A Review of Pyroptosis in Liver Disease

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Abstract: Pyroptosis is a new form of programmed cell death that is different from cell necrosis, apoptosis, and autophagy. It is characterized by the rupture of cell membranes mediated by Gasdermin and the release of cell contents and pro-inflammatory factors. This study systematically integrated the role of pyroptosis in liver disease and the mechanism of its impact. The researchers explored the relationship between pyroptosis and ALD, NAFLD, viral hepatitis, liver fibrosis, and HCC. The pyroptosis signaling pathway is divided into the classical pathway that relies on cysteine aspartase-1 and the non-classical pathway that depends on caspase-4, 5, and 11, in which the activation of caspase-1 in the classical pathway depends on the inflammasome, and the non-classical pathway directly activates caspase-4, 5, and 11, induces the formation of membrane pores, and IL-1β, IL-18 matures and is released, and the cell membrane ruptures and pyroptosis occurs. Eventually, it has an effect on the liver. Therefore, this paper focuses on the mechanism of pyroptosis, and summarizes the research progress of pyroptosis in the occurrence and development of non-alcoholic fatty liver disease, alcoholic liver disease, viral hepatitis, liver cirrhosis. By studying the influencing mechanism of pyroptosis, can provide new ideas and strategies for the prevention and treatment of these diseases.

1 Introduction

Cell death is a ubiquitous phenomenon in biology, at the same time, pyroptosis, could act as a new form of cell death, greatly impact on immune defense mechanisms. Which cause irreversible damage to the human body and seriously affect the patients' life quality. To further explore pathogenesis of liver diseases and clarify the relationship between pyroptosis and the emergence and development of liver diseases. Therefore, this paper aims to summarize the latest literature, and to explain the mechanism of cell death and the role of pyroptosis in liver diseases.[1]

2 Mechanism of Pyroptosis

Pyroptosis is a part of the process of animal growth, tissue homeostasis and aging (Shi, 2017), which is a process of necrotizing and inflammatory and programmed cell death induced by inflammatory cysteine aspartate protease, which is the body's natural immune response to defend against external pathogens, but excessive occurrence of pyroptosis may cause inflammatory response and immune system diseases. The classical pyroptosis pathway is closely related to the inflammasome and is a caspase-1-dependent pyroptosis pathway. Receptor PRRs activate inflammasomes by recognizing PAMPs and DAMPs. Procaspase-1 in its inactive form is recruited and hydrolyzed by the CARD domain (CARD) and the thermoprotein domain (PYD) to become active caspase-1. Mature caspase-1 is key to cleavage interleukin-1β (IL-1β), which triggers receptor activation and oligomerization when endogenous danger signals or pathogens are recognized by receptors in the cytoplasm. Active caspase-1 turns IL-1β precursors and IL-18 precursors into active IL-1β and IL-18 and cleaves gas-dermin-D, whose N-terminus forms pores in the cell membrane, causing cells to swell and rupture, and inflammatory factors are released in large quantities outside the cell, thus triggering pyroptosis of cells. The non-canonical pyroptosis pathway is mediated by caspase-4, caspase-5, and caspase-11 (caspase-4 and cas-pase-5 in humans and caspase-11 in murine humans), and these proteins directly recognize endotoxin wall lipopolysaccharide (LPS) of gram-negative bacteria, and pyroptosis is the main response to their activation. Unlike caspase-1 activation, which occurs in macrophages or dendritic cells, caspase-4, caspase-5, and caspase-11 occur in macrophages and non-macrophages, and can directly induce the maturation and release of IL-1β and IL-18 under the action of TLR3/TLR4-TRIF, resulting in pyroptosis (Shi, 2017). When the CARD domain of caspase-11 binds to LPS, it accelerates its own oligomerization and activation, thereby producing protease activity, cleaving GSDMD to rapidly form membrane pores with a diameter of 10~15nm on the cell membrane at its N-terminus, thereby inducing pyroptosis. In short, pyroptosis produces IL-1β and IL-18, which are the main causes of acute and chronic inflammation in the human body, which are endogenous pyrogens and the main factors of fever. [2-6]

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3 The Relationship Between Pyroptosis and Liver Disease

