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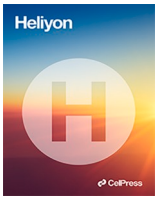

Review article

Programmed cell death, from liver Ischemia–Reperfusion injury perspective: An overview

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ABSTRACT

Liver ischemia-reperfusion injury (LIRI) commonly occurs in liver resection, liver transplantation, shock, and other hemorrhagic conditions, resulting in profound local and systemic effects via associated inflammatory responses and hepatic cell death. Hepatocyte death is a significant component of LIRI and its mechanism was previously thought to be limited to apoptosis and necrosis. With the discovery of novel types of programmed cell death (PCD), necroptosis, ferroptosis, pyroptosis, autophagy, NETosis, and parthanatos have been shown to be involved in LIRI. Understanding the mechanisms underlying cell death following LIRI is indispensable to mitigating the widespread effects of LIRI. Here, we review the roles of different PCD and discuss potential therapy in LIRI.

1. Introduction

Ischemia-reperfusion injury occurs in numerous diseases, resulting in cell death and organ damage. Liver ischemia-reperfusion injury (LIRI) is involved in hepatic resection, liver transplantation, or hypotensive shock [1]. There are two phases involved in LIRI: the local ischemic insult and the reperfusion injury that are interconnected [2]. During the ischemia period, oxygen is exhausted and ATP production decreases, thus resulting in edema and swelling of cells [3]. Previous researches have shown that cell death is the major underlying mechanisms of LIRI [4, 5]. In the past decades, it has been considered that necrosis and apoptosis are mainly in LIRI [6]. In recent years, various forms of programmed cell death (PCD) that are distinct from apoptosis have been reported. Our review will primarily focus on PCD in LIRI, as well as potential therapeutic targets for various types of PCD (Fig. 1).

2. Cell death is one of the major mechanisms for LIRI

There are two types of cells in the liver:hepatocytes and nonparenchymal cells, including Kuffer cells (KCs), liver sinusoidal endothelial cells (LSECs) and hepatic stellate cells [7]. Donor livers are kept in cold storage during transport, which are exposed to cold ischemia [8]. Then, preserved livers are implanted into surgical recipients, leading to warm ischemia, which is triggered by hepatocellular injury [9]. Initiation of blood flow is achieved by reconstructing the vasculature (end of warm ischemia) [10]. Cold and warm ischemia injury lead to immune activation and comprehensive hepatocytes damage in the early stages of LIRI [11].

Despite the similar mechanisms behind cold and warm ischemic insults, hepatocytes and LSECs respond differently to these two

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ischemic stresses [12]. During liver transplantation, injured hepatocytes and LSECs release damage-associated molecular patterns (DAMPs) and cause a pro-inflammatory phenotype in KCs [11]. Owing to a disrupted respiratory chain in hepatocytes in LIRI, reactive oxygen species (ROS) are produced from the mitochondria and cause tissue damage [13]. The ROS produced in the early stage of ischemia-reperfusion lead to protein denaturation and damage of biofilm through lipid peroxidation. In addition, the mass ROS can activate macrophages and lymphocytes, causing local and systemic inflammatory damage. The activation of inflammatory cells through migration, chemotactic aggregation of hepatic sinuses, resulting in liver reflow phenomenon [14]. Inflammatory mediators aggravate the damage of surrounding liver tissue, manifested as apoptosis and necrosis of liver cells [12]. LSECs are highly vulnerable to injury during cold preservation [15]. When platelets adhere to LSECs, LSEC death and microcirculatory congestion can occur during LIRI [16].

