


Review

Autophagy, Ferroptosis, Apoptosis and Pyroptosis in Metabolic Dysfunction-Associated Steatotic Liver Disease

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) has a global prevalence of 25% and is a leading cause of cirrhosis and hepatocellular carcinoma. The prevalence of MASLD has been increasing, mirroring the global increase in diabetes and metabolic syndrome. MASLD is a chronic and progressive condition characterized by inflammation, oxidative stress, insulin resistance, and disruptions in lipid metabolism. Programmed cell death (PCD) plays a pivotal role in determining the pathological aspects of MASLD, including liver inflammation, fibrosis, and even the potential for malignant transformation. PCD is a dominant process that is fundamental for eukaryotic growth and serves as a regulatory factor in MASLD. PCD encompasses various pathways, including autophagy, ferroptosis, apoptosis, and pyroptosis. These PCD pathways can be activated at different stages of MASLD. The key effector molecules involved in these processes are central focal points in the development of therapeutic interventions for MASLD. Here, we comprehensively review the idea that targeted the modulation of the PCD pathway may be an effective approach for the prevention and/or treatment of MASLD.

Keywords: autophagy; ferroptosis; apoptosis; pyroptosis; metabolic dysfunction-associated steatotic liver disease

1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is emerging as the leading chronic liver disease worldwide. It is estimated to afflict one billion individuals globally and may be present in approximately one in four of the world population [1]. However, there are notable disparities in the prevalence of MASLD across diverse geographic regions. The Middle East and South America exhibit the highest prevalence, while Africa reports the lowest prevalence of MASLD [2]. Globally, the prevalence of MASLD in individuals who are not classified as obese typically falls within the range of 10–30% in both Western and Eastern countries [3]. MASLD is therefore a worldwide health issue that imposes a significant socioeconomic burden.

MASLD is a leading contributor to liver-related morbidity and mortality, as well as being the fastest growing cause of hepatocellular carcinoma (HCC) [4]. This disease encompasses a spectrum of liver disorders, ranging from simple fat accumulation in the liver (non-alcoholic fatty liver, NAFL) to a more severe form known as metabolic dysfunction-associated steatohepatitis (MASH). The latter is characterized by inflammation and rapid progression of fibrosis, each with its own variable trajectory, but with the potential to progress to cirrhosis and HCC [5]. MASLD is also closely associated with the metabolic syndrome, type 2 diabetes, extra-hepatic cancers, and its associated complications. The most severe among the extra-hepatic can-

cers cancer, mainly in the elderly [6]. The pathogenesis of MASLD involves a buildup of fats such as triglycerides in hepatocytes, accompanied by insulin resistance (IR), oxidative stress and endoplasmic reticulum (ER) stress, lipotoxicity, mitochondrial dysfunction, hepatocyte lipoapoptosis, etc [7]. The pathogenesis of MASLD is complicated and involves multisystem abnormality and dysfunction. To date, there is still no ideal approved drug for the prevention and cure of this disease. Therefore, MASLD and its more severe forms constitute a growing worldwide epidemic with a high unmet medical need.

Cells can undergo two distinct modes of cell death: accidental cell death (ACD) and regulated cell death (RCD). RCD, commonly known as programmed cell death (PCD), is a strictly controlled form of cell death triggered by complex signaling [8]. PCD plays a crucial role in maintaining body homeostasis, but excessive activation or insensitivity to PCD can contribute to the development and progression of various diseases [9]. In the context of MASLD, PCD emerges as a pivotal factor that influences the severity and outcome of liver injury [10]. The death of hepatocytes is an important event in the progression of MASLD, causing inflammation that subsequently leads to fibrosis, cirrhosis, and even HCC [11]. Recent investigations have identified various types of PCD, including mainly apoptosis, autophagy, necroptosis, pyroptosis, and ferroptosis. All of these have been studied for their involvement in the pathogenesis of MASLD. They have unique characteris-



tics while also exhibiting many similarities, overlap and crosstalk. Consequently, it is plausible that multiple types of PCD coexist. In this review, we discuss the known signaling cascades associated with each PCD and explore their implications in MASLD.

2. Autophagy and MASLD

2.1 Autophagy

Autophagy is the process by which eukaryotic cells degrade their cytoplasmic proteins and damaged organelles by lysosomes under the control of autophagy-related genes [12]. On the one hand, autophagy can prevent cell damage and ensure that cells survive in the absence of nutrition. On the other hand, autophagy can respond to cytotoxic stimuli [13]. This form of PCD encompasses both basic autophagy occurring under physiological conditions, and induced autophagy triggered by stress conditions [14]. The former serves as a cellular self-protection mechanism, contributing to cell growth and development, and protecting cells from metabolic stress and oxidative damage. It plays a crucial role in maintaining intracellular homeostasis and governing the synthesis, degradation and recycling of cellular products [15]. However, it is worth noting that while generally beneficial, autophagy can also potentially induce metabolic stress, facilitate the degradation of cellular components under certain circumstances and even contribute to cell death [16]. Studies have shown that autophagy plays a very important role in many physiological and pathological processes, including cell homeostasis, aging, immunity, tumorigenesis and neurodegenerative diseases [17].

2.2 Autophagy in MASLD

MASLD is a clinicopathological syndrome with similar histological changes in the liver as to alcoholic liver disease, but without a patient history of excessive drinking [18]. Autophagy can regulate the homeostasis of the intracellular environment, and is therefore closely associated with development, progression and prognosis of MASLD [19]. Autophagy of liver endothelial cells in MASH patients is reduced compared to patients with simple steatosis or normal liver [20]. At present, drugs that can induce autophagy of hepatocytes may have potential therapeutic effects on MASLD [21]. However, the only treatment option for MASLD is still lifestyle intervention, which usually involves modification of diet and physical exercise [22]. Calorie restriction and physical exercise are the two main ways to stimulate autophagy [23]. MASLD is therefore closely related to autophagy.

Triglycerides (TG) in liver cells mainly exist in the form of lipid droplets. These droplets contain a lipid core composed of TG, with the surface covered by a single layer of phospholipids. The single layer of phospholipids is embedded with structurally-related PAT family proteins, including lipid droplet coating protein (perilipin) and lipogenesis-related protein [24]. Lipid droplets play

an important role in lipid metabolism and storage, membrane transport and protein degradation. Moreover, autophagy has been shown to decompose fat and lipid droplets [25]. When the autophagy bodies surrounding lipid droplets fuse with lysosomes, the lipid droplets are degraded into free fatty acids, which are then oxidized in mitochondria to generate ATP [26]. Under starvation conditions, LC3 appears on the surface of lipid droplets and LC3II interacts with lipid droplet coating proteins to degrade lipids through autophagy. This is mediated by autophagosomes which recognize lipid droplet coating proteins on the surface of lipid droplets [27]. More recent research has shown that autophagy can regulate lipid metabolism, improve insulin resistance, reduce oxidative stress and improve MASLD [28]. Lipid metabolism in hepatocytes is closely related to autophagy. Autophagy exerts a direct influence on lipid metabolism by facilitating the degradation of lipid droplets. Moreover, it indirectly regulates lipid metabolism by maintaining the normal functions of organelles and proteases that are integral to lipid metabolism [29]. The process of intracellular lipid transport through autophagosomes and leading to lysosomal decomposition is called lipophagy [30]. However, long-term chronic lipid deposition in MASLD leads to abnormal autophagy function in hepatocytes [31]. Impaired autophagy function could therefore be one of the internal mechanisms of lipid deposition in MASLD hepatocytes. As lipids accumulate in the liver, the level of autophagy decreases, the membrane structure of autophagosomes changes, and the combination of autophagosomes with lysosomes is inhibited, thus affecting the role of autophagy in lipid degradation [32]. In an *in vitro* model of MASH, lipid metabolism and inflammatory reactions are elevated following the treatment of hepatocytes with the autophagy inhibitor 3-methylindole [33]. Other studies have shown that when the autophagy level is reduced due to excessive lipid accumulation in the liver, simple inflammation can evolve to MASLD and its associated complications. If lipid accumulation in the liver is reduced, the autophagy level can be restored and the occurrence of liver injury or MASLD and its complications can be prevented [34].