3.1 Relationship between pyroptosis and ALD

Therefore, understanding the pathogenesis and molecular regulatory mechanisms of ALD will help to develop good diagnostic indicators, prevention and treatment methods. Recently, it has been discovered that pyroptosis may be a key mechanism for the occurrence and progression of ALD. ALD is a rare genetic disorder caused by abnormal lipid metabolism in the body, causing demyelination of the central nervous system and atrophy or dysplasia of the adrenal cortex, as well as abnormal peroxidase in cells. ALD can limit dietary intake of VLCFA. It is the most common in children, more than 5-12 years old, the initial manifestations are inattention, memory loss, learning difficulties, unsteady gait, abnormal behavior, etc., and gradually appear vision and (or) hearing loss, dysarthria, ataxia, paralysis, seizures, dementia and other symptoms, gradually progress, and finally complete paralysis, blindness or deafness, may have convulsions, and even status convulsiveus. There is currently no specific treatment for ALD. NLRP3 inflammasomes are involved in the emergence and development of ALD, and the effect of alcohol on pyroptosis is triggered by PAMP and DAMP, which could be released from ethanol-induced damaged primary hepatocytes and this will trigger the inflammatory-dependent cytokines to speed up and maintain the inflammatory cycle of ALD. In addition, alcohol can also reduce the expression of miRNA-148a in hepatocytes and induce the overexpression of thioredoxin-interacting protein through forkhead box protein O1(Mirshafiee et al., 2018). TXNIP binds to and promotes the activation of the NLRP3 inflammasome, leading to caspase-1-mediated pyroptosis. Some studies have demonstrated that hepatocyte-specific expression of miRNA-148a caused by lentiviral delivery can directly inhibit the interaction between thioredoxin and NLRP3, thereby slowing down pyroptosis and reducing the incidence of ALD. The above report provides evidence and direction that NLRP3 inflammasomes are pathogenic in the development of ALD, however, the triggers that initiate NLRP3 activation have yet to be identified. [3-10]

3.2 Relationship Between Pyroptosis and NAFLD

Non-alcoholic fatty liver disease (NAFLD) is characterized by hepatic lipid accumulation with insulin resistance, and diagnosis requires histologic analysis of more than 5% hepatocyte steatosis, or proton density fat (PDFF) measured by proton magnetic resonance spectroscopy (1 H-MRS) or quantitative water selective MRI fraction provides a rough estimate of the proportion of lipids in the liver) in excess of 5.6%. NAFLD consists of two distinct pathological states corresponding to different prognosis: nonalcoholic fatty liver disease (NAFL) and nonalcoholic steatohepatitis (NASH); The latter also covers a wider range of severities, including liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). Nonalcoholic fatty liver disease (NAFLD) is a metabolic syndrome. Nonalcoholic fatty liver disease is closely related to insulin resistance, which is an important feature of metabolic syndrome and is associated with other metabolic disorders such as obesity, hypertension, and hyperglycemia. If a patient has a chronic excessive alcohol consumption but no obvious abnormalities on liver histology, although the serum aminotransferases are mildly elevated, it does not fall under the category of alcoholic liver disease but is simple fatty liver disease. It may be caused by excessive fat deposition in liver cells due to long-term heavy alcohol consumption. According to the pathological characteristics, it can be divided into simple fatty liver disease, steatohepatitis, fatty liver fibrosis and fatty cirrhosis. The course includes isolated fatty liver disease, steatohepatitis, and fatty liver fibrosis, which may eventually progress to cirrhosis and HCC. At present, the understanding of the pathological mechanism of NALFD is still shallow, and there is a lack of effective treatment countermeasures, so how to delay the progression of NAFLD and try to reverse this process has been a topic of great concern (Knorr et al.,2021). Pyroptosis plays a vital role in the development of NAFLD into NASH, and the activation of NLRP3 inflammasome could accelerates this pathological process and this will aggravates the inflammatory response of the liver. NLRP3 can accelerate the pathological progression of NAFLD by activating inflammatory factors associated with insulin resistance. In addition, in the NAFLD state, hepatocytes are subjected to excessive oxidative stress, producing excess ROS. TXNIP was separated from thioredoxin, which activated NLRP3. Inhibiting the process of NLRP3 inflammasome formation and activation can attenuate the liver inflammation response, cell damage and steatosis caused by hepatocyte pyroptosis, and has the effect of slowing down NAFLD to a certain extent.

