately triggering caspase-3, -6 and -7 activation and apoptosis (Fig. 3) (23).

Apoptosis in MetS. Among various PCD modalities, apoptosis is one of the most extensively characterized forms of PCD contributing to MetS progression, particularly in pancreatic β-cell dysfunction, adipose tissue remodeling and hepatic injury. In MetS, apoptosis is not merely a consequence of metabolic stress but also an active driver of disease progression through tissue remodeling and amplification of inflammatory responses. In obesity, adipose tissue expansion is not limitless. When adipocytes enlarge beyond their vascular support and metabolic capabilities, hypoxia, lipotoxicity and endoplasmic reticulum stress (ERS) occur (24). Nutrient overload and elevated FFAs stimulate excessive lipid and protein synthesis in the ER, activating the unfolded protein response (UPR) (25). Severe, prolonged ERS shifts the UPR from promoting cell survival towards apoptosis, primarily mediated by protein kinase R-like ER kinase-eukaryotic translation initiation factor 2 subunit 1-activating transcription factor 4 (ATF4) and inositol-requiring enzyme 1α-apoptosis signal-regulating kinase 1-JNK signaling pathways (26). ATF4 upregulates the pro-apoptotic protein C/EBP homologous protein, while JNK pathway activation phosphorylates and inhibits anti-apoptotic Bcl-2, simultaneously activating pro-apoptotic proteins Bad and Bim. This disrupts cellular balance between survival and apoptosis (27). Together with elevated FFAs, these signals promote mitochondrial membrane potential collapse, resulting in cytochrome C release. Macrophages recognize, engulf and become activated by apoptotic adipocytes, subsequently secreting abundant pro-inflammatory cytokines. This exacerbates local inflammation and induces apoptosis in neighboring adipocytes through paracrine signaling (28).

Although apoptotic hepatocytes can no longer perform their normal metabolic functions, including glucose metabolism, their death process releases 'find-me' and 'eat-me' signals. These signals recruit and activate Kupffer cells, resident hepatic macrophages (29). Activated Kupffer cells secrete inflammatory cytokines such as TNF-α, impairing insulin signaling in adjacent hepatocytes. A previous study indicated that inhibiting adipocyte apoptosis enhances systemic insulin sensitivity, suggesting apoptosis as a pathogenic contributor to IR (30). In T2DM, glucotoxicity and lipotoxicity synergistically drive pancreatic β-cell apoptosis. Sustained hyperglycemia increases mitochondrial oxidative phosphorylation, producing excessive reactive oxygen species (ROS) that exceed cellular antioxidant capacity, causing oxidative stress and cellular damage (31). Moreover, inflammatory mediators secreted by insulin-resistant tissues, and cytokines (IL-1β, TNF-α and IFN-γ) from immune cells infiltrating pancreatic islets, directly activate β-cell apoptotic mechanisms (32). Although β-cell apoptosis is 'silent' and non-inflammatory, its consequences are profound. It leads to irreversible loss of functional β-cell mass, absolute insulin deficiency and uncontrolled hyperglycemia.

Hypertension induces apoptosis in vascular smooth muscle cells (VSMCs) and vascular endothelial cells (VECs) due to stress from the vascular wall and shear forces from blood flow. Prolonged pressure overload alters the expression of proteins such as p53, Bax and Bcl-2, thus affecting the regulatory balance between proliferation and apoptosis in VSMCs (33). Studies have demonstrated that caspase-3 is involved in apoptosis of hypoxic VECs (34). During the progression of hypertension, accumulated apoptosis results in thinning of the myocardial microvascular network, compromising blood supply and exacerbating myocardial cell death (35). Notably, sustained vasoconstriction simultaneously promotes apoptosis, vascular wall thickening, atherosclerosis, luminal narrowing and increased vessel stiffness, consequently aggravating hypertensive complications (36). Hyperlipidemia, particularly elevated FFAs and oxidized low-density lipoprotein (ox-LDL), acts as a critical stressor triggering various apoptotic pathways. Palmitic acid serves as a precursor for ceramide synthesis, inducing mitochondrial dysfunction, increased ROS production and cytochrome C release, thereby strongly activating mitochondrial apoptosis (37). In macrophages, apoptosis triggered by ox-LDL is essential for necrotic core formation

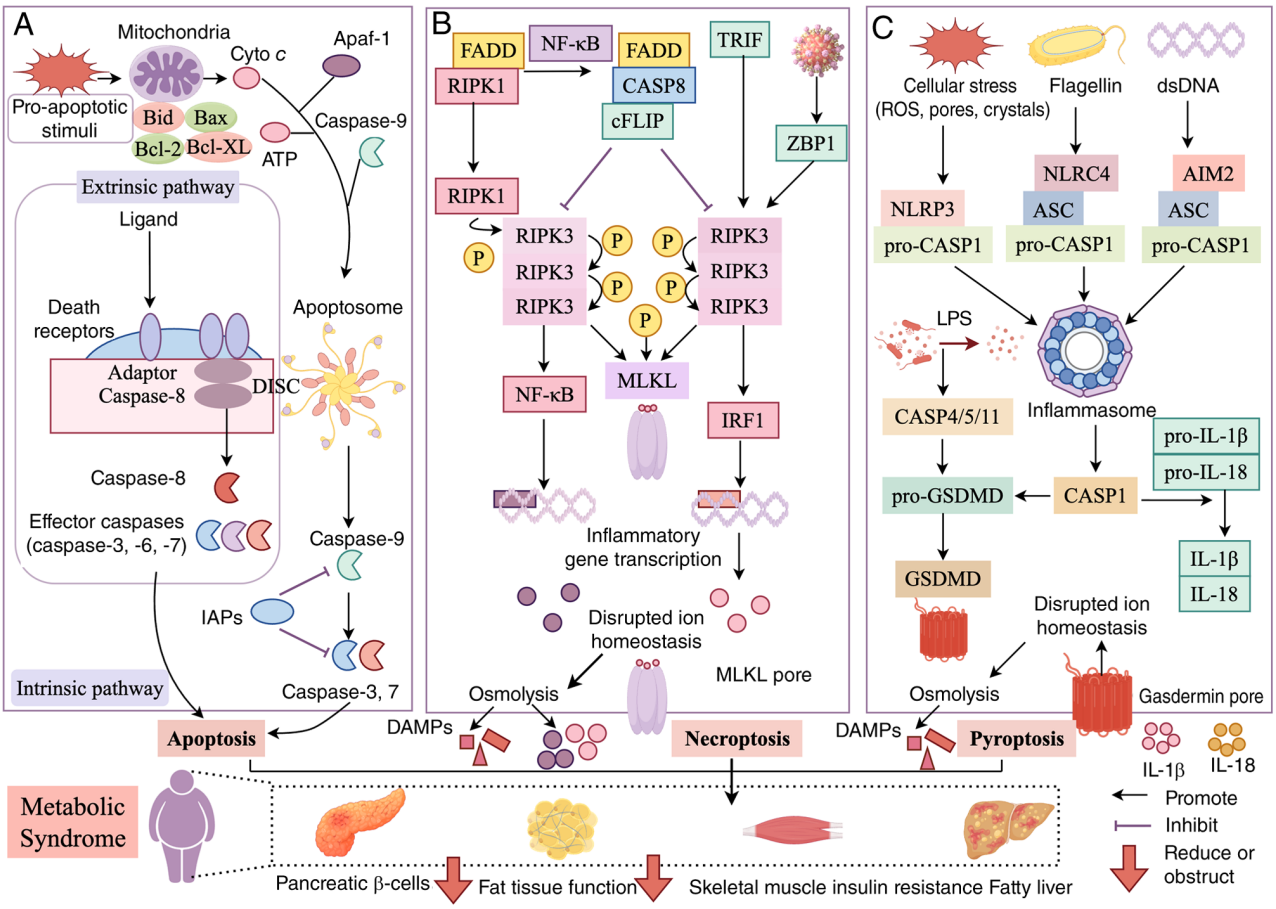

Figure 3. Schematic diagram of apoptosis, necroptosis, and pyroptosis mechanisms in MetS. (A) Exogenous apoptosis pathway: Death receptor binds ligand, recruits adaptor proteins to form a complex with caspase-8 (DISC), activating caspase-3. Intrinsic apoptosis pathway: Metabolic stress induces mitochondria to release cyto *c*, which binds Apaf-1 to form an apoptosome, activating caspase-9, which ultimately activates effector caspases. In MetS, this pathway can cause tissue damage, such as to pancreatic β-cells. (B) Necroptosis: Regulated by proteins such as RIPK1 and RIPK3. When caspase-8 is inhibited (such as by cFLIP), RIPK1 and RIPK3 bind and become phosphorylated, further activating the MLKL protein. MLKL aggregates and forms pores in the cell membrane, disrupting ion homeostasis and ultimately leading to osmotic lysis. This process activates pathways such as NF-κB to trigger inflammatory gene transcription while releasing large amounts of DAMPs. In MetS, this can damage adipose tissue, skeletal muscle and other tissues, exacerbating insulin resistance. (C) Pyroptosis: Different stimuli, such as cellular stress, bacterial flagella and double-stranded DNA, activate corresponding inflammasomes NLRP3, NLRC4 and AIM2, respectively. These complexes activate caspase-1; caspase-1 cleaves the GSDMD protein to form pores that disrupt the cell membrane, while simultaneously processing pro-IL-1β and pro-IL-18 into active cytokines IL-1β and IL-18. Ultimately, cells lyse and release pro-inflammatory factors, exacerbating pathological processes such as fatty liver disease and adipose tissue inflammation in MetS. The figure was created using Figdraw (www.figdraw.com). MetS, metabolic syndrome; DISC, death-inducing signaling complex; RIPK, receptor-interacting serine/threonine-protein kinase; MLKL, mixed lineage kinase domain like pseudokinase; DAMPs, damage-associated molecular patterns; NLRP3, NLR family pyrin domain containing 3; GSDMD, gasdermin D.

within atherosclerotic plaques. If apoptotic macrophages are not cleared efficiently, they undergo secondary necrosis, releasing pro-inflammatory components (38). Current evidence supporting the involvement of apoptosis in MetS is relatively strong, based on consistent findings from animal models, human pancreatic tissue studies and clinical observations linking β-cell loss to metabolic deterioration.

Pyroptosis

Mechanism of pyroptosis. The classical pyroptosis pathway primarily involves activation of intracellular multiprotein complexes known as inflammasomes. Inflammasomes detect and respond to various endogenous and exogenous danger signals, including pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) (39). Upon activation, inflammasome sensors recruit the adaptor protein apoptosis-associated speck-like protein containing a CARD (ASC), primarily via pyrin domain interactions. ASC aggregation subsequently exposes its caspase recruitment domain (CARD), facilitating interaction with procaspase-1 and linking inflammasome sensors with procaspase-1 (40). Additionally, certain CARD-containing sensors can directly recruit procaspase-1. Elevated local concentrations of procaspase-1 drive its heterodimerization, self-cleavage and activation to caspase-1. Activated caspase-1 then cleaves pro-IL-1β/pro-IL-18 and gasdermin D (GSDMD), generating an N-terminal fragment (NT). GSDMD-NT integrates into the cell membrane lipid bilayer, forming pores that induce pyroptotic cell death and facilitate the release of mature IL-1β and IL-18 into the extracellular space (41). The non-canonical pathway involves human caspase-4/5 or murine caspase-11 as direct intracellular receptors for LPS. Upon sensing LPS, these caspases cleave GSDMD, initiating pyroptosis (42). Recent findings also suggest alternative pyroptosis pathways mediated by caspase-3, caspase-8 and granzyme (Fig. 3) (43).

Pyroptosis in MetS. In obesity, excessive nutrient intake induces adipose tissue dysfunction, ultimately impairing insulin sensitivity. A previous study demonstrated increased NLR family pyrin domain containing 3 (NLRP3), IL-1β and IL-18 expression in adipose tissues of high-fat diet-fed mice, associating with reduced insulin sensitivity. Conversely, NLRP3 knockout mice exhibited improved insulin sensitivity under identical dietary conditions (44). In 10 male patients with T2DM, weight reduction achieved through caloric restriction and exercise led to decreased adipose tissue expression of NLRP3 and IL-18, accompanied by enhanced insulin sensitivity (45). Sehgal *et al* (46) proposed that adipose tissue inflammation mediated by the NLRP3 inflammasome markedly reduces insulin sensitivity, a hypothesis supported by other research. In a study involving 98 subjects, targeted NLRP3 inhibition via small interfering RNA substantially decreased LPS-induced expression of fibrosis-associated molecules in adipocytes, alleviating inflammation and fibrosis (47). Additionally, melatonin has been reported to attenuate inflammasome-mediated pyroptosis in murine adipose tissue by inhibiting NF-κB/GSDMD signaling (48).

Inflammation is intrinsically associated with diabetes. Research has demonstrated that hyperglycemia increases levels of advanced glycation end products (AGEs) and ROS, thereby activating inflammasomes and triggering pyroptosis (49). Ma *et al* (50) confirmed that pyroptosis exacerbates β-cell destruction, ultimately impairing glucose metabolism. Furthermore, Carlos *et al* (51) observed an increased proportion of macrophages expressing caspase-1 in pancreatic lymph nodes of streptozotocin-induced diabetic mice, whereas this proportion decreased in NLRP3-knockout mice. Furthermore, knockout of NLRP3 and IL-1R genes markedly elevated insulin levels and reduced hyperglycemia. Luo *et al* (52) separately reported increased expression of NLRP3, caspase-1 and IL-1β as critical factors driving diabetic cardiomyopathy progression. Experimental NLRP3-microRNA (miRNA) therapy effectively reduced myocardial inflammation by inhibiting IL-1β, IL-18, TNF-α and IL-6 release. Moreover, NLRP3 gene silencing attenuated myocardial inflammation, cardiac pyroptosis and left ventricular fibrosis, thereby improving diabetic cardiomyopathy progression in T2DM rat models.

Low-grade or persistent inflammation is crucial in hypertension progression. For example, Dalekos *et al* (53) proposed that inflammasome activation and pyroptosis notably contribute to elevated blood pressure. Inflammasome activation leads to caspase-1 activation, which subsequently cleaves GSDMD, mediates pyroptosis and releases additional inflammatory mediators into the extracellular space, further exacerbating inflammation and hypertension. NF-κB is a primary activator of the pyroptosis-related inflammasome NLRP3. NF-κB knockout markedly attenuated NLRP3 and caspase-1 activation, thereby inhibiting salt-sensitive hypertension progression in rats (54). Research has further confirmed that after 25 days of treatment with the NLRP3 inhibitor MCC950, hypertensive mice exhibited marked improvements in blood pressure, urine volume, osmolarity and proteinuria (55). Levels of NLRP3 inflammasome components, including apoptosis-associated speck-like protein, pro-caspase-1 and inflammatory markers (pro-IL-18, pro-IL-1β and TNF-α), were markedly reduced compared with the baseline. These findings indicate that pharmacological inhibition of the NLRP3 inflammasome represents a promising therapeutic approach for hypertension. Another animal study demonstrated that NLRP3 inflammasome inhibition effectively alleviates kidney injury resulting from pyroptosis (56). Current evidence implicating pyroptosis in MetS is primarily derived from experimental models and human tissue studies, particularly in adipose inflammation and NAFLD, while large-scale clinical validation remains limited.

Autophagy

Mechanisms of autophagy. Autophagy is a critical metabolic recycling process in eukaryotic cells, mediated by lysosomes or vacuoles, involving the degradation and reuse of intracellular components. Autophagy regulation involves several signaling pathways, among which adenosine monophosphate-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) pathways are most prominent (57). AMPK functions as a conserved energy sensor, activating autophagy initiation under metabolic stress conditions, such as energy deprivation (58). Conversely, mTOR acts as a major negative regulator of autophagy, integrating upstream signals including PI3K, insulin-like growth factor (IGF-1/IGF-2) and AMPK to inhibit autophagic activity (59). Specifically, mTOR kinase activates signaling pathways involving AKT and MAPK, thereby suppressing autophagy. The AMPK and p53 signaling pathways negatively regulate mTOR activity, thus promoting autophagy (60). Under normal physiological conditions, mTOR inhibits autophagy; however, during stress states such as nutrient deprivation or starvation, autophagy initiation occurs via the mTOR/autophagy-related gene (Atg) 1/Atg13 signaling axis (61). During autophagy, the selective adaptor protein p62 specifically targets certain proteins and organelles for sorting and degradation. Mitophagy exemplifies selective autophagy and is essential for maintaining cardiomyocyte homeostasis. In this process, damaged or dysfunctional mitochondria are selectively recognized via the Pink1-Parkin signaling pathway or other mitochondrial autophagy receptors and subsequently degraded by acidic lysosomal hydrolases (Fig. 4) (62).

