

NLRP3 inflammasome as a novel therapeutic target for heart failure

ABSTRACT

Heart failure (HF) is a leading cause of mortality worldwide. The pathogenesis of HF is complex and has not yet been fully elucidated, which has slowed drug development and long-term treatments. Inflammasome-mediated responses occur during the progression of HF. It has been reported that energy metabolism and metabolites of intestinal flora are also involved in the process of HF, and they interact with each other to promote the progression of HF. NLR family pyrin domain containing 3 (NLRP3) inflammasome may be a key target in the relationship between inflammation-mediated energy metabolism and metabolites of intestinal flora. Elucidating the relationship among the above three factors may help to identify new molecular targets for the prevention and treatment of HF and ultimately affect the course of HF. In this study, we systematically summarize evidence regarding the relationship among NLRP3 inflammasome, energy metabolism, intestinal microflora metabolites, and inflammation, as well as highlight advantages of NLRP3 inflammasome in treating HF.

Keywords: heart failure, inflammation, NLRP3, metabolism, flora

INTRODUCTION

Heart failure (HF) is the end stage of a variety of heart diseases, which has the characteristics of high hospitalization rate and high mortality. Although the treatment of HF has made great progress, the re-hospitalization and mortality rates are still high. Therefore, there is an urgent need to identify new targets for delaying HF (1).

At present, the pathogenesis of HF has been demonstrated to include hemodynamic abnormalities, ventricular remodeling, nervous system activation, fibrosis, and inflammasome responses. However, the relationship among different pathogenic components have not been fully characterized, and most of the current treatment programs are not comprehensive in ameliorating all of these components. Patients with HF often have energy metabolism disorder, such that the reaction substrate changes from free fatty acids to glucose, which further aggravates the process of HF (2, 3). Energy metabolism is closely related to inflammasome reactions. Patients with HF often have intestinal congestion, higher permeability of the intestinal wall, and unstable composition and content of intestinal microflora (4), which can promote the release of inflammasome factors, induce inflammasome reactions (5), and ultimately accelerate the development of HF (6, 7).

Taken together, HF often consists of energy metabolism disorder and intestinal microflora metabolite disorder, accompanied by inflammasome activation, namely NLR family pyrin domain containing 3 (NLRP3) inflammasome. Therefore, it is speculated that inhibition of NLRP3 inflammasome can prevent and treat HF through modulating inflammation-related energy metabolism and intestinal microflora metabolites.

Heart failure consists of energy metabolism disorder and intestinal flora metabolite disorder

Energy metabolism disorder in heart failure

Changes in energy metabolism pathways in HF mainly involve the metabolic disorder of myocardial lipids and glucose as well as other substances, which eventually

REVIEW

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leads to ventricular remodeling. Some researchers have referred to this metabolic abnormality as myocardial metabolic remodeling (8). Ventricular remodeling is the main pathological basis of HF. Myocardial metabolic remodeling occurs earlier than ventricular remodeling, which will accelerate the process of ventricular remodeling. Therefore, the effect of improving myocardial metabolic remodeling is better than that of single-intervention ventricular remodeling (9). Wenjing et al. (10) confirmed that the metabolic remodeling of myocardial substrate in the early stage of HF is an adaptive response, and the late stage will cause the disorder of internal environment and accelerate the process of HF. Improving myocardial substrate metabolism can better protect and improve myocardial function and provide new targets and strategies for the treatment of heart failure. Noordali et al. (11) confirmed that there were significant changes in cardiac energy metabolism in patients with HF, and severe metabolic imbalance was considered to be an overall feature of HF. Therefore, we believe that energy metabolism disorder runs through HF.

The energy metabolism disorder implicated in HF involves myocardial metabolism reconstruction. With the development of HF, a decrease in capillary density decreases oxygen supply to the heart, and an increase in the load before and after the heart in the circulation intensifies myocardial energy shortage. To meet the increased energy demand in HF, the metabolic substrate of the myocardium is transformed from fatty acids to glucose (12). For the same oxygen consumption, glucose oxidation produces more ATP than does fatty acid oxidation (13). However, at the end of HF, severe hypoxia leads to a decline in insulin resistance and mitochondrial oxidation capacity. Pyruvate enters tricarboxylic acid cycle (TCA) and is reduced to lactate, which leads to severe reduction of ATP production. Meanwhile, a decrease in fatty acid β oxidation by cardiomyocytes, increase of fatty acids in the myocardium, and accumulation of lipotoxic substances, such as ceramide, aggravate the progression of HF (14). Moreover, evidence shows that energy metabolism disorder occurs in chronic HF and is accompanied by inflammation (15).