3.3 Relationship Between Pyroptosis and Viral Hepatitis

Viral Hepatitis includes types such as viral hepatitis C (hepatitis C) and viral hepatitis E (hepatitis E). Hepatitis C is caused by hepatitis C virus infection, mainly through blood transfusion and other ways of transmission, treatment is mainly by taking small molecule drugs, the cure rate is very high. The epidemic characteristics of hepatitis E resemble hepatitis A, through the fecal-oral route transmission, is contagious, treatment can usually be cured, mainly by symptomatic support treatment. Viral hepatitis is a liver inflammation in which hepatitis viruses infect liver cells and cause a high mortality rate, about 90% of which can be attributed to chronic infections caused by HBV and HCV, and severe viral hepatitis progresses to liver fibrosis, cirrhosis and even HCC. It is important to note that NLRP3 inflammasomes are a potential factor in the development and development of viral hepatitis. In addition, NLRP3 inflammasome can also stimulate the formation of lipid

droplets in hepatocytes, thereby promoting the morphological change and replication of HCV, and accelerating the deterioration of liver diseases. Therefore, further study of the relationship between HBV and HCV and hepatocyte pyroptosis can further explore the pathogenic mechanism of human hepatitis virus-induced liver disease (Xiang et al.,2018).

3.4 The Relationship Between Pyroptosis and Liver Fibrosis

Liver fibrosis is the result of the liver's scar repair response to various acute and chronic liver injuries, and is a common link in the progression of various chronic liver diseases to cirrhosis. Liver fibrosis is a serious liver disease state. Liver fibrosis, the abnormal proliferation of fibrous connective tissue in the liver, is an important process in the progression of chronic liver disease to cirrhosis. Its severity cannot be ignored because it not only affects the normal function of the liver, but can also lead to serious consequences such as cirrhosis and liver cancer. Early liver fibrosis may present with hepatic discomfort, fatigue, loss of appetite, and weight loss. First, liver discomfort. Early liver fibrosis can cause the liver to enlarge and compress surrounding tissues, causing local pain or discomfort. The symptoms are predominantly in the liver area and may present as persistent or intermittent pain or discomfort. Second, Fatigue. Liver fibrosis can affect the liver's detoxification and metabolic functions, resulting in an inadequate energy supply to the body, which can lead to fatigue symptoms. Fatigue is a generalized sensation that people may feel weak and exhausted. Third, loss of appetite. Liver fibrosis interferes with the secretion and excretion of bile, affecting the digestion and absorption of food, which in turn leads to loss of appetite. This symptom usually manifests as a decrease in interest in food and a decrease in the amount of food eaten. Last, weight loss. Early liver fibrosis may lead to weight loss due to loss of appetite and metabolic abnormalities. In addition, weight loss can also be caused by increased malnutrition and protein consumption.

There are various causes of liver fibrosis, including viral hepatitis, alcoholic liver disease, autoimmune liver disease, etc. These causes act on the liver for a long time, causing liver cell damage, which in turn leads to the proliferation of fibrous tissue. Its main feature is the imbalance between the generation and degradation of extracellular matrix (ECM), mainly collagen, and excessive deposition in the liver. Activated hepatic stellate cells (HSCs) are the main source of ECM during the occurrence of liver fibrosis. HSC proliferation, migration, and phenotype transformation after continuous activation become myofibroblast like cells, which are the core link in the occurrence and development of liver fibrosis. Activated HSCs have the following characteristics: (1) synthesis and secretion of various ECM such as interstitial collagen; (2) Autocrine production of fibrogenic cytokines such as transforming growth factor (TGF) β 1; (3) Release collagenase inhibitor tissue metalloproteinase inhibitor (TIMP); (4) Secreting chemokines and other inflammatory cytokines; (5) Has cell contraction characteristics; (6) Synthesize matrix metalloproteinases (MMPs) to cause abnormal degradation of ECM; (7) Tolerance to apoptotic stimuli, etc. Many signaling molecules and pathways are involved in regulating the fibrosis related biological characteristics of HSCs, and their mechanisms of action are complex. HSC has pro-fibrotic and pro-inflammatory effects, and secretes a variety of ECM components during activation. NLRP3 inflammasome activation in HSCs can lead to an increase in the number of SMA-positive cells. Therefore, NLRP3 inflammasome activation can activate HSC, which in turn leads to the emergence and development of liver fibrosis.

