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The Role of NLRP3 Inflammasome in the Pathogenesis and Progression of Metabolic Dysfunction-Associated Steatotic Liver Disease

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a common chronic liver disease characterized by excessive hepatic lipid accumulation and closely associated with metabolic disorders. Its progression involves not only abnormal lipid metabolism but also inflammatory responses, oxidative stress, mitochondrial dysfunction, and fibrosis formation. The NLRP3 inflammasome, as an important component of innate immunity, plays a key role in regulating inflammation under metabolic stress conditions. When activated by factors such as lipid overload, reactive oxygen species production, mitochondrial damage, and gut-derived inflammatory signals, the NLRP3 inflammasome promotes the activation of Caspase-1 and the release of inflammatory cytokines, including interleukin-1β and interleukin-18. These inflammatory responses affect hepatocytes, Kupffer cells, and hepatic stellate cells, contributing to liver inflammation and fibrosis during MASLD progression. This paper discusses the biological characteristics and activation mechanisms of the NLRP3 inflammasome and analyzes its involvement in hepatic lipid accumulation, chronic inflammation, metabolic disorders, and fibrosis development. The interaction between NLRP3 signaling and oxidative stress, insulin resistance, and the gut-liver axis is also examined. Targeting the NLRP3 inflammasome may provide a potential approach for MASLD management, although further studies are needed to clarify its clinical application and safety.

Keywords: NLRP3 inflammasome, metabolic dysfunction-associated steatotic liver disease, hepatic inflammation, oxidative stress, liver fibrosis, innate immunity

1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a common chronic liver disease characterized by excessive fat accumulation in the liver and is closely associated with metabolic disorders such as obesity, insulin resistance, type 2 diabetes, and dyslipidemia. Compared with simple hepatic steatosis, MASLD may cause continuous liver injury and can progress to metabolic dysfunction-associated steatohepatitis (MASH), liver fibrosis, cirrhosis, and even liver cancer. The increasing prevalence of metabolic disorders has made MASLD an important health problem worldwide.

The development of MASLD is not caused by lipid accumulation alone. Excessive fatty acid

deposition in hepatocytes can disturb normal cellular metabolism and induce lipotoxicity. This process may increase oxidative stress, damage mitochondria, and trigger inflammatory responses in the liver. Immune cells in the liver, especially Kupffer cells, respond to metabolic stress signals and release inflammatory mediators. Persistent inflammation can aggravate hepatocyte injury and promote the activation of hepatic stellate cells, which contributes to liver fibrosis. These changes show that inflammation and immune regulation are important parts of MASLD progression.

The NLRP3 inflammasome is an important component of the innate immune system and plays a key role in inflammatory responses. It is composed of the NLRP3 protein, the adaptor protein ASC, and Caspase-1. When activated by metabolic stress signals, the NLRP3 inflammasome promotes the maturation and release of inflammatory cytokines such as interleukin-1β (IL-1β) and interleukin-18 (IL-18). These inflammatory factors can affect liver cells and immune cells, creating an inflammatory environment that contributes to liver damage.

Recent studies have shown that NLRP3 inflammasome activation is closely related to the occurrence and progression of MASLD. Abnormal lipid metabolism, oxidative stress, mitochondrial dysfunction, and changes in the gut-liver axis may activate NLRP3 signaling in the liver. Activated NLRP3 inflammasome can promote hepatic inflammation, increase hepatocyte injury, and accelerate fibrosis formation. The regulation of NLRP3 activity has therefore attracted attention as a possible approach for controlling MASLD progression.

This paper discusses the role of the NLRP3 inflammasome in MASLD pathogenesis, focusing on its effects on hepatic lipid accumulation, inflammatory responses, and liver fibrosis. The relationship between NLRP3 activation and major metabolic pathways is also examined to provide a clearer understanding of how immune regulation participates in MASLD development.

2. Biological Characteristics and Activation Mechanisms of NLRP3 Inflammasome

2.1 Structure and Components of NLRP3 Inflammasome

The NLRP3 inflammasome is an intracellular protein complex that plays an important role in innate immune responses. It can recognize different types of danger signals produced by infection, tissue damage, and metabolic disorders. Unlike adaptive immunity, innate immunity responds quickly to harmful changes in the internal environment. The NLRP3 inflammasome acts as a key sensor that connects cellular stress signals with inflammatory reactions.