The activation of Kupffer cells is pivotal in LIRI for contributing to inflammatory responce [17]. In the initial stages of an ischemic insult, DAMPs is released from damaged cells, leading to an increase in ROS, reactive nitrogen species [18], and pro-inflammatory cytokines (IL-10) being produced by Kupffer cells after reperfusion [18]. Additionally, proinflammatory cytokines are also responsible for creating a positive feedback loop that leads to an increase in the activity of KCs [19]. Neutrophils are attracted to liver tissue by CCL2 in LIRI, secreted by the KCs [20]. At the same time, KCs are also responding to LIRI by producing IL-10 [21]. This study suggests that KCs may play a self-limiting role in the development of IRI after liver transplantation. Further studies should be conducted to clarify the effects of warm ischemic reperfusion injury on LSEC phenotype and KCs function.

3. Programmed cell death in LIRI

The Nomenclature Committee on Cell Death states that all cell deaths other than accidental cell deaths are defined using biochemical characteristics, which are programmed by internal mechanisms, and thus are termed programmed cell death (PCD) [22]. PCD is mainly attributed to necrotic and apoptotic pathways [23–25]. Although it may appear that LIRI mostly as a consequence of lytic necrosis, many divergent forms of regulated cell death are often complementary or overlap each other in different parts of the liver [26]. Ischemia and reperfusion injury can initiate several cellular processes, which are associated with some type of PCD, including apoptosis, necroptosis, ferroptosis, pyroptosis, autophagy, NETosis and parthanatos (Table 1) [27–31]. In this review, we