Autophagy dysfunction: A double-edged regulator of MetS. Although autophagy is generally regarded as a protective mechanism maintaining cellular homeostasis, accumulating evidence indicates that its role in MetS is highly context-dependent and involves dual regulatory effects (63). The metabolic effects of autophagy are influenced by multiple factors, including tissue type, disease stage, nutritional status and autophagic flux efficiency (64). Physiological activation of autophagy maintains metabolic homeostasis by eliminating damaged mitochondria and regulating lipid metabolism (65). In insulin-sensitive tissues, basal autophagy is essential for metabolic regulation. For example, a previous study involving tissue-specific deletion of autophagy-related genes demonstrated the indispensable role of autophagy in preventing metabolic deterioration (66). Liver-specific Atg7 knockout mice exhibit impaired autophagic flux, hepatic lipid accumulation, increased oxidative stress and spontaneous steatosis, whereas restoration of autophagic activity ameliorates metabolic abnormalities (67). Similarly, loss of autophagy-related gene function in pancreatic β-cells results in mitochondrial dysfunction and impaired insulin secretion, highlighting the protective role of autophagy in maintaining β-cell

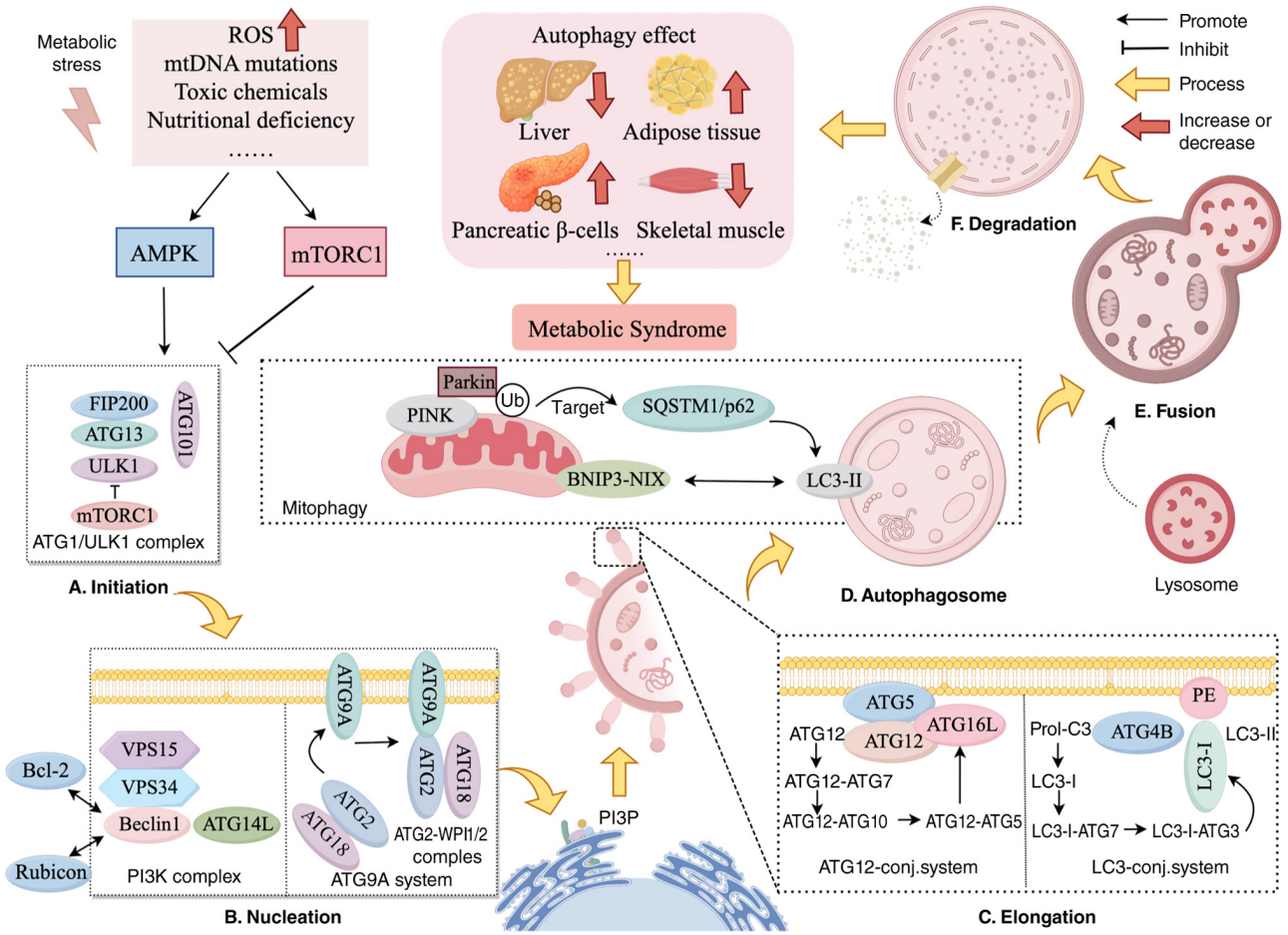

Figure 4. Schematic diagram of autophagy mechanisms in MetS. When metabolic stress occurs, such as increased ROS, mtDNA mutations or toxin/nutrient deprivation, autophagy is regulated through two core pathways: AMPK pathway activation promotes autophagy initiation by forming the ATG1/ULK1 complex; mTORC1 pathway inhibition releases its suppression of autophagy, jointly driving the process. Complete autophagy process: (A) Initiation: ATG1/ULK1 complex formation prepares for autophagy; (B) nucleation: PI3K complex, ATG9A system and others form the autophagosome precursor membrane; (C) elongation: Proteins including ATG12 and LC3 systems assist in extending the precursor membrane, forming a double-layered structure enveloping 'substances awaiting clearance'; (D) autophagosome (E) fusion and (F) degradation: Autophagosomes fuse with lysosomes, degrading and recycling their contents. Among these, mitophagy represents a specialized form of autophagy. Damaged mitochondria are marked through pathways such as PINK/Parkin and BNIP3-NIX, ultimately engulfed by autophagosomes for degradation, thereby preventing metabolic disorders triggered by mitochondrial dysfunction. Ultimately, this affects the function of the liver, skeletal muscle, adipose tissue and pancreatic β-cells, contributing to the onset and progression of MetS. The figure was created using Figdraw (www.figdraw.com). MetS, metabolic syndrome; ROS, reactive oxygen species; ULK1, autophagy-light chain kinase 1; ATG, autophagy-related gene; mtDNA, mitochondrial DNA.

function (68). However, excessive or dysregulated autophagy may become maladaptive under certain pathological conditions. Persistent nutrient stress or chronic inflammation can disrupt the balance between autophagic degradation and cellular regeneration, leading to excessive organelle turnover and cellular dysfunction (69).

In adipose tissue, enhanced autophagic activity may facilitate adipocyte remodeling and lipid mobilization, while in advanced metabolic disorders, sustained autophagic activity may fail to restore cellular homeostasis due to impaired lysosomal function (70) Autophagy serves an essential role in adipocyte differentiation and maturation, with obesity further influencing autophagic activity during MetS. Dyslipidemia, hypertension and hyperglycemia primarily contribute to altered autophagy in obese individuals. Conversely, impaired autophagy, especially its suppression, accelerates obesity and metabolic disorders (71). Mice with systemic or tissue-specific knockouts of autophagy-related proteins, including Beclin 2, Atg7, lysosomal membrane-associated protein 2, transcription factor EB (TFEB) and Bif-1, exhibit increased susceptibility to obesity phenotypes (72). For example, liver-specific deletion of Atg7 or TFEB causes hepatic steatosis and increased body weight in mice, whereas their overexpression prevents weight gain and MetS (73). Furthermore, autophagy regulation in the central nervous system is closely linked to obesity; inhibiting autophagy in specific neuronal populations stimulates appetite and promotes obesity (74). This creates a vicious cycle wherein defective autophagy accelerates lifestyle-induced obesity, further suppressing autophagy in liver, muscle, and adipose tissues and exacerbating MetS symptoms.

Elevated blood glucose activates the IGF-1R pathway, promoting PI3K translocation to membranes and subsequent activation of AKT/PKB signaling. This inhibits the tuberous sclerosis complex (TSC), activating mTOR, which impairs autophagic flux in cardiac microvascular endothelial cells (75). A previous study showed reduced levels of hepatic autophagy markers (LC3II) and increased p62 expression in hyperinsulinemic conditions, high-fat diet-induced obesity and ob/ob

mouse models, indicating impaired autophagy (76). Under glucose deprivation, decreased ATP levels activate AMPK. Activated AMPK suppresses mTORC1 by stimulating the TSC1-TSC2 complex and directly initiates autophagy via the autophagy-light chain kinase 1 complex (77). Zhao *et al* (78) demonstrated that treating HUVECs with ox-LDL or AGEs altered endothelial autophagic flux, while AGE-induced autophagy blockade increased mitochondrial ROS production. Stimulation of autophagy by the mTOR inhibitor rapamycin or TFEB overexpression prevented AGE/ox-LDL-induced mitochondrial ROS accumulation, enhanced eNOS dimerization and ameliorated diabetic endothelial dysfunction (79). Furthermore, autophagy-deficient mice fed a high-fat diet showed increased susceptibility to diabetic symptoms, mitochondrial injury and pancreatic β-cell dysfunction (80).

Under normal conditions, hyperlipidemia reduces basal autophagy levels. Enhanced lipolysis in adipocytes and IR elevate blood lipid levels, potentially impairing autophagy by blocking autophagosome-lysosome fusion, lysosomal acidification and lysosomal enzyme activities. A previous study demonstrated that in high-fat diet-induced obese mouse models, elevated blood lipids suppressed autophagosome-lysosome fusion, disrupting intracellular Ca^{2+} regulation, damaging mitochondria and inducing apoptosis (81). Intracellular fatty acid derivatives, such as ceramides, diacylglycerols and fatty acyl-CoA, further disrupt autophagic homeostasis, thereby promoting IR and steatohepatitis (82). Knockout of protein tyrosine phosphatase 1B (PTP1B) alleviates cardiomyocyte damage induced by a high-fat diet in mice by restoring cardiac autophagy through an AMPK-dependent mechanism (83). Although autophagy inhibition alone is insufficient for lipid accumulation and steatosis development, it promotes lipid deposition when combined with other factors, such as prolonged high-fat diet exposure or obesity-related genetic mutations (84). Therefore, autophagy should not be simply considered either beneficial or detrimental in MetS. Instead, its biological effects depend on whether autophagic flux is maintained at an appropriate level. Therapeutic strategies should aim to restore physiological autophagy rather than indiscriminately activate or inhibit this pathway.

Ferroptosis

Mechanism of ferroptosis. Ferroptosis is closely linked to intracellular iron accumulation. Under normal physiological conditions, Fe^{3+} binds to transferrin (TF) and enters cells via the TF receptor 1 (TFR1) on the cell membrane (85). Upon entering the cell, Fe^{3+} is reduced to Fe^{2+}, subsequently entering the labile iron pool (LIP). Disturbances in iron metabolism lead to abnormal Fe^{2+} accumulation within the LIP. This excess Fe^{2+} initiates lipid peroxidation through the Fenton reaction, generating abundant lipid-ROS that damage cell membranes and induce ferroptosis (86). During ferroptosis, Fe^{3+}-catalyzed free radicals primarily target membrane polyunsaturated fatty acids (PUFAs), such as arachidonic acid (AA) and adrenocortical acid (AdA) (87). Under catalysis by ACSL4, these fatty acids bind to coenzyme A (CoA) to form AA-CoA or AdA-CoA intermediates. Subsequently, these intermediates are esterified by lysophospholipid acyltransferase 5 (LPCAT3) into phosphatidylethanolamine-linked forms (PE-AA or PE-AdA). Lipoxygenases (LOXs) then enzymatically convert these forms into peroxidized products (PE-AA/AdA-OOH), ultimately causing ferroptosis (88). Glutathione peroxidase 4 (GPX4) serves a crucial role in cellular antioxidant defense by catalyzing the reduction of toxic lipid hydroperoxides (LOOH) into non-toxic phospholipids, while converting reduced glutathione (GSH) to oxidized GSH (89). When GSH availability decreases, GPX4 activity declines, causing ROS accumulation and ferroptotic cell death (Fig. 5).

Ferroptosis in MetS. High intracellular iron levels disrupt adipocyte differentiation, contributing to metabolic dysfunction. Liposomes, which store triglycerides (TGs) as neutral lipids, are enveloped by Fas-associated factor 1 (FAF1) to protect against Fe^{2+} exposure (90). TGs within liposomes undergo hydrolysis of ester bonds to form glycerol and FFAs. Under conditions of Fe^{2+} overload, cytoplasmic FFAs trigger lipid peroxidation through the Fenton reaction, rapidly generating PUFA-OOH (91). In the presence of excess Fe^{2+}, PUFA-OOH readily oxidizes further, initiating chain reactions of lipid oxidation by extracting hydrogen atoms from neighboring PUFAs. This disrupts membrane integrity, ultimately leading to cell death (92). A previous study demonstrated that reducing iron accumulation in white adipose tissue limits intestinal lipid absorption, thus protecting against metabolic disturbances induced by high-fat diets (93). Further research indicates (94) that lowering intracellular iron inhibits adipogenic gene expression and reduces lipid synthesis. Elevated iron levels also promote persistent adipokine secretion, creating an inflammatory environment that attracts macrophage infiltration and drives obesity progression.

A previous epidemiological study suggested a possible relationship between excess body iron storage and the risk of T2DM (95). Iron overload reduces insulin sensitivity, lowers adiponectin secretion and increases leptin levels, thus promoting IR (96). A previous prospective study reported a positive association between IR and elevated serum ferritin concentrations (97). Disrupted iron metabolism contributes to mitochondrial dysfunction, thereby impairing insulin signaling pathways. Additionally, GPX4-deficient mice exhibit adipocyte hypertrophy and IR, indicating that iron metabolism disturbances induce IR by impairing mitochondrial function and altering adipocyte cytokine production (98). Research findings also show that increased body iron stores elevate T2DM risk (99). For instance, mouse models of hereditary hemochromatosis, characterized by systemic iron overload, exhibit iron accumulation in skeletal muscles, enhanced fatty acid oxidation and diminished glucose oxidation, collectively aggravating IR (100). A previous study aiming to improve diabetes outcomes demonstrated enhanced insulin secretion and sensitivity following reductions in systemic iron stores (101). However, it is noteworthy that serum ferritin-based assessments of body iron storage are not entirely reliable indicators, as ferritin levels also increase in conditions such as inflammation, cancer and liver diseases (102).

A previous study demonstrated that iron overload is closely linked to atherosclerosis risk factors, including abnormal iron metabolism, which is frequently observed in obese and hypertensive individuals (103). Excessive iron intake aggravates dyslipidemia, particularly by increasing TG levels. Moreover, iron overload and lipid metabolic disturbances synergistically accelerate atherosclerosis progression. Iron chelation therapy

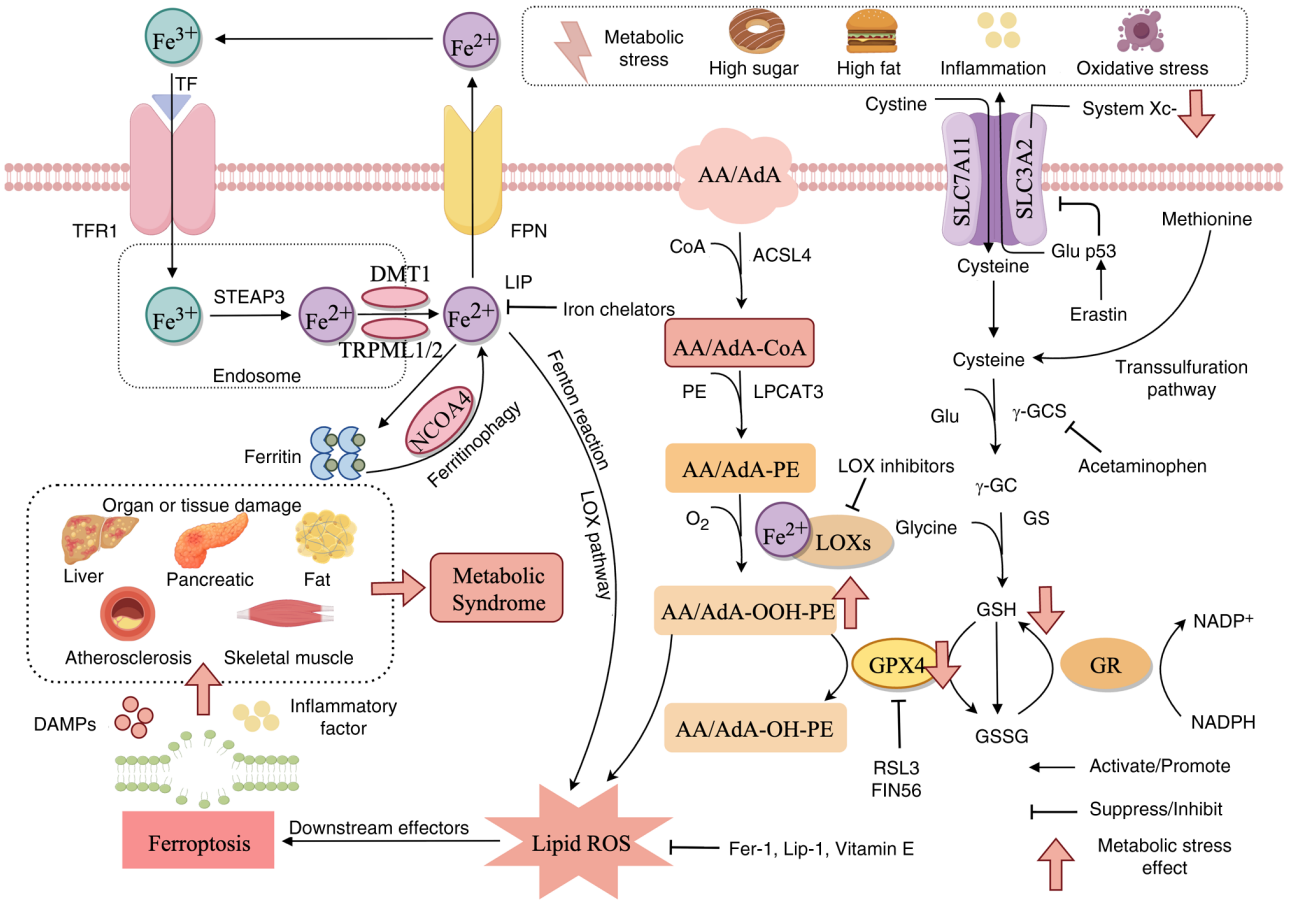

Figure 5. Schematic diagram of ferroptosis mechanisms in MetS. Iron enters cells via the TFR1 receptor, is reduced to Fe^{2+} by STEAP3 in endosomes and then transported to the cytoplasm by DMT1. Cytoplasmic Fe^{2+} is partially stored by ferritin, while the remainder exists as an LIP. Under metabolic stress, ferritin is degraded via ferritinophagy, releasing large amounts of Fe^{2+}. Concurrently, impaired function of the iron export protein FPN leads to intracellular Fe^{2+} accumulation. Excess Fe^{2+} catalyzes lipid peroxidation through the Fenton reaction, ultimately triggering ferroptosis. Metabolic stress also inhibits System Xc-, causing intracellular cysteine deficiency and reduced GSH synthesis. This GSH depletion prevents GPX4 from scavenging lipid ROS. Concurrently, AA/AdA undergoes enzymatic modification by ACSL4, LPCAT3 and others into lipid substrates. Under the influence of Fe^{2+} and LOXs, these substrates generate substantial lipid peroxides, ultimately damaging cell membranes and triggering ferroptosis. Following ferroptosis, DAMPs and inflammatory cytokines are released, exacerbating tissue damage in the liver, pancreas and vasculature, thereby driving the progression of MetS. Conversely, iron chelators and GPX4 activators (such as vitamin E) can mitigate ferroptosis by reducing Fe^{2+} or inhibiting lipid peroxidation. The figure was created using Figdraw (www.figdraw.com). MetS, metabolic syndrome; ROS, reactive oxygen species; DAMPs, damage-associated molecular patterns; GPX4, glutathione peroxidase 4; FPN, ferroportin; TFR1, transferrin receptor 1; STEAP3, six-transmembrane epithelial antigen of prostate 3; LIP, labile iron pool; GSH, glutathione; AA/AdA, arachidonic acid/adrenic acid; LOXs, lipoxygenases; ACSL4, acyl-CoA synthetase long-chain family member 4; LPCAT3, lysophosphatidylcholine acyltransferase 3; DMT1, divalent metal transporter 1.

and dietary iron restriction stabilize atherosclerotic plaques and protect against endothelial injury (104). In addition, inhibition of GPX4 promotes lipid peroxide accumulation, induces ferroptosis and contributes to atherosclerotic plaque formation. Ferroptosis-related LOXs accelerate atherosclerosis development, whereas inhibition of 12/15-LOX reduces LDL oxidation and attenuates atherosclerosis progression (105). Iron overload also serves a critical role in the progression of metabolic-associated fatty liver disease (MAFLD). Excessive systemic iron induces intracellular lipid peroxidation, damages hepatocytes and promotes liver fibrosis. Ferroptosis in this context is accompanied by collapse of intracellular antioxidant defenses, particularly depletion of GSH and GPX4, rendering hepatocytes more vulnerable to oxidative stress and further exacerbating MAFLD progression (106). Although ferroptosis has been increasingly implicated in NAFLD/MASH progression, most available evidence is derived from cellular and animal models, and its clinical relevance requires further validation.