The NLRP3 inflammasome mainly consists of three components: the NLRP3 sensor protein, the ASC adaptor protein, and Caspase-1. NLRP3 is responsible for detecting abnormal signals inside cells. It belongs to the nucleotide-binding oligomerization domain-like receptor family and can respond to various stimuli, including metabolic stress, oxidative damage, and cellular injury. However, NLRP3 does not directly produce inflammatory factors. It needs to interact with other proteins to form an active inflammasome complex.

ASC is an adaptor protein that connects NLRP3 with Caspase-1. After NLRP3 recognizes danger signals, ASC helps assemble the inflammasome structure and promotes the activation of Caspase-1. Caspase-1 is an important inflammatory enzyme that controls the maturation of several inflammatory cytokines. Through the activation of Caspase-1, inactive forms of IL-1β and IL-18 are converted into their active forms and released outside cells.

In the liver, the NLRP3 inflammasome is mainly expressed in immune cells such as Kupffer cells, but it can also be activated in hepatocytes and other liver-related cells under metabolic stress conditions. Normal activation of NLRP3 helps remove harmful stimuli and maintain tissue balance. However, excessive or continuous activation may lead to chronic inflammation and contribute to liver injury. This process is closely related to the development of MASLD.

2.2 Activation Signals of NLRP3 Inflammasome

The activation of the NLRP3 inflammasome requires multiple signals from the cellular environment. In MASLD, metabolic disorders create conditions that can continuously stimulate NLRP3 activation. Excessive lipid accumulation, oxidative stress, mitochondrial damage, and inflammatory signals from the gut are important factors involved in this process.

Excessive lipid accumulation is one of the main metabolic changes in MASLD. When large amounts of free fatty acids enter hepatocytes, normal lipid metabolism becomes disrupted.

Some fatty acids cannot be effectively processed and may cause lipotoxicity. Lipid overload can damage cellular structures and stimulate inflammatory pathways, including NLRP3 activation. Activated NLRP3 then promotes the release of inflammatory factors, which further affects liver cell function.

Reactive oxygen species (ROS) production is another important signal for NLRP3 activation. Under metabolic stress, mitochondria may produce excessive ROS due to impaired energy metabolism. High levels of ROS can damage proteins, lipids, and DNA within cells. These changes can be recognized as danger signals and activate the NLRP3 inflammasome. In MASLD, oxidative stress and NLRP3 activation often form a continuous cycle, where metabolic damage increases inflammation and inflammation further worsens cellular injury.

Mitochondrial dysfunction also contributes to NLRP3 activation. Mitochondria are responsible for energy production and play an important role in maintaining cellular metabolism. In MASLD, abnormal lipid metabolism can impair mitochondrial function, resulting in reduced energy efficiency and increased production of harmful molecules. Damaged mitochondria may release signals that activate NLRP3 and promote inflammatory responses.

Endotoxin stimulation from the gut-liver axis is another factor involved in NLRP3 activation. Changes in intestinal microbiota and impaired intestinal barrier function may increase the entry of bacterial products such as lipopolysaccharide (LPS) into circulation. When LPS reaches the liver, it can activate immune cells and promote inflammatory signaling. This pathway provides an important connection between intestinal changes and hepatic inflammation in MASLD.

2.3 Inflammatory Responses Mediated by NLRP3 Inflammasome

After activation, the NLRP3 inflammasome triggers a series of inflammatory reactions through Caspase-1. Activated Caspase-1 promotes the processing of inactive IL-1β and IL-18 into mature inflammatory cytokines. These cytokines are then released from cells and participate in local and systemic inflammatory responses.

IL-1β is one of the major inflammatory mediators produced through NLRP3 activation. In the liver, increased IL-1β levels can promote the recruitment of immune cells and enhance inflammatory responses. It can also affect hepatocyte metabolism and increase liver injury under metabolic stress conditions. Continuous production of IL-1β may maintain a chronic inflammatory environment, which is commonly observed during MASLD progression.