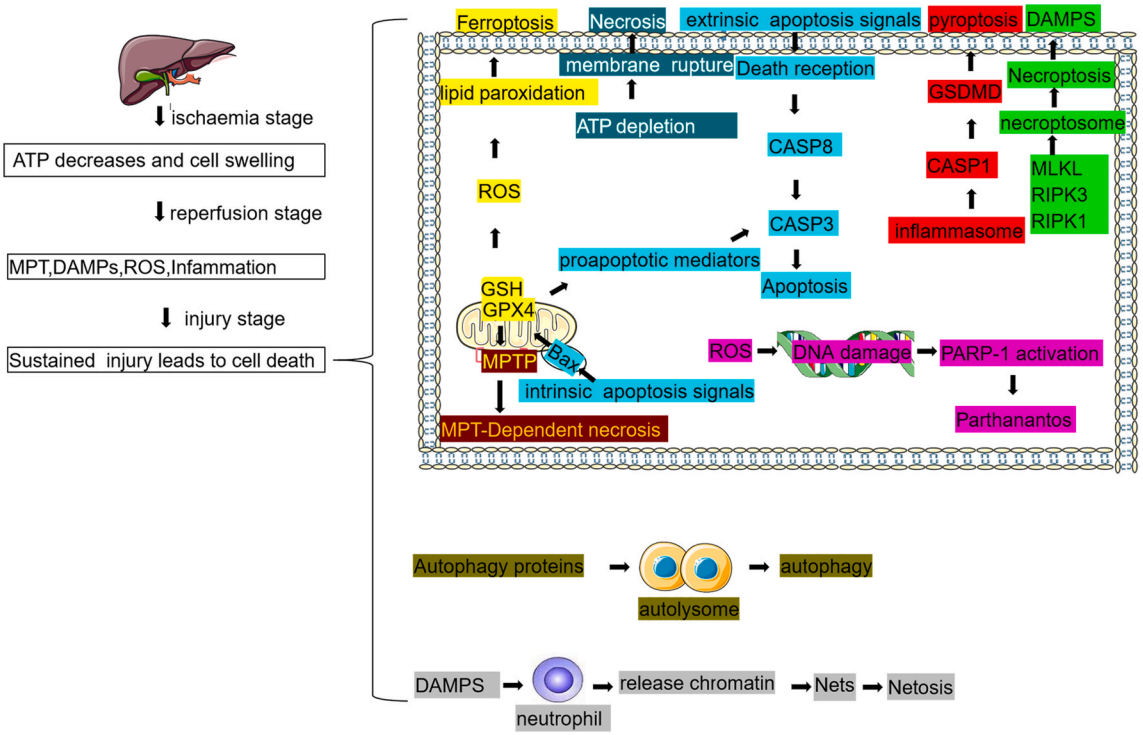

Fig. 1. Programmed cell death pathways in liver ischemia-reperfusion injury (LIRI). During ischemia, the affected hepatocytes are deprived of oxygen, resulting in decreased ATP production. Following reperfusion, ROS accumulation can lead to inflammasome formation, which may initiate pyroptosis (red), or excess ROS can damage DNA, leading to PARP overactivation and parthanatos (purple). Ferroptosis is mediated by erastin, whose activation leads to iron-dependent ROS accumulation, iron overload and lipid peroxidation (yellow). Activation of caspase-8 stimulates formation of necroptosomes, which are composed of RIPK1, RIPK3 and MLKL (green). NETosis occurs in response to various stimuli such as DAMPs, and neutrophils expel their chromatin, resulting in a sticky NET that can capture and kill pathogens (gray). ROS, reactive oxygen species; DAMPs, damage-associated molecular patterns; PARP, poly ADP-ribose polymerase; RIPK, receptor interacting protein kinase; MLKL,mixed lineage domain-like protein. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Summary of different programmed cell death types in liver ischemia–reperfusion injury.

	MPT-Necrosis	Apoptosis intrinsic	Apoptosis extrinsic	Necroptosis	Ferroptosis	Pyroptosis	Autophagy	NETosis	Parthanatos
Triggered by	ROS	intracellular signals	TNF-α	TLR3/4 receptor activation	Fe^{2+} overload	Inflammation	Ischemia	ROS	DNA damage
Inflammatory	Yes	No	NO	Yes	Yes	Yes	Partially have autolysosomes	Yes	No
Main mechanism	Mitochondrial dysfunction	Caspase-3 cleavage	Caspase cascade	Necrosome complex	Lipid peroxidation	Caspase-1 activation		Inflammation	RARP activation
Key players	MPTP	Caspase-3 and 9	Caspase-8	RIPK1、RIPK3、MLKL	LPO and ROS	Caspase-1,caspase-4 and 11, Gasdermin D	ATGs	Activated neutrophils	RARP-1,PAR, AIF
Inhibitors	ATP	Bcl-2	Bcl-2	Caspase-8	GPX4	Inflammation inhibitors	Bcl-2	NETs inhibitors	Caspase-3
Morphology	Mitochondrial membranes rupture	Apoptotic bodies	Outer mitochondrial membrane pores	Lytic death	Condensed mitochondrial	Membrane rupture	Autophagic- vacuoles cellular degradation	NETs	Nuclear translocation
ATP slump	Yes	No	No	No	No	No	Yes	No	Yes
DNA damage	No	Yes	Yes	No	No	No	No	No	Yes
Role in LIRI	Promote	Promote	Promote	Promote	Promote	Promote	Suppress	Promote	Promote
(Refs.)	(32-36)	(37–39)	(40–43)	(44–46)	(47–50)	(51–53)	(54–57)	(58–62)	(63–65)

ROS: reactive oxygen species; MPTP: Mitochondrial Permeability Transition Pore; Bcl-2:B-cell lymphoma-2; TNF:tumor necrosis factor; TLR:Toll-like receptors; RIPK: Receptor-interacting serine/threonine-protein kinase; PARP-1: polymerase-1; MLKL: mixed lineage kinase domain-like; LPO:lipid peroxide; GPX4:glutathione peroxidase-4; NLRP3: NOD-like receptor protein 3; ATGs: autophagy-related genes; AIF: apoptosis-inducing factor; NETs: Neutrophil extracellular traps.

focus on the different types and roles of PCD that are closely to LIRI.