Recent studies have shown that activation of AMP-activated protein kinase (AMPK) can increase the autophagy level of hepatocytes and promote fatty acid oxidation [35]. Under conditions of sufficient glucose, active mammalian target of rapamycin (mTOR) inhibits the activation of unc-51-like kinase 1 (ULK1) and the initiation of autophagy by phosphorylating a specific site in ULK1 (Ser 757), thereby destroying the interaction between ULK1 and AMPK. Under conditions of glucose deficiency, AMPK is activated, the phosphorylation of mTOR is inhibited by AMPK, and ULK1 can interact with AMPK and be phosphorylated by AMPK, thus enabling the activated ULK1 to start autophagy [36–38]. Liver Kinase B1 (LKB1) is an upstream regulatory protein of AMPK (Fig. 1). Following activation of the LKB1-AMPK-mTOR pathway, the

mRNA levels of *CPT1 α* and *PPAR α* were observed to increase, while triglyceride and cholesterol levels decreased [39]. In addition, hyperinsulinemia and insulin resistance are related to changes in the autophagy level [40]. A high carbohydrate diet can induce MASLD, which is closely related to hyperlipidemia and diabetes. Activation of the ChREBP/PPAR γ pathway has been reported to induce the activation of factors related to fat autophagy, thereby regulating lipid metabolism [41]. The liver expression levels of ATG7, LC3 and ULK1 are significantly decreased in patients with MASLD. However through fasting it was found that autophagy mediated by activated fibroblast growth factor 21 was responsible for lipid degradation [42].

The influence of obesity-induced liver lipid metabolism disorders on human health has attracted much attention in recent years. The research described above shows that autophagy plays a key role in hepatic lipid metabolism, mainly by degrading intracellular lipid droplets and reducing lipid accumulation in the liver, thereby improving lipid metabolism disorders (Fig. 1). Study of the molecular mechanism of autophagy in hepatic lipid metabolism should clarify the pathogenesis of liver lipid metabolism disorder caused by obesity and lead to improvement in drug treatments.

3. Ferroptosis and MASLD

3.1 Ferroptosis

Dixon first introduced the concept of ferroptosis in 2012 to describe a form of iron-dependent, non-apoptotic cell death observed in cancer cells with *KRAS* mutations. The cellular features of ferroptosis include: (a) Iron homeostasis, (b) lipid peroxidation, and (c) depletion of glutathione peroxidase 4 (GPX4) [43]. Several key biological processes in the human body are based on the ability of iron to fluctuate between oxidized (Fe^{3+}) and reduced (Fe^{2+}) forms [44]. Intracellular iron levels are kept in balance by an intracellular transport system. Fe^{2+} is absorbed by epithelial cells in the small intestine and released following erythrocyte degradation. It is then oxidized to Fe^{3+} when free outside the cell.

Free extracellular Fe^{3+} enters the cell via endocytosis after first binding to transferrin (TF) to form TF- Fe^{3+} and then binding to transferrin receptor 1 (TFR1) on the cell membrane [45]. Fe^{3+} that enters the cell is reduced to Fe^{2+} in the cytoplasm by STEAP family member 3 (STEAP3). Under the regulation of divalent metal ion transport protein 1 (DMT1), Fe^{2+} is mainly stored in a nontoxic and stable manner in ferritin. The remainder is stored in a free state in the labile iron pool (LIP). When the intracellular Fe^{2+} content is too high, ferroportin (FPN) can oxidize the excess Fe^{2+} to Fe^{3+} and secrete it from the cell. In this way, ferrous ions in the body are recirculated to enable strict control of intracellular iron homeostasis. Ferritin is a protein complex with 24 subunits and consisting of

ferritin heavy and light chains, a nano-sized hydrated iron oxide core, and a protein shell with cage-like structure that stores 4500 iron atoms [46]. Ferritin heavy chain (FTH) has iron oxidase activity, while ferritin light chain (FTL) promotes the nucleation of iron [47]. Fe^{2+} binds to FTH through the pore space of ferritin and is oxidized to Fe^{3+} , thereby rendering Fe^{3+} inert for deposition and unable to generate toxic effects and reactive oxygen species (ROS) inside the cell. Ferritin is a very important antioxidant and is essential for the prevention of oxidative stress mediated by iron overload. Increased ferritin expression somewhat limits the occurrence of ferroptosis. The onset of ferroptosis requires iron to be released from ferritin and reduced to Fe^{2+} [48]. The degradation of ferritin is dependent on autophagy. Nuclear receptor coactivator 4 (NCOA4), a selective autophagy-targeted receptor that binds to FTH, transports ferritin to the lysosome for degradation and the releases of ferric ions. This increases the intracellular destabilized iron content and promotes ROS accumulation, thus driving ferroptosis. Sensitivity to ferroptosis is affected by the expression level of NCOA4 [49]. Depletion of NCOA4 increases FTH expression, limits ferritin degradation, reduces intracellular free iron and oxidative stress, and decreases sensitivity to ferroptosis [50]. In contrast, overexpression of NCOA4 increases the ferritin autophagic flux, thereby increasing sensitivity to ferroptosis [51].

3.2 Lipid Peroxidation and Depletion of GPX4 in Ferroptosis

Polyunsaturated fatty acids (PUFAs) are the primary substrates for peroxidation in cell membranes during ferroptosis. Elevated PUFA synthesis enhances susceptibility to ferroptosis by a process that is positively modulated by acyl coenzyme A (CoA) synthetase long-chain family member 4 (ACSL4) [52]. Lipid peroxidation can cause great damage to cells. The accumulation of propylene glycol, the end product of lipid peroxidation, can cause polymerization of proteins and nucleic acids, leading to irreversible damage to membrane structure and ultimately to cell death [53]. Glutathione (GSH) functions as a substrate for the antioxidant enzyme GPX4, which mitigates the presence of toxic lipid ROS during ferroptosis. GPX4 is an intracellular antioxidant that catalyzes the transformation of GSH into oxidized glutathione while concurrently converting phospholipid hydroperoxides (PLOOH) into corresponding phospholipid alcohols. This enzymatic process effectively inhibits lipid peroxidation and is a pivotal mechanism in the prevention of ferroptosis. Additionally, the transmembrane protein system Xc $^-$ comprising solute carrier family 7 member 11 (SLC7A11) and solute carrier family 3 member 2 (SLC3A2) mediates the exchange of extracellular cystine with intracellular glutamate in a 1:1 ratio across the cell membrane [54].