IL-18 is another important cytokine regulated by NLRP3 inflammasome activation. It participates in immune regulation and influences the activity of different immune cells. Abnormal IL-18 production may affect the balance between protective immune responses and excessive inflammation. In the context of MASLD, changes in IL-18 signaling are associated with liver inflammation and metabolic dysfunction.

Persistent activation of the NLRP3 inflammasome can cause long-term inflammatory damage in the liver. Continuous release of inflammatory cytokines affects hepatocytes, Kupffer cells, and hepatic stellate cells. Injured hepatocytes release additional danger signals, which further activate immune responses. At the same time, inflammatory mediators can stimulate hepatic stellate cells and promote extracellular matrix deposition, increasing the risk of liver fibrosis.

The activation of NLRP3 is therefore not only an inflammatory event but also a process that links metabolic stress with liver tissue damage. In MASLD, abnormal metabolic conditions can maintain NLRP3 activation, leading to continuous inflammation and promoting disease progression.

3. Role of NLRP3 Inflammasome in the Pathogenesis of MASLD

3.1 NLRP3 Inflammasome and Hepatic Lipid Accumulation

Excessive lipid accumulation in hepatocytes is a key feature of MASLD. Under normal conditions, the liver maintains lipid balance through fatty acid uptake, synthesis, oxidation, and export. When metabolic disorders occur, this balance is disrupted, leading to increased lipid storage in liver cells. The accumulation of triglycerides and free fatty acids creates metabolic stress and provides important signals for NLRP3 inflammasome activation.

High levels of free fatty acids, especially saturated fatty acids, can directly affect hepatocyte function. Excess fatty acids may cause endoplasmic reticulum stress, mitochondrial damage, and oxidative stress. These changes can

stimulate inflammatory signaling pathways and promote NLRP3 activation. In addition, excessive lipid deposition may change the internal environment of hepatocytes, making cells more sensitive to inflammatory stimulation.

Lipid droplets are important structures involved in hepatic fat storage. In MASLD, increased formation and enlargement of lipid droplets are commonly observed in hepatocytes. Although lipid droplets can temporarily reduce the harmful effects of free fatty acids by storing excess lipids, excessive lipid accumulation may lead to lipotoxicity. Lipotoxicity occurs when accumulated lipids interfere with normal cellular functions and cause cell injury. Damaged hepatocytes can release danger signals that activate NLRP3 inflammasome-related pathways.

The activation of NLRP3 also affects hepatic lipid metabolism. Inflammatory cytokines released after NLRP3 activation, including IL-1β and IL-18, can interfere with metabolic processes in hepatocytes. IL-1β may reduce insulin sensitivity and disturb lipid metabolism, which increases fatty acid accumulation in the liver. This creates a continuous cycle in which metabolic disorders activate inflammation, while inflammation further worsens metabolic imbalance.

NLRP3 activation is therefore closely connected with the early stage of MASLD. It links excessive lipid storage with inflammatory responses and helps explain why simple steatosis may gradually develop into more severe liver injury.

3.2 NLRP3 Inflammasome and Hepatic Inflammation

Inflammation is a major factor involved in the progression of MASLD. The liver contains various immune cells that respond to metabolic stress, and Kupffer cells are the main resident macrophages in the liver. These cells can detect harmful signals caused by lipid overload, oxidative stress, and damaged hepatocytes. NLRP3 inflammasome activation in Kupffer cells is an important process that promotes hepatic inflammation.

When Kupffer cells are exposed to metabolic stress signals, NLRP3 inflammasome activation increases Caspase-1 activity and promotes the release of IL-1β and IL-18. These inflammatory cytokines can enhance the recruitment and activation of other immune cells in the liver. The increased inflammatory response may cause further damage to hepatocytes and maintain a chronic inflammatory environment.

IL-1β plays an important role in MASLD-related inflammation. It can promote the production of additional inflammatory mediators and increase immune cell activation. Elevated IL-1β levels are associated with hepatocyte injury and metabolic abnormalities. Persistent IL-1β signaling may interfere with normal liver function and accelerate the transition from simple steatosis to inflammatory liver disease.