3.1. Mitochondrial permeability transition (MPT)-dependent necrosis

MPT-dependent necrosis is a typical form of PCD regulated by the mitochondria and widely involved in LIRI [32]. MPT, which occurs in uncontrolled mitochondria during LIRI, causes ATP depletion, generates ROS, and accelerates membrane potential dissipation [33,34]. Reperfusion injury after ischemia causes mitochondrial membrane permeabilization and depolarization. Peptidyl-prolyl isomerase F and cyclophilin D (CypD) are involved in forming permeability transition pores in the mitochondrial membrane [35]. As CypD binds to the mitochondrial surface and becomes phosphorylated, it accelerates connection with the adenine nucleotide translocator in LIRI and the Ca^{2+}-mediated MPT [35, 36].

Studies have shown that necrosis is considerably decreased after CypD knockout in animal models of renal, cardiac and liver ischemia-reperfusion [66–68]. Thus, MPT onset is a causative factor contributing to MPT-dependent necrosis after reperfusion in hepatocytes [69]. It has been shown that MPT is directly related to apoptosis in the sense that MPT can release cytochrome-c and other pro-apoptotic molecules from the intracellular microenvironment directly into the cytosol as part of the process of apoptosis [70,71]. However, no consensus exists regarding what pathogenetic mechanisms of MPT development play roles in LIRI.

3.2. Apoptosis

Apoptosis is a form of PCD induced by DNA stability imbalance, ROS overload and oxidative stress [72–75]. DNA fragmentation, chromatin condensation and plasma membrane blebbing are characteristic of apoptotic bodies, which are non-membrane-bound particles containing portions of the cytoplasm and fragmented organelles [76]. The two types of caspase-activation mechanisms are intrinsic and extrinsic pathways, which activate caspases [37]. A mitochondrial insult increases the permeability of the mitochondrial membrane, which, in turn, triggers the activation of caspases-9 and caspase-3 in intrinsic pathways [38]. Apoptosis-inducing ligands associated with tumor necrosis factor receptors (TNF-R) and TNF-related apoptosis receptors activate the caspase-8 intrinsic pathway via the death receptors [39]. This process prevents DAMPs from leaching out by prompting cells to actively produce anti-inflammatory signals [77]. During extrinsic apoptosis, ligands react with their receptors on the cell surface to activate procaspase-8 [40]. These events bring about MPT, which further initiates the process of apoptosis [41]. Thus, colony stimulating factors are released, and they induce apoptosis of cells [41]. A study conducted in LIRI suggests that a small proportion of hepatocytes undergo apoptosis as a result of the stress [42]. As a consequence of apoptosis in hepatocytes and LSECs, cytochrome-c is released into tissue and caspase is activated [43]. In the ischemic stage of the liver, apoptosis of hepatic nonparenchymal cells, including KCs and LSECs, activates the TNFα-induced apoptosis mechanism and increases reperfusion injury in hepatocytes [40]. When the mitochondrial structure gets injuryed due to LIRI, the apoptosis proteins release from the intermembrane space and enter the cytoplasm [43]. Some biomarkers related to apoptosis have been identified by researchers, including the activated caspase family and cytochrome-c [40]. These biomarkers should be investigated further in LIRI. Nrf2 activators therapeutically suppress apoptosis during LIRI by regulating inflammatory responses [78]. Antioxidant activators exhibit a modest protective effect against LIRI by preventing apoptosis [79]. Previous research studies have elucidated that the potential benefit of Ginsenoside is that it alleviates LIRI by inhibiting apoptosis-related proteins and inflammation mediators, which represents an effective method to prevent LIRI [80]. The mitochondrial pathways are considered as reliable regulators of apoptosis. In clinical practice, they are considered as a new treatment option that prevents the occurrence of LIRI.

3.3. Necroptosis

Necroptosis is a form of PCD that can be classified into a number of different types depending on its molecular mechanism, although it is activated by receptor signaling pathways that are unrelated to apoptosis [81]. Mixed lineage domain-like protein (MLKL) pores trigger production of DAMPs and other inflammatory molecules, demonstrating the importance of necroptosis in non-alcoholic steatohepatitis and LIRI [82, 83]. It is thought that necroptosis of cells may be a critical factor in the development of non-alcoholic fatty liver disease, both of which are leading indications for liver transplantation [44]. MLKL-knockout animals displayed lower hepatic neutrophil infiltration and were more resistant to LIRI due to enhanced MLKL-mediated necroptosis [44].