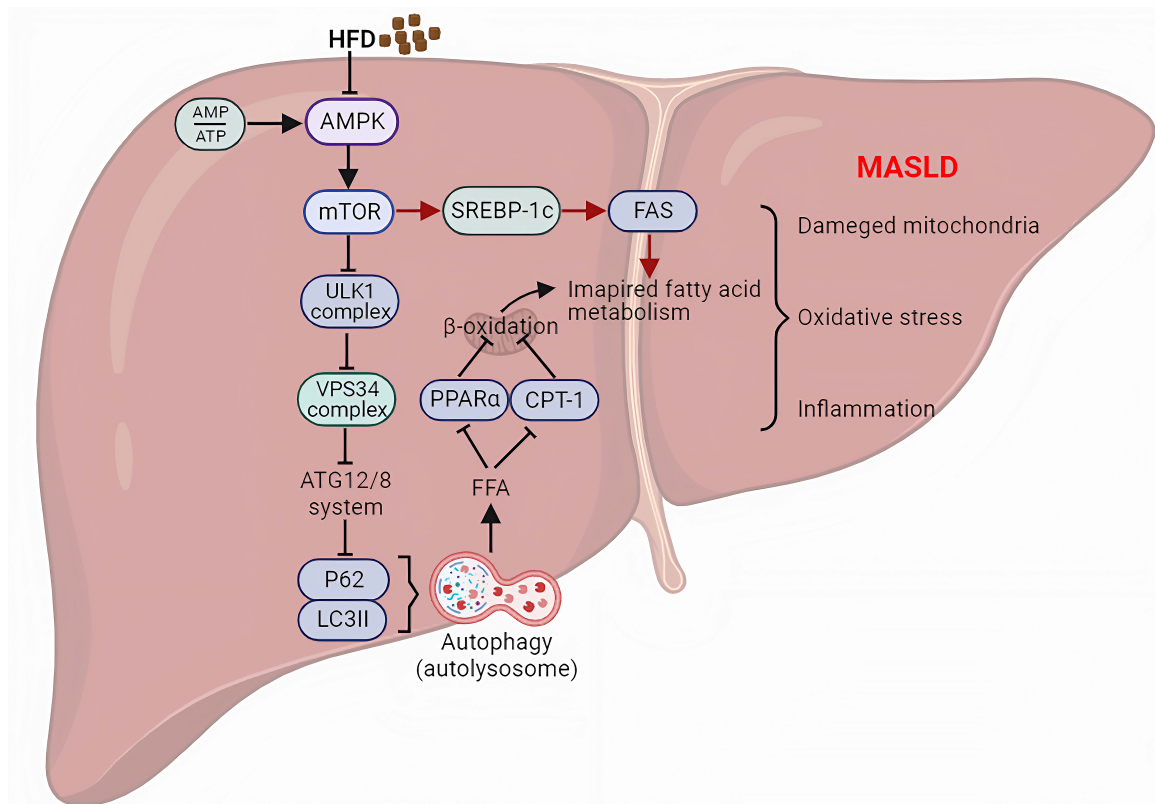


Fig. 1. Autophagy and MASLD. The AMPK pathway is considered a key factor in slowing the progression of MASLD. When excessive fat accumulates in the liver, AMPK is inhibited. This promotes hepatic fatty acid synthesis, while concurrently suppressing fatty acid oxidation and hence reducing fatty acid consumption. This increases intracellular lipid accumulation and favors the onset and progression of MASLD. AMPK also regulates autophagy through its effects on the clearance of cellular waste and the maintenance of energy balance. AMPK activation can directly phosphorylate ULK1 to initiate autophagy. AMPK can also indirectly promote autophagy by inhibiting mTOR. Thus, AMPK-mediated autophagy facilitates the degradation of cellular waste, such as fatty acids. Abbreviations: MASLD, metabolic dysfunction-associated steatotic liver disease; HFD, high-fat diet; AMPK, AMP-activated protein kinase; ULK1, unc-51-like kinase 1; mTOR, mammalian target of rapamycin; LC3, microtubule-associated proteins 1A/1B light chain 3; FFA, free fatty acids; SREBP-1c, sterol regulatory element binding protein 1c; FAS, fatty acid synthase; PPAR α , peroxisome proliferation-activated receptor α ; CPT1, carnitine palmitoyltransferase 1. Created with [BioRender.com](https://www.biorender.com).

3.3 Ferroptosis in MASLD

MASLD is a progressive liver disease that can progress to MASH, liver fibrosis, and even to HCC [55]. The liver is an important organ for fat metabolism and nutrient metabolism. It is also an important site for iron storage, accounting for about one-third of the body's stored iron reserve. Iron in the liver has a dual role in that hepatocytes maintain iron homeostasis through the production and secretion of hepcidin (Hepc), while iron metabolism and excessive accumulation of lipid peroxides in hepatocytes also causes ferroptosis [56]. Ferroptosis occurs during the progression of various types of liver diseases, such as alcoholic liver disease, non-alcoholic steatohepatitis, and HCC [57]. These are characterized by iron deficiency or iron overload in hepatocytes [58]. Specific inhibition of lipid peroxidation, modulation of iron metabolism and GPX4 (Fig. 2), and amelioration of excessive ferroptosis in the liver have become important approaches to combat MASLD.

3.3.1 Iron homeostasis in MASLD

As the main iron storage organ in the body, the liver is important for maintaining iron homeostasis. Normally, iron is stored in hepatic ferritin. By binding to ferritin and transporting it to the lysosomes, NCOA4 causes iron overload, resulting ultimately in the releases of large amounts of Fe^{2+} (Fig. 2). The reaction of Fe^{2+} with hydrogen peroxide (H_2O_2) generates Fe^{3+} and hydroxyl radicals ($\text{HO}\cdot$) via the Fenton reaction. The attack of $\text{HO}\cdot$ on polyunsaturated fatty acids in the membrane leads to increased lipid peroxidation, which then induces ferroptosis. Ferroptosis may be an important trigger for MASLD [59]. Although the total iron concentration in the liver of a mouse model of MASLD was not significantly altered, the Fe^{2+} concentration was elevated [60]. Hepatocellular steatosis and the progression of hepatic fibrosis leads to massive degradation of ferritin and large-scale release of free iron, resulting in significantly increased sensitivity of hepatocytes to ferroptosis.

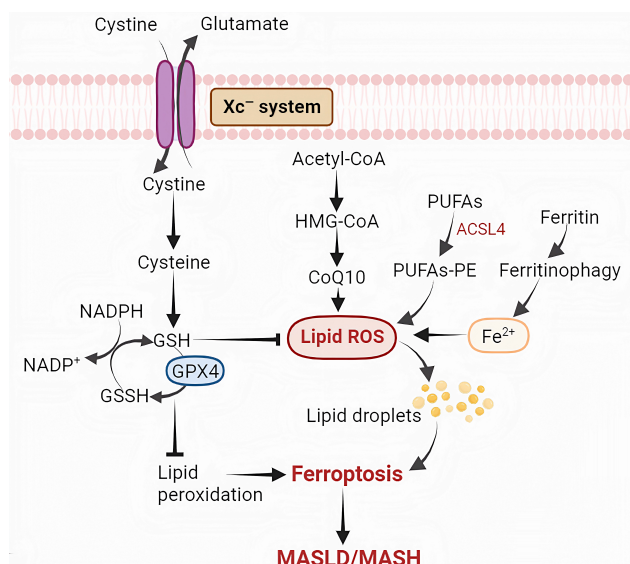


Fig. 2. Ferroptosis and MASLD. Ferroptosis can be initiated by inhibiting the Xc^- /GSH/GPX4 system axis, or lipid peroxidation. Blocking the Xc^- /GSH/GPX4 axis leads to reduced intracellular cysteine levels and inhibition of the lipid repair function of GPX4. Consequently, the disruption of cellular antioxidant capacity becomes a contributing factor to the onset and progression of ferroptosis. In MASLD, the key characteristics of ferroptosis include elevation of the intracellular Fe^{2+} concentration, and abnormal accumulation of lipid ROS. Additionally, ferritinophagy may modulate the generation of lipid ROS by regulating intracellular Fe^{2+} levels, thereby helping to maintain the lipid redox balance. Abbreviations: GSH, glutathione; ROS, reactive oxygen species; GPX4, glutathione peroxidase 4; PUFAs, polyunsaturated fatty acids; ACSL4, acyl-CoA synthetase long chain family member 4. Created with BioRender.com.

tos. Specific inhibition of hepatocyte ferroptosis and liver tissue inflammation were almost completely suppressed in the NASH mouse model. Treatment with ferroptosis inhibitors decreased the liver tissue iron levels and increased the relative expression levels of FTH and FTL. Ferroptosis inhibitors almost completely reversed hepatocyte cell death in the early stages of MASH and improved liver function [61].