IL-18 also participates in liver immune regulation. It affects the activity of immune cells and influences inflammatory responses within the liver. Appropriate IL-18 signaling may contribute to immune balance, but excessive production may promote chronic inflammation. Abnormal regulation of IL-18 has been linked to metabolic disorders and liver injury in MASLD.

Chronic low-grade inflammation is a common feature of MASLD. Unlike acute inflammation caused by infection or severe injury, metabolic inflammation usually occurs at a lower intensity but lasts for a longer period. Continuous activation of NLRP3 maintains the production of inflammatory cytokines and prevents the liver from returning to a normal metabolic state. This persistent inflammatory condition contributes to hepatocyte damage and provides conditions for further disease progression.

3.3 NLRP3 Inflammasome and Liver Fibrosis Development

Liver fibrosis is an important stage in the progression of MASLD. It occurs when repeated liver injury causes excessive production and accumulation of extracellular matrix components. Hepatic stellate cells are the main cells responsible for producing collagen during fibrosis. Their activation is closely related to inflammatory signals released from damaged hepatocytes and immune cells.

NLRP3 inflammasome activation contributes to hepatic stellate cell activation through inflammatory mediators. Cytokines such as IL-1β can promote the expression of fibrosis-related molecules and increase collagen production. Activated hepatic stellate cells gradually transform into a fibrotic state, leading to extracellular matrix deposition and structural changes in liver tissue.

Kupffer cells also participate in this process. After NLRP3 activation, Kupffer cells release inflammatory cytokines and other signaling molecules that influence nearby hepatic stellate cells. This interaction between immune cells and

fibrosis-related cells creates an environment that supports continuous tissue repair and collagen accumulation. When this process continues for a long time, normal liver structure may be replaced by fibrotic tissue.

The role of NLRP3 becomes more significant during the transition from MASLD to metabolic dysfunction-associated steatohepatitis (MASH). MASH is characterized by increased inflammation and hepatocyte injury compared with simple steatosis. NLRP3 activation connects metabolic stress, immune responses, and fibrosis formation, making it an important pathway in this transition.

Although fibrosis development involves multiple signaling pathways, NLRP3 inflammasome activation provides a direct link between metabolic abnormalities and chronic liver damage. Regulation of NLRP3 activity may help reduce inflammatory injury and slow fibrosis progression in MASLD.

4. Interaction Between NLRP3 Inflammasome and Metabolic Pathways in MASLD

4.1 NLRP3 Inflammasome and Oxidative Stress

Oxidative stress is an important factor involved in the development of MASLD and has a close relationship with NLRP3 inflammasome activation. Under normal conditions, cells maintain a balance between reactive oxygen species (ROS) production and antioxidant defense systems. In metabolic disorders, excessive lipid accumulation and mitochondrial dysfunction can increase ROS production. When ROS levels exceed the ability of cells to remove them, oxidative stress occurs and causes damage to liver cells.

Mitochondria are one of the main sources of ROS in hepatocytes. In MASLD, excessive fatty acid metabolism increases the burden on mitochondria and affects normal energy production. Damaged mitochondria may release more ROS and other danger signals, which can activate the NLRP3 inflammasome. This process allows NLRP3 to sense cellular stress and initiate inflammatory responses.

Oxidative stress and NLRP3 activation can influence each other. Increased ROS production promotes NLRP3 activation, while inflammatory responses caused by NLRP3 may further damage mitochondria and increase oxidative stress. This interaction creates a continuous cycle that aggravates hepatocyte injury. Inflammatory cytokines released after NLRP3 activation, such as IL-1β and IL-18, can enhance oxidative damage and affect normal liver metabolism.

Oxidative stress also contributes to changes in liver tissue structure. Excessive ROS can damage cell membranes, proteins, and genetic materials, leading to hepatocyte dysfunction or death. Damaged hepatocytes release additional inflammatory signals, which activate immune cells and maintain NLRP3-related inflammation. Therefore, oxidative stress is not only a result of metabolic imbalance but also an important factor that promotes NLRP3-mediated liver injury.