Necroptosis

Mechanisms of necroptosis. Necroptosis is a form of regulated cellular death occurring when apoptosis pathways are inhibited. While its underlying mechanism shares similarities with apoptosis, its morphological features closely resemble necrosis. Dysregulated necroptosis contributes to multiple inflammatory diseases, infections and neurodegenerative conditions (107). Numerous stimuli can initiate necroptosis, but the classical pathway involves the TNF-α/TNFR-induced RIPK1-RIPK3-mixed lineage kinase domain like pseudokinase (MLKL) cascade (108). Upon TNF-α binding, TNFR1 undergoes conformational changes and recruits multiple proteins, including RIPK1, TRADD, cellular inhibitor of apoptosis proteins (cIAP1, cIAP2), TNFR2 and TNFR5, forming Complex I at the cell membrane. Following internalization and modification, TNFR1 dissociates from Complex I, and RIPK1 subsequently assembles Complex II together with TRADD, FADD and caspase-8. When caspase-8 activity

is suppressed, RIPK1 phosphorylation initiates the necroptosis pathway, interacting with RIPK3 to form a necrosome complex. RIPK3 autophosphorylation then activates MLKL, which oligomerizes, relocates to the plasma membrane and forms pores. This pore formation causes an influx of Na^+ and Ca^{2+}, elevating intracellular osmotic pressure and resulting in plasma membrane rupture. This event releases DAMPs, causing inflammation and tissue injury (Fig. 3) (109).

Necroptosis in MetS. In obese adipose tissue, hypertrophic adipocytes are among the first cells to undergo necroptosis. Consequently, intracellular contents, including DAMPs such as ATP, DNA, HMGB1 and IL-33, are extensively released into the extracellular matrix (110). These DAMPs act as 'danger signals', activating macrophages via classical inflammatory pathways, including NF-κB and the NLRP3 inflammasome. This activation leads to abundant cytokine secretion (TNF-α, IL-1β, IL-6 and MCP-1), further amplifying adipocyte death (111). Experimental evidence demonstrates marked upregulation of RIPK3 and MLKL at both protein and mRNA levels in adipose tissues from diet-induced obese and ob/ob mice, associating strongly with inflammatory severity (112). In skeletal muscle and liver tissues, inflammatory signals increase the expression of key gluconeogenic enzymes. Consequently, hepatic glucose production continues despite insulin presence, exacerbating fasting hyperglycemia. Additionally, these inflammatory signals can induce damage and death in healthy β-cells, triggering a cascade effect and accelerating β-cell mass depletion (113). Furthermore, sublethal activation of RIPK1/RIPK3 may impair β-cell insulin secretion, leading to defective insulin release. Notably, human pancreatic tissues affected by T2DM frequently exhibit islet amyloid polypeptide (IAPP) deposits. These oligomerized IAPP aggregates are internalized by phagocytes, inducing lysosomal membrane rupture and content leakage, which strongly activates the NLRP3 inflammasome and subsequently triggers necroptosis (114). When LDL levels increase, LDL enters the vascular endothelium and oxidizes into ox-LDL, which induces ERS and mitochondrial dysfunction, activating RIPK3 (115). When cholesterol reverse transport is compromised, free cholesterol accumulates intracellularly, forming cholesterol crystals (CCs). These crystals, upon phagocytosis into lysosomes, puncture the lysosomal membrane due to their rigidity, releasing cathepsins into the cytoplasm. This directly activates the NLRP3 inflammasome and downstream caspase-1 in a RIPK3-dependent manner, potentially triggering MLKL activation (116).

Emerging PCD mechanisms in MetS

PANoptosis in MetS. PANoptosis represents an emerging form of regulated cell death implicated in metabolic inflammation (117). Unlike the simultaneous activation of multiple independent cell death pathways, PANoptosis is mediated by the formation of a supramolecular complex termed the PANoptosome, which coordinates key regulators from different death programs, including Z-DNA binding protein 1 (ZBP1), RIPK3, caspase-8 and inflammasome components (118,119). Although PANoptosis has attracted increasing attention in inflammatory diseases, its direct contribution to MetS remains largely unexplored. Current evidence linking PANoptosis to MetS-associated disorders is mainly based on observations of shared inflammatory pathways, including NLRP3 inflammasome activation, caspase signaling and RIPK-dependent inflammatory responses (120,121). In obesity and MASLD, chronic metabolic stress induces persistent activation of inflammatory signaling pathways that overlap with known PANoptosis-related mechanisms (122). For example, saturated fatty acids, mitochondrial dysfunction and oxidative stress can activate inflammasome pathways and inflammatory caspase signaling, thereby theoretically providing a favorable environment for PANoptotic responses (123,124). However, direct evidence demonstrating a causal role of PANoptosis in MetS remains limited. It remains unclear whether functional PANoptosome complexes are assembled in metabolic tissues such as adipose tissue, the liver or the pancreas. Future studies using genetic models and single-cell approaches are required to determine the precise contribution of PANoptosis to MetS progression. (Fig. 6).

Disulfidptosis in MetS. Disulfidptosis is a novel cell death mechanism recently identified by Liu *et al* (125) in 2023. It is characterized by the disruption of cytoskeletal integrity triggered by abnormal intracellular accumulation of disulfide bonds. Under conditions of glucose deprivation or inhibition of glucose transporters, the pentose phosphate pathway becomes impaired, reducing NADPH generation and inhibiting the reduction of cystine to cysteine. This metabolic dysfunction leads to the abnormal accumulation of intracellular cystine and excessive disulfide bond formation. These disulfide bonds aberrantly cross-link with free cysteine residues on cytoskeletal proteins such as actin, disrupting the filamentous actin network, impairing cellular contractility, and ultimately causing plasma membrane rupture (126). Notably, overexpression of the cystine/glutamate antiporter solute carrier family 7 member 11 (SLC7A11) exacerbates disulfidptosis by enhancing cystine uptake and further consuming NADPH reserves (Fig. 7) (127). Compared with classical PCD pathways such as apoptosis, pyroptosis and ferroptosis, evidence supporting the direct involvement of disulfidptosis in MetS remains extremely limited. A previous study primarily focused on cancer metabolism and cellular stress-related models rather than metabolic diseases (128). Nevertheless, several metabolic features of MetS, including glucose imbalance, oxidative stress and redox dysregulation, share biological similarities with cellular stress conditions known to induce disulfidptosis (129). Therefore, disulfidptosis may represent a potential but currently unvalidated mechanism linking metabolic stress to cellular injury. Future investigations should determine whether disulfidptosis is activated in metabolic tissues affected by MetS, including adipose tissue, the liver and vascular endothelium, and whether modulation of SLC7A11-dependent cystine metabolism influences metabolic disease progression.

In summary, emerging PCD pathways provide new perspectives for understanding metabolic disorders. However, their relevance to MetS remains at an early stage. Several key questions remain unresolved: First, whether PANoptosome formation occurs in metabolic tissues under physiological and pathological conditions; second, whether disulfidptosis represents a genuine metabolic disease-associated death mechanism or merely a cellular stress response; and third, how these emerging pathways interact with established PCD programs during disease progression. The key characteristics, regulatory molecules, biological consequences and representative

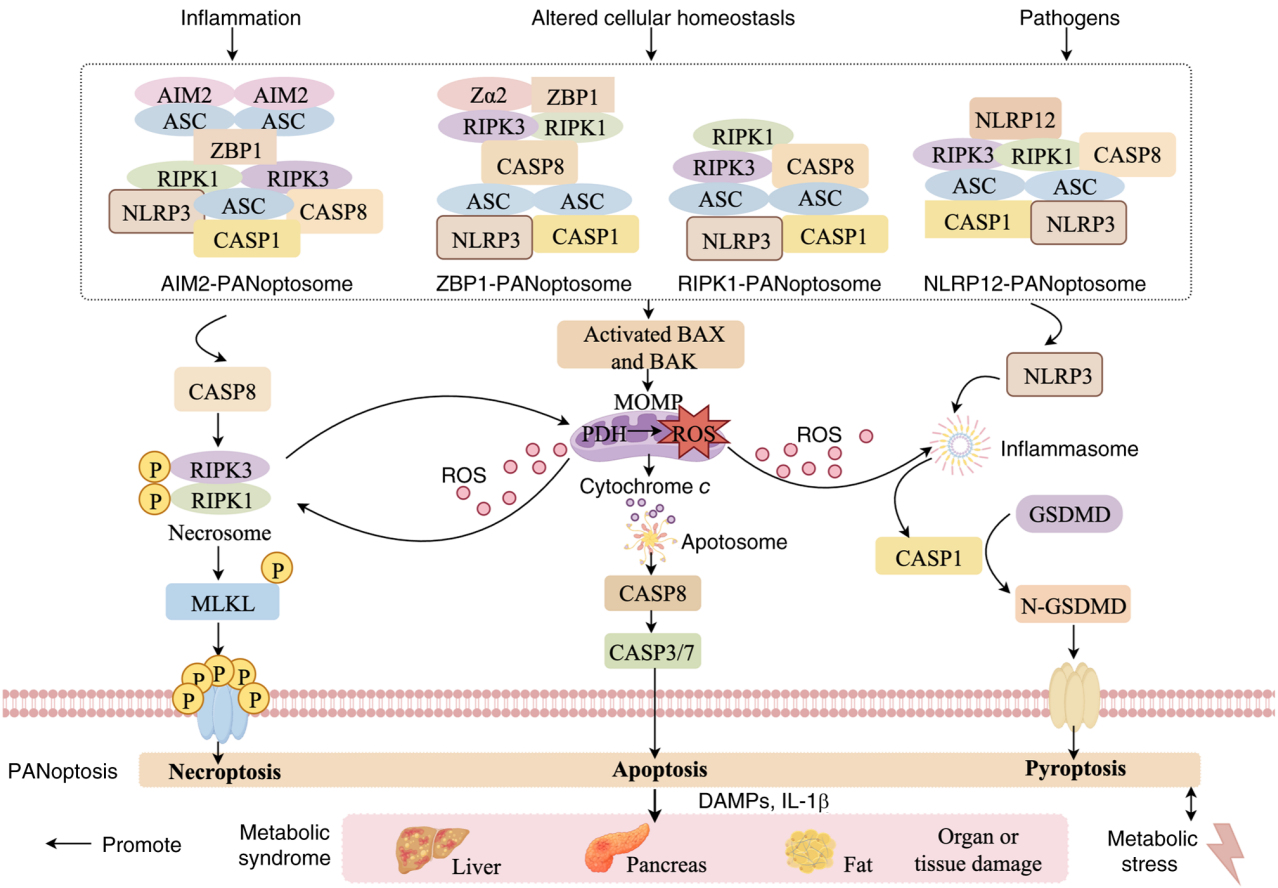

Figure 6. Schematic of PANoptosis assembly mechanisms in MetS. Different stimuli induce distinct PANoptosome complex assembly: Inflammatory stimuli form AIM2-PANoptosomes, cellular homeostasis disruption forms ZBP1-PANoptosomes and RIPK1-PANoptosomes, while pathogen stimulation forms NLRP12-PANoptosomes. PANoptosis may concurrently promote the release of DAMPs and proinflammatory factors, exacerbating tissue damage in the liver, pancreas, and adipose tissue, thereby contributing to the initiation and progression of MetS. Conversely, metabolic stress further enhances PANoptotic activation, establishing a vicious cycle. The figure was created using Figdraw (www.figdraw.com). MetS, metabolic syndrome; AIM2, absent in melanoma 2; ZBP1, Z-DNA-binding protein 1; RIPK, receptor-interacting serine/threonine-protein kinase; NLRP12, NLR family pyrin domain containing 12; DAMPs, damage-associated molecular patterns; GSDMD, gasdermin D; CASP, caspase; NLRP3, NLR family pyrin domain containing 3; ROS, reactive oxygen species.

evidence for the major PCD pathways involved in MetS are summarized in Table I (20,43,57,85,107,120,127).

5. Molecular crosstalk and network regulation among PCD pathways in MetS

In MetS, the interaction between distinct cell death pathways forms a highly intricate and dynamically regulated network. This crosstalk markedly amplifies tissue inflammation and damage, functioning as a crucial mechanism driving the progression of MetS toward end-organ complications. Different PCD pathways share common upstream signals, regulatory molecules and cellular stress responses, forming a complex cell death regulatory network that determines cell fate under metabolic stress conditions. Importantly, the biological outcome of PCD activation is highly context-dependent. The predominant cell death pathway varies depending on tissue type, metabolic environment, disease stage and stress intensity. Furthermore, inhibition of one PCD pathway may induce compensatory activation of alternative cell death pathways, thereby limiting the therapeutic efficacy of single-pathway interventions. Therefore, understanding the molecular crosstalk and hierarchical regulation among PCD pathways is essential for developing more precise therapeutic strategies for MetS.

Shared molecular nodes controlling the transition among PCD pathways

RIPK1/RIPK3 signaling as a molecular switch. The RIPK1/RIPK3 signaling axis represents one of the best-characterized molecular switches regulating the transition between different forms of PCD. Under physiological conditions, activation of death receptors such as TNFR1 can induce apoptosis through the activation of caspase-8 (130). However, when caspase-8 activity is inhibited or impaired, RIPK1 interacts with RIPK3 to form the necrosome complex, resulting in RIPK3-mediated phosphorylation of MLKL and subsequent necroptosis (131). In MetS, chronic inflammatory signals and metabolic stress may disrupt the balance between apoptosis and necroptosis. For example, obesity-associated inflammatory cytokines and excessive FFAs can activate TNF-α signaling, thereby enhancing RIPK1/RIPK3 signaling in adipose tissue and liver (132). Although apoptosis may initially function as a controlled mechanism for eliminating damaged cells, persistent metabolic stress may shift cell fate from apoptosis toward necroptosis, resulting in membrane rupture and DAMP release, thereby amplifying metabolic inflammation (133). Moreover, a previous study suggested that RIPK1/RIPK3 signaling may interact with inflammasome activation, thereby establishing a potential link between necroptosis and pyroptosis (134).

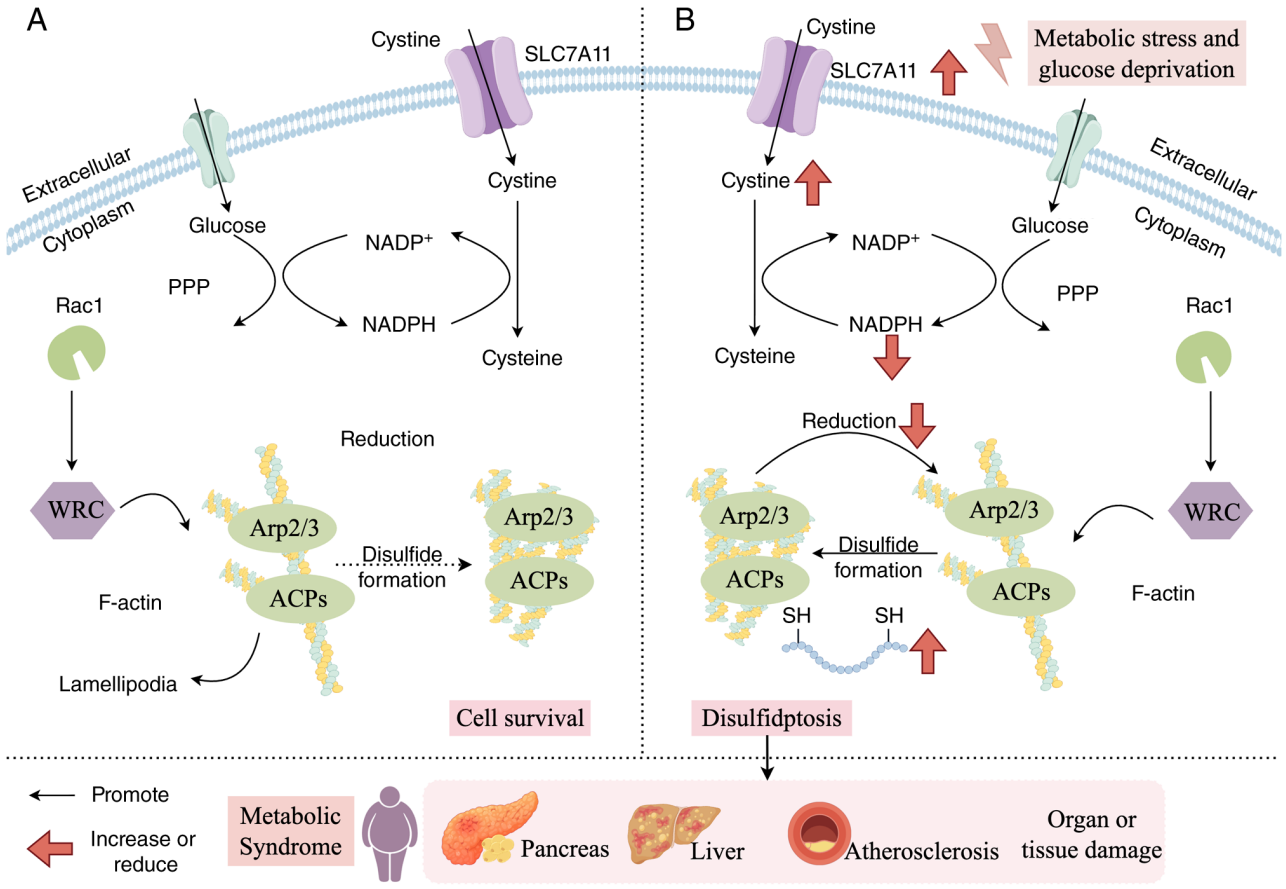

Figure 7. Schematic diagram of disulfidptosis mechanisms in MetS. (A) Under normal conditions glucose metabolism is balanced, the pentose phosphate pathway functions normally, generating sufficient NADPH to maintain GSH levels and ensure intracellular redox homeostasis. Cysteine entering cells via the transporter SLC7A11 is effectively reduced and utilized, preserving cytoskeletal stability. (B) During disulfidptosis, under the high-glucose and insulin-resistant conditions of MetS, cellular glucose metabolism becomes imbalanced. NADPH is extensively depleted with insufficient regeneration, leading to GSH exhaustion. Despite continued SLC7A11-mediated cystine influx, the loss of reducing capacity causes abnormal intracellular cystine accumulation. Cystine then forms extensive abnormal disulfide bonds with intracellular proteins, directly attacking and cross-linking cytoskeletal proteins (such as actin). This triggers cytoskeletal network disintegration, ultimately inducing cell death. This mechanism drives metabolic vascular complications and tissue fibrosis. The figure was created using Figdraw (www.figdraw.com). MetS, metabolic syndrome; SLC7A11, solute carrier family 7 member 11; GSH, glutathione.

