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The relevance of pyroptosis in the pathogenesis of liver diseases

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ABSTRACT

Pyroptosis is a novel programmed cell death form which is distinct from other types of cell death. As an inherently inflammatory process, it plays a vital role in cellular lysis and release of pro-inflammatory cytokines when hosts defend against infections. Recent studies have reported that pyroptosis was involved in liver diseases and had important functions in the progress and development of liver diseases. Here, we addressed the potential role of pyroptosis in liver diseases on the basis of brief introduction of the morphological characteristics, molecular and pathophysiological mechanisms of pyroptosis.

1. Introduction

Programmed cell death plays an essential and fundamental role in the development and survival of the hosts in the body's defense against infections [1]. There are six main types of programmed cell death including apoptosis, necrosis, pyroptosis, ferroptosis, autophagy and efferocytosis [2].To date, the apoptosis is the most extensively studied while the research of pyroptosis is neither comprehensive nor concrete [3]. Pyroptosis is a novel programmed cell death form responsible for both the cellular lysis and the extracellular release of many pro-inflammatory cytokines such as IL-1β and IL-18 when triggered by inflammatory stimuli [4]. It is an inherently inflammatory process, which can sense both infectious microorganisms such as Francisella, Salmonella, Legionella and non-infectious stimuli like some host factors [3]. It was first reported in 1996 that there was a cell death pathway uniquely programmed by the inflammatory caspase-1 rather than the apoptosis executor-caspase-3. The pharmacological inhibition of caspase-1 and its genetic deletion could enhanced the resistance of mice to microbial infections [5–7].Based on a serial of later researches, a novel programmed cell death named pyroptosis was uncovered, which was obviously different from apoptosis [8]. Firstly, the occurrence of apoptosis mainly depends on initiator caspases (caspase-2, -8, -9, -10) and effector caspases (caspase-3, -6, -7). In contrast, the pyroptotic caspases include caspases 1, 4 and 5 in humans and caspases 1 and 11 in mice [9]. Secondly, the pores formed on the plasma membrane during pyroptosis are between 1.1 and 2.4 nm in diameter, which cause the swell and lysis of cells leading to the release of the cell content. However, apoptosis forms membrane blebbing rather than forming pores on the membrane and it can form special membrane-enclosed apoptotic bodies [10,11]. Thirdly, the pyroptosis and apoptosis both have chromatin condensation and DNA damage, but pyroptosis is characterized by the intact nucleus, the absence of DNA laddering and the positivity in TUNEL and Annexin V staining [12].

2. Molecular mechanisms of pyroptosis

2.1. The canonical inflammasome-induced pyroptosis

There are two pathways to activate pyroptosis including the canonical pathway and the non-canonical pathway. The canonical pathway induces pyroptosis through cytoplasmic multiprotein complexes named inflammasome [13]. Four main prototypes of inflammasomes have been identified so far— NLR family pyrin domain containing 1 (NLRP1), NLRC4, melanoma-2 (AIM2) and NLRP3 [14]. These inflammasomes can sense various stimuli to induce pyroptosis. As an extensively -studied inflammasome, NLRP3 could be activated by a serial of microbe- and host-derived triggers, including bacteria, viruses, DAMPs, pore-forming toxins etc. [15,16]. Similarly, the AIM2 inflammasome responds to cytosolic double-stranded DNA [17]. The NLRC4 inflammasome recognizes cytosolic bacterial flagellin and PrgJ (a conserved component of pathogen-associated type III secretion systems) and the NLRP1 inflammasome detects anthracis [18–20]. After these interactions, inflammasomes bind to a caspase recruitment domain (ASC), then ASC recruits and cleaves pro-caspase-1, and eventually activates caspase-1 [21]. Specially, the NLRC4 can directly recruit the pro-caspase-1 without the formation of ASC [22,23].The