4.2 NLRP3 Inflammasome and Insulin Resistance

Insulin resistance is a common metabolic feature of MASLD and plays an important role in abnormal lipid metabolism. Under normal conditions, insulin helps regulate glucose utilization and lipid storage. When insulin signaling is impaired, the ability of cells to respond to insulin decreases, leading to increased glucose production and abnormal fat metabolism. These changes promote lipid accumulation in the liver.

Inflammation caused by NLRP3 activation can interfere with insulin signaling pathways. IL-1β released after NLRP3 activation may reduce insulin sensitivity by affecting key molecules involved in insulin signal transmission. When insulin signaling is weakened, hepatocytes have difficulty maintaining normal metabolic balance, which increases fatty acid synthesis and reduces lipid breakdown.

Insulin resistance can also promote NLRP3 activation. Increased circulating fatty acids and glucose levels caused by metabolic disorders can increase oxidative stress and mitochondrial dysfunction. These changes provide activation signals for NLRP3 inflammasome formation. As a result, insulin resistance and NLRP3 activation may influence each other during MASLD progression.

The relationship between insulin resistance and NLRP3 activation shows the connection between metabolic disorders and inflammation. Abnormal glucose and lipid metabolism provide the conditions for inflammatory activation, while inflammatory responses further worsen metabolic dysfunction. This interaction contributes to continued liver fat accumulation and increases the risk of inflammatory liver injury.

4.3 NLRP3 Inflammasome and the Gut-Liver Axis

The gut-liver axis is an important pathway connecting intestinal changes with liver metabolism and immune responses. The liver receives most of its blood supply from the portal vein, which allows substances from the intestine to directly influence liver function. Changes in intestinal microbiota and intestinal barrier integrity can therefore affect hepatic inflammatory responses.

In MASLD, metabolic disorders may cause changes in gut microbiota composition. An imbalance in intestinal bacteria can reduce the production of beneficial metabolites and increase the release of harmful bacterial products. At the same time, damage to the intestinal barrier may increase intestinal permeability, allowing substances such as lipopolysaccharide (LPS) to enter circulation and reach the liver.

LPS can activate immune cells in the liver through inflammatory signaling pathways. When Kupffer cells recognize LPS, they may produce inflammatory mediators and promote NLRP3 inflammasome activation. Activated NLRP3 then increases the production of IL-1β and IL-18, which enhances hepatic inflammation and contributes to liver injury.

The gut-liver axis also interacts with metabolic stress pathways. Changes in intestinal microorganisms can influence lipid metabolism, insulin sensitivity, and oxidative stress, which are closely related to NLRP3 activation. This connection explains why intestinal disorders can affect the severity of liver inflammation in MASLD.

Regulating the gut-liver axis may provide another approach for controlling NLRP3-related inflammation. Improving intestinal barrier function, maintaining microbial balance, and reducing harmful inflammatory signals may help decrease excessive NLRP3 activation and protect liver function.

5. Therapeutic Potential of Targeting NLRP3 Inflammasome in MASLD

5.1 Direct Inhibition of NLRP3 Inflammasome

The important role of NLRP3 inflammasome in MASLD has attracted attention to NLRP3 as a potential therapeutic target. Since excessive NLRP3 activation promotes liver inflammation and fibrosis, directly reducing its activity may help control inflammatory damage and slow disease progression. Current studies have explored different strategies to block NLRP3 signaling, including inhibition of NLRP3 assembly, suppression of Caspase-1 activation, and reduction of downstream inflammatory cytokine release.

Direct inhibition of NLRP3 can reduce the production of IL-1β and IL-18, which are key inflammatory factors involved in liver injury. By decreasing the release of these cytokines, NLRP3 inhibition may reduce immune cell activation and improve the inflammatory environment in the liver. This approach may also limit the activation of hepatic stellate cells and reduce extracellular matrix accumulation, thereby slowing fibrosis development.

Several small-molecule compounds have been studied for their ability to regulate NLRP3 activity. These compounds may affect different steps of inflammasome activation, such as preventing NLRP3 oligomerization or reducing Caspase-1 activation. Experimental studies have shown that blocking NLRP3-related pathways can reduce hepatic inflammation and improve metabolic disorders in MASLD models.