It has also been shown that ferroptosis and damage to liver cells can occur in the absence of iron overload. The multifunctional protein poly (C) binding protein (PCBP1) is a receptor that acts as a cytoplasmic iron chaperone and binds and transfers iron to mammalian cells. GSH binds Fe^{2+} through its free sulfhydryl group to form the Fe-GSH complex. Ninety-five percent of LIP consists of PCBP1 with the Fe-GSH complexes [62]. Knockdown of PCBP1 increased the highly reactive iron content in LIP in mouse hepatocytes, leading to generation of ROS. This resulted in increased lipid peroxidation, exacerbation of lipid denaturation, and ferroptosis in hepatocytes without iron over-

load. PCBP1 may therefore ameliorate MASLD by regulating LIP and inhibiting ferroptosis [63]. In summary, important factors in the development of MASLD may be the increase in lipid peroxides triggered by iron overload and ferroptosis. The reduction of iron overload and targeting of PCBP1 may have a mitigating effect on the development of MASLD.

Oxidative stress caused by lipid peroxides is thought to be one of the important factors in the development of MASLD, and the accumulation of lipid peroxides is also a cause of ferroptosis. Thus ferroptosis may be a contributing key factor to MASLD [64]. Lipid peroxidation products can damage hepatocytes, and there may be a synergistic relationship between the lipid peroxidation substrate arachidonic acid (AA) and Fe^{2+} . This triggers programmed hepatocyte death with the involvement of Fe^{2+} , depletes intracellular antioxidants, leads to GSH and vitamin E deficiency, and creates a vicious circle of oxidative imbalance. This causes the lethal and emergency effect of hepatocyte injury, thereby accelerating the development of MASLD. The lipid peroxidation product MDA and the Fe^{2+} content were significantly increased in MASLD mice induced by a high-fat diet [60]. During the course of MASH accompanied by a rise in AA, ferroptosis inhibitors can ameliorate lipid accumulation and iron overload, resulting in a decrease in the degree of MASH. ACSL4 is a key enzyme in the generation of lipid peroxidases from PUFA, and ACSL4 expression was significantly elevated in a rat model of MASH. Inhibition of ACSL4 expression of ACSL4 can alleviate MASH [60] (Fig. 2). In summary, the inhibition of lipid peroxidation and ferroptosis may be a viable treatment for MASLD.

3.3.2 Depletion of GPX4 in MASLD

Oxidative stress is one of the most important mechanisms of liver injury in MASLD. Large amounts of ROS are generated and target the double bonds of PUFAs, resulting in the formation of lipid peroxides that can induce ferroptosis and exacerbate hepatocyte injury. GSH/GPX4 is an antioxidant system that targets lipid peroxide accumulation. Inhibition of the GSH/GPX4 system leads to peroxidative damage to cell membranes and ferroptosis (Fig. 2). GPX4 activators were found to be effective at alleviating MASH [65]. Nuclear factor E2-related factor 2 (Nrf2) is an alkaline leucine zipper protein and a key transcription factor for many antioxidant proteins. Nrf2 can directly regulate GPX4 transcription, and is also an important regulator of *de novo* GSH synthesis. Studies have shown that Nrf2 expression is reduced in MASLD mice, and enhancing the Nrf2-HO1 pathway can effectively prevent the development of MASLD [66,67]. Knockdown of Nrf2 in MASLD mice effectively reduces lipid accumulation and decreases PPAR γ levels [68].

Numerous studies have confirmed that ferroptosis is involved in the progression of MASLD/MASH. Moreover,

pathological processes such as lipid accumulation, hepatic steatosis, inflammatory cell infiltration, fibrosis, and mitochondrial damage are associated with ferroptosis in MASLD. Iron overload and oxidative stress-induced lipid peroxidation may mediate the progression of MASLD, and the major antioxidant mechanisms and iron metabolism regulators may be potential targets in future studies.

4. Apoptosis and MASLD

4.1 Apoptosis and the Activation of Caspases in MASLD/MASH

Apoptosis exhibits distinctive morphological features, including cellular shrinkage, a dense cytoplasm with tightly packed organelles, and pyknosis resulting from characteristic condensation and fragmentation of chromatin [69]. The biochemical process of apoptosis is induced by the activation of both initiator and executioner caspases. These caspases facilitate cell demise by cleaving proteins and subsequently activating nucleases, which in turn cleave DNA into shorter, uniform fragments. A recent study found a strong correlation between active caspases 3 and 7, increased expression of Fas receptors in MASH specimens, and the subsequent association of hepatocyte apoptosis with the progression of MASH [70]. Activation of caspase 3 and the occurrence of hepatocyte apoptosis are well-established hallmarks observed in various experimental models of MASLD, and in human MASLD [71] (Fig. 3). These phenomena have consistently shown a positive correlation with the severity of the disease.

The pharmacological pan-caspase inhibitor VX-166, an inhibitor of hepatic apoptosis, can decrease liver cell death in mice suffering from MASH. This could ultimately prevent the development of fibrosis [72]. Patients with MASH display increased levels of active caspase 2, active caspase 3, and apoptosis in their livers [71]. In addition, ballooned hepatocytes downregulate caspase 9, which is a crucial enzyme responsible for initiating mitochondrial apoptosis [73]. The absence of caspase 8 in hepatocytes attenuates the methionine-choline deficient (MCD)-induced increase in apoptosis, resulting in decreased production of pro-inflammatory cytokines, and reduced infiltration in the liver [74]. These observations highlight the crucial role of caspase 8 in MASH pathogenesis. Caspase 2 is considered an initial trigger in the process of lipid-induced cytotoxicity, specifically lipo-apoptosis, contributing significantly to MASH pathogenesis [75]. Its involvement in hepatocyte apoptosis induced by lipids is closely linked to the generation of apoptosis-associated fibrogenic factors. Furthermore, mice with MASH, show reduced levels of free CoA in the liver. This decrease correlated with elevated caspase 2 activity, and was associated with more severe liver cell death, inflammation, and fibrosis [75].