Therefore, the RIPK1/RIPK3 signaling axis does not simply represent a necroptotic pathway but functions as a molecular switch that integrates inflammatory and metabolic signals to determine cell fate.

NLRP3 inflammasome as a convergence hub. The NLRP3 inflammasome represents another critical regulatory hub linking metabolic stress to inflammatory PCD. In response to metabolic stimuli and cellular stress signals, including saturated fatty acids, CCs, mitochondrial ROS and ERS, NLRP3 activation promotes caspase-1 cleavage and subsequent GSDMD-mediated pyroptosis (135). However, the role of NLRP3 extends beyond pyroptosis induction. Inflammasome activation can also influence other PCD pathways through inflammatory amplification, mitochondrial dysfunction and metabolic stress responses. For example, excessive NLRP3 activation promotes IL-1β and IL-18 secretion, which further aggravates IR, hepatic inflammation and adipose tissue dysfunction (136). Meanwhile, metabolic stress-induced mitochondrial damage enhances ROS production, creating a positive feedback loop among mitochondrial dysfunction, pyroptosis and other forms of cell death. In adipose tissue, NLRP3-mediated macrophage pyroptosis contributes to chronic inflammation and IR (137). In the liver, Kupffer cell pyroptosis promotes inflammatory responses and accelerates steatohepatitis progression (29). In pancreatic β-cells, inflammasome activation contributes to inflammatory injury and impaired insulin secretion (31). These findings indicate that pyroptosis functions as an important inflammatory amplifier within the broader PCD network.

Mitochondria as a central regulator linking apoptosis, autophagy and ferroptosis. Mitochondria serve as a central regulatory platform connecting multiple PCD pathways in MetS. As metabolic organs are highly dependent on mitochondrial function, nutrient overload and lipid accumulation can induce mitochondrial dysfunction, characterized by impaired oxidative phosphorylation, excessive ROS generation, mitochondrial membrane potential disruption and defective mitochondrial quality control (138,139). Mitochondrial dysfunction directly activates apoptosis through cytochrome *c* release and subsequent activation of the caspase cascade (140). Meanwhile, defective mitophagy impairs mitochondrial clearance, resulting in the accumulation of damaged mitochondria and further enhancing oxidative stress and inflammatory signaling (141). Thus, mitophagy dysfunction may increase cellular susceptibility to apoptosis and other stress-induced death pathways. In addition, mitochondria-mediated oxidative

Table I. Biochemical characteristics of cell death pathways, key regulatory factors, pathogenesis in MetS, representative tissues, evidence source and evidence level in MetS.

Mode of cell death	Biochemical features	Key regulatory factors	Pathogenesis in MetS	Representative tissues	Evidence source	Evidence level	(Refs.)
Apoptosis	Release cytochrome c, activate pro-apoptotic proteins of the Bcl-2 family to form apoptosomes, initiate the caspase processing cascade, leading to DNA fragmentation	1. Caspase-8, -9, -3 2. Bcl-2 family proteins 3. p53 4. MAPK signaling pathway	1. Reduction in pancreatic β- cells 2. Endothelial cell dysfunction 3. Adipose tissue remodeling	Pancreas, adipose tissue, liver	Human studies and animal models	A/B	(20)
Pyroptosis	Caspase-dependent cleavage of gasdermin triggers inflammation and releases IL-18 and IL-1β	1. NLRP3, caspase-1/4/5/11 2. GSDMD 3. IL-1β, IL-18	1. The core link connecting metabolic inflammation 2. Insulin resistance 3. Adipose tissue inflammation	Liver, muscle, adipose tissue	Animal models and mechanistic studies	B	(43)
Autophagy	Increased lysosomal activity, degradation of p62 protein, autophagosome formation, no inflammatory response	1. ATG 2. mTOR pathway (inhibits autophagy), AMPK pathway (activates autophagy) 3. Beclin-1, LC3-II	1. Protective: Basal levels of autophagy maintain β-cell function and insulin sensitivity 2. Destructive: Excessive autophagy activation or dysfunction contributes to β-cell exhaustion and tissue damage	Liver, cardiovascular system	Cell/animal studies	A/B	(57)
Ferroptosis	Intracellular Fe^{2+} levels increase, generating large amounts of ROS, depleting GSH, and reducing GPX4 activity, leading to the accumulation of lipid peroxides	1. GPX4, SLC7A11, GSH, Nrf2 2. ACSL4, free iron, LOXs	1. Lipid peroxidation-driven 2. Liver injury 3. Pancreatic β-cell damage 4. Cardiomyopathy	Adipose tissue, liver	Animal models	B	(85)
Necroptosis	Decreased ATP levels activate RIP1 and RIP3, and MLKL releases DAMP, triggering a secondary inflammatory response	1. RIPK1, RIPK3, MLKL 2. Caspase-8	1. Exacerbate tissue inflammation 2. Damage insulin target organs 3. Promote atherosclerosis	Adipose tissue, liver, pancreas	Animal and human tissue	C	(107)

Table I. Continued.

Mode of cell death	Biochemical features	Key regulatory factors	Pathogenesis in MetS	Representative tissues	Evidence source	Evidence level	(Refs.)
PANoptosis	Activation of caspase-8 cleaves GSDMD/GSDME during pyroptosis; activation of MLKL perforates the plasma membrane during necroptosis; activation of caspase-3/7 cleaves substrates during apoptosis	1. RIPK1, RIPK3 2. Caspase-8 3. Caspase-3/7 4. MLKL 5. GSDME	This phenomenon may occur when multiple pathways such as apoptosis and necroptosis are simultaneously activated within the complex stress environment of MetS	Immune cells, metabolic tissues	Preclinical	D	(120)
Disulfidptosis	Glucose deprivation induces high expression of SLC7A11, leading to excessive cystine uptake by cells. This depletes NADPH and forms numerous abnormal disulfide bonds within cytoskeletal proteins such as actin. Consequently, the cytoskeletal network undergoes contraction, aggregation, and fragmentation	1. NADPH levels 2. SLC7A11 3. Actin cytoskeletal proteins 4. Oxidative-reductive imbalance	Glucose-deprivation stress	Unknown/ under investigation	Limited studies	D	(127)

NLRP3, NLR family pyrin domain containing 3; GSDMD, gasdermin D; IL-1β, interleukin-1β; IL-18, interleukin-18; ATG, autophagy-related gene; mTOR, mechanistic target of rapamycin; AMPK, AMP-activated protein kinase; LC3-II, microtubule-associated protein 1 light chain 3-II; GPX4, glutathione peroxidase 4; SLC7A11, solute carrier family 7 member 11; GSH, glutathione; Nrf2, nuclear factor erythroid 2-related factor 2; ACSL4, acyl-CoA synthetase long-chain family member 4; LOXs, lipoxygenases; RIPK1, receptor-interacting serine/threonine-protein kinase 1; RIPK3, receptor-interacting serine/threonine-protein kinase 3; MLKL, mixed lineage kinase domain-like protein; DAMPs, damage-associated molecular patterns; NADPH, nicotinamide adenine dinucleotide phosphate.

imbalance contributes to ferroptosis by promoting iron-dependent lipid peroxidation (142). Excessive mitochondrial ROS production facilitates the oxidation of polyunsaturated fatty acids and compromises antioxidant defense systems, particularly the GPX4-dependent pathway (143). Therefore, mitochondrial homeostasis represents a critical determinant of whether cells undergo adaptive survival responses or irreversible death under metabolic stress.

GPX4/SLC7A11 axis connecting ferroptosis and disulfidptosis. Redox regulation represents another important regulatory interface between ferroptosis and the emerging disulfidptosis pathway. Ferroptosis is primarily driven by iron-dependent lipid peroxidation, whereas disulfidptosis is associated with abnormal disulfide stress caused by impaired cystine metabolism. The SLC7A11/GSH system represents a shared regulatory axis connecting these pathways. SLC7A11 promotes cystine uptake, maintaining intracellular GSH synthesis and supporting GPX4 activity, thereby preventing the accumulation of lipid peroxides and ferroptotic cell death (144,145). Under conditions of severe metabolic stress, particularly glucose deprivation, impaired cystine utilization may disrupt redox homeostasis, leading to excessive disulfide accumulation and cytoskeletal collapse (146). Although direct evidence linking disulfidptosis to MetS remains limited, the

metabolic regulation of SLC7A11 suggests potential interactions between ferroptosis and newly recognized forms of PCD. Further studies are required to determine whether modulation of this axis contributes to metabolic disease progression.

Tissue-specific dominance and compensation of PCD pathways in MetS. Although multiple PCD pathways coexist within metabolic tissues, their relative contributions vary according to tissue characteristics and disease stage. Therapeutic inhibition of one pathway may result in compensatory activation of alternative cell death pathways. Therefore, identifying dominant PCD patterns in different organs is essential for understanding MetS pathogenesis and designing targeted interventions. Adipose tissue dysfunction is a central feature of obesity-associated MetS. Under conditions of excessive nutrient accumulation, adipocyte hypertrophy induces hypoxia, ERS and mitochondrial dysfunction, resulting in increased apoptosis (29). Dying adipocytes release inflammatory signals that recruit macrophages and promote chronic adipose inflammation. Meanwhile, macrophage activation stimulates NLRP3 inflammasome formation and pyroptosis, leading to enhanced production of IL-1β and IL-18 (51). Thus, apoptosis and pyroptosis cooperate to establish an inflammatory microenvironment that promotes IR.

The liver is one of the major target organs affected by MetS. In MASLD, excessive lipid accumulation induces mitochondrial dysfunction, oxidative stress and iron imbalance (147). Although hepatocyte apoptosis contributes to liver injury, increasing evidence suggests that ferroptosis serves a critical role in lipid peroxidation-associated hepatic damage. Impaired antioxidant defense, particularly reduced GPX4 activity, increases susceptibility to ferroptosis (148). Meanwhile, defective mitophagy further aggravates mitochondrial injury and lipid accumulation, creating a vicious cycle among mitophagy impairment, ferroptosis and inflammation.

Pancreatic β-cells are particularly vulnerable to metabolic stress due to their limited antioxidant capacity. Chronic hyperglycemia, inflammatory cytokines and ERS induce β-cell apoptosis, leading to progressive loss of insulin-producing cells (30). In addition, inflammasome activation promotes β-cell pyroptosis, further impairing insulin secretion. Therefore, apoptosis and pyroptosis represent complementary mechanisms contributing to pancreatic dysfunction in MetS. Vascular endothelial dysfunction is a major complication of MetS. Hyperglycemia, dyslipidemia and oxidative stress impair endothelial mitochondrial function and activate apoptotic pathways (149). Emerging evidence also suggests that ferroptosis contributes to endothelial lipid peroxidation and vascular inflammation (150). Therefore, endothelial PCD regulation may represent an important therapeutic target for preventing cardiovascular complications associated with MetS.

Therapeutic importance of targeting multiple PCD pathways. Due to the extensive crosstalk and compensatory mechanisms among PCD pathways, targeting a single cell death modality may offer limited therapeutic efficacy. For example, inhibition of pyroptosis may reduce inflammatory injury but cannot fully ameliorate mitochondrial dysfunction or oxidative stress. Similarly, ferroptosis inhibition may protect hepatocytes from lipid peroxidation-induced injury but may not completely resolve metabolic inflammation. Therefore, future therapeutic strategies should consider coordinated modulation of multiple PCD pathways rather than selective targeting of individual death programs. Pharmacological approaches targeting common upstream events, such as mitochondrial dysfunction, oxidative stress, inflammasome activation and metabolic dysregulation, may provide broader protective effects. For instance, AMPK activation can simultaneously enhance autophagy, improve mitochondrial function and suppress inflammatory signaling. Similarly, modulation of Nrf2 signaling may simultaneously enhance antioxidant defense, regulate ferroptosis susceptibility and modulate inflammatory responses. However, multi-target regulation also presents challenges, including tissue specificity, potential interference with physiological cell death processes, and difficulties in determining optimal timing and dosage. Future studies integrating single-cell sequencing, multi-omics approaches and data from human clinical cohorts are needed to identify precise PCD regulatory networks and develop individualized therapeutic strategies for MetS.

6. Research on novel regulatory mechanisms in MetS

In MetS, epigenetic modifications, exosomes, and PCD form a dynamic and mutually regulated network that drives chronic inflammation and tissue injury. The high-glucose, high-fat, inflammatory environment associated with MetS induces epigenetic alterations, affecting the expression of genes involved in PCD. These epigenetic changes can be encapsulated into exosomes, released into the circulation and subsequently delivered to distant tissues. Exosomes transfer these aberrant signals, altering PCD processes in recipient cells, thus exacerbating metabolic dysfunction and organ damage (151). Therefore, targeting epigenetic mechanisms or using engineered exosomes to modulate PCD represents an innovative strategy for disrupting this detrimental cycle.

Epigenetic regulation of PCD in MetS. Epigenetic modifications precisely control the initiation and execution of PCD by regulating gene expression via DNA methylation, histone modifications and non-coding RNAs, without altering the underlying DNA sequence (152). Concurrently, epigenetic mechanisms regulate autophagy during nutritional excess or deficiency. A previous study revealed that coactivator-associated arginine methyltransferase 1-mediated methylation of histone arginine residues critically regulates autophagy, particularly activating autophagic processes during starvation (153). Experimental evidence indicates that obesity-induced epigenetic changes in adipocytes establish cellular 'memory', increasing susceptibility to weight regain following caloric restriction and activating hepatic inflammatory pathways (154). Hypermethylation at cg02814054 promotes obesity by reducing microtubule associated serine/threonine kinase 3 expression, whereas hypomethylation at cg06028605 elevates obesity risk by downregulating SLC5A11 (155). Despite substantial evidence linking epigenetic modifications to obesity onset and progression, mechanisms governing epigenetic regulation of autophagy in response to drastic nutritional changes remain unclear. Laha *et al* (156) demonstrated that homocysteine modifies the epigenome, promoting lipogenesis and impairing fatty acid metabolism through Zfp407-mediated

pyroptosis and peroxisome proliferator-activated receptor γ-dependent pathways, contributing notably to obesity and related metabolic dysfunctions. Extensive research has also examined epigenetic abnormalities, including DNA methylation, histone modifications and miRNAs, in type 1 diabetes. DNA methylation and miRNAs are proposed biomarkers predicting pancreatic β-cell death (157). Abnormal histone acetylation and deacetylation mechanisms are involved in hypertension; A previous study confirmed that elevated histone H3 acetylation associates with primary hypertension progression (158).

Exosome-mediated regulation of PCD in MetS. Exosomes are nanoscale extracellular vesicles secreted by cells, carrying proteins, lipids, DNA and abundant non-coding RNAs. They function as crucial mediators of inter-organ communication (159). DNA methyltransferases or histone-modifying enzymes carried by exosomes can enter the nucleus of recipient cells, directly altering the epigenetic state of genes associated with PCD. Under MetS conditions, the composition of exosomes secreted by adipose tissue, liver and muscle cells undergoes notable alterations. Persistent hyperglycemia activates monocytes/macrophages, causing an imbalance in M1/M2 polarization. These activated cells release exosomes enriched with miR-30a, interacting with renal tubular epithelial cells to activate the transient receptor potential canonical 6-calcineurin A-nuclear factor of activated T cells pathway, thus triggering PCD (160). Adipocyte-derived exosomes in MetS contain elevated pro-inflammatory miRNAs (miR-27a and miR-155) and pro-PCD miRNAs, whereas protective miRNAs (miR-30a and miR-124) are decreased. For instance, a previous study demonstrated that extracellular adipocyte-derived miR-1224 suppresses M2 macrophage polarization in obesity-induced inflammation via the Musashi RNA-binding protein 2-regulated Wnt/β-catenin signaling axis (161). Additionally, exosome-transported long non-coding RNAs (lncRNAs) and circular RNAs function as competitive endogenous RNAs (ceRNAs) by sequestering miRNAs in recipient cells, thus releasing their suppression of PCD-related gene expression. For instance, lncRNAs from adipocyte-derived exosomes are taken up by hepatocytes, promoting pyroptosis and hepatic steatosis through the miR-34a/sirtuin 1 pathway. Exosomes may also carry inflammasome components (such as NLRP3) or DAMPs, directly seeding inflammation and pyroptosis in recipient cells. Xiong *et al* (162) reported that astragaloside IV inhibits diabetic endothelial cell pyroptosis by enhancing exosome release from endothelial progenitor cells and modulating PI3KR2/SPRED1 signaling. Yan *et al* (163) demonstrated that a high-fat diet reduces adipocyte AMPKα1 activity, decreasing exosome secretion and inhibiting NAFLD progression both *in vivo* and *in vitro*, highlighting the potential of blocking exosome release from white adipose tissue as a novel therapeutic approach for NAFLD.