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following molecular mechanism that ultimately mediated pyroptosis was obscure for a long time. However, recent studies show that a protein from the gasdermin family with unknown function is a key substrate to regulate pyroptosis—the Gasdermin-D (GSDMD) [24]. Human GSDMD protein belongs to a family of proteins with Gasdermin domain, which is composed of six family members with 45% sequence homology, including GSDMA, GSDMB, GSDMC, GSDMD, GSDME (also known as DFNA5) and DFNB59. They are closely related to occurrence and development of many diseases (such as deafness, alopecia, tumors, immune diseases and nervous system diseases) [25].Activated caspase-1 cleaves the Gasdermin-D into a 22-kDa C-terminal fragment and a 31-kDa N-terminal fragment which causes pores via lysing phosphoinositide/cardiolipin-containing liposomes of the cell membrane and initiates pyroptosis [26–28]. At the same time, the cleaved caspase-1 can also cut the pro-IL-1β and the pro-IL-18 into IL-1β and IL-18, which are released extracellularly as a result of the formation of the pores on the cell membrane.

2.2. The non-canonical inflammasome-induced pyroptosis

Owing to the caspase-11 is able to direct pyroptosis independently, the caspase-11 –mediated pyroptosis was termed as the non-canonical pathway. In response to bacterial lipopolysaccharide (LPS) molecules, outer membrane vesicles (OMV) produced by Gram-negative bacteria deliver LPS to the cytosol and trigger caspase-11-dependent effector responses in vitro and in vivo [29–31]. After interaction with LPS, the cleaved caspase-11 also activates the Gasdermin-D to form pores on the membrane of cells. Meanwhile, the N-terminal fragment of Gasdermin-D activates the NLRP3 inflammasome and induces pyroptosis via the canonical pathway [1].

3. Pyroptosis in liver diseases

Normally, moderate pyroptosis is helpful to delete infected cells timely, but excessive activation of pyroptosis can lead to massive cell death, severe tissue damage and organ failure, which is related with pathogeneses of some diseases [8]. Nowadays liver diseases have become a serious health problem in the world because of its increasing incidence. Some of them gradually develop into cirrhosis and hepatocellular carcinoma (HCC) which seriously threaten the human life. Furthermore, recent studies have reported that pyroptosis is responsible for the development of liver diseases. Since there exists intestine-liver axis in the body, the intestinal flora can enter into liver when the imbalance of gut microflora occurs. Then, the bacterial LPS can induce pyroptosis of liver cells as an important factor in the initiation of pyroptosis. [32]. Moreover, the liver inflammation, has been confirmed to be relate with pyroptosis during the development of cirrhosis, infection-induced liver fibrosis (LF) and HCC. Therefore, pyroptosis plays an important role in the occurrence and development of liver diseases.