3.5 Relationship Between Pyroptosis and HCC

Hepatocellular carcinoma (HCC) is a primary liver cancer with a high mortality rate. HCC accounts for more than 90% of primary liver cancers and is a common type of liver cancer in China. Hepatocellular carcinoma generally refers to malignant neoplastic diseases originating from hepatocytes, and the causes of hepatocellular carcinoma are usually due to hepatitis virus infection, aflatoxin infection, chemical infection, etc. If left untreated, the patient's condition will gradually worsen, and he will be prone to symptoms such as liver pain, jaundice, progressive weight loss, and fatigue. Hepatocellular carcinoma is one of the types of liver cancer, which is a relatively serious disease that may lead to life-threatening conditions if not treated in time. Causes include cirrhosis of the liver, hepatitis B and C virus infection, aflatoxin exposure, smoking, obesity, diabetes, etc Surgical excision is considered one of the standard treatments. However, HCC still shows a high rate of postoperative recurrence, rapid progression, and a very poor prognosis. There is an urgent need to find new therapeutic targets for HCC. As a new mode of programmed cell death, pyroptosis may be a new treatment for HCC after cell senescence and apoptosis. Factors such as 17β-estradiol (E2) and estrogen receptor (ER) β have also been taken into account the gender differences in the incidence of HCC. Studies have shown that ERβ expression is also reduced in HCC tissues, and it has been found that NLRP3 inflammasomes activated with E2 ultimately improve HCC progression by HCC cell lines (SMMC7721, BEL7402, and HepG2 cells) treated with E2/ERβ/MAPK signaling. In addition, E2 treatment-activated NLRP3 inflammasomes induce caspase-1-dependent apoptosis in HepG2 cells, resulting in inhibition of HCC progression. The results showed that E2 and ERβ exerted anticancer effects by activating the NLRP3 inflammasome to trigger pyrophosphorylation. In summary, the factors related to pyroptosis have dual mechanisms that promote and inhibit tumorigenesis. Pharmacologically targeting NLRP3 inflammasomes may inhibit HCC proliferation and metastasis, suggesting that this may be a new therapeutic strategy (Wang et al.,2021).

4 The Role of Pyroptosis in Liver Disease

The increase in the incidence of liver disease has been an important problem that seriously threatens health in China for a long time, and some patients with liver disease due to various reasons gradually develop liver cirrhosis and liver cancer.

4.1 Pyroptosis and Viral Hepatitis

Hepatitis as a common digestive disorder, including viral hepatitis and autoimmune hepatitis. Viral hepatitis refers to liver inflammation caused by viral infection of liver cells, which has a high mortality rate (Ning et al., 2019). Viral hepatitis B and hepatitis C are the main diseases, which can develop into liver fibrosis, and even lead to liver cirrhosis and liver cancer. Bacterial endotoxins can highly induce pyroptosis in hepatocytes, which may also trigger pyroptosis and affect the progression of liver disease. It has been documented that the occurrence and development of hepatitis B and C are related to pyroptosis in viral hepatitis. Recognition of viral DNA/RNA and pattern PRRs induces inflammasome activation and leads to pyroptosis. The TM domain of the metastatic receptor may reduce the expression of pyroptosis markers, including cleaved caspase-1 and IL-1β, by blocking AIM2-dependent signaling pathways during multiple viral infections. Hepatitis B virus inhibits lipopolysaccharide-induced expression of NLRP3 and IL-1β by inhibiting the nuclear transcription alfactor Kappa B molecular signaling pathway and the synthesis of reactive oxygen species. Under hydrogen peroxide-stimulated conditions, the NLRP3 inflammasome is activated by high levels of mitoROS and mediates hepatitis B virus x protein-induced liver inflammation and hepatocyte pyroptosis. Hepatitis C virus can mediate pyroptosis through caspase-1 and caspase-3 signaling. In hepatocytes, the formation of lipid droplets is closely related to NLRP3, leading to morphological changes and replication of HCV, which plays a role in the development of liver disease. In chronic HCV, IL-1β produced by Kupffer cells has been associated with an inflammatory response and has been shown to be a major source of IL-1β. Therefore, in order to clarify the occurrence and development mechanism of viral hepatitis, it is necessary to study the relationship between pyroptosis and viral hepatitis B and C, so as to provide directions for the treatment of the disease (Beier et al. ,2018).