7. Therapeutic strategies targeting PCD: From experimental evidence to clinical translation

Pharmacological modulation. Due to the contribution of multiple PCD pathways to MetS progression, pharmacological modulation of specific cell death pathways has emerged as a potential therapeutic strategy. Several small-molecule regulators targeting apoptosis, pyroptosis, ferroptosis, necroptosis and autophagy-associated pathways have demonstrated protective effects in experimental models of metabolic diseases. However, most evidence is derived from preclinical studies, and clinical translation remains challenging. Apoptosis is the most extensively studied form of PCD. The serine protease inhibitor camostat mesilate was shown to alleviate hypertension and renal injury in MetS rats by inhibiting podocyte apoptosis and reducing podocyte injury through both dependent and independent mechanisms (164). Methyl-β-cyclodextrin, a cyclic oligosaccharide commonly used to lower membrane cholesterol, induces apoptosis in mesenchymal stromal cells, improves glucose transport and endoplasmic reticulum function, enhances antioxidant capacity, and effectively treats metabolic disorders such as IR, MetS and diabetes (165). Epigallocatechin-3-gallate (EGCG), a compound extracted from green tea known for its antioxidant and anti-inflammatory effects, alleviates bladder apoptosis and ovarian hormone deficiency in rat models of MetS and ovarian dysfunction (166). Strategies targeting pyroptosis have mainly focused on inhibiting inflammasome activation or gasdermin-mediated membrane pore formation. MCC950 is a selective NLRP3 inflammasome inhibitor that exerts anti-inflammatory effects in experimental models of obesity, IR and MASLD by reducing caspase-1 activation and IL-1β production; however, caution is warranted due to the reported hepatotoxicity of MCC950 (55). Disulfiram, traditionally used for alcohol dependence, has been reported to inhibit GSDMD pore formation and suppress pyroptosis-related inflammatory responses in preclinical studies (167,168). However, the safety profile and long-term efficacy of inflammasome inhibition require further evaluation because inflammasomes also contribute to host defense against infection. Exercise can notably enhance metabolic health by suppressing inflammatory pyroptosis, representing a novel therapeutic target for chronic disorders such as age-related obesity, muscle atrophy and IR/T2DM (169). Therefore, exercise constitutes a promising strategy to inhibit pyroptosis, reduce inflammation and promote metabolic health.

Unlike numerous classical PCD pathways, autophagy exhibits a dual role in MetS, and therapeutic modulation requires careful consideration of disease stage and tissue context. Rapamycin-induced autophagy activation has demonstrated beneficial effects in experimental models by improving mitochondrial quality control and lipid metabolism (79). Conversely, excessive inhibition of autophagy may aggravate metabolic dysfunction, highlighting the importance of precise regulation rather than indiscriminate activation or inhibition. Peng *et al* (170) demonstrated that EGCG inhibits obesity and glucose intolerance induced by a high-fat diet in C57BL/6 mice by modulating autophagy and lipolysis. Furthermore, compounds including luteolin (171), berberine (172), ferulic acid (173), MSI-1436 (174), elamipretide (175) and melatonin (176) exhibit therapeutic potential in MetS by regulating autophagy and ferroptosis pathways. Lim *et al* (177) identified a small molecule named MSL through chemical library screening, which enhances autophagic flux and improves metabolic profiles in obese and MetS mice, thus representing a promising therapeutic candidate. Drugs such as

memantine (178) and moxonidine (179) have shown beneficial effects in MetS model rats by modulating autophagy. Cai (180) conducted a randomized controlled trial involving 84 patients with MetS who were classified according to the Traditional Chinese Medicine (TCM) syndrome differentiation framework as having Qi stagnation and phlegm-stasis syndrome, a TCM diagnostic pattern characterized by impaired Qi circulation and the accumulation of phlegm and blood stasis. Participants were randomized into a control group receiving conventional Western medical treatment and a treatment group receiving conventional treatment combined with Shugan Wendan Decoction, a traditional Chinese herbal formula. After 12 weeks, the results indicated that Shugan Wendan Decoction improves IR, glucose and lipid metabolism, and oxidative stress in patients with MetS by upregulating liver X receptor α and mediating autophagy/apoptosis pathways. Additionally, the PTP1B inhibitor MSI-1436 has entered Phase 1 and 1b clinical trials, although currently only for obesity and T2DM treatment (NCT00606112, 2008; NCT00806338, 2009) (174). Regarding non-pharmacological interventions, a previous study demonstrated that intermittent fasting and ketogenic diets enhance insulin sensitivity, promote autophagy, reduce inflammation and improve metabolic indicators in patients with MetS and T2DM, including reductions in HbA1c, fasting blood glucose, body weight and TGs (181). Additionally, chronic intermittent hypobaric hypoxia protects vascular endothelium by modulating autophagy in MetS rat models (182).

Ferroptosis has attracted increasing attention as a potential therapeutic target for metabolic liver diseases due to its close association with lipid peroxidation and oxidative stress. Ferrostatin-1, a classical ferroptosis inhibitor, suppresses lipid peroxidation by preventing iron-dependent oxidative damage (183). In cellular and animal models of metabolic liver injury, inhibition of ferroptosis has been shown to preserve hepatocyte viability, reduce oxidative stress and alleviate inflammatory responses (184). Similar protective effects have been reported for liproxstatin-1, another ferroptosis inhibitor, particularly in experimental models of hepatic injury (185). Nevertheless, whether ferroptosis inhibition provides long-term metabolic benefits remains uncertain because ferroptosis may also participate in physiological iron metabolism and immune regulation. In addition, although GPX4 activators can alleviate ferroptosis by inhibiting lipid peroxidation, they also exhibit limited target specificity. Therapeutic inhibition of necroptosis has mainly focused on targeting the RIPK1/RIPK3/MLKL signaling axis. Necrostatin-1 (Nec-1), a selective RIPK1 inhibitor, has been widely used as a pharmacological tool to suppress necroptosis. In experimental models of metabolic disorders, inhibition of RIPK1 signaling has been shown to reduce inflammatory responses, improve insulin sensitivity and attenuate tissue injury (186). For example, Nec-1 treatment reduced inflammatory signaling activation and cell death in models of obesity-associated metabolic dysfunction and hepatic injury (187). However, the application of Nec-1 in clinical settings is limited by concerns regarding target specificity, pharmacokinetic properties and the physiological roles of necroptosis in immune regulation. Additional compounds, including orientin (188), dihydroquercetin (189), clofibrate (190), astaxanthin (191), longan flower water extract (192), 5-azacytidine/resveratrol (193) and clomiphene (194), have also been investigated for their potential effects on PCD-related processes in experimental models. Representative compounds and drugs targeting PCD pathways for the treatment of MetS are summarized in Table II (164-166,170-176,179,180,188-197).

Current clinical status and challenges for translation. Due to the extensive crosstalk among PCD pathways, simultaneous modulation of multiple cell death programs may provide superior therapeutic effects compared with single-pathway inhibition. Targeting PCD represents a promising therapeutic strategy for MetS. However, translating mechanistic discoveries into clinical applications remains challenging. Current therapeutic strategies are mainly supported by preclinical studies, with most approaches focusing on pharmacological modulation of specific PCD pathways. Therefore, beyond the identification of potential therapeutic agents, it is essential to critically evaluate the translational barriers, including target specificity, tissue selectivity, biomarker availability and long-term safety. Despite promising preclinical findings, no PCD-targeting agent has yet been approved specifically for the treatment of MetS. Most available evidence is derived from cellular and animal studies, and several barriers limit clinical translation: i) Limited clinical evidence: Although several metabolic interventions indirectly influence PCD pathways, including lifestyle interventions and existing metabolic therapies, direct clinical trials targeting specific PCD pathways in MetS or MASLD remain scarce; ii) off-target effects: Numerous PCD regulators participate in physiological processes beyond cell death regulation; for example, inhibition of apoptosis or inflammasome signaling may interfere with immune surveillance and tissue homeostasis; iii) tissue specificity: A major challenge is achieving tissue-specific modulation; a PCD pathway that is harmful in one tissue may be protective in another, therefore systemic inhibition may produce unpredictable outcomes; and iv) long-term safety: Because PCD pathways are essential for normal development, immune regulation and tissue renewal, long-term safety evaluation is required before clinical application.

8. Conclusions and outlook

MetS is a complex metabolic disorder characterized by a markedly high global prevalence. The primary drivers of MetS include IR, chronic inflammation and adipose tissue dysfunction, which collectively pose substantial challenges for effective management. Current evidence indicates that PCD is not only a consequence but also a critical pathological factor influencing the onset and progression of MetS. Various forms of PCD interact with metabolic tissue injury, such as in adipose tissue, liver, pancreatic islets and blood vessels, triggering cascading reactions leading ultimately to systemic metabolic dysfunction. Specifically, apoptosis of pancreatic β-cells reduces insulin secretion, while adipocyte apoptosis intensifies adipose dysfunction and promotes pro-inflammatory adipokine release. Metabolic stress-induced necroptosis exacerbates inflammation and strongly associates with fatty liver disease and IR. Lipotoxicity, hyperglycemia and related stressors activate the NLRP3 inflammasome, inducing pyroptosis and amplifying chronic, low-grade inflammation in

Table II. Representative compounds/drugs targeting programmed cell death for MetS treatment.

Compounds/drugs	Research model	Target molecule	Mechanism	(Refs.)
Camostat mesilate	MetS model rats	TG ↓, TC ↓, Bax/Bcl-2 ↓, pro-caspase-3 ↓	Apoptosis ↓	(164)
Methyl-β-cyclodextrin	Horse MetS model	ROS ↓, SOD ↑, iNOS ↑, Bcl-2 ↓, p53 ↑, Bax ↑	Apoptosis ↑	(165)
Epigallocatechin-3-gallate	MetS model rats	Apoptotic cells ↓, Bcl-2 ↑, GRP78 ↓, CHOP ↓, caspase-12 ↓	Apoptosis ↓	(166)
	MetS mouse model	PPARγ ↓, C/EBPα ↓, FASN ↓, HSL ↑, ATGL ↑, LC3 ↓, p62 ↓	Autophagy ↑	(170)
Luteolin	Rat model of MetS-induced cardiac injury	BCL-2 ↓, CASP-3 ↑, CASP-9 ↑, NR4A2 ↓, p53 ↓, IL-6 ↓, IL-1β ↓, TNF-α ↓	Apoptosis ↓, autophagy ↑	(171)
Berberine	Rat model of MetS combined with carotid stenosis	Wnt/GSK-3β/β-catenin pathway activity ↓	Apoptosis ↓	(172)
Ferulic acid	MetS hepatocyte model	MMP ↓, ROS ↓, ATP ↑, AMPK ↑, SIRT1 ↑	Autophagy ↑	(173)
MSI-1436	Horse MetS model	IL-1β ↓, TNF-α ↓, TGF-β ↓, hs70 ↑, Beclin-1 ↑, MFN2 ↑, PINK1 ↑, CHOP ↓, ATF6 ↓, HSPA5 ↓, XBP1 ↓, LC3A ↑, LC3B-I ↓, LC3B-II ↓	Autophagy ↑	(174)
Elamipretide	MetS pig kidney cell model	p62 ↑, ATG5-12 ↑, mTOR ↑, AMPK ↑, ULK-1 ↑, cytochrome *c* ↑	Autophagy ↑, apoptosis ↓	(175)
Melatonin	MetS hamster model	mTOR ↑, LC3-II ↑, LC3-II/LC3-I ↑, Beclin1 ↑	Autophagy ↑	(176)
Moxonidine	MetS model rats	IL-6 ↓, c-TnI ↓, caspase-3 ↓, TGF-β1 ↓, MMP-9 ↓, NR4A2 ↓, p53 ↑, LC3A/B ↑, Beclin-1 ↑, SQSTM1 ↓, p62 ↓	Autophagy ↑, apoptosis ↓	(179)
Shugan Wendan decoction	Patients with MetS	FPG ↓, HbA1c ↓, FINS ↓, HOMA-IR ↓, TC ↓, TG ↓, LDL-C ↓, HOMA-IR ↓, MDA ↓, HDL-C ↑, SOD ↑, GSH-PX ↑	Autophagy ↑, apoptosis ↓	(180)
Orientin	Horse MetS model	Bax/Bcl-2 ↓, p21 ↓, TP53, ROS ↓, SOD1 ↑	Apoptosis ↑	(188)
Dihydroquercetin	MetS model rats	GSH-Px ↑, GSH ↑, TNF-α ↓, IL-1β ↓, BDNF ↑, ROS, apoptotic cells ↓	Apoptosis ↓	(189)
Clofibrate	MetS model rats	IL-1β ↓, IL-6 ↓, TNF-α ↓, MMP-2 ↓, apoptotic cells ↓	Apoptosis ↓	(190)
Astaxanthin	Horse MetS model	p21 ↓, p53 ↓, Bax ↓, caspase-3 ↓, caspase-8 ↓, caspase-9 ↓, Bcl-2 ↑, SOD1 ↑, SOD2 ↑	Apoptosis ↓	(191)
Longan flower water extract	MetS model rats	Fas ↓, FADD ↓, caspase-8 ↓, caspase-3 ↓, Bax ↓, Bak ↓, Bax/Bcl-2 ↓, Bak/Bcl-xL ↓, IGF-1R ↑, Bcl-2 ↑	Apoptosis ↓	(192)
5-azacytidine, resveratrol	Horse MetS model	p21 ↓, Bax ↑, Bcl-2 ↑, Beclin-3 ↓, LC3 ↓, LAMP-2 ↑, MMP ↑, SOD ↑, p62 ↑, LAMP-2 ↑, mTOR ↓	Autophagy ↑	(193)
Clomiphene citrate	MetS mouse model	LC3-II ↑, p62 ↑, LAMP2 ↑, CTSB ↑, CTSD ↑, ATGL ↑, HSL ↑, MGL ↑, LAL ↑	Autophagy ↑	(194)
Pioglitazone	MetS model rats	Apoptotic cells ↓, p62 ↑, LC3 ↑	Autophagy ↑, apoptosis ↓	(195)
Chaiqi decoction	MetS model rats	LC3 ↑, LC3II/I ↑, Beclin-1 ↑	Autophagy ↑	(196)

Table II. Continued.

Compounds/drugs	Research model	Target molecule	Mechanism	(Refs.)
Metformin	MetS mouse model	ROS ↓, Nrf2 ↑, SLC7A11 ↑, GPX4 ↑, MDA ↓, GSH ↓	Ferroptosis ↓	(197)

↑, increased expression levels; ↓, decreased expression levels; MetS, metabolic syndrome; TG, triglycerides; TC, total cholesterol; Bax, BCL2-associated X protein; Bcl-2, B-cell lymphoma 2; ROS, reactive oxygen species; SOD, superoxide dismutase; iNOS, inducible nitric oxide synthase; p53, tumor protein p53; GRP78, glucose-regulated protein 78; CHOP, C/EBP homologous protein; PPARγ, peroxisome proliferator-activated receptor γ; C/EBPα, CCAAT/enhancer-binding protein α; FASN, fatty acid synthase; HSL, hormone-sensitive lipase; ATGL, adipose triglyceride lipase; LC3, microtubule-associated protein 1 light chain 3; NR4A2, nuclear receptor subfamily 4 group A member 2; IL-6, interleukin-6; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α; Wnt, Wingless-related integration site; GSK-3β, glycogen synthase kinase 3β; MMP, matrix metalloproteinase; ATP, adenosine triphosphate; AMPK, AMP-activated protein kinase; SIRT1, sirtuin 1; TGF-β, transforming growth factor-β; HSPA5, heat shock protein family A member 5; MFN2, mitofusin 2; PINK1, PTEN-induced kinase 1; ATF6, activating transcription factor 6; XBP1, X-box binding protein 1; LC3A/B, microtubule-associated protein 1 light chain 3 A/B; ATG5-12, autophagy-related 5-12 conjugate; mTOR, mechanistic target of rapamycin; ULK1, unc-51-like autophagy activating kinase 1; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; FINS, fasting insulin; HOMA-IR, homeostatic model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; MDA, malondialdehyde; HDL-C, high-density lipoprotein cholesterol; GSH-Px, glutathione peroxidase; TP53, tumor protein p53; SOD, superoxide dismutase; GSH, glutathione; BDNF, brain-derived neurotrophic factor; Fas, Fas cell surface death receptor; FADD, Fas-associated death domain protein; Bak, BCL2 antagonist/killer 1; Bcl-xL, B-cell lymphoma-extra large; IGF-1R, insulin-like growth factor 1 receptor; LAMP-2, lysosomal-associated membrane protein 2; CTSB, cathepsin B; CTSD, cathepsin D; MGL, monoglyceride lipase; LAL, lysosomal acid lipase; Nrf2, nuclear factor erythroid 2-related factor 2; SLC7A11, solute carrier family 7 member 11; GPX4, glutathione peroxidase 4.

MetS. Ferroptosis, marked by iron-dependent lipid peroxidation, correlates closely with hepatocyte loss and endothelial injury in NASH. Autophagy exerts protective functions in insulin-sensitive tissues, whereas impaired autophagy accelerates metabolic deterioration. Recently discovered mechanisms such as PANoptosis and disulfidptosis provide novel insights into the complex pathophysiology of MetS. Furthermore, innovative regulatory mechanisms involving epigenetics and exosomes notably influence chronic inflammation and tissue damage in MetS by modulating PCD, highlighting their potential as therapeutic targets.

Although substantial progress has been achieved in understanding the role of PCD in MetS, several fundamental questions remain unresolved. First, the precise mechanisms determining cell fate selection among different PCD pathways remain unclear. Under metabolic stress, cells may undergo apoptosis, pyroptosis, ferroptosis or interconnected forms of cell death; however, the molecular switches controlling these transitions require further investigation. Second, the tissue-specific regulation of PCD networks remains poorly understood. Different metabolic organs exhibit distinct metabolic environments and stress responses, suggesting that universal PCD-targeting strategies may not be optimal. Third, clinically applicable biomarkers for monitoring PCD activity are urgently needed. Current assessment of PCD activity mainly relies on experimental markers, whereas circulating indicators capable of predicting disease progression and therapeutic response remain limited. Fourth, future therapeutic development should move beyond single-pathway interventions toward precision regulation of PCD networks. Emerging approaches, including targeted nanoparticles, tissue-specific delivery systems and multi-omics-guided treatment strategies, may provide new opportunities for personalized management of MetS. Fifth, the current understanding of PCD in MetS is largely based on experimental models, and differences in disease models, tissue specificity and methodological approaches limit direct clinical translation.