Previous research suggests that necroptosis contributes to LIRI. In steatotic mice with LIRI, necroptosis markers were increased [45]. Blocking necroptosis can effectively diminish oxidative stress, endoplasmic reticular stress and inflammation [81]. Necroptosis has widespread negative effects on solid organ transplantation [46,84]. Owing to the complexity of the role of necroptosis in LIRI, it is essential that further molecular studies are conducted.

3.4. Ferroptosis

Ferroptosis is a type of PCD that is closely be associated with iron metabolism cycle in vivo, which involves lipid peroxide (LPO) accumulation and glutathione (GSH) depletion in the intracellular microenvironment [85–87]. The main characteristic of ferroptosis is the presence of mitochondria with condensed densities of mitochondria, as well as a ruptured outer membrane barrier [88,47]. Owing to its function in limiting lipid peroxidation, glutathione peroxidase 4 (GPX4) also function as an inhibitor of ferroptosis, implying that its activity is reliant on GSH [48]. A murine model of LIRI showed marked upregulation of the ferroptosis marker, Ptgs2 [49]. In LIRI, ferroptosis is involved in small molecules that inhibits glutathione biosynthesis, which causes ROS accumulation and mitochondrial damage [50]. Quantitative comparisons of LPO and liver injury have shown that LPO can cause parenchymal cell death after

reperfusion [48]. Fer-1 inhibits extracellular iron levels of hepatocytes and macrophages, which are highly susceptible to the effects of extracellular iron [89]. Liver plays an important role in regulating the systemic iron homeostasis [90]. Overexpressing adipose-specific lipin-1 mice accumulated large amounts of iron and had poor ferroptotic gene expression in LIRI [91]. Some potential therapeutic targets, such as desferrioxamine, Fer-1, and glutathione, reduce harmful damage caused by ferroptosis in LIRI [49, 92]. ROS accumulation is a critical component of ferroptosis in LIRI [93]. Consequently, the balance between GSH and ROS may influence LIRI. Future research will consider whether ferroptosis is necessary for cell death in LIRI models using GPX4-knockout mice.

3.5. Pyroptosis

Pyroptosis involves a unique PCD-associated mechanism that exerts a more intense inflammatory response [94,95]. Pyroptosis is a proinflammatory cytosolic death mode mediated by the gasdermin family through pore formation and pyrotopic-related inflammatory reactions [96,97]. The classical pyroptosis pathway is a proinflammatory form of PCD mediated by caspase-1 [98, 51]. By recruiting inflammasomes and NOD-like receptor protein 3 (NLRP3), the apoptosis-associated adapter protein can form a focus called the "pyroptosome" that is activated during apoptosis [52]. A mouse model of LIRI showed that the NLRP3 inflammasome was involved in generating interleukin (IL)-1, and NLRP3 silencing has a protective effect in LIRI, mostly by downregulating caspase-1 activation and decreasing inflammatory factor release [53]. Researchers have demonstrated that LIRI can be alleviated by targeting the NLRP3 and pyroptosis [99].

The non-classical pathway of pyroptosis is caspase-4 and caspase-11-dependent under stimulation of various infectious factors such as the gram-negative bacterial surface endotoxin, lipopolysaccharide (LPS) [100,101]. It was traditionally believed that apoptosis and pyroptosis were mutually exclusive. These researches showed that there was significant crosstalk between apoptosis and pyroptosis. Moreover, the secretion of pro-inflammatory cytokines was suppressed [102]. Gasdermin D (GSDMD) causes mitochondrial membranes damage and potential oxidative phosphorylation [103]. The caspase-11 (GSDMD) pathway aggravates neutrophilic infiltration via pyroptotic cell production of inflammatory factors [104]. Future research should evaluate the impact of GSDMD inhibition on LIRI in mice. The possibility that pyroptotic pathways target cells in liver disease should also be studied.