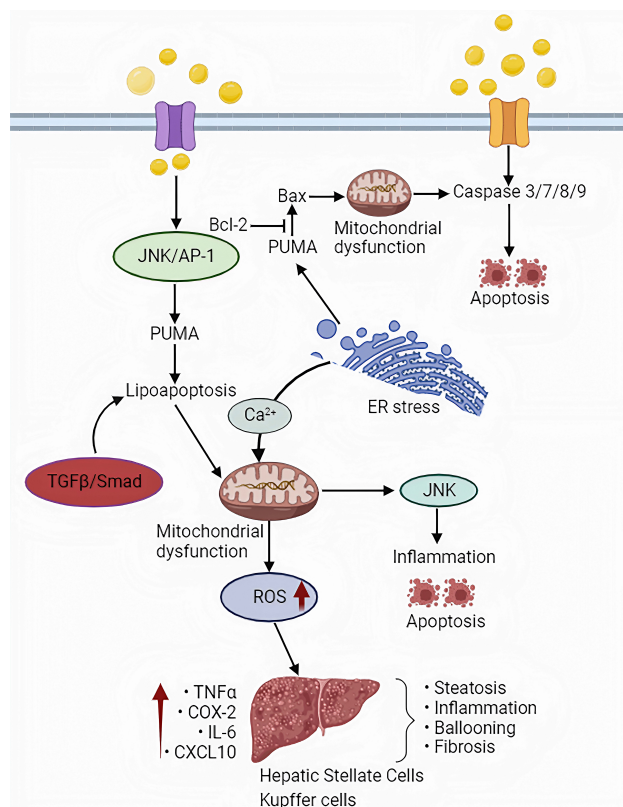


Fig. 3. Apoptosis and MASLD. Saturated FFAs exacerbate hepatocyte lipoapoptosis linked to JNK activation by promoting the activity of proapoptotic Bcl-2 proteins, notably Bax. Among these proteins, Bax assumes a pivotal role in initiating the intrinsic apoptotic pathway. Additionally, the apoptosis-modulator, PUMA, participates in FFA-induced lipoapoptosis in hepatocytes through the JNK/AP-1 complex. The transcriptional upregulation of PUMA, coupled with subsequent Bax activation, represents a critical step in the initiation of apoptosis mediated by saturated FFAs. Consequently, mitochondria emerge as central regulators in facilitating the elimination of fatty acids and inducing changes that enable hepatocytes to counteract excessive fat accumulation. Impaired mitochondrial function is implicated in various pathogenetic mechanisms of MASH. Abbreviations: JNK, c-Jun N-terminal kinase; AP-1, activator protein-1; Bcl-2, B-cell lymphoma-2; Bax, Bcl2-associated X; PUMA, p53-upregulated modulator of apoptosis; TNF α , tumor necrosis factor α ; ER, endoplasmic reticulum. Created with [BioRender.com](https://www.biorender.com).

4.2 Bcl-2 Family Members and Mitochondria in the Progression of MASLD/MASH

In patients with MASH, liver injury is associated with two key factors: apoptosis and the activation of NF- κ B, despite strong expression of the anti-apoptotic protein B-cell lymphoma 2 (Bcl-2) [76]. Surprisingly, serum Bcl-2 concentrations were significantly higher in the simple fatty liver patients than in the MASH ones [77]. All these alterations are dependent on caspases and involve mitochondrial

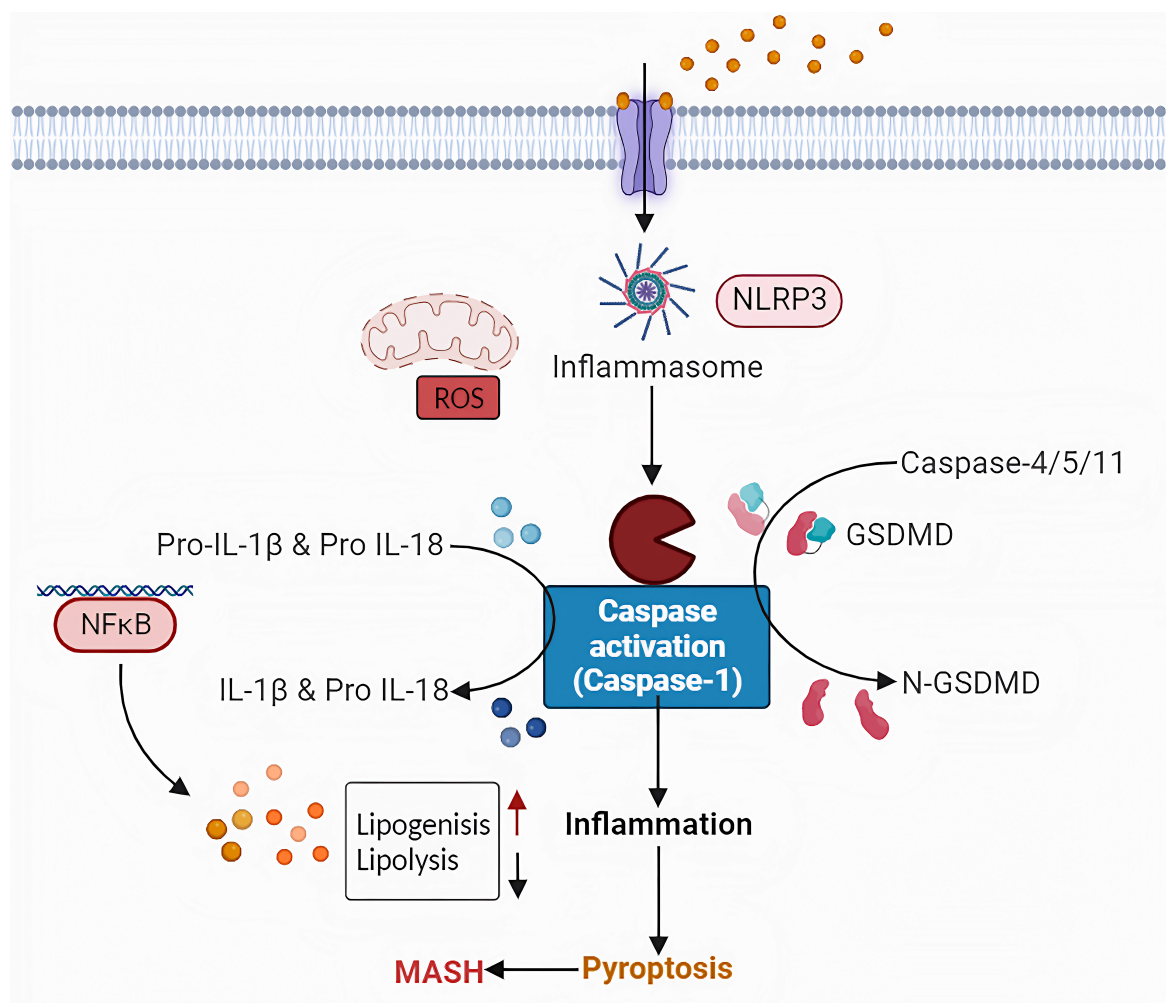


Fig. 4. Pyroptosis and MASLD. Cellular damage occurs during the progression of MASH due to factors such as oxidative stress, endoplasmic reticulum stress, and inflammatory responses. This can activate the formation of inflammasomes, with NLRP3 being a common factor. Activated inflammasomes, through the activation of caspase-1, subsequently induce the cleavage of Gasdermin D and the triggering of pyroptosis. Pyroptosis leads to cell rupture and the release of cellular contents, including pro-inflammatory cytokines such as IL-1 β and IL-18, which then initiate an inflammatory response. In MASLD, this inflammatory reaction may exacerbate liver damage, fibrosis, and disease progression. Abbreviations: NLRP3, NOD-like receptor family, pyrin domain-containing 3; IL-18, interleukin 18; IL-1 β , interleukin 1 β ; GSDMD, Gasdermin D. Created with [BioRender.com](https://www.biorender.com).

membrane disruption, leading to the release of cytochrome c and initiation of mitochondrial apoptosis pathways. This process involves the activation of proteins such as Bcl-2-associated X (Bax) and Bcl-2-interacting mediator of cell death (Bim) [10]. Of note, however, patients with MASH typically exhibit significantly reduced levels of Bcl-2 [10] (Fig. 3). Furthermore, there is an inverse correlation between the degree of apoptosis and the level of Bcl-2.

