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Mechanism of Pyroptosis in Acute Liver Injury and Prospect of Targeted Therapy

Jiaoxue Guo

School of Business, Naval Medical University, Shanghai, China
2794855670@qq.com

Abstract. Acute liver injury is a critical clinical syndrome characterized by rapid necrosis of hepatocytes and severe inflammatory reaction. At present, effective treatments for its fundamental pathogenic connections are lacking. In recent years, studies have found that pyroptosis, as a programmed inflammatory cell death mode mediated by gasdermin protein, plays a central role in the occurrence and development of a variety of acute liver injury. In this process, the inflammasome senses danger signals and activates caspase-1, which in turn cleaves GSDMD protein and forms cell membrane pores, ultimately leading to cell osmotic lysis and the release of a large number of pro-inflammatory factors. This article systematically elaborated the specific activation pathways and mechanisms of pyroptosis in different types of liver injury, such as drug-induced liver injury, ischemia-reperfusion injury, viral / autoimmune hepatitis and sepsis, and discussed the therapeutic prospect of targeted intervention on the key nodes of pyroptosis. Despite the challenges of crosstalk coexistence of cell death modes and safety of targeted therapy, the development of specific GSDMD inhibitors, analysis of cell heterogeneity using single-cell technology, and exploration of combination treatment strategies still bring new hope to this field. A thorough understanding of pyroptosis mechanism will provide crucial theoretical underpinnings and innovative ideas for the precise prevention and management of acute liver injury.

Keywords: pyroptosis, acute liver injury, GasderminD, targeted therapy

1. Introduction

1.1. Overview of acute liver injury

Acute liver injury is a syndrome of rapid deterioration of liver function caused by a variety of etiologies, characterized by massive necrosis of hepatocytes in a short period of time, which can lead to jaundice, coagulation dysfunction, hepatic encephalopathy and other clinical manifestations, and severe cases progress to acute liver failure [1]. Globally, liver damage brought on by drugs [2], viral hepatitis, alcohol-related liver damage [3] and liver ischemia-reperfusion injury are the main causes of the disease. The core pathological mechanism of the disease is massive death of hepatocytes and secondary strong inflammatory reaction. Necrotic hepatocytes release damage-associated molecular patterns (DAMPs) , activate Kupffer cells, further recruit and activate neutrophils and macrophages, forming an inflammatory storm [4]. Excessive inflammation not only

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aggravates liver injury, but also induces systemic inflammatory response and multiple organ failure, which is a key factor determining the prognosis.

At present, the clinical treatment is mainly supportive treatment, and there is a lack of specific drugs for hepatocyte death and inflammatory cascade. Although N-acetylcysteine can be used for acetaminophen poisoning, antiviral treatment is effective for some hepatitis. However, targeted therapy for the core pathological links is still very limited [5]. Therefore, it has become the research focus in this field to deeply reveal its molecular mechanism and find key intervention targets.

1.2. Discovery and concept of pyroptosis

In the past, programmed cell death was equated with "apoptosis". That is, a non inflammatory way of cell clearance. While "necrosis" is regarded as passive and disordered cell death, which often causes inflammation. In 2001, Cookson et al proposed the concept of "pyroptosis", which is defined as a cell death mode dependent on caspase-1 [6]. Gasdermin family proteins are responsible for the planned inflammatory cell death known as pyroptosis. The mechanism is that cells assemble inflammasomes after sensing pathogens or danger signals, and then activate caspase-1 [7]. Activated caspase-1 cleaves gasdermin D protein and releases its N-terminal domain, which can oligomerize into pores on cell membrane [8], resulting in imbalance of cell osmotic pressure, swelling and rupture, while generating damage-associated molecular patterns and pro-inflammatory substances like IL-1β and IL-18 to intensely trigger the immune response and create local and even systemic inflammation.