Because of the enterohepatic axis in the liver, hepatic portal blockage causes stasis of the mesenteric venous vein, allowing gram-negative bacteria in the intestinal tract to enter the blood [105]. LPS is the strongest activator of liver macrophages such as KCs [102]. LPS binds to cell surface receptors through the toll-like receptor pathway to activate KCs [103]. Because caspase-11 is a natural receptor of LPS, LPS can bind to caspase-11 in cells and activate it, thus initiating the caspase-11-dependent non-classical pathway of cell death [97]. Future research should investigate whether and how pyroptosis of parenchymal and nonparenchymal liver cells regulates LIRI.

3.6. Autophagy

Autophagy is a conserved intracellular pathway to maintain homeostasis, involving the degradation of organelles [106–108]. Thus, in response to cellular stress, autophagy may represent an adaptive response [109]. Autophagic responses have been primarily observed in the large perivenular hepatocyte subpopulation [54]. During the early stage of LIRI, autophagy plays a protective role [55]. During LIRI, dysfunctional mitochondria triggers the activition of NLRP3 and damages hepatocytes [56]. Meanwhile, ROS also activates the PINK1/Parkin pathway, which further induces mitophagy and inhibits the NLRP3 inflammatory pathway [57]. Adding autophagy inhibitor to liver preservation solution reduced IRI after rat liver implantation, and Beclin-1 (autophagy protein) is decreased in hepatocytes during LIRI [110, 111]. Zinc protoporphyrin reduces heme oxygenase expression, which inhibits autophagy and exacerbates LIRI[112]. Regarding perfusion injury, application of appropriate interventions along the autophagy regulatory pathway based on the states of damaged cells and autophagy can effectively protect hepatocyte from LIRI.

3.7. NETosis

During inflammation responce, neutrophils are one of the first cells to be recruited supplemented [113]. Consequently, neutrophils are key components of the early response to tissue injury [114,115]. NETosis is a type of PCD associated with neutrophil activation, which involves decondensed chromatin with granule enzymes, myeloperoxidase release, and ROS [116, 117]. During NETosis, neutrophils expel chromatin, resulting in sticky neutrophil extracellular trap (NET) that captures and inhibits pathogens [58]. Neutrophils are attracted to the liver intracellular microenvironment in LIRI [59]. Neutrophils are increased in the liver as soon as ischemia occurs, but they only cause damage later when neutrophils become exosmotic and directly cling to stressed hepatocytes [60]. The widespread presence of NETosis aggravates LIRI, which is linked to NET formation properties [61]. Other NET proteins, such as neutrophil elastase, inhibit normal physiological functions of hepatocytes in LIRI [62]. Treatment with DNase I or peptidyl-arginine-deiminase inhibitors considerably reduces inflammation after LIRI by inhibiting NET formation [59]. Previous studies demonstrated that both extracellular histones and high-mobility group boxes directly caused serious inflammatory responses via TLR-9 or TLR-4 in LIRI [118, 119]. KCs, which account for the largest proportion of nonparenchymal cells, attract neutrophils by releasing chemoattractants in LIRI [120]. In LIRI, IL-33 is released, which promotes NETosis of infiltrating neutrophils and amplifies negative effects [121]. Therefore, this newly discovered mode of PCD with activated NETs as effectors provides viable therapeutic targets for LIRI.