4.3 Activation of JNK and Apoptosis in MASLD/MASH

The onset of ER stress-associated c-Jun N-terminal kinase (JNK) initiates apoptosis by modulating the expression and function of pro-apoptotic members from the Bcl-2 family. This includes Bcl-2 homology 3 (BH3) proteins like Bim and the p53-upregulated modulator of apoptosis

(PUMA) [78]. PUMA, in turn, facilitates the activation of Bax, leading to permeabilization of the mitochondrial outer membrane and causing these pro-apoptotic factors to relocate to the cytosol [78]. The interaction between phosphorylated JNK and mitochondrial Sab results in compromised respiration, the generation of ROS, prolonged JNK activation, and apoptosis in the presence of lipid-induced lipotoxicity. These ultimately contribute to the pathogenesis of MASH [79] (Fig. 3). Therefore, the JNK signaling pathway plays a crucial role in the apoptosis that occurs during MASLD and MASH.

4.4 Pro-Inflammatory Cytokines, Chemokines, Oxidative Stress and Apoptosis in MASLD/MASH

Overexpression of the tumor necrosis factor (TNF) receptors 1 and 2 aggravate hepatic steatosis and fibrosis. At

the same time, they promote hepatic induction of TNF- α , vascular cell adhesion molecule 1, and intracellular adhesion molecule 1 [80]. This highlights the potential to target and inhibit the signaling pathways of TNF receptors 1 and 2 in patients with MASH [81]. The signaling pathway involving TNF receptor 1 contributes to the progression of “simple steatosis” towards the “MASH” phenotype. In rats with MASH, cyclooxygenase (COX)-2 can facilitate hepatocellular apoptosis by interacting with TNF- α and IL6 [82]. Of note, COX-2 is expressed at elevated levels in MASH. The secretion of pathophysiological extracellular ATP through the pannexin1 pathway during lipoapoptosis can trigger the migration of human monocytes in individuals with MASH. Lipids were also found to increase the mRNA expression of IL1 β and IL6 in bone marrow-derived macrophages in mice [83]. Recent findings have highlighted the significant involvement of C-X-C motif chemokine 10 (CXCL10), a well-known pro-inflammatory chemokine, in the development of MASH. Through its binding to the CXCR3 receptor, CXCL10 facilitates the recruitment of activated CXCR3⁺ T lymphocytes and macrophages into the liver tissue, thereby promoting inflammation, apoptosis, and fibrosis within the parenchyma [84]. In summary, inflammasomes and cytokines are pivotal factors that instigate apoptosis and respond to hepatocyte apoptosis in the context of MASLD and MASH.

Additionally, studies have suggested the presence of oxidized phosphatidylcholine within apoptotic hepatocytes in the livers of patients with steatotic disorders. This implies that oxidized phosphatidylcholine is generated within hepatocytes that have been subjected to oxidative damage [85]. Moreover, transforming growth factor β (TGF β) has the potential to modulate the p53 signaling pathway, thereby influencing the development of ROS, apoptosis, and MASH. TGF β signaling is responsible for activating Smad- and TGF β -activated kinase 1-dependent pathways, thus regulating cell survival, proliferation, fibrosis, and tumorigenesis. TGF β signaling is implicated in hepatocyte apoptosis and in the accumulation of lipids by Smad signaling and ROS, which ultimately contributes to the progression of MASH. Oxidative stress is a central element in the pathogenesis of MASH, with ROS serving as key markers of this oxidative stress. Mitochondrial dysfunction is the primary contributor to ROS in fatty liver diseases, being intricately interconnected with ER stress. Fueled by lipotoxicity, these factors, form a self-perpetuating cycle of organelle damage, which ultimately leads to sterile inflammation and apoptosis in MASH [10].

5. Pyroptosis and MASLD

Pyroptosis is a highly inflammatory form of PCD triggered by inflammatory microorganisms. These can detect cell cytosolic contamination or disturbance. Pyroptosis serves as a crucial component of the innate immune response. It has a significant role in promoting inflammation by releas-

ing cytokines such as interleukin 1 β (IL-1 β), IL-18, and various other inflammatory substances [86] (Fig. 4). Accumulating evidence suggests that pyroptosis contributes to the development of various diseases, including those associated with MASLD. Excessive cholesterol levels in patients with MASH disrupt the stability of lysosomal membranes, resulting in lysosomal damage and the release of their contents. This sequence of events subsequently triggers activation of the NOD-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome and pyroptosis [87]. Additionally, oxidative stress-generated ROS in MASH has the ability to activate the NLRP3 inflammasome, which in turn activates caspase-1 to initiate the process of pyroptosis (Fig. 4). Unrepressed NLRP3 activation has been showed to reduce hepatocyte survival, hepatic inflammation, and activation of hepatic stellate cells (HSCs), ultimately resulting in collagen deposition and liver fibrosis [88]. Pyroptosis relies primarily on the activation of caspase-1. Caspase-1 cleaves IL-1 β precursors to generate active IL-1 β , which subsequently recruits and activates other immune cells. This process promotes the synthesis of chemokines (e.g., IL-18), inflammatory factors (e.g., IL-6) and adhesion factors. Consequently, this sets off a “cascade effect”, that amplifies the inflammatory response [89].

In a mouse model fed the MCD diet, inflammasome-mediated dysbiosis was found to modulate the pathogenesis of MASLD and obesity. Aggravation of liver injury was also apparent in interleukin-18 knockout (*IL-18 KO*) mice. Notably, when NLRP3 deficiency was selectively confined to the immune system, the severity of MASH was not significantly different to wild-type animals [90]. MCC950, an NLRP3 inhibitor, attenuated the elevated levels of aspartate transaminase (AST) and alanine transaminase (ALT) in a mouse model of MASH, leading to reduced activation of NF- κ B. This reduction subsequently diminished liver inflammation and overall enhancement in the MASLD activity score. Higher levels of active caspase-1 and IL-1 β were observed in MCD-fed mice, but these were reduced after inhibition of NLRP3. Notably, the inhibition of NLRP3 delayed hepatic fibrosis, as indicated by lower levels of fibrotic markers and reduced infiltration of macrophages and neutrophils in MASH models [70]. Mitigation of pyroptosis through inhibition of the NLRP3 inflammasome attenuated the tendency towards ballooned hepatocytes. Gasdermin D (GSDMD), the primary effector of pyroptosis downstream of caspase-1, 4, 5, and 11, shows increased expression in MASLD patients and in various animal models of MASH. GSDMD expression was markedly elevated in mice fed an MCD diet, whereas mice lacking GSDMD showed attenuated MASH, lower ALT and TG levels, and improved liver fibrosis [91,92]. Additionally, GSDMD deficiency led to an improved hepatic cytokine profile, characterized by reduced levels of TNF, and IL-1 β .

6. Key Liver Cell Types in PCD in the Context of MASLD

6.1 Hepatic Stellate Cells (HSCs)

HSCs are key players in liver fibrosis, which is a common feature of advanced MASLD. PCD in activated HSCs encompasses autophagy, necroptosis, and pyroptosis. These may contribute to the resolution of fibrosis, or exacerbate tissue damage. While an association between autophagy and fibrosis is acknowledged, a correlation with hepatic fibrosis remains inconclusive. A recent study found that inducing autophagy in HSCs can hold promise for alleviating liver fibrosis. This therapeutic effect is attributed to a decrease in the secretion of extracellular vesicles carrying fibrotic components derived from activated HSCs [93]. Furthermore, the significance of mitophagy in the context of liver fibrosis deserves attention, thereby highlighting an additional dimension to the intricate processes involved in this pathological condition. Studies have indicated that the suppression of mitophagy in HSCs significantly activates these cells, thereby worsening hepatic fibrosis [94]. Conversely, another study reported that enhancement of autophagy in HSCs accelerates their activation, thereby promoting liver fibrosis [95]. Similarly, the formation of inflammasomes during pyroptosis can lead to liver injury and fibrosis, while inhibition of their activity can potentially reduce hepatic fibrosis caused by MASLD [96]. The activation of HSCs by inflammasomes released during hepatocyte pyroptosis constitutes a pivotal mechanism in liver fibrosis. Pyroptosis-induced dead hepatic cells can release high mobility group-1 (HMGB1), which serves as a damage-associated molecular pattern (DAMP), thereby promoting the activation of HSCs. Inhibiting pyroptosis typically reduces inflammation and liver fibrosis [97].