1.3. Purpose of this article

Based on the close relationship between pyroptosis and inflammatory response, its role in the pathogenesis of acute liver injury has attracted increasing attention. This review systematically expounds pyroptosis's central function in acute hepatic injury caused by various etiologies, analyzes its molecular pathway from inflammasome activation to gasdermin D execution, discusses the interaction between hepatocytes and Kupffer cells in this process, and looks forward to the potential of targeted intervention of pyroptosis pathway as a therapeutic strategy, in order to give clinical liver injury avoidance and therapy a theoretical foundation.

2. The core molecular mechanism of pyroptosis

2.1. Priming signal: activation of inflammasome

The core of pyroptosis is the inflammasome, a multiprotein complex that senses intracellular danger signals and activates caspase-1. In acute liver injury, the NLRP3 inflammasome is one of the most intensively studied and critical types [9]. The receptor protein NLRP3, the adaptor protein ASC, and the effector protein pro-caspase-1 make up the NLRP3 inflammasome.Its activation usually requires two steps: the first is the "priming signal", which activates the NF-κB pathway through Toll like receptors by pathogen-associated molecular patterns or damage-associated molecular patterns, and upregulates the expression of components such as NLRP3 and pro-IL-1β. The second is the "activation signal", which is brought on by things like the release of volatile oxygen compounds, K+ efflux, mitochondrial dysfunction or lysosome rupture, which are common in acute liver injury [10]. These signals prompt NLRP3 to oligomerize and recruit pro-caspase-1 through ASC proteins. Turn it into active caspase-1 by self cleavage. In addition to NLRP3, AIM2 inflammasome, which senses

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cytosolic DNA, and NLRC4 inflammasome, which senses bacterial flagellin, are also activated in specific liver injury to jointly initiate the pyroptosis program.

2.2. Execution phase: the core role of gasdermin D protein

Activated caspase-1 is the key executor of pyroptosis, and its core role is to cleave the substrate gasdermin D. GSDMD protein maintains an inactive state through an autoinhibitory linker region, where caspase-1, mouse caspase-11 and human caspase-4/5, can particularly cleave [7]. The GSDMD-N-terminal domain released after cleavage has intrinsic membrane drilling activity. This fragment will rapidly translocate to the inner side of the cell membrane and form a stable β- barrel pore by binding to the membrane phospholipid phosphatidylinositol and oligomerization [8]. These pores allow ions and small molecules to pass freely, but block macromolecular proteins, thus completely destroying the osmotic pressure balance of the cell. The direct consequence is that a large amount of water flows in, and the cell undergoes osmotic swelling, which eventually leads to cell membrane rupture and cell disintegration. Therefore, GSDMD mediated pore formation is an irreversible terminal link in the execution stage of pyroptosis, and it is also a morphological sign that distinguishes it from other forms of cell death.

2.3. Effector stage: release of inflammatory factors

The "inflammatory" characteristic of pyroptosis is fully reflected at this stage. After the formation of GSDMD pores, two waves of key inflammatory mediators will be triggered: the first is the "active" release. While cleaving GSDMD, activated caspase-1 also processes another important substrate, the inactive pro-IL-1β and pro-IL-18, to convert them into mature and highly active forms [11]. These mature cytokines with small molecular weight (about 17kDa) can be released to the extracellular in large quantities directly through the GSDMD pore. The second is passive release: as the cells are finally completely lysed due to osmotic imbalance, such as high mobility group box 1, ATP, S100 protein and other damage-associated molecular patterns are released into the tissue microenvironment.

The released IL-1β and IL-18 are potent proinflammatory factors, which can strongly recruit and activate neutrophils, lymphocytes, etc., and rapidly amplify inflammatory signals. At the same time, the released damage-associated molecular patterns act as danger alarms, activating pattern recognition receptors of peripheral cells, triggering a new round of inflammasome activation and pyroptosis. This self amplifying positive feedback loop has formed an "inflammatory storm" in local tissues, which has become the core molecular basis for the severe inflammatory response and tissue destruction in acute liver injury.