To address these limitations, future research should focus on several key areas. At the mechanistic level, multi-omics techniques, including single-cell sequencing, spatial transcriptomics and proteomics, should be utilized to systematically decipher tissue-specific activation patterns of distinct forms of PCD across various MetS-related tissues. Such analyses will clarify the complex interactions between PCD pathways and factors such as metabolic reprogramming, gut microbiome dysbiosis and epigenetic modifications, thus identifying crucial regulatory molecules and signaling cascades. These insights will enable more precise therapeutic targeting. Additionally, greater emphasis should be placed on exploring the interactions between different PCD subtypes, examining their synergistic or antagonistic roles in disease progression, thereby revealing multidimensional regulatory mechanisms driving MetS development. Regarding model optimization, more clinically relevant models, such as gene-edited animal models and patient-derived organoid systems, should be developed to improve replication of human disease features. These advanced models will provide robust platforms for validating molecular mechanisms and screening potential therapeutics. Furthermore, establishing a comprehensive clinical database of PCD characteristics through multicenter cohort studies involving patients with MetS will be beneficial. Integrating clinical phenotypes with prognostic data will help clarify the clinical relevance of PCD-related biomarkers. In the context of clinical translation, accelerating the development and clinical trials of PCD-targeted therapies should become a priority, emphasizing combination treatment strategies to enhance therapeutic efficacy and minimize adverse effects. Concurrently, research into personalized treatments based on genetic backgrounds, metabolic profiles and individual patterns of PCD activation should be intensified. Precision

medicine methodologies should be adopted to identify populations that would most benefit, enabling targeted prevention and intervention in MetS. Additionally, efforts should focus on developing standardized, highly specific and sensitive biomarker detection systems for PCD, facilitating their clinical adoption for early diagnosis, monitoring therapeutic efficacy and prognostic evaluation.

In summary, the importance of PCD in MetS is becoming increasingly clear, and numerous therapeutic targets are actively being investigated. Future studies should prioritize elucidating intricate interactions among these pathways and accelerating their translation into clinical practice. These steps are crucial for developing precise, effective therapeutics for MetS, ultimately reducing the substantial global burden posed by this widespread health issue.

Acknowledgements

Not applicable.

Funding

The present work was supported by the Noncommunicable Chronic Diseases-National Science and Technology Major Project (grant no. 2023ZD0509400) and The National Natural Science Foundation of China (grant no. 82574805).

Availability of data and materials

Not applicable.

Authors' contributions

JZ and QC designed and conceptualized the article; JZ and MZ prepared and wrote the article; YZ, CG and YD conducted literature searching and initial reviewing; LS, DZ and QZ did the study selection and assessment; QC reviewed the draft and provided suggestions for revision. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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.

References

1. Eckel RH, Grundy SM and Zimmet PZ: The metabolic syndrome. Lancet 365: 1415-1428, 2005.
2. Liang X, Or B, Tsoi MF, Cheung CL and Cheung BMY: Prevalence of metabolic syndrome in the United States National health and nutrition examination survey 2011-18. Postgrad Med J 99: 985-992, 2023.
3. Li Y, Zhao L, Yu D, Wang Z and Ding G: Metabolic syndrome prevalence and its risk factors among adults in China: A nationally representative cross-sectional study. PLoS One 13: e0199293, 2018.
4. Hu Y, Li W, Nie J, Zhang C, Zhou J, Hu Z, Zhou H and Lei X: Association between the atherogenic index of plasma and major adverse cardiovascular events in individuals with metabolic syndrome: findings from the UK biobank. Cardiovasc Diabetol 24: 444, 2025.
5. Kassi E, Pervanidou P, Kaltsas G and Chrousos G: Metabolic syndrome: definitions and controversies. BMC Med 9: 48, 2011.
6. Hsu CN, Hou CY, Hsu WH and Tain YL: Early-life origins of metabolic syndrome: Mechanisms and preventive aspects. Int J Mol Sci 22: 11872, 2021.
7. Wang M, Yu F, Zhang Y and Li P: Programmed cell death in tumor immunity: Mechanistic insights and clinical implications. Front Immunol 14: 1309635, 2024.
8. Guicciardi ME, Malhi H, Mott JL and Gores GJ: Apoptosis and necrosis in the liver. Compr Physiol 3: 977-1010, 2013.
9. Zhao X, Zhang H, Ding X, Wu H, Li M, Yin N, Gao J, Xu Y, Wang R, Qi Z, *et al*: ATP6AP2 ameliorates inflammation and pyroptosis in heart failure by promoting lysosome-dependent STING degradation. Apoptosis 31: 202, 2026.
10. Liu P, Anandhan A, Chen J, Shakya A, Dodson M, Ooi A, Chapman E, White E, Garcia JG and Zhang DD: Decreased autophagosome biogenesis, reduced NRF2, and enhanced ferroptotic cell death are underlying molecular mechanisms of non-alcoholic fatty liver disease. Redox Biol 59: 102570, 2023.
11. Parums DV: Editorial: Review articles, systematic reviews, meta-analysis, and the updated preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2020 Guidelines. Med Sci Monit 27: e934475, 2021.
12. Gluvic Z, Zaric B, Resanovic I, Obradovic M, Mitrovic A, Radak D and Isenovic ER: Link between metabolic syndrome and insulin resistance. Curr Vasc Pharmacol 15: 30-39, 2017.
13. Ramasubbu K and Devi Rajeswari V: Impairment of insulin signaling pathway PI3K/Akt/mTOR and insulin resistance induced AGEs on diabetes mellitus and neurodegenerative diseases: A perspective review. Mol Cell Biochem 478: 1307-1324, 2023.
14. Tripathy D, Mohanty P, Dhindsa S, Syed T, Ghanim H, Aljada A and Dandona P: Elevation of free fatty acids induces inflammation and impairs vascular reactivity in healthy subjects. Diabetes 52: 2882-2887, 2003.
15. Murakami T, Michelagnoli S, Longhi R, Gianfranceschi G, Pazzucconi F, Calabresi L, Sirtori CR and Franceschini G: Triglycerides are major determinants of cholesterol esterification/transfer and HDL remodeling in human plasma. Arterioscler Thromb Vasc Biol 15: 1819-1828, 1995.
16. Esteve E, Ricart W and Fernandez-Real JM: Adipocytokines and insulin resistance: The possible role of lipocalin-2, retinol binding protein-4, and adiponectin. Diabetes Care 32 (Suppl 2): S362-S367, 2009.
17. Bellingan GJ, Xu P, Cooksley H, Cauldwell H, Shock A, Bottoms S, Haslett C, Mutsaers SE and Laurent GJ: Adhesion molecule-dependent mechanisms regulate the rate of macrophage clearance during the resolution of peritoneal inflammation. J Exp Med 196: 1515-1521, 2002.
18. Burcelin R, Luche E, Serino M and Amar J: The gut microbiota ecology: A new opportunity for the treatment of metabolic diseases? Front Biosci (Landmark Ed) 14: 5107-5117, 2009.
19. Armougom F, Henry M, Vialettes B, Raccah D and Raoult D: Monitoring bacterial community of human gut microbiota reveals an increase in Lactobacillus in obese patients and Methanogens in anorexic patients. PLoS One 4: e7125, 2009.
20. Obeng E: Apoptosis (programmed cell death) and its signals-A review. Braz J Biol 81: 1133-1143, 2020.
21. Zhu M, Liu D, Liu G, Zhang M and Pan F: Caspase-linked programmed cell death in prostate cancer: From apoptosis, necroptosis, and pyroptosis to PANoptosis. Biomolecules 13: 1715, 2023.
22. Rajesh Y and Kanneganti TD: Innate immune cell death in neuroinflammation and Alzheimer's disease. Cells 11: 1885, 2022.
23. Zhou Z, Arroum T, Luo X, Kang R, Lee YJ, Tang D, Hüttemann M and Song X: Diverse functions of cytochrome c in cell death and disease. Cell Death Differ 31: 387-404, 2024.
24. Ma J, Liu Y, Valladolid-Acebes I, Recio-López P, Peng G, Li J, Berggren PO, Juntti-Berggren L and Tong N: ATF5 is a regulator of ER stress and β-cell apoptosis in different mouse models of genetic- and diet-induced obesity and diabetes mellitus. Cell Signal 102: 110535, 2023.

25. Liu Y, Yang Y, Xu C, Liu J, Chen J, Li G, Huang B, Pan Y, Zhang Y, Wei Q, *et al*: Circular RNA circGlis3 protects against islet β-cell dysfunction and apoptosis in obesity. Nat Commun 14: 351, 2023.
26. Liu Y, Li Q, Tian G, Zhou X, Chen P, Chen B, Shan Z and Qi B: Neuronal PRDX-2-mediated ROS signaling regulates food digestion via peripheral UPRmt activation. Nat Commun 15: 10582, 2024.
27. Uddandrao VVS, Eraniappan S, Balakrishnan Ramajayam A, Singaravel S, Roy A, Parim BN, Ponnusamy C, Ganapathy S, Ponnusamy P and Sasikumar V: Hydroxycitric acid and capsaicin combination alleviates obesity-induced testicular apoptosis, oxidative stress and inflammation. Syst Biol Reprod Med 70: 20-37, 2024.
28. Nelson-Dooley C, Della-Fera MA, Hamrick M and Baile CA: Novel treatments for obesity and osteoporosis: Targeting apoptotic pathways in adipocytes. Curr Med Chem 12: 2215-2225, 2005.
29. Jamalat Y, Gamallat Y, Jaceline Gislaine PS, Meyiah A, Shopit A, Li H, Ahmed B, Chu P, Wang H, Li X, *et al*: Phosphocreatine attenuates endoplasmic reticulum stress-mediated hepatocellular apoptosis ameliorates insulin resistance in diabetes model. Biochem Biophys Res Commun 506: 611-618, 2018.
30. Osmanlıoğlu HÖ and Nazıroğlu M: Resveratrol modulates diabetes-induced neuropathic pain, apoptosis, and oxidative neurotoxicity in mice through TRPV4 channel inhibition. Mol Neurobiol 61: 7269-7286, 2024.
31. Guo Z, Wan X, Luo Y, Liang F, Jiang S, Yuan X and Mo Z: The vicious circle of UHRF1 down-regulation and KEAP1/NRF2/HO-1 pathway impairment promotes oxidative stress-induced endothelial cell apoptosis in diabetes. Diabet Med 40: e15026, 2023.
32. Eizirik DL and Darville MI: Beta-cell apoptosis and defense mechanisms: Lessons from type 1 diabetes. Diabetes 50 (Suppl 1): S64-S69, 2001.
33. Intengan HD and Schiffrin EL: Vascular remodeling in hypertension: Roles of apoptosis, inflammation, and fibrosis. Hypertension 38 (3 Pt 2): 581-587, 2001.
34. Wang Q, Cui Y, Lin N and Pang S: Correlation of cardiomyocyte apoptosis with duration of hypertension, severity of hypertension and caspase-3 expression in hypertensive rats. Exp Ther Med 17: 2741-2745, 2019.
35. Zhang F, Guo Z, Wu M, Lin G, Chen H, Zheng H, Zhang D, Jiang M, Xie Y, Chen Y, *et al*: Trifolin attenuates hypertension-mediated cardiac injury by inhibiting cardiomyocyte apoptosis: Mechanistic insights and therapeutic potential. Eur J Pharmacol 985: 177125, 2024.
36. Sakao S, Tatsumi K and Voelkel NF: Endothelial cells and pulmonary arterial hypertension: Apoptosis, proliferation, interaction and transdifferentiation. Respir Res 10: 95, 2009.
37. Mu YM, Yanase T, Nishi Y, Tanaka A, Saito M, Jin CH, Mukasa C, Okabe T, Nomura M, Goto K and Nawata H: Saturated FFAs, palmitic acid and stearic acid, induce apoptosis in human granulosa cells. Endocrinology 142: 3590-3597, 2001.
38. Lin F, Pei L, Zhang Q, Han W, Jiang S, Lin Y, Dong B, Cui L and Li M: Ox-LDL induces endothelial cell apoptosis and macrophage migration by regulating caveolin-1 phosphorylation. J Cell Physiol 233: 6683-6692, 2018.
39. Broz P and Dixit VM: Inflammasomes: Mechanism of assembly, regulation and signalling. Nat Rev Immunol 16: 407-420, 2016.
40. Lu A, Li Y, Schmidt FI, Yin Q, Chen S, Fu TM, Tong AB, Ploegh HL, Mao Y and Wu H: Molecular basis of caspase-1 polymerization and its inhibition by a new capping mechanism. Nat Struct Mol Biol 23: 416-425, 2016.
41. Heilig R, Dick MS, Sborgi L, Meunier E, Hiller S and Broz P: The Gasdermin-D pore acts as a conduit for IL-1β secretion in mice. Eur J Immunol 48: 584-592, 2018.
42. Man SM, Karki R and Kanneganti TD: Molecular mechanisms and functions of pyroptosis, inflammatory caspases and inflammasomes in infectious diseases. Immunol Rev 277: 61-75, 2017.
43. Zhou Z, He H, Wang K, Shi X, Wang Y, Su Y, Wang Y, Li D, Liu W, Zhang Y, *et al*: Granzyme A from cytotoxic lymphocytes cleaves GSDMB to trigger pyroptosis in target cells. Science 368: eaaz7548, 2020.
44. Yuan X, Chen P, Luan X, Yu C, Miao L, Zuo Y, Liu A, Sun T and Di G: NLRP3 deficiency protects against acetaminophen-induced liver injury by inhibiting hepatocyte pyroptosis. Mol Med Rep 29: 61, 2024.
45. Vandanmagsar B, Youm YH, Ravussin A, Galgani JE, Stadler K, Mynatt RL, Ravussin E, Stephens JM and Dixit VD: The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. Nat Med 17: 179-188, 2011.
46. Sehgal A, Behl T, Kaur I, Singh S, Sharma N and Aleya L: Targeting NLRP3 inflammasome as a chief instigator of obesity, contributing to local adipose tissue inflammation and insulin resistance. Environ Sci Pollut Res Int 28: 43102-43113, 2021.
47. Unamuno X, Gómez-Ambrosi J, Ramírez B, Rodríguez A, Becerril S, Valentí V, Moncada R, Silva C, Salvador J, Frühbeck G and Catalán V: NLRP3 inflammasome blockade reduces adipose tissue inflammation and extracellular matrix remodeling. Cell Mol Immunol 18: 1045-1057, 2021.
48. Liu Z, Gan L, Xu Y, Luo D, Ren Q, Wu S and Sun C: Melatonin alleviates inflammasome-induced pyroptosis through inhibiting NF-κB/GSDMD signal in mice adipose tissue. J Pineal Res 63: c12414, 2017.
49. Khalid M, Petroianu G and Adem A: Advanced glycation end products and diabetes mellitus: mechanisms and perspectives. Biomolecules 12: 542, 2022.
50. Ma H, Jeppesen JF and Jaenisch R: Human T cells expressing a CD19 CAR-T receptor provide insights into mechanisms of human CD19-positive B cell destruction. Cell Rep Med 1: 100097, 2020.
51. Carlos D, Costa FR, Pereira CA, Rocha FA, Yaochite JN, Oliveira GG, Carneiro FS, Tostes RC, Ramos SG, Zamboni DS, *et al*: Mitochondrial DNA activates the NLRP3 inflammasome and predisposes to type 1 diabetes in murine model. Front Immunol 8: 164, 2017.
52. Luo B, Li B, Wang W, Liu X, Liu X, Xia Y, Zhang C, Zhang Y, Zhang M and An F: Rosuvastatin alleviates diabetic cardiomyopathy by inhibiting NLRP3 inflammasome and MAPK pathways in a type 2 diabetes rat model. Cardiovasc Drugs Ther 28: 33-43, 2014.
53. Dalekos GN, Elisaf M, Bairaktari E, Tsolas O and Siamopoulos KC: Increased serum levels of interleukin-1beta in the systemic circulation of patients with essential hypertension: Additional risk factor for atherogenesis in hypertensive patients? J Lab Clin Med 129: 300-308, 1997.
54. Qi J, Yu XJ, Shi XL, Gao HL, Yi QY, Tan H, Fan XY, Zhang Y, Song XA, Cui W, *et al*: NF-κB blockade in hypothalamic paraventricular nucleus inhibits high-salt-induced hypertension through NLRP3 and caspase-1. Cardiovasc Toxicol 16: 345-354, 2016.
55. Krishnan SM, Ling YH, Huuskes BM, Ferens DM, Saini N, Chan CT, Diep H, Kett MM, Samuel CS, Kemp-Harper BK, *et al*: Pharmacological inhibition of the NLRP3 inflammasome reduces blood pressure, renal damage, and dysfunction in salt-sensitive hypertension. Cardiovasc Res 115: 776-787, 2019.
56. Chi K, Geng X, Liu C, Cai G and Hong Q: Research progress on the role of inflammasomes in kidney disease. Mediators Inflamm 2020: 8032797, 2020.
57. Glick D, Barth S and Macleod KF: Autophagy: Cellular and molecular mechanisms. J Pathol 221: 3-12, 2010.
58. Hu Y, Chen H, Zhang L, Lin X, Li X, Zhuang H, Fan H, Meng T, He Z, Huang H, *et al*: The AMPK-MFN2 axis regulates MAM dynamics and autophagy induced by energy stresses. Autophagy 17: 1142-1156, 2021.
59. Kim YC and Guan KL: mTOR: A pharmacologic target for autophagy regulation. J Clin Invest 125: 25-32, 2015.
60. Kim J, Kundu M, Viollet B and Guan KL: AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. Nat Cell Biol 13: 132-141, 2011.
61. Fu L, Wu W, Sun X and Zhang P: Glucocorticoids enhanced osteoclast autophagy through the PI3K/Akt/mTOR signaling pathway. Calcif Tissue Int 107: 60-71, 2020.
62. Eiyama A and Okamoto K: PINK1/Parkin-mediated mitophagy in mammalian cells. Curr Opin Cell Biol 33: 95-101, 2015.
63. Eldakhakhny B, Bima A, Alamoudi AA, Alnami A, Abo-Elkhair SM, Sakr H, Almoghrabi Y, Ghoneim FM, Nagib RM and Elsamanoudy A: The role of low-carbohydrate, high-fat diet in modulating autophagy and endoplasmic reticulum stress in aortic endothelial dysfunction of metabolic syndrome animal model. Front Nutr 11: 1467719, 2024.
64. Li H, Ye Z, Zheng G and Su Z: Polysaccharides targeting autophagy to alleviate metabolic syndrome. Int J Biol Macromol 283 (Pt 1): 137393, 2024.
65. Zhao J, Duan L, Li J, Yao C, Wang G, Mi J, Yu Y, Ding L, Zhao Y, Yan G, *et al*: New insights into the interplay between autophagy, gut microbiota and insulin resistance in metabolic syndrome. Biomed Pharmacother 176: 116807, 2024.