4.2 Pyroptosis and Alcoholic Liver Disease

Alcoholic liver disease is liver damage and inflammation caused by excessive alcohol consumption, is a disease with a high mortality rate, and an important factor in liver fibrosis and cirrhosis, characterized by abnormal lipid deposition of hepatocytes and excessive oxidative stress. The pathological changes of alcoholic liver disease are mainly bullous and bullolar, or accompanied by vesicular mixed hepatocellular steatosis, which can be pathologically divided into alcoholic fatty liver, alcoholic hepatitis, alcoholic liver fibrosis and alcoholic cirrhosis according to whether the diseased liver tissue is accompanied by inflammatory response and fibrosis.

Liver damage caused by the hereditary hereditary diagnosis of alcoholic fatty liver disease is first manifested as hepatocyte steatosis, and mildly manifested as scattered single stem cells or small patches of hepatocyte involvement, mainly distributed in the central lobular area, and the disease will further develop to lead to diffuse distribution. Alcoholic hepatitis is characterized by liver fibrosis, hepatocyte necrosis, neutrophil infiltration, alcoholic hyaline bodies and alcoholic cirrhosis in the hepatocytes of the central lobular area, complete destruction of the lobular structure of the liver, replaced by pseudolobular formation and extensive fibrosis, and the general morphology is micronodular cirrhosis, which can be divided into active and quiescent according to whether there is interface hepatitis in the fibrous septum.

While several studies have identified several typical alcohol-induced hepatocyte injury pathways, including endoplasmic reticulum stress, oxidative stress, pyroptosis, apoptosis, and autophagy, how these mechanisms contribute to exacerbation remains to be tested. The study noted that RNA sequencing analysis showed that the expression levels of caspase-4 and caspase-11 genes in the liver tissues of ALD patients and mice were increased in the experiment. The NL-RP3 oligomer inhibitor MCC950 can significantly improve cell viability and protect hepatocytes from ethanol-induced pyroptosis, which fully indicates that the activation of NLRP3 inflammasome plays an important role in the occurrence and development of ALD. NLRP3 has been reported to recruit apoptosis-associated dot-like proteins and Procaspase-1 to become mature caspase-1, thereby inducing liver injury. The inflammasome activation of NLRP3 is closely related to ROS, and the main source is mitochondria. Many studies have confirmed that mitochondria-related energy metabolism, signal transduction, and ROS production are key to programmed cell death. Under the action of alcohol, the expression of miRNA-148a in hepatocytes is reduced, and thiori interacting protein can be overexpressed, and the overexpression of TXNIP can activate the NLRP3 inflammasome, resulting in caspase-1-mediated pyroptosis. The above results suggest that NLRP3 inflammasome plays a key role in the occurrence and development of ALD, while the activation mechanism of NLRP3 is not fully understood (Meng et al.,2023).

4.3 Pyroptosis and Liver Fibrosis

Hepatic Fibrosis (HF) refers to the abnormal amount of scar tissue formed in the liver as the liver attempts to repair and replace damaged cells. It is a reversible pathophysiological phenomenon that can be caused by viral hepatitis, alcohol, aflatoxin and other causes. Liver fibrosis is an important stage in the development of chronic liver disease to cirrhosis, and its four key indicators are of great significance for evaluating the

disease. The four indicators are hyaluronidase, type III procollagen, laminin, and type IV collagen. Hyaluronidase is a matrix component synthesized by liver stromal cells, which can sensitively reflect the amount of fiber produced in the liver and the condition of liver damage, and is a sensitive indicator of liver fibrosis and liver cirrhosis. The amount of type III procollagen in serum is closely related to the degree of liver fibrosis, and the higher its index, the more severe the degree of liver fibrosis may be. Laminin is a non-collagenous structural protein unique to the basement membrane, and its levels can reflect the degree of liver fibrosis activity and portal venous pressure. Finally, the increase in the content of type IV collagen, as the main component of the basement membrane, can sensitively reflect the process of liver fibrosis, which is one of the early markers of liver fibrosis.