3. Specific role of pyroptosis in different types of acute liver injury

A key factor in the pathophysiology of acute liver injury is pyroptosis, a type of controlled cell death.It promotes hepatocyte death and inflammatory cascade through inflammasome activation and membrane pore formation mediated by gasdermin protein family. The pathogenic factors of different types of acute liver injury can activate inflammasomes or downstream pyroptosis related proteins through specific molecular pathways, and finally aggravate liver injury through hepatocyte rupture and the release of inflammatory factors.

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3.1. Liver damage caused by drugs

The main cause of clinical acute liver failure is drug-induced liver injury. Of these, the mechanism of acetaminophen (APAP) overdose-induced liver injury has been researched the most, and pyroptosis is a crucial part of this process. N-acetyl-p-benzoquinone imine (NAPQI), a toxic intermediate produced by APAP metabolism in the liver, can rapidly deplete intracellular glutathione reserves, bind to mitochondrial proteins, and trigger mitochondrial dysfunction and a large number of reactive oxygen species (ROS) production [12].The intracellular NLRP3 inflammasome is triggered by these endogenous hazard messages, which function as damage-associated molecular patterns [13]. Through the adaptor protein ASC, the triggered NLRP3 inflammasome recruits pro-caspase-1, causing it to self-cleave into enzymatically active caspase-1. It then cleaves GSDMD, creating cell membrane pores that facilitate the maturing and discharge of IL-1β and IL-18. IL-18 released during pyroptosis can further act as a potent chemoattractant for neutrophils to infiltrate the liver tissue and expand the local inflammatory response [14]. In addition, Kupffer cells that colonize the liver also undergo pyroptosis under the activation of NAPQI, and continuously release pro-inflammatory factors, which has become a key factor for the continued spread of inflammation in APAP hepatotoxicity [15].

3.2. Hepatic ischemia-reperfusion injury

Cell pyroptosis brought on by hypoxia reoxygenation is a key factor in the process of harm in liver ischemia-reperfusion injury, a common pathophysiological reaction in the clinical procedures of liver transplantation, shock resuscitation, and other procedures. In the ischemic phase, the interruption of oxygen supply leads to the disorder of hepatocyte energy metabolism and the impairment of mitochondrial function; During the reperfusion phase, accompanied by the re supply of oxygen, the mitochondrial respiratory chain produces a large amount of ROS in an explosive manner, and the cell necrosis caused by ischemia releases DAMPs such as HMGB1 and ATP, which together activate the NLRP3 inflammasome [16]. In this process, the pyroptosis of hepatocytes and Kupffer cells forms a synergistic injury effect: the hepatocyte pyroptosis directly generates the integrity of the liver's structure and function is destroyed by the depletion of liver peripheral cells; Kupffer cells, as intrahepatic macrophages, undergo pyroptosis under the activation of ROS and other signals, and release inflammatory mediators like IL-1β and IL-6, which even more recruit peripheral immunity cells to infiltrate the liver and activate hepatic stellate cells, exacerbate the inflammatory response and tissue edema, and form a malignant cycle [17].

3.3. Autoimmune hepatitis and viral hepatitis

In the course of autoimmune hepatitis and viral hepatitis, pyroptosis has become a key bridge between immune abnormalities and liver cell damage by recognizing disease self antigens or pathogen-associated molecular patterns. In viral hepatitis, double stranded DNA produced during hepatitis B virus (HBV) replication can be recognized by cytosolic AIM2 inflammasome, while single stranded RNA of hepatitis C virus (HCV) can activate downstream inflammasome assembly through RIG-I-like receptor signaling pathway. The study found that the expression of AIM2 in liver tissue of patients with HBV was significantly increased, and was positively correlated with the levels of caspase-1 and IL-1β, suggesting that AIM2 mediated pyroptosis pathway is involved in the inflammatory injury caused by HBV infection. The continuous replication of virus can break the body's immune tolerance. The continuous activation of inflammasome induces pyroptosis of

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hepatocytes. The released inflammatory factors further recruit immune cell infiltration, forming a vicious cycle of "virus replication-pyroptosis activation-inflammation amplification". In autoimmune hepatitis, autoantigens can activate NLRP3 inflammasome in macrophages and hepatocytes to initiate caspase-1-dependent pyroptosis. Animal model experiments confirmed that pyroptosis's involvement in the process of liver injury is further supported by the fact that the degree of GSDMD cleavage was substantially higher in the liver tissue of the autoimmune hepatitis model than in normal hepatic tissue [18].