3.8. Parthanatos

Parthanatos is a type of PCD which is based on poly ADP-ribose polymerase-1 (PARP-1) that damages organs by causing sterile inflammation [122]. It seems that apoptosis contributes considerably to cell death processes; however, in studies, caspase suppression failed to completely halt cell death[123]. The PARP-1 enzyme is a DNA-repairing enzyme that is activated by high genomic stress, and its function is to bind ADP-ribose and to form branching PAR polymers which initiate the repair process of the DNA[124]. When DNA damage is mild, PARP-1 mobilizes DNA repair proteins to facilitate the repair of the impaired DNA[125]. PARP-1 overactivation and PAR polymerization occurs as a result of severe DNA damage and stress response. After PAR polymers have been cleaved from proteins, they are then shuttled to mitochondria where they stimulate the nuclear translocation of the mitochondrial protein, apoptosis-inducing factor (AIF), which in turn results in the translocation of AIF from mitochondria to the nuclear envelope, which is the final step to the formation of parthanatos [126,127].

PARP may be critical in the interplay of inflammation and DNA damage in clinical situations [63]. The programmed cell death is induced in a redox-dependent manner by activated PARP[64]. PARP may thus have a significant role in liver damage and inflammation following ischemic reperfusion [65]. Necroptosis may have a link to parthanatos in that RIPK1 and RIPK3 activate PARP-1 enzymes, promote ATP depletion and AIF release [128,129]. The proinflammatory effects of PARP in parenchymal and non-parenchymal cells in LIRI need to be further investigated in order to better understand its mechanisms.

3.9. Other modes of PCD

Copper-induced cell death, a newly discovered type of PCD, is regulated by copper metabolism balance in vivo [130]. Cuproptosis is characterized by mitochondrial stress caused by the aggregation of lipoylated mitochondrial enzymes [131]. Cu acts as an active transition metal of vital enzymes [132]. However, cells are injured when they are exposed to excess copper [133]. Previous research shows that treatment with copper sulfide at a dose of 20 mg/kg can increase the amount of ROS produced in the liver and reduce the levels of antioxidant enzymes in the liver of rats when using this treatment [134]. A chronic exposure to excess Cu can cause an increase in ROS in the livers of mice and promote apoptosis [135]. Lipoylated proteins, which are highly correlated with copper metabolism, lead to proteotoxic stress [130]. In certain circumstances, a disordered Cu homeostasis can lead to harmful consequences, such as Wilson's disease and Menkes disease [136]. Future studies should focus on confirming whether cuproptosis occurs and the specific mechanism in LIRI.

Lysosome-dependent cell death is a type of PCD that occurs via permeabilization of lysosomal membranes [137]. By causing lysosomal disruption and activating cathepsin B, accumulation of free fatty acids in liver cells is directly implicated in mitochondrial dysfunction [138]. Previous research suggests that lysosomal-dependent cell death may be a relevant factor in non-alcoholic fatty liver disease [139]. And impaired lysosomal functions associated with alcoholic liver disease [140]. Cathepsins are commonly overexpressed and activated in many cancerous tissues, including liver cancer [141]. However, neither copper-induced nor lysosome-dependent cell death have been explored in LIRI. Further experiments are needed to determine whether they play roles in LIRI.

3.10. Modulators of PCD against IRI

Programmed cell death of endothelial and parenchymal cells is recognized as the promising intervening target [16]. IR injury is attenuated by nonmedicine interventions, but their beneficial effects are limited. In order to reduce IR injury in both clinical and preclinical trials, small molecules are designed and applied. Moreover, only several small molecules directly target the origin of IR injury, but alleviate IR injury effectively. Therapies of the ideal combination of small molecules targeting multiple cell types have shown potent synergetic therapeutic effects, laying the foundation for novel strategies to attenuate IR injury. Recent studies have reported a potential risk of these drug interactions when it comes to IR injury, which encourages us to pay more attention to novel mechanisms and possible therapeutic targets.

4. Interactions between different forms of PCD in LIRI

Cell death complexity arises from the interactions between the different types of cell death. Various factors can influence the death of cell, including cellular organelles as well as environmental factors. There is also evidence that the biochemical change of cell death may have a influence on the activity of another type of cell death as well. The underlying mechanism behind the process of cell death within a cell is therefore determined by the interaction of different signaling pathways and the context within which the cell is situated.