In developing countries such as Asia and Africa, viral hepatitis is the main cause of liver fibrosis, while in Western developed countries, alcohol or obesity are common causes. Local long-term stimulation of liver caused by various inducements leads to activation of hepatic astrocytes, which forms liver fibrosis. The basis for these changes is the imbalance between fibrogenesis and fibrolysis caused by chronic liver injury. Mouse and human hepatocytes can undergo pyroptosis upon NLRP3 inflammasome activation and subsequently release NLRP3 inflammasomes, thereby promoting and maintaining inflammasome-driven fibrosis. Inhibition of the activation of caspase-1 and GSDMD inhibits the occurrence of pyroptosis. Studies have shown that GSDMD-knocking human hepatocellular carcinoma HepG2 cells or GSDMD-knocking mouse primary hepatocytes are both resistant to inflammasome-induced pyroptosis, suggesting that hepatocyte death is dependent on GSDMD activation. The study also pointed out that overactivation of hepatocyte NLRP3 leads to hepatocyte pyroptosis and inflammasome secretion into the extracellular space. Caspase-1 activity is present in the liver tissue of patients with NASH, and serum caspase-1 activity is related to the degree of liver damage, especially the degree of liver fibrosis. Activated caspase-1, IL-1β, and IL-18 can activate NL-RP3, and IL-1β and IL-18 induce collagen deposition and are important for the formation of liver fibrosis. Pyroptosis is closely related to liver fibrosis, and in-depth research should be carried out on the mechanism of liver fibrosis caused by NLRP3 inflammasome, so as to better control the occurrence and development of this disease (Xiang et al., 2018).

4.4 Pyroptosis and Hepatocellular Carcinoma

Primary hepatocellular carcinoma is common in liver disease and is a highly aggressive primary tumor in gastrointestinal malignancy, and the search for new therapeutic targets has become an urgent need for HCC treatment. Inflammasome is a complex of polymeric cytoplasmic proteins, leading to activation of the inflammatory response, this also mediate host immune responses to pathogen infection and cellular damage. In the microenvironment of the tumor, chronic inflammation plays a key role in the development of tumors. Inflammasomes also act as a "double-edged sword" role in different kinds of cancer, being both promoters and suppressors of tumors. The components of the NL-RP3 inflammasome were greatly down-regulated in hepatoma cells, and pyroptosis in hepatoma tissues and cells was inhibited. As a novel regulator, long non-coding RNAs are key in the process of tumorigenesis and development, including pyroptosis, proliferation, apoptosis, and cell cycle progression. Relevant studies showed that the expression of SNHG7 and SIRT1 genes was up-regulated, and the expression of miR-34a gene was down-regulated in hepatocellular carcinoma tissues and cell lines. SNHG7 inhibits miR-34a and upregulates the expression of SIRT1, thereby inhibiting NLRP3-induced pyroptosis. These phenomena suggest that the SNHG7/miR-34a/SIRT1 axis may be a target for the treatment of liver cancer. IL-1 receptor-associated kinases include a class of serine threonine kinases. Some studies have confirmed that IRAKs are involved in metabolic, inflammatory, and pathophysiological processes in malignant diseases. The down-regulation of IRAK1 in the biological function and regulatory mechanism of hepatocellular carcinoma progression can inhibit the activation of NLRP3 inflammasome, prevent the invasion, proliferation and migration of hepatocellular carcinoma cells, and promote the apoptosis of hepatoma cells.

5 Conclusion

As a new form of cell death, pyroptosis plays an important role in maintaining metabolism and immune homeostasis. As a research hotspot in recent years, pyroptosis has attracted the attention of researchers and clinicians at home and abroad to provide new solutions for the treatment of liver diseases. The activation of NLRP3 inflammasome is an important regulator of pyroptosis and plays different roles in the occurrence and development of liver diseases including HBV, HCV, NAFLD, HCC, and fibrosis.

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