3.4. Sepsis related liver injury

Acute liver damage brought on by sepsis is a significant symptom of systemic inflammatory response involving the liver, and its core mechanism is that endotoxin directly induces hepatocyte death through the non-canonical pyroptosis pathway [19]. After Gram-negative bacteria infection, the level of lipopolysaccharide (LPS) in the circulation increases. The liver sinusoidal epithelium barrier can be penetrated by LPS and enter the cytoplasm of hepatocytes, directly bind to and activate caspase-4/5 [20]. Unlike the canonical pathway, activated caspase-4/5 can directly cleave GSDMD without the involvement of inflammasomes, and its N-terminal segment creates holes in the cell barrier, triggering cell swelling and rupture. At the same time, potassium ion efflux caused by pyroptosis can retroactively activate inflammasome NLRP3, promote IL-18 and IL-1β maturation through the canonical pathway, and further amplify the systemic inflammatory response. In the sepsis mouse model constructed by cecal ligation and perforation, the expression of caspase-11 and GSDMD in liver tissue was significantly upregulated , and the degree of hepatocyte pyroptosis was positively correlated with liver injury score. The use of pyroptosis inhibitor Shuanglun can significantly reduce the level of inflammatory factors in serum and reduce liver tissue necrosis [21]. In addition, mitochondrial microvesicles containing GSDMD-N-terminal fragments released by pyroptosis of Kupffer cells in sepsis can lead to mitochondrial dysfunction in hepatocytes, exacerbate metabolic disorders and inflammatory damage. Recent studies have also found that STING signaling pathway can further activate immune cell pyroptosis by sensing the level of circulating free DNA, forming an inflammatory cascade amplification network, providing a novel molecular target for the focused management of liver damage associated with sepsis [22].

4. Conclusions and prospects

This review systematically expounds the central role of pyroptosis in acute liver injury. Studies have shown that pyroptosis, through its unique molecular mechanism, has become an important bridge between the initial injury factors and the amplification effect of liver inflammation under a variety of pathological conditions, such as drug-related liver injury, liver injury caused by ischemia-reperfusion, viral hepatitis and sepsis related liver injury. This mechanism not only explains the vicious cycle formed between hepatocyte death and excessive inflammatory response, but also reveals its key position in the pathogenesis of acute liver injury.

Although targeting pyroptosis provides a new idea for the treatment of acute liver injury, the field still faces many challenges. First, there is a complex crosstalk between pyroptosis and other cell death modes such as apoptosis and necrosis, which makes it difficult to accurately distinguish and specifically intervene. Secondly, the safety of targeted therapy is prominent. As pyroptosis is an important part of the body's immune defense, its excessive inhibition may lead to immune deficiency and increase the risk of infection. In addition, different cells in the liver have different

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mechanisms of action in the process of pyroptosis, and this cell specificity has brought great challenges to the precise implementation of targeted therapy.

In view of the current dilemma, future research should focus on three directions: First, developing more specific small molecule inhibitors targeting GSDMD will enhance therapeutic efficacy and minimize systemic side effects. Second, utilizing state-of-the-art methods like sequencing of single cells will enable the mapping of pyroptosis signals in the liver under different etiological conditions, providing a theoretical basis for precise intervention. Finally, we should actively explore combination treatment strategies, such as combining pyroptosis inhibitors with traditional hepatoprotective drugs, to open up a new path for the clinical treatment of acute liver injury through multi-target synergy.

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