3.1. Pyroptosis in the NAFLD

Nonalcoholic-fatty-liver disease (NAFLD) has become a growing health problem for its high prevalence and association with the high risk of developing cirrhosis and hepatocellular carcinoma [33]. With the deepening of studies on liver diseases, people are becoming more aware of the importance of pyroptosis in the pathogenesis of NAFLD. NAFLD is histologically further categorized into non-alcoholic fatty liver (NAFL), which is characterized by triglyceride accumulation in hepatocytes and non-alcoholic steatohepatitis (NASH— a more serious stage of NAFLD characterized by cell injury, hepatocyte ballooning and inflammatory cell infiltration that may further progress to fibrosis, cirrhosis, and hepatocellular carcinoma). This classification is based on the absence or presence of hepatocellular inflammatory injury [34]. At the NAFL stage, the Nlrp3 inflammasome induced caspase-1 cleavage which induces pyroptosis after sensing lipotoxicity-associated ceramide [35]. However, the damage to the body is relatively mild for the inflammation caused by pyroptosis was not obvious. Comparatively speaking, at the NASH stage, pyroptosis induced-inflammation or fibrosis was much more severe so that pyroptosis did great harm to the body. Wu et al. had proved that the pyroptosis-inducing fragment GSDMD-N was upregulated in NAFLD and showed even higher levels in NASH. In addition, MCD (methionine-choline deficient) -fed Gsdmd −/− mice showed milder degree of steatosis and inflammation compared with WT mice through the regulation of lipogenic and lipolytic genes. These all indicated that pyroptosis executor— GSDMD-N played an important role in the pathogenesis of NAFLD via several signals including the regulation of lipogenesis, the activation of NF-κb and cytokine secretion [36]. As the pyroptosis was downstream of inflammasome, many researches revealed that the NLRP3 inflammasome activation can also influence the severity of NAFLD via regulating pyroptosis. It was reported that in Nlrp3 −/− mice with a choline deficient amino acid-defined (CDAA) diet, the degrees of liver inflammation, fibrogenesis and injury reduced [37]. Besides, As2O3 could cause NASH/NAFLD via inducing hepatocyte pyroptosis through activation of NLRP3 inflammasome mediated by cytoplasmic cathepsin B [4]. Moreover, the NLRP3 selective inhibitor—MCC950, alleviated inflammation and fibrosis of NAFLD in obese diabetic mice and MCD-fed mice via reducing hepatic caspase 1, MCP-1, IL-6, IL-1β expression and suppressing migration of macrophages and neutrophils in the liver [38].Our group and others verified that the thioredoxin interacting protein (TXNIP) was a positive regulator in activating NLRP3 inflammasome and an important oxidative stress factor in the body [39,40]. However, He et al. thought differently since they found that the genetic deficiency of thioredoxin-interacting protein (TXNIP) enhanced the activation of NLRP3 inflammasome and pyroptosis leading to aggravation of liver injury, which suggested that TXNIP plays a protective and anti-inflammatory role in the development of NAFLD by inhibiting the activation of NLRP3 and preventing pyroptosis [41]. This might be because TXNIP is an important molecule related to the host immune response, the genetic deficiency also affects many normal physiological functions which leading to the aggravation of NAFLD. Thus, the inhibition of NLRP3 inflammasome and GSDMD is able to decrease the severity of liver inflammation and fibrosis through regulating pyroptosis pathways, and eventually improving NAFLD.

3.2. Pyroptosis in the AH

Alcoholic hepatitis (AH) is a disease with high mortality due to liver injury and inflammation caused by excessive alcohol intake. Since the molecule mechanism of alcoholic hepatitis is still unclear, there are no effective treatment strategies at present. However, excessive alcohol consumption often related with various cell death including pyroptosis. Elena et al. recently discovered that after CASP11/4 activation, the activated Gasdermin-D also induced pyroptosis through the CASP11/4-GSDMD pathway, which may play a central role in the pathogenesis of AH. Inexplicably, as the central part in the process of pyroptosis, the caspase-1 did not change in this AH mouse model, which may need further investigation. Besides, it had demonstrated that pharmacological inhibition of CCR2/5 signaling could alleviate alcohol-induced liver injury by means of reducing cleaved Gasdermin D levels [42]. Furthermore, alcohol was able to decrease miR-148a expression in hepatocytes through FoxO1, leading to TXNIP overexpression and NLRP3 inflammasome activation, which induced hepatocyte pyroptosis [43]. The selenium-enriched spirulina platensis was found to have a protective role in alcohol-induced liver injury by the reduction of caspase-1-induced pyroptosis [44]. In conclusion, the above important findings provide us novel insights in pyroptosis-based therapies for reducing progression and incidence of AH.

3.3. Pyroptosis in the hepatitis

3.3.1. Pyroptosis in viral hepatitis

As the most common viral hepatitis in the world, the hepatitis B and C have been proved to be associated with pyroptosis. Kei et al. had found that the recognition between the viral DNA/RNA and pattern recognition receptors (PRRs) induced the activation of the inflammasomes resulting in pyroptosis. TFRTM tetherin decreased the pyroptosis markers such as cleaved caspase-1 and IL-1β probably through blocking the AIM2-dependent signaling pathway during viral infections. HBV also inhibited LPS-induced expression of NLRP3 and IL-1β via the inhibition of NF-κb signaling pathway and the production of reactive oxygen species (ROS) [45]. Furthermore, they also found that HBcAg induced the secretion of another marker of pyroptosis— IL-18, which implied that HBcAg invasion was one of the major inducers in HBV-mediated pyroptosis [46]. For hepatitis C, HCV was verified to induce pyroptosis mediated by both caspase-1 and caspase-3 signaling. Caspase-1-mediated pyroptosis was shown in either HCV infected or bystander cells, which was closely related with the pathogenesis of hepatitis C [47].Due to the hepatitis is closely related with pyroptosis, researchers begin to explore how to improve hepatitis via inhibiting pyroptosis.