Intestinal flora metabolite disorder in HF

In recent years, it has been confirmed that cardiovascular disease (CVD) is closely related to dysfunction of intestinal microbiota. The metabolites of intestinal flora directly and/or indirectly affect changes in cardiac energy metabolism in HF. At present, the following four metabolites are most implicated; trimethylamine oxide (TMAO), short-chain fatty acids (SCFAs), bile acid, and endotoxins.

HIGHLIGHTS

- NLRP3 is the new target for the treatment of heart failure (HF).
- In this review, we investigate the role of energy metabolism disorder, inflammation, intestinal flora metabolites, and other aspects in HF.
- This study serves to provide a theoretical basis for experimental research and clinical treatment.

TMAO is a key metabolite of intestinal flora and is produced by dietary precursors containing TMA, such as phosphatidylcholine, choline, and L-carnitine. Clinical research shows that increased plasma TMAO is related to diastolic dysfunction, indicating that TMAO may affect myocardial tissue mechanics (16); this also confirms that plasma TMAO levels are more effective than are BNP levels in predicting the prognosis of HF and the rate of re-hospitalization (17).

SCFAs are another key metabolite of intestinal flora. The gut microbiota in the distal intestine promote fermentation, which usually produces SCFAs, which are the main nutrient source of the cecum and colon epithelium (18). SCFAs not only maintain stability of the intestinal barrier, but also regulate the immune system and play a defensive function against the invasion of pathogenic bacteria and harmful substances. In addition, results have shown that SCFAs can improve the prognosis of HF by inhibiting ventricular remodeling (19, 20).

Bile acid is also a key metabolite of intestinal flora. Bile acids are traditionally considered to act as emulsifiers for the gut to absorb fat and fat-soluble vitamins. Primary bile acids are usually synthesized in the liver (21). These major bile acids are usually reabsorbed (>95%). Intestinal microflora can further metabolize bile acids that have not been reabsorbed and produce secondary bile acids (22, 23). Relevant clinical studies have shown that the ratio of primary bile acid to secondary bile acid is decreased in patients with HF (24).

Endotoxins, also known as lipopolysaccharides (LPS), represent typical pathogen-related molecules, and mainly signal through toll-like receptor 4 (TLR4) to induce the expression of downstream inflammasome products (25). This effect occurs in cardiomyocytes and cardiac fibroblasts (26). There is also evidence that bacterial translocation increases during HF owing to one or more mechanisms, including changes in gastrointestinal structure and function caused by visceral congestion and host immune defense abnormalities (27). Furthermore, intestinal microbiome dysfunction, especially metabolite dysfunction, also accelerates the process of HF (28).

INTERACTION BETWEEN ENERGY METABOLISM DISORDER AND INTESTINAL METABOLITE DISORDER IN HEART FAILURE

Energy metabolism disorder induces dysfunction of intestinal flora and related metabolites

The pathogenesis of HF is complex and is accompanied by energy metabolism disorder, which causes different degrees of intestinal barrier dysfunction (25). Fatty acids can have antibacterial action or can be used as metabolic substrates by intestinal bacteria, which can affect the intestinal flora and its metabolites. The composition of intestinal flora in mice on a low-fat diet is different from that of other groups, indicating that the metabolism of fatty acids in vivo affects the composition of intestinal flora in mice (29). Studies have shown that a high-fat diet can increase intestinal permeability and induce barrier dysfunction by changing bile acid concentration (30). It can also induce intestinal flora disorder (31). Changes in microorganisms induced by a high-sug-

ar diet, including a decrease in diversity, increase in Proteus bacilli, and a decrease in pseudobacilli have common characteristics with microbial group disorders related to metabolic diseases, inflammatory bowel disease, and other human diseases (32). Therefore, energy metabolism disorder in HF leads to dysfunction of intestinal flora and related metabolites (33).

Energy metabolism disorder caused by intestinal metabolite disorder

The main metabolite disorders in the intestine consist of dysfunction of TMAO, SCFAs, and bile acids. An increased TMAO concentration will damage the oxidation of pyruvate and fatty acids in myocardial mitochondria, thus leading to energy metabolism disorder and further aggravating HF (34). Acetate is a type of SCFA. In a clinical study of SCFAs, it was found that acetate has a protective effect on hypertrophic heart (19). Bile acid, as a signaling molecule, can activate different receptors to participate in energy homeostasis and participates in the process of HF (35). In conclusion, harmful metabolites of intestinal flora are increased, and beneficial metabolites are decreased in chronic HF, which leads to energy metabolism disorder (36).

DISTURBANCES IN ENERGY METABOLISM AND INTESTINAL FLORA METABOLITES CAN ACTIVATE NLRP3 INFLAMMASOME IN HEART FAILURE

Activation of inflammasome corpuscles in NLRP3 inflammasome

The activation of NLRP3 inflammasome corpuscles induced by the binding of NLRP3 to the adaptor ASC through the interaction of pyd-pyd, and results in the aggregation of ASC into a large mottled structure (37). NLRP3 protein