66. Rodrigues SF, Stokes KY, Festuccia WT and Martins JO: Editorial: Interplay between autophagy and metabolic syndrome: Causes, consequences and therapeutic challenges. Front Cell Dev Biol 9: 765778, 2021.
67. Sciarretta S, Zhai P, Shao D, Maejima Y, Robbins J, Volpe M, Condorelli G and Sadoshima J: Rheb is a critical regulator of autophagy during myocardial ischemia: Pathophysiological implications in obesity and metabolic syndrome. Circulation 125: 1134-1146, 2012.
68. Álvarez-Mercado AI, Rojano-Alfonso C, Micó-Carnero M, Caballeria-Casals A, Peralta C and Casillas-Ramírez A: New insights into the role of autophagy in liver surgery in the setting of metabolic syndrome and related diseases. Front Cell Dev Biol 9: 670273, 2021.
69. Xu J, Kitada M, Ogura Y and Koya D: Relationship between autophagy and metabolic syndrome characteristics in the pathogenesis of atherosclerosis. Front Cell Dev Biol 9: 641852, 2021.
70. Kornicka K, Houston J and Marycz K: Dysfunction of mesenchymal stem cells isolated from metabolic syndrome and type 2 diabetic patients as result of oxidative stress and autophagy may limit their potential therapeutic use. Stem Cell Rev Rep 14: 337-345, 2018.
71. Kim KH and Lee MS: Autophagy-a key player in cellular and body metabolism. Nat Rev Endocrinol 10: 322-337, 2014.
72. He C, Wei Y, Sun K, Li B, Dong X, Zou Z, Liu Y, Kinch LN, Khan S, Sinha S, *et al*: Beclin 2 functions in autophagy, degradation of G protein-coupled receptors, and metabolism. Cell 154: 1085-1099, 2013.
73. Settembre C, De Cegli R, Mansueto G, Saha PK, Vetrini F, Visvikis O, Huynh T, Carissimo A, Palmer D, Klisch TJ, *et al*: TFEB controls cellular lipid metabolism through a starvation-induced autoregulatory loop. Nat Cell Biol 15: 647-658, 2013.
74. Quan W, Kim HK, Moon EY, Kim SS, Choi CS, Komatsu M, Jeong YT, Lee MK, Kim KW, Kim MS and Lee MS: Role of hypothalamic proopiomelanocortin neuron autophagy in the control of appetite and leptin response. Endocrinology 153: 1817-1826, 2012.
75. Kumariya S, Ubba V, Jha RK and Gayen JR: Autophagy in ovary and polycystic ovary syndrome: role, dispute and future perspective. Autophagy 17: 2706-2733, 2021.
76. Song YM, Lee YH, Kim JW, Ham DS, Kang ES, Cha BS, Lee HC and Lee BW: Metformin alleviates hepatosteatosis by restoring SIRT1-mediated autophagy induction via an AMP-activated protein kinase-independent pathway. Autophagy 11: 46-59, 2015.
77. Maiese K: Novel nervous and multi-system regenerative therapeutic strategies for diabetes mellitus with mTOR. Neural Regen Res 11: 372-385, 2016.
78. Zhao L, Zhang CL, He L, Chen Q, Liu L, Kang L, Liu J, Luo JY, Gou L, Qu D, *et al*: Restoration of autophagic flux improves endothelial function in diabetes through lowering mitochondrial ROS-Mediated eNOS monomerization. Diabetes 71: 1099-1114, 2022.
79. Zhang Z, Zhang S, Wang Y, Yang M, Zhang N, Jin Z, Ding L, Jiang W, Yang J, Sun Z, *et al*: Autophagy inhibits high glucose induced cardiac microvascular endothelial cells apoptosis by MTOR signal pathway. Apoptosis 22: 1510-1523, 2017.
80. Da Cruz LL, Vesentini G, Sinzato YK, Villaverde AISB, Volpato GT and Damasceno DC: Effects of high-fat diet-induced diabetes on autophagy in the murine liver: A systematic review and meta-analysis. Life Sci 309: 121012, 2022.
81. Koga H, Kaushik S and Cuervo AM: Altered lipid content inhibits autophagic vesicular fusion. FASEB J 24: 3052-3065, 2010.
82. Engin A: Non-alcoholic fatty liver disease. Adv Exp Med Biol 960: 443-467, 2017.
83. Kandadi MR, Panzhinskiy E, Roe ND, Nair S, Hu D and Sun A: Deletion of protein tyrosine phosphatase 1B rescues against myocardial anomalies in high fat diet-induced obesity: Role of AMPK-dependent autophagy. Biochim Biophys Acta 1852: 299-309, 2015.
84. Zheng P, Ma W, Gu Y, Wu H, Bian Z, Liu N, Yang D and Chen X: High-fat diet causes mitochondrial damage and downregulation of mitofusin-2 and optic atrophy-1 in multiple organs. J Clin Biochem Nutr 73: 61-76, 2023.
85. Wang Q, Sun J, Chen T, Song S, Hou Y, Feng L, Fan C and Li M: Ferroptosis, pyroptosis, and cuproptosis in Alzheimer's disease. ACS Chem Neurosci 14: 3564-3587, 2023.
86. Chavoshinezhad S, Beirami E, Izadpanah E, Feligioni M and Hassanzadeh K: Molecular mechanism and potential therapeutic targets of necroptosis and ferroptosis in Alzheimer's disease. Biomed Pharmacother 168: 115656, 2023.
87. Liang D, Minikes AM and Jiang X: Ferroptosis at the intersection of lipid metabolism and cellular signaling. Mol Cell 82: 2215-2227, 2022.
88. Tang D, Chen X, Kang R and Kroemer G: Ferroptosis: Molecular mechanisms and health implications. Cell Res 31: 107-125, 2021.
89. Liu J, Kang R and Tang D: Signaling pathways and defense mechanisms of ferroptosis. FEBS J 289:7038-7050, 2022.
90. Ursini F and Maiorino M: Lipid peroxidation and ferroptosis: The role of GSH and GPx4. Free Radic Biol Med 152: 175-185, 2020.
91. Mandal PK, Seiler A, Perisic T, Kölle P, Banjac Canak A, Förster H, Weiss N, Kremmer E, Lieberman MW, Bannai S, *et al*: System x(c)- and thioredoxin reductase 1 cooperatively rescue glutathione deficiency. J Biol Chem 285: 22244-22253, 2010.
92. Abdelmagid SA, Clarke SE, Nielsen DE, Badawi A, El-Sohemy A, Mutch DM and Ma DW: Comprehensive profiling of plasma fatty acid concentrations in young healthy Canadian adults. PLoS One 10: e0116195, 2015.
93. Zhang Z, Funcke JB, Zi Z, Zhao S, Straub LG, Zhu Y, Zhu Q, Crewe C, An YA, Chen S, *et al*: Adipocyte iron levels impinge on a fat-gut crosstalk to regulate intestinal lipid absorption and mediate protection from obesity. Cell Metab 33: 1624-1639.e9, 2021.
94. Wang X, Wu Q, Zhong M, Chen Y, Wang Y, Li X, Zhao W, Ge C, Wang X, Yu Y, *et al*: Adipocyte-derived ferroptotic signaling mitigates obesity. Cell Metab 37: 673-691.e7, 2025.
95. Kose T, Vera-Aviles M, Sharp PA and Latunde-Dada GO: Curcumin and (-)- epigallocatechin-3-gallate protect murine MIN6 pancreatic beta-cells against iron toxicity and erastin-induced ferroptosis. Pharmaceuticals (Basel) 12: 26, 2019.
96. Suárez-Ortegón MF, Ensaldo-Carrasco E, Shi T, McLachlan S, Fernández-Real JM and Wild SH: Ferritin, metabolic syndrome and its components: A systematic review and meta-analysis. Atherosclerosis 275: 97-106, 2018.
97. Fernández-Real JM, Ricart-Engel W, Arroyo E, Balançá R, Casamitjana-Abella R, Cabrero D, Fernández-Castañer M and Soler J: Serum ferritin as a component of the insulin resistance syndrome. Diabetes Care 21: 62-68, 1998.
98. Schwärzler J, Mayr L, Radlinger B, Grabherr F, Philipp M, Texler B, Grander C, Ritsch A, Hunjadi M, Enrich B, *et al*: Adipocyte GPX4 protects against inflammation, hepatic insulin resistance and metabolic dysregulation. Int J Obes (Lond) 46: 951-959, 2022.
99. Jehn M, Clark JM and Guallar E: Serum ferritin and risk of the metabolic syndrome in U.S. adults. Diabetes Care 27: 2422-2428, 2004.
100. Huang J, Jones D, Luo B, Sanderson M, Soto J, Abel ED, Cooksey RC and McClain DA: Iron overload and diabetes risk: A shift from glucose to Fatty Acid oxidation and increased hepatic glucose production in a mouse model of hereditary hemochromatosis. Diabetes 60: 80-87, 2011.
101. Houschyar KS, Lüdtke R, Dobos GJ, Kalus U, Broecker-Preuss M, Rampp T, Brinkhaus B and Michalsen A: Effects of phlebotomy-induced reduction of body iron stores on metabolic syndrome: Results from a randomized clinical trial. BMC Med 10: 54, 2012.
102. Wang W, Knovich MA, Coffman LG, Torti FM and Torti SV: Serum ferritin: Past, present and future. Biochim Biophys Acta 1800: 760-769, 2010.
103. Vinchi F, Porto G, Simmelbauer A, Altamura S, Passos ST, Garbowski M, Silva AMN, Spaich S, Seide SE, Sparla R, *et al*: Atherosclerosis is aggravated by iron overload and ameliorated by dietary and pharmacological iron restriction. Eur Heart J 41: 2681-2695, 2020.
104. Ito F, Sono Y and Ito T: Measurement and clinical significance of lipid peroxidation as a biomarker of oxidative stress: Oxidative stress in diabetes, atherosclerosis, and chronic inflammation. Antioxidants (Basel) 8: 72, 2019.
105. Li C, Chen JW, Liu ZH, Shen Y, Ding FH, Gu G, Liu J, Qiu JP, Gao J, Zhang RY, *et al*: CTRP5 promotes transcytosis and oxidative modification of low-density lipoprotein and the development of atherosclerosis. Atherosclerosis 278: 197-209, 2018.
106. Tong J, Li D, Meng H, Sun D, Lan X, Ni M, Ma J, Zeng F, Sun S, Fu J, *et al*: Targeting a novel inducible GPX4 alternative isoform to alleviate ferroptosis and treat metabolic-associated fatty liver disease. Acta Pharm Sin B 12: 3650-3666, 2022.
107. Ma D, Wang X, Liu J, Cui Y, Luo S and Wang F: The development of necroptosis: What we can learn. Cell Stress Chaperones 28: 969-987, 2023.

108. Ai Y, Meng Y, Yan B, Zhou Q and Wang X: The biochemical pathways of apoptotic, necroptotic, pyroptotic, and ferroptotic cell death. Mol Cell 84: 170-179, 2024.
109. He R, Wang Z, Dong S, Chen Z and Zhou W: Understanding necroptosis in pancreatic diseases. Biomolecules 12: 828, 2022.
110. Chen R, Kang R and Tang D: The mechanism of HMGB1 secretion and release. Exp Mol Med 54: 91-102, 2022.
111. Lo CH and Zeng J: TNF as a mediator of metabolic inflammation and body-brain interaction in obesity-driven neuroinflammation and neurodegeneration. Ageing Res Rev 112: 102891, 2025.
112. Tye H, Conos SA, Djajawi TM, Gottschalk TA, Abdoulkader N, Kong IY, Kammoun HL, Narayana VK, Kratina T, Speir M, *et al*: Divergent roles of RIPK3 and MLKL in high-fat diet-induced obesity and MAFLD in mice. Life Sci Alliance 8: e202302446, 2024.
113. Vankayalapati A, Durojaye O, Mukherjee T, Paidipally P, Owusu-Afriyie B, Vankayalapati R and Radhakrishnan RK: Metabolic changes enhance necroptosis of type 2 diabetes mellitus mice infected with Mycobacterium tuberculosis. PLoS Pathog 20: e1012148, 2024.
114. Rojas J, Bermudez V, Palmar J, Martínez MS, Olivar LC, Nava M, Tomey D, Rojas M, Salazar J, Garicano C and Velasco M: Pancreatic beta cell death: Novel potential mechanisms in diabetes therapy. J Diabetes Res 2018: 9601801, 2018.
115. Wu H, Gao W, Ma Y, Zhong X, Qian J, Huang D and Ge J: TRIM25-mediated XRCC1 ubiquitination accelerates atherosclerosis by inducing macrophage M1 polarization and programmed death. Inflamm Res 73: 1445-1458, 2024.
116. Chtourou Y, Slima AB, Makni M, Gdoura R and Fetoui H: Naringenin protects cardiac hypercholesterolemia-induced oxidative stress and subsequent necroptosis in rats. Pharmacol Rep 67: 1090-1097, 2015.
117. Malireddi RKS, Kesavardhana S and Kanneganti TD: ZBP1 and TAK1: Master regulators of NLRP3 inflammasome/pyroptosis, apoptosis, and necroptosis (PAN-optosis). Front Cell Infect Microbiol 9: 406, 2019.
118. Karki R, Sharma BR, Lee E, Banoth B, Malireddi RKS, Samir P, Tuladhar S, Mummareddy H, Burton AR, Vogel P and Kanneganti TD: Interferon regulatory factor 1 regulates PANoptosis to prevent colorectal cancer. JCI Insight 5: e136720, 2020.
119. Liu Y, Hu C, Luo S, Han Y, Li L, Wei L, Chen W and Yang M: S14G-humanin (HNG) ameliorates diabetic nephropathy tubular injury by inhibiting Z-DNA/ZBP1-mediated necroptosis. Eur J Pharmacol 1031: 179175, 2026.
120. Hou Y, Feng Q, Wei C, Cao F, Liu D, Pan S, Shi Y, Liu Z and Liu F: Emerging role of PANoptosis in kidney diseases: Molecular mechanisms and therapeutic opportunities. Apoptosis 30: 579-596, 2025.
121. Zhang X, Tang B, Luo J, Yang Y, Weng Q, Fang S, Zhao Z, Tu J, Chen M and Ji J: Cuproptosis, ferroptosis and PANoptosis in tumor immune microenvironment remodeling and immunotherapy: Culprits or new hope. Mol Cancer 23: 255, 2024.
122. Neira G, Becerril S, Valentí V, Moncada R, Catalán V, Gómez-Ambrosi J, Colina I, Silva C, Escalada J, Frühbeck G and Rodríguez A: FNDC4 reduces hepatocyte inflammatory cell death via AMPKα in metabolic dysfunction-associated steatotic liver disease. Clin Nutr 43: 2221-2233, 2024.
123. Wang Y, Tao Y, Zhang S, Wang Q, Liu Z, Lin S, Wang Y, Huang Y, Zhang T, Mayala HA, *et al*: Pseudostellaria heterophylla polysaccharides attenuate diabetic lower limb ischemia via CYP2E1-mediated mitochondrial homeostasis and PANoptosis regulation. Phytomedicine 148: 157252, 2025.
124. Lee S, Karki R, Wang Y, Nguyen LN, Kalathur RC and Kanneganti TD: AIM2 forms a complex with pyrin and ZBP1 to drive PANoptosis and host defence. Nature 597: 415-419, 2021.
125. Liu X, Nie L, Zhang Y, Yan Y, Wang C, Colic M, Olszewski K, Horbath A, Chen X, Lei G, *et al*: Actin cytoskeleton vulnerability to disulfide stress mediates disulfidptosis. Nat Cell Biol 25: 404-414, 2023.
126. Xiao F, Li HL, Yang B, Che H, Xu F, Li G, Zhou CH and Wang S: Disulfidptosis: A new type of cell death. Apoptosis 29: 1309-1329, 2024.
127. Qiu H, Liu J, Shao N, Zhao J, Chen C, Jiang Y, Zhao X and Xu L: SLC7A11 as a bridge between ferroptosis and disulfidptosis: A promising target for tumor treatment. Cell Commun Signal 23: 460, 2025.
128. Sastre J, Pérez S, Sabater L and Rius-Pérez S: Redox signaling in the pancreas in health and disease. Physiol Rev 105: 593-650, 2025.
129. Li F: Study on the correlation between crucial disulfidptosis regulators and diabetic nephropathy. Master's thesis. Nanchang University, 2024 (In Chinese).
130. Tu Y, Liu W, Sang T, Pan L, Wu W, Fang Q, Liu Y, Liu B and Wan Y: Rhein protects against renal aging and fibrotic injury by multiple targets through inhibition of TNF-α-mediated autophagy and necroptosis crosstalk. Front Pharmacol 17: 1693000, 2026.
131. Lei X, Chen Y, Lien E and Fitzgerald KA: MLKL-driven inflammasome activation and caspase-8 mediate inflammatory cell death in influenza A virus infection. mBio 14: e0011023, 2023.
132. Ma S, Sun C, Wang Y, Zhang X and Kuang H: Interconnected cell death pathways: central mechanisms and therapeutic targets in impaired follicular development of polycystic ovary syndrome. J Ovarian Res 19: 183, 2026.
133. Espín E, Yang C, Shannon CP, Checkervarty AK, Kim S, Lapp L, Assadian S, Grunau B, Goldfarb DM, Hutton J, *et al*: Pilot longitudinal integrated transcriptomic-metabolomic study reveals immune and metabolic signatures in non-hospitalized healthcare workers with long COVID. Front Cell Infect Microbiol 16: 1808564, 2026.
134. Iba T, Okada H, Nagaoka I, Ferrer R and Levy JH: Regulated cell death in sepsis: Reframing NETosis within the spectrum of apoptosis and inflammatory lytic death. Inflamm Res 75: 106, 2026.
135. Ji L and Gu H: The anti-obesity effects of rhein on improving insulin resistance (IR) and blood lipid levels are involved in endoplasmic reticulum stress (ERs), inflammation, and oxidative stress in vivo and vitro. Bioengineered 12: 5797-5813, 2021.
136. Shen K, Wang P, Zhang H, Wang X, Fu H, Li J, Chen J, Zhao P, Cheng W, Wang Y, *et al*: MiR-24-3p delivered by adipose derived stem cells exosomes alleviate macrophage pyroptosis via NLRP3/Caspase1/GSDMD in sepsis ALI. Stem Cell Res Ther 16: 582, 2025.
137. Karunakaran D, Turner AW, Duchez AC, Soubeyrand S, Rasheed A, Smyth D, Cook DP, Nikpay M, Kandiah JW, Pan C, *et al*: RIPK1 gene variants associate with obesity in humans and can be therapeutically silenced to reduce obesity in mice. Nat Metab 2: 1113-1125, 2020.
138. Saller BS, Wöhrle S, Fischer L, Dufossez C, Ingerl IL, Kessler S, Mateo-Tortola M, Gorka O, Lange F, Cheng Y, *et al*: Acute suppression of mitochondrial ATP production prevents apoptosis and provides an essential signal for NLRP3 inflammasome activation. Immunity 58: 90-107.e11, 2025.
139. Albright JM and Holian A: Contribution of particle-induced lysosome membrane permeabilization to NLRP3 inflammasome activation and mitochondrial ROS production. Toxicol Sci 208: 357-368, 2025.
140. Thakkar AB, Subramanian RB, Thakkar VR, Thakkar SS, Prajapati J, Goswami D and Thakor P: Biochanin A, an isoflavone isolated from Dalbergia sissoo Roxb. ex DC., leaves promote ROS-mediated and caspase-dependent apoptosis in lung adenocarcinoma cells. J Biomol Struct Dyn 44: 2328-2352, 2026.
141. Wan H, Wei J, Wang Y, Ge L, Hu Q, Li Y, Zhou B and Zeng X: A novel non-nad-based PARP1 inhibitor, Japoflavone B, triggered Caspase-3/GSDME-mediated pyroptosis through ROS/p38/p53 pathway in NSCLC. Chem Biol Interact 420: 111693, 2025.
142. Cevallos C, Jarmoluk P, Sviercz F, Freiberger RN, López CAM, Delpino MV and Quarleri J: Ferroptosis and mitochondrial ROS are central to SARS-CoV-2-induced hepatocyte death. Front Cell Infect Microbiol 15: 1625928, 2025.
143. Dohl J, Burns G and Singh M: The intersection of mitochondria, lipids, and ferroptosis: A new avenue for dry age-related macular degeneration. Apoptosis 30: 2526-2546, 2025.
144. Song Z, Yao Q, Huang L, Cui D, Xie J, Wu L, Huang J, Zhai B, Liu D and Xu X: Glucose deprivation-induced disulfidptosis via the SLC7A11-INF2 axis: Pan-cancer prognostic exploration and therapeutic validation. Adv Sci (Weinh) 12: e08556, 2025.
145. Ni X, Duan L, Bao Y, Li J, Zhang X, Jia D and Wu N: Circ_005077 accelerates myocardial lipotoxicity induced by high-fat diet via CyPA/p47PHOX mediated ferroptosis. Cardiovasc Diabetol 23: 129, 2024.
146. Li R, Wang J, Li W and Qian L: Disulfidptosis: Mechanisms, evidence boundaries, and translational opportunities. Redox Biol 95: 104306, 2026.
147. Li ZY, Zhao YB, Wu ZY, Wang HJ, Hu YZ, Zhang XF, Kang X, Su C, Zhang T and Liu AD: Exposure to endocrine-disrupting chemicals, iron metabolism, and risk of metabolic dysfunction-associated steatotic liver disease: A nationwide cross-sectional study in China. Biomed Environ Sci 39: 677-689, 2026.