3.3.2. Pyroptosis in autoimmune hepatitis

It was found that the caspase-1-dependent pyroptosis also occurred in ConA-induced hepatitis (a model of autoimmune hepatitis) and the human interleukin-1 receptor antagonist (rhIL-1Ra) could strongly suppressed liver inflammation via the inhibition of NLRP3 inflammasome induced-pyroptosis [48]. TNF superfamily receptor OX40 was demonstrated to active the expression of caspase-1 via TNF receptor-associated factor 6-mediated recruitment of the paracaspase MALT1. Thus, targeting the pyroptosis-related molecule protein OX40 merits further study in the treatment of hepatitis [49].

3.4. Pyroptosis in the liver cancer

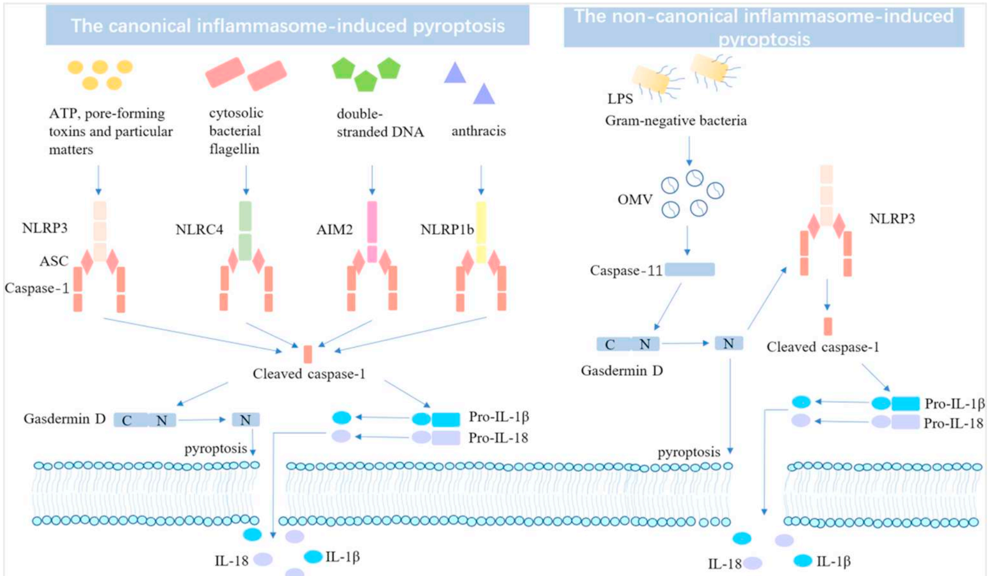
Similarly, pyroptosis is also involved in the pathogenesis of hepatocellular carcinoma, one of the most common malignant tumors in the world. Compared with normal liver tissues, the expression of NLRP3 in hepatocellular carcinoma tissues decreased significantly, thus the pyroptosis in HCC reduced [50]. Moreover, the administration of berberine, a natural isoquinoline alkaloid which was reported to activate caspase-1 and pyroptosis, had strong inhibitive effects on the proliferation and migration of hepatocellular carcinoma cells. Caspase-1 inhibitor Ac-YVAD-CMK attenuated these effects via suppressing berberine-induced pyroptosis in xenograft mouse model. The above studies suggested that pyroptosis might be a new target in the treatment of HCC [51].