4.1. Crosstalk between apoptosis and pyroptosis

Recent research describes that the various PCD processes are molecularly linked and ultimately result in cell death of heterogeneous phenotypes [97]. Apoptosis and pyroptosis are characterized by chromatin condensation and caspase-dependence [142]. It has been found that pyroptosis is an inflammatory cell lysis that occurs when apoptotic cells are not scavenged [143]. It is well known that caspase-1-GSDMD is a classical pathway responsible for regulating apoptosis as well as pyroptosis [144]. Both apoptosis and pyroptosis entail activation of protease caspases, with pyroptosis-inducing caspase-1 activating downstream apoptotic signaling [145]. During apoptosis and pyroptosis, caspase-8 serves as a molecular switch [146]. The caspase-8 protein, which is part of the caspase family, can

link up with the pyroptotic adapter protein in order to induce apoptosis [104]. Apoptosis is promoted by an activated caspase-8. When caspase-8 gene is inactive, pyroptosis is accelerated by stimulating the formation of apoptosis-associated speck-like protein [147]. In addition to caspase-3, there is another essential link between apoptosis and pyroptosis that needs to be discussed. Caspase-3, the executioner of apoptosis, may activate gasdermin E which is structurally and functionally identical to the pyroptotic effector [147]. Glycyrrhizin, binding directly with HMGB1 to inhibit its activity and the subsequent KCs pyroptosis. Hua et al. has established that glycyrrhizin can attenuates LIRI by suppressing the effect of pyroptosis and apoptosis simultaneously, but the molecular mechanism is unclear [64].

4.2. Crosstalk between necroptosis and apoptosis

Apoptosis is closely related to necroptosis, which occurs when apoptosis is restricted or downregulated [148]. Activation of caspase-8 inhibits functioning of the negative regulator of necroptosis, RIP1, by cleaving it and thus causing the cell to become apoptotic [149]. Caspase-8 inhibition results in the formation of a complex between the RIP1/RIP3 and the caspase-8 complex, thus initiating necroptosis [150]. During LIRI, ATP production is decreased to a level that is insufficient to keep caspase-8 activity and functioning [44]. Research need to be made in the future to explore the mechanisms of crosstalk between necroptosis and apoptosis.

5. Conclusion

Due to the extensive cross-talk among PCD, it seems promising to develop therapy designed to inhibit multiple types of PCD at the same time [151]. Researchers have elucidated the relationship between the proportion of PCD and injury severity of LIRI in published research, demonstrating the importance of PCD in the treatment of LIRI [152]. Whether this mode of cell death is predominant in hepatocytes, cholangiocytes, and nonparenchymal cells remains controversial.

An intrinsic cellular mechanism that different modes of PCD has been discovered and identified. However, the chronological and spatial distributions of the various modes of cell death in LIRI and how the modes of PCD connect and interfere with each other remain uncertain. Moreover, necrotic cells release many factors and contents into the surrounding environment, and whether these substances affect subsequent cell death is unclear. Despite decades of research, the process of hepatocyte death remains poorly understood pathologically, resulting in a limited capacity to prevent LIRI. Regarding potential therapy, how to effectively suppress PCD and reduce the cascade of cell death in LIRI remains a challenge. Mitochondrial pathway targeting, ferroptosis inhibition, apoptotic signal transmission, autophagosome formation, PARP-1 activation and inflammatory responses might be beneficial. Further research is underway to explore the exact mechanisms of these types of PCD, which will develop new therapies for LIRI.

CRediT authorship contribution statement

Shaobin Luo: Writing – original draft. **Rongkun Luo:** Methodology. **Gang Deng:** Visualization. **Feizhou Huang:** Investigation. **Zhao Lei:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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