148. Wang K, An G, Park J, Cunha E Rocha K, Zeng Z, Qin H, Farrell A, Schlotthauer A, Lim W and Ying W: Labile iron starvation in embryonic Kupffer cells aggravates MASH via mitochondrial failure and macrophage dysfunction. Cell Death Dis: Jun 18, 2026 (Epub ahead of print).
149. Zhang C, Huang P, Pak M, Korchak JA and Zubair AC: Extracellular vesicles derived from VEGF mRNA-Engineered mesenchymal stem cells promote endothelial cell survival. Cells 15: 717, 2026.
150. Du Y, Shen Y, Wang R, Ren X and Ye S: Role of lipid droplet-mediated lipid peroxidation by GPX4 in docosahexaenoic acid-induced EA.hy926 endothelial cell ferroptosis. Biochim Biophys Acta Mol Cell Biol Lipids 1871: 159748, 2026.
151. Adil M, Kanwal S, Rasheed S, Iqbal M and Abbas G: Cancer chemoresistance; Recent challenges and future considerations. Cancer Treat Res 185: 237-253, 2023.
152. Yang X, Liu Y, Cao J, Wu C, Tang L, Bian W, Chen Y, Yu L, Wu Y, Li S, *et al*: Targeting epigenetic and post-translational modifications of NRF2: Key regulatory factors in disease treatment. Cell Death Discov 11: 189, 2025.
153. Shin HJ, Kim H, Oh S, Lee JG, Kee M, Ko HJ, Kweon MN, Won KJ and Baek SH: AMPK-SKP2-CARM1 signalling cascade in transcriptional regulation of autophagy. Nature 534: 553-557, 2016.
154. Fischer IP, Irmler M, Meyer CW, Sachs SJ, Neff F, Hrabě de Angelis M, Beckers J, Tschöp MH, Hofmann SM and Ussar S: A history of obesity leaves an inflammatory fingerprint in liver and adipose tissue. Int J Obes (Lond) 42: 507-517, 2018.
155. Nikpay M, Ravati S, Dent R and McPherson R: Epigenome-wide study identified methylation sites associated with the risk of obesity. Nutrients 13: 1984, 2021.
156. Laha A, Majumder A, Singh M and Tyagi SC: Connecting homocysteine and obesity through pyroptosis, gut microbiome, epigenetics, peroxisome proliferator-activated receptor γ, and zinc finger protein 407. Can J Physiol Pharmacol 96: 971-976, 2018.
157. Xie Z, Chang C, Huang G and Zhou Z: The role of epigenetics in type 1 diabetes. Adv Exp Med Biol 1253: 223-257, 2020.
158. Millis RM: Epigenetics and hypertension. Curr Hypertens Rep 13: 21-28, 2011.
159. Pedrosa MA, Labandeira CM, Lago-Baameiro N, Valenzuela R, Pardo M, Labandeira-Garcia JL and Rodriguez-Perez AI: Extracellular vesicles and their renin-angiotensin cargo as a link between metabolic syndrome and Parkinson's disease. Antioxidants (Basel) 12: 2045, 2023.
160. Hao J, Wang S, Guo X, Guo X and Hao L: The axis of miR-30a/AIF-1/TRPC6/calcineurin A/NFAT2 regulated the death modalities and inflammation of renal tubular epithelial cells in diabetic kidney disease via exosome. Life Sci 377: 123760, 2025.
161. Zhang D, Yao X, Teng Y, Zhao T, Lin L, Li Y, Shang H, Jin Y and Jin Q: Adipocytes-derived Exosomal microRNA-1224 inhibits M2 macrophage polarization in obesity-induced adipose tissue inflammation via MSI2-mediated Wnt/β-catenin Axis. Mol Nutr Food Res 66: 2100889, 2022.
162. Xiong W, Zhang X, Zhou J, Chen J, Liu Y, Yan Y, Tan M, Huang H, Si Y and Wei Y: Astragaloside IV promotes exosome secretion of endothelial progenitor cells to regulate PI3KR2/SPRED1 signaling and inhibit pyroptosis of diabetic endothelial cells. Cytotherapy 26: 36-50, 2024.
163. Yan C, Tian X, Li J, Liu D, Ye D, Xie Z, Han Y and Zou MH: A high-fat diet attenuates AMPK α1 in adipocytes to induce exosome shedding and nonalcoholic fatty liver development in vivo. Diabetes 70: 577-588, 2021.
164. Mizumoto T, Kakizoe Y, Nakagawa T, Iwata Y, Miyasato Y, Uchimura K, Adachi M, Deng Q, Hayata M, Morinaga J, *et al*: A serine protease inhibitor camostat mesilate prevents podocyte apoptosis and attenuates podocyte injury in metabolic syndrome model rats. J Pharmacol Sci 146: 192-199, 2021.
165. Szydlarska J, Weiss C and Marycz K: The Effect of Methyl-β-cyclodextrin on apoptosis, proliferative activity, and oxidative stress in adipose-derived mesenchymal stromal cells of horses suffering from metabolic syndrome (EMS). Molecules 23: 287, 2018.
166. Lee YL, Lin KL, Wu BN, Chuang SM, Wu WJ, Lee YC, Ho WT and Juan YS: Epigallocatechin-3-gallate alleviates bladder overactivity in a rat model with metabolic syndrome and ovarian hormone deficiency through mitochondria apoptosis pathways. Sci Rep 8: 5358, 2018.
167. Li WD, Shen XY, Jiang XL, Wen HF, Shen Y, Zhang MQ and Tan WT: Disulfiram alleviates cardiac hypertrophic injury by inhibiting TAK1-mediated PANoptosis. Sheng Li Xue Bao 77: 222-230, 2025 (In Chinese).
168. Liu Z, Zhao J, Ding Y, Yan Z, An H, Yu L, Kang Y, Ye X, Cai Y and Ye Q: Quinone-amine sonosensitizer nanoplatform loaded with a GSDMD-activating agent for dual-pathway pyroptosis-augmented sonodynamic immunotherapy against glioblastoma. Acta Biomater S1742-7061(26)00499-X, 2026 (Epub ahead of print).
169. Gong L, Tong T and Zhang E: Editorial: Exercise intervention on metabolic syndrome: Focus on pyroptosis. Front Endocrinol (Lausanne) 15: 1461283, 2024.
170. Peng H, Cheng Q, Chen J, Wang Y, Du M, Lin X, Zhao Q, Chen S, Zhang J and Wang X: Green tea epigallocatechin-3-gallate ameliorates lipid accumulation and obesity-associated metabolic syndrome via regulating autophagy and lipolysis in preadipocytes and adipose tissue. J Agric Food Chem 73: 12272-12291, 2025.
171. Dai X, Liang B and Sun Y: Luteolin ameliorates rat model of metabolic syndrome-induced cardiac injury by apoptosis suppression and autophagy promotion via NR4A2/p53 regulation. BMC Complement Med Ther 25: 14, 2025.
172. Zhang JJ: Effect of ferberine on carotid artery stenosis in rats with metabolic syndrome. Doctoral dissertation. Tianjin Medical University, 2021 (In Chinese).
173. Li Y, Zhao W, Sair AT, Li T and Liu RH: Ferulic acid restores mitochondrial dynamics and autophagy via AMPK signaling pathway in a palmitate-induced hepatocyte model of metabolic syndrome. Sci Rep 14: 18970, 2024.
174. Bourebaba L, Serwotka-Suszczak A, Pielok A, Sikora M, Mularczyk M and Marycz K: The PTP1B inhibitor MSI-1436 ameliorates liver insulin sensitivity by modulating autophagy, ER stress and systemic inflammation in Equine metabolic syndrome affected horses. Front Endocrinol (Lausanne) 14: 1149610, 2023.
175. Hong S, Ghandriz R, Siddiqi S, Zhu XY, Saadiq IM, Jordan KL, Tang H, Ali KA, Lerman A, Eirin A and Lerman LO: Effects of elamipretide on autophagy in renal cells of pigs with metabolic syndrome. Cells 11: 2891, 2022.
176. Santos-Ledo A, Luxán-Delgado B, Caballero B, Potes Y, Rodríguez-González S, Boga JA, Coto-Montes A and García-Macia M: Melatonin ameliorates autophagy impairment in a metabolic syndrome model. Antioxidants (Basel) 10: 796, 2021.
177. Lim H, Lim YM, Kim KH, Jeon YE, Park K, Kim J, Hwang HY, Lee DJ, Pagire H, Kwon HJ, *et al*: A novel autophagy enhancer as a therapeutic agent against metabolic syndrome and diabetes. Nat Commun 9: 1438, 2018.
178. Zakaria EM, Abdel-Ghany RH, Elgharbawy AS, Alsemeh AE and Metwally SS: A novel approach to repositioning memantine for metabolic syndrome-induced steatohepatitis: Modulation of hepatic autophagy, inflammation, and fibrosis. Life Sci 319: 121509, 2023.
179. El-Sayed SS, Rezq S, Alsemeh AE and Mahmoud MF: Moxonidine ameliorates cardiac injury in rats with metabolic syndrome by regulating autophagy. Life Sci 312: 121210, 2023.
180. Cai HR: The study of effects and mechanism of Shugan Wendan decoction in improving insulin resistance in metabolic syndrome. Doctoral dissertation. Guangzhou University of Chinese Medicine, 2021 (In Chinese).
181. Delrue C, Speeckaert R and Speeckaert MM: The role of intermittent fasting and ketogenic diet in metabolic syndrome and type 2 diabetes. Acta Clin Belg 80: 100-114, 2025.
182. Cui F, Guan Y, Guo J, Tian YM, Hu HF, Zhang XJ and Zhang Y: Chronic intermittent hypobaric hypoxia protects vascular endothelium by ameliorating autophagy in metabolic syndrome rats. Life Sci 205: 145-154, 2018.
183. Shao Q, Xu X, Han X, Liang Z, Zhang Q, Hu J and Qian X: CSF1 inhibits ferroptosis in colorectal cancer cells by autocrine activation of the JAK/STAT3 signaling pathway. Biochem Pharmacol 253 (Pt 1): 118298, 2026.
184. Li ZC, Xu FF, Zhao Y, Shen CR, Song XY, Xu YP, Guo H, Fu JT, Tao XY, Ren J, *et al*: Exercise suppresses IP6K3 to modulate BCAA metabolism and ferroptosis in MASLD. Cell Mol Biol Lett: Jul 8, 2026 (Epub ahead of print).
185. Rokop ZP, Zhang W, Ghosh N, Biswas N, Das A, Lin J, Sen CK and Kubal C: Exacerbated ischemia-reperfusion injury in fatty livers is mediated by lipid peroxidation stress and ferroptosis. Surgery 175: 1539-1546, 2024.

186. Al-Farhan A, Nayal OS and Pratt DA: Suppression of lipid peroxidation by necrostatins and their potential for dual targeting of ferroptosis and necroptosis. J Med Chem 69: 17508-17523, 2026.
187. Kondo T, Macdonald S, Engelmann C, Habtesion A, Macnaughtan J, Mehta G, Mookerjee RP, Davies N, Pavesi M, Moreau R, *et al*: The role of RIPK1 mediated cell death in acute on chronic liver failure. Cell Death Dis 13: 5, 2021.
188. Orzoł D, Kępska M and Zyzak M: Orientin reverses premature senescence in equine adipose stromal cells affected by equine metabolic syndrome through oxidative stress modulation. Int J Mol Sci 26: 6867, 2025.
189. Fu Y, Yuan P, Zeng M, Zhang Q, Hou Y, Gao L, Wei Y, Zheng Y, Feng W and Zheng X: Dihydroquercetin regulates HIF-1α/AKT/NR2B signalling to improve impaired brain function in rats with metabolic syndrome. Heliyon 10: e29807, 2024.
190. Sánchez-Aguilar M, Ibarra-Lara L, Cano-Martínez A, Soria-Castro E, Castrejón-Téllez V, Pavón N, Osorio-Yáñez C, Díaz-Díaz E and Rubio-Ruíz ME: PPAR alpha activation by clofibrate alleviates ischemia/reperfusion injury in metabolic syndrome rats by decreasing cardiac inflammation and remodeling and by regulating the atrial natriuretic peptide compensatory response. Int J Mol Sci 24: 5321, 2023.
191. Mularczyk M, Bourebaba N, Marycz K and Bourebaba L: Astaxanthin carotenoid modulates oxidative stress in adipose-derived stromal cells isolated from equine metabolic syndrome affected horses by targeting mitochondrial biogenesis. Biomolecules 12: 1039, 2022.
192. Cheng SM, Kumar VB, Wu LY, Chang HC, Kuo CH, Wei LS, Lin YM, Padma VV, Lee SD and Huang CY: Anti-apoptotic and pro-survival effects of longan flower extracts on rat hearts with fructose-induced metabolic syndrome. Environ Toxicol 36: 1021-1030, 2021.
193. Marycz K, Houston JMI, Weiss C, Röcken M and Kornicka K: 5-Azacytidine and resveratrol enhance chondrogenic differentiation of metabolic syndrome-derived mesenchymal stem cells by modulating autophagy. Oxid Med Cell Longev 2019: 1523140, 2019.
194. Li L, Lin J, Huang C, Liu J, Yuan Y, Liu Z, Li Y, Li W and Diao A: The TFEB activator clomiphene citrate ameliorates lipid metabolic syndrome pathology by activating lipophagy and lipolysis. Biochem Pharmacol 232: 116694, 2025.
195. Cayli S, Alimogullari E, Piskin I, Bilginoglu A and Nakkas H: Effect of pioglitazone on the expression of ubiquitin proteasome system and autophagic proteins in rat pancreas with metabolic syndrome. J Mol Histol 52: 929-942, 2021.
196. Chen X, Yan XR, Liu J and Zhang LP: Chaiqi decoction ameliorates vascular endothelial injury in metabolic syndrome by upregulating autophagy. Am J Transl Res 12: 4902-4922, 2020.
197. Xu L, Li W, Chen Y, Liu S, Liu G, Luo W, Cao G and Wang S: Metformin regulates cardiac ferroptosis to reduce metabolic syndrome-induced cardiac dysfunction. Appl Biochem Biotechnol 197: 179-193, 2025.