3.5. Pyroptosis in the liver fibrosis

Pyroptosis was shown to be associated with liver fibrosis in NASH [36]. HSC (hepatic stellate cell), the major source of fibrosis-related protein CTGF (connective tissue growth factor) and TIMP1 (tissues inhibitor of metalloproteinases 1), was found to be activated and generate collagen deposition via pyroptosis [52]. IL-1β procured proliferation of HSC possibly through the IL-1R1, JNK, and AP-1 pathways in rat and it also induced fibrosis by enhancing the expressions of collagen and TGF-β [53,54]. In addition to HSC, eosinophils were shown to induce hepatic fibrosis through pyroptosis. It induced secretion of IL-1β and IL-18, or even death of hepatocytes, resulting in liver fibrosis. This process could be suppressed by caspase-1 inhibitors, indicating that the infiltrated eosinophils induced hepatic fibrosis through pyroptosis [55]. In mice liver fibrosis models fed with MCD for 8 weeks, the expression levels of α-SMA and TGF-β 1 genes in GSDMD −/− mice were lower than those of WT mice, and the content of hydroxyproline in GSDMD −/− mice was obviously reduced, suggesting that the pyroptosis executor –GSDMD plays an important role in the development of MCD-induced liver fibrosis [36]. Wree et al. demonstrated that pyroptosis induced by NLRP3 was able to increase the expression of CTGF, TIMP1 and enhance collagen deposition. Accordingly, in mutant Nlrp3 knock-in mice models, it was reported that NLRP3- initiated pyroptosis resulted in more severe liver inflammation and fibrosis because of NLRP3 hyperactivation. In contrast, the NLRP3 deficiency can protect liver from thioacetamide (TAA) or carbon tetrachloride—induced liver fibrosis [54].

4. Conclusions

As outlined in this review, during the inflammation-related cell programmed death–pyroptosis, a serial of stimuli activate both caspase-1/4/5/11 inflammasomes and the production of GSDMD-N, eventually inducing cell lysis, the release of intracellular contents and inflammatory factors. As a result, the release of IL-1β and IL-18 and the increase expression of GSDMD-N are contributing to the occurrence and development of various liver diseases. NLRP3 inflammasome is one of the most important molecules in the process of pyroptosis. By inhibiting its activation, the pyroptosis can be suppressed and the symptoms of liver diseases can be improved. Thus, many its inhibitors have been put into clinical trials to testify their treatment effects [56]. Although the pyroptosis was demonstrated to be closely correlated with the progress of liver diseases, many aspects about it are still elusive and need further investigations, such as how the pyroptosis causes liver damage, how it functions in the progress of disease and whether these NLRP3 inflammasomes inhibitors are suitable for the clinical application, etc. Indeed, pyroptosis acts as a double-edged sword. The inflammatory factors released during the pyroptosis not only can enhance the immunity of the body to the pathogenic factors, but also inhibit the proliferation and migration of hepatocellular carcinoma cells via inducing their pyroptosis. However, excessive activation of pyroptosis aggravates the inflammatory responses, causes liver damage and even induces progression to liver fibrosis and HCC. Therefore, the exploration in the relationship of pyroptosis with liver diseases can provide new strategies for the prevention and treatment of liver diseases.



Molecular basis of the canonical inflammasome-induced pyroptosis and the non-canonical inflammasome-induced pyroptosis.

In the canonical pathway, various stimuli activate their respective inflammasome sensors including NLRP1b, NLRP3, NLRC4, and AIM2.These activated inflammasome sensors trigger formation of the caspase recruitment domain ASC and the recruitment of pro-caspase-1 which induce the cleavage of pro-caspase-1. The cleaved caspase-1 then directly cut gasdermin D, pro-IL-1β and pro-IL-18 into GSDMD-N, IL-1β and IL-18 respectively. The GSDMD-N form pores on the cell membrane and induce pyroptosis, the IL-1β and IL-18 are released extracellularly through these pores. In the non-canonical pathway, LPS is delivered to the cytosol by OMV produced by Gram-negative bacteria and triggers the activation of caspase-11. As a result, caspase-11 cleave gasdermin D into GSDMD-C and GSDMD-N which form pores on the cell membrane and induce pyroptosis. Besides, GSDMD-N also activates the NLRP3 inflammasome and then produces IL-1β and IL-18 to cause inflammation as the canonical pathway.

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Author contributions

Huiting Guo wrote the manuscript and prepared figures; Min Zheng, Cheng Zhou, and Mingjie Xie provided expert comments and edits. All authors reviewed the manuscript.

Conflicts of interest

The authors declare no financial conflicts of interests.

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