However, direct targeting of NLRP3 requires careful consideration. NLRP3 is not only involved in disease-related inflammation but also participates in normal immune defense. Complete and long-term suppression of NLRP3 activity may affect the body's ability to respond to infections or tissue damage. A more precise regulation of NLRP3 activation rather than complete inhibition may provide a safer therapeutic approach.

5.2 Regulation of Upstream Metabolic Factors

NLRP3 activation in MASLD is closely influenced by metabolic abnormalities. Regulating the factors that trigger NLRP3 activation may provide another way to reduce inflammation. These approaches focus on improving lipid metabolism, reducing oxidative stress, and restoring metabolic balance.

Abnormal lipid metabolism is an important trigger of NLRP3 activation. Excessive fatty acid accumulation can cause lipotoxicity and promote inflammatory responses in the liver. Improving lipid metabolism may reduce the stress signals that activate NLRP3. Weight control, dietary adjustment, and increased physical activity can reduce hepatic fat accumulation and improve metabolic function. These lifestyle changes remain important approaches for managing MASLD.

Oxidative stress is another major factor involved in NLRP3 activation. Reducing excessive ROS production and improving mitochondrial function may help prevent unnecessary inflammasome activation. Antioxidant strategies and metabolic regulation methods have been studied for their ability to reduce oxidative damage and protect hepatocytes. By improving the cellular environment, these approaches may indirectly decrease NLRP3-related inflammation.

Metabolic-targeted therapies may also influence NLRP3 activity. Treatments that improve insulin sensitivity or regulate glucose and lipid metabolism can reduce the metabolic stress associated with MASLD. Improved insulin signaling decreases abnormal lipid accumulation and reduces inflammatory stimulation in liver cells. Some metabolic drugs have shown potential effects on liver inflammation, although their specific influence on NLRP3 pathways requires further investigation.

The gut-liver axis is another potential target for regulating NLRP3 activation. Maintaining intestinal barrier integrity and improving gut microbiota balance may reduce the entry of inflammatory signals into the liver. These strategies may decrease immune activation and help maintain a healthier liver environment.

5.3 Challenges and Future Perspectives of NLRP3-Based Therapy

Although NLRP3 inflammasome has shown potential as a therapeutic target for MASLD, several challenges remain. NLRP3 activation is controlled by multiple signals, including metabolic stress, oxidative damage, mitochondrial changes, and immune responses. The complex regulation of this pathway makes it difficult to determine the appropriate level and timing of intervention.

The effects of NLRP3 regulation on normal immune function also need attention. NLRP3 plays a role in protecting the body against harmful stimuli and infections. Excessive inhibition may weaken normal immune responses. Future therapies need to balance the reduction of harmful inflammation with the maintenance of necessary immune activity.

Another challenge is the difference between experimental studies and clinical application. Many NLRP3-related treatments have shown beneficial effects in animal models, but their safety and effectiveness in patients with MASLD require further clinical evaluation. Factors such as disease stage, metabolic status, and individual differences may influence treatment outcomes. Future research may focus on more accurate regulation of NLRP3 signaling. Combining NLRP3-targeted strategies with metabolic improvement, lifestyle intervention, or other anti-inflammatory approaches may provide better therapeutic effects. A clearer understanding of NLRP3-related mechanisms will help develop treatments that can reduce liver inflammation while maintaining normal physiological functions.

6. Conclusion

The NLRP3 inflammasome is closely involved in the development of MASLD through its effects on lipid metabolism, inflammatory responses, and liver fibrosis. Metabolic stress caused by lipid accumulation, oxidative damage, mitochondrial dysfunction, and gut-liver axis imbalance can activate NLRP3 signaling in the liver. The activated inflammasome promotes the release of inflammatory cytokines, which affects hepatocytes, immune cells, and hepatic stellate cells, contributing to continuous liver injury. Understanding the role of NLRP3 inflammasome provides a clearer view of how metabolic disorders are connected with chronic liver inflammation. Regulation of NLRP3 activity may offer new possibilities for MASLD treatment, but further studies are needed to clarify its safety, effectiveness, and clinical application.

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