Necroptosis is a variant of programmed lytic cell death and has parallels with necrosis. Both modalities share similar characteristics, including enlarged cell volume, organelle swelling, and compromised membrane integrity. These lead to the release of DAMPs, which in turn induce inflammatory responses and consequential secondary injury [98]. In the context of MASH, necroptosis serves to intensify inflammation. DAMPs from necroptotic hepatocytes play a pivotal role in tissue inflammation and in triggering the activation of HSCs. However, the role of necroptosis in HSCs appears to be different to that in hepatocytes. Previous research has shown that induced necroptosis in HSCs substantially reduces liver fibrosis [99]. In summary, the modulation of PCD in HSCs may be a potential therapeutic approach to regulate liver fibrogenesis in MASLD.

6.2 Kupffer Cells (KCs)

KCs are resident macrophages in the liver responsible for identifying tissue damage and initiating an inflammatory response. KCs are closely associated with MASLD. The inflammatory response triggered by fat accumulation in MASLD may activate KCs [69], causing them to re-

lease inflammatory factors and thus further exacerbating liver inflammation and damage. KCs also play a role in clearing free radicals and responding to oxidative stress, thereby maintaining the hepatic redox balance [100]. The increased oxidative stress in MASLD can challenge the antioxidant function of KCs. Pyroptosis appears to be more prominent in macrophages during liver injury induced by MASLD/MASH, and it also contributes to the progression of liver fibrosis. The DAMP SA1008 is elevated in fibrotic liver tissue and has the capacity to mediate pyroptosis of KCs [101]. SA1008, released from deceased macrophages, activates HSCs, thereby promoting liver fibrosis. The pyroptosis of KCs effectively alleviates liver fibrosis by suppressing the nicotinamide adenine dinucleotide phosphate oxidase (NOX2)/NLRP3 pathway [102].

Autophagy within KCs is a robust protective mechanism for liver homeostasis during the initiation and progression of hepatic fibrosis. The autophagic process in KCs has a safeguard effect on hepatocytes during instances of hepatic injury. This protective role is manifested through the suppression of hepatic inflammation and fibrogenesis, as shown by the inhibition of ROS-induced IL-1 α/β secretion in murine models subjected to carbon tetrachloride treatment, and in rats exposed to N-diethylnitrosamine feeding [103]. Necroptosis is therefore a pivotal mechanism for macrophages, as highlighted by the induction of necroptosis in liver-resident macrophages, and specifically KCs [104]. The expeditious clearance of dying cells by macrophages is imperative for the onset of liver fibrosis subsequent to hepatocyte necroptosis. Nevertheless, macrophages encounter challenges in effectively eliminating necroptotic hepatocytes, with research showing that phagocytosis is compromised in the context of MASH.

7. Crosstalk between Different Types of PCD in MASLD

7.1 Apoptosis, Pyroptosis and Necroptosis

There are clear parallels between apoptosis and necroptosis in the context of liver injury, particularly in MASH. Specifically, the upregulation of activating transcription factor 3 in MASH induces increased expression of receptor-interacting serine-threonine kinase 3 (RIPK3) [105]. As a consequence, this molecular change prompts a transition in the predominant mode of cell death within hepatocytes, shifting from apoptosis to necroptosis and thereby aggravating hepatic steatosis. In contrast to pyroptosis, necroptosis represents a distinct form of PCD characterized by distinctive triggering factors and morphological features. Both modalities exhibit shared features in terms of membrane rupture and the initiation of inflammation within the context of MASLD/MASH [10]. Additionally, caspase-10 intricately regulates both pyroptosis and necroptosis by cleaving RIPK1, thereby hindering the assembly of the NLRP3 inflammasome in hepatic macrophages [106]. This regulatory mechanism markedly reduces the

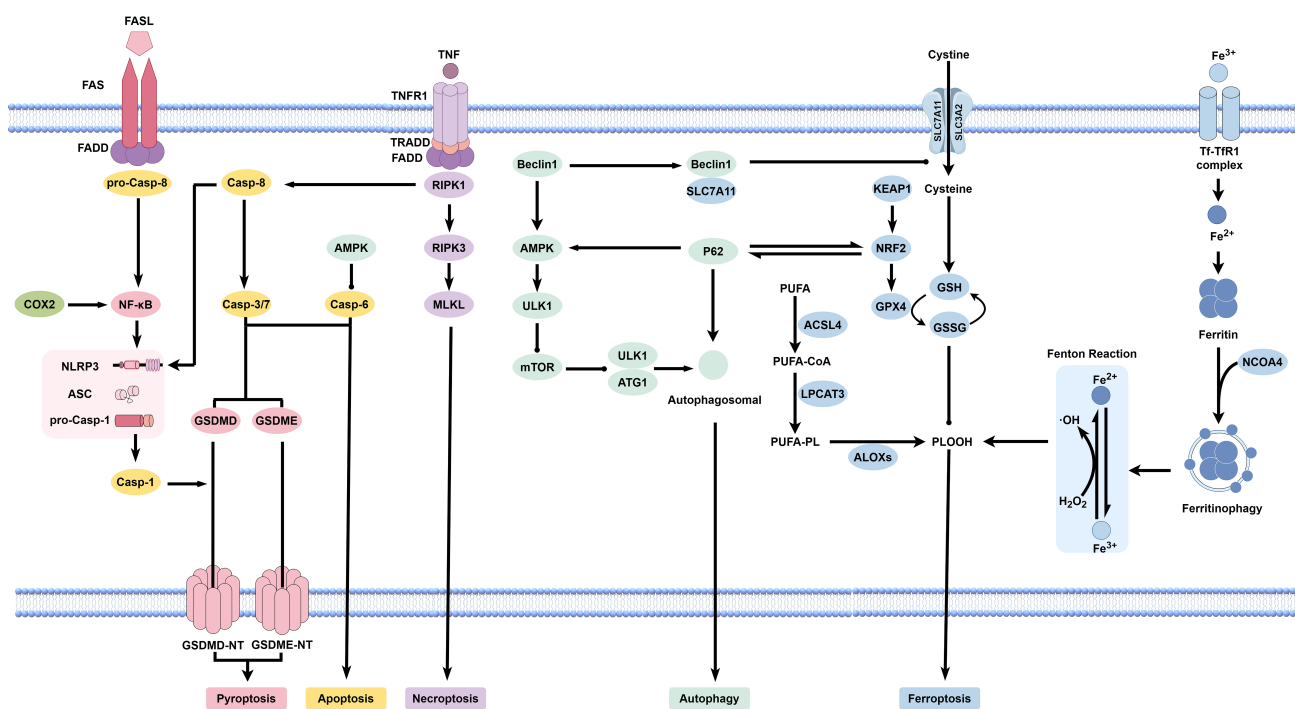


Fig. 5. Interplay among diverse forms of PCD gives rise to a complex regulatory network influencing the fate of cells. Key nodes in this intricate interaction, crucial for the survival or demise of macrophages, include AMPK, mTOR, Caspase-8, RIPK3, Bcl-2, and p62. These components play pivotal roles in the interconnection of pyroptosis, apoptosis, necroptosis, autophagy, and ferroptosis within the cell death network. Abbreviations: ASC, apoptosis-associated speck-like protein; NCOA4, nuclear receptor coactivator 4; NLRP3, NOD-like receptor thermal protein domain associated protein 3; COX-2, cyclooxygenase-2; TFR1, transferrin receptor 1; NRF2, nuclear factor erythroid 2-related factor 2. By Figdraw.

incidence of necroptosis and pyroptosis in macrophages, leading to a concomitant reduction in the release of inflammatory cytokines (Fig. 5). As a result, this action attenuates cirrhosis and suppresses the activation of HSCs. The three distinct modes of cellular death, namely apoptosis, necroptosis, and pyroptosis, collectively constitute the pro-inflammatory form of PCD known as PANoptosis. Caspase-6 and caspase-8 are the two most important regulators of PANoptosis (Fig. 5). This phenomenon has been implicated in the context of liver fibrosis, whereby RIPK1 is as a key driver of PANoptosis within KCs. NASH subsequently intensifies and is characterized by steatosis, inflammation, and fibrosis [107]. Experimental evidence indicates that inhibition of PANoptosis in hepatocytes is effective at ameliorating liver injury and fibrosis induced by fatty liver disease associated with metabolic dysfunctions [107].

7.2 Ferroptosis, Autophagy and Other Forms of PCD

A distinctive feature of ferroptosis involves the increased levels of intracellular ROS. This shared characteristic extends across diverse forms of PCD, encompassing apoptosis, necroptosis, and pyroptosis. It implies the presence of interactive regulatory relationships between ferroptosis and other pathways of PCD. A previous study reported

that administration of a GPX4 inhibitor can induce ferroptosis and concurrently activate apoptosis by upregulating early growth response-1 (EGR1) expression. Ferroptosis subsequently initiates necroptosis through the generation of ROS. The therapeutic efficacy of ferroptosis inhibition in the context of MASLD is demonstrated by improvement of apoptosis, necroptosis, and pyroptosis [108,109]. Overexpression of yes-associated protein (YAP) facilitates liver fibrosis, ferroptosis, and necroptosis in MASLD/MASH and can be mitigated by the administration of exosomes derived from huMSC cells [109]. These exosomes have the capacity to secrete Beclin-1, an autophagy regulator, by mediating ferritinophagy, thereby diminishing the system Xc⁻/GPX4 axis to significantly increase susceptibility to ferroptosis.

The process of autophagy in hepatocytes initiates apoptosis, subsequently triggering the transdifferentiation of HSCs into myofibroblasts. The facilitation of mitophagy enhances apoptosis in HSCs, thereby mitigating liver fibrosis [95]. Furthermore, the induction of necroptosis is also contingent upon autophagic processes. In the presence of ATG5, necroptosis has the capability to eliminate activated HSCs, thereby mitigating liver fibrosis [110]. While the complex interplay between autophagy and pyroptosis in the context of liver fibrosis remains incompletely

Table 1. The potential therapeutic applications of different types of PCD inducers in MASLD.

Drugs	Effects on the PCD	Benefits of MASLD	Refs
Ferrostatin-1	A ferroptosis inhibitor and prevents lipid ROS accumulation and inhibits lipid peroxidation	Ameliorate MASLD/MASH and fibrosis	[112]
Liproxstatin-1	As a ferroptosis inhibitor, serves as a radical-trapping antioxidant to impede the process of lipid peroxidation	Alleviates MASLD	[113]
Deferoxamine	As an iron chelator, has affinity with Fe^{3+}	Ameliorate MASLD/MASH and fibrosis	[114]
Deferasirox	As an iron chelator, suppresses oxidative stress and HSC activation	Ameliorate MASLD/MASH and fibrosis	[115]
Deferiprone	As an iron chelator, attenuates hepatic inflammation	Alleviates MASLD	[107]
Necrostatin-1	As a necroptosis inhibitors, attenuates hepatic inflammation	Alleviates liver injury and ischemia reperfusion injury in MASLD	[116]
Necrosulfonamide	As a necroptosis inhibitors, decreases hepatic de novo fat synthesis and chemokine ligand expressions	Has protective effects in MASH	[117]
Emricasan	As an apoptosis inhibitor, decreases ALT and biomarkers	Has protective effects and ameliorate fibrosis in MASH	[118]
GS-9450	As an apoptosis inhibitor, decreases ALT	Has protective effects in MASH	[119]
Disulfiram	As a pyroptosis inhibitor, modulates the gut microbiota and bile acid metabolism	Ameliorates MASH	[120]
PX-478	As a pyroptosis inhibitor, reduces weight and abdominal adipocyte hypertrophy	May ameliorate fatty liver disease	[121]
Rapamycin	As an autophagy activator, attenuates steatosis, inflammation, and increases fatty acid oxidation	Ameliorates MASH and fibrosis	[122]
Trehalose	As an autophagy activator, increases transcription of genes, regulates mitochondrial energy metabolism	Ameliorates MASLD and inflammation	[123]
Metformin	As an autophagy activator, alleviates hepatic steatosis, protects of hepatocyte necroptosis, and induces lipophagy	Ameliorates MASLD and fibrosis	[10]
Spermidine	As an autophagy activator, enhances mitochondrial activity and fatty acid β -oxidation	Ameliorates MASH	[124]
Resveratrol	As an autophagy activator, improves glucose metabolism, lipid profile, and steatosis	Ameliorates MASLD/MASH and liver fibrosis	[125]

PCD, Programmed cell death; MASLD, Metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; ALT, alanine transaminase.

elucidated, valuable insights into their interaction can be gleaned from observations in other liver diseases. For example, increasing the level of autophagy in hepatocytes promotes pyroptosis of in an arsenic-induced MASLD animal model. Conversely, the suppression of mitophagy has been shown to alleviate the pyroptosis of hepatocytes in FFA-induced MASH [111]. Given the associations between various types of PCD and MASLD mentioned above, we have compiled the therapeutic applications of different types of PCD inducers for MASLD, as illustrated in Table 1 (Ref. [10,107,112–125]).

8. Conclusions

The concept of PCD has brought about a paradigm shift in our comprehension of cell death, while stimulating an entire realm of research in MASLD. Accumulating evidence indicates that PCD plays a significant role in metabolic liver disease and holds promise as a therapeutic target for MASLD/MASH. In the context of MASLD, PCD is a major driving force for fat accumulation, liver inflammation, liver injury and fibrosis. Nevertheless, several cru-

cial questions still need to be addressed through experimental research prior to clinical applications. Further research is needed to fully elucidate the molecular conditions in which the various PCD mechanisms regulate cell death. Understanding the precise signaling pathways that govern PCD in MASLD should enable researchers to target therapeutics to specific molecules, thereby mitigating subsequent liver injury, inflammation, and fibrosis. More importantly, various PCD modes coexist in MASLD, and hepatocytes are able to transition between different death subroutines. Future investigations should aim to understand the substantial crosstalk among the various PCD modes and signaling cascades in MASLD. A better understanding of the intricacies and connections involved in the pathogenesis of MASLD will be instrumental for the development of targeted therapeutics.

Author Contributions

SSZ and XZY designed the study. SSZ, YG and XZY collected and analyzed the literatures. SSZ and XZY wrote the manuscript. YG and XZY discussed and critically re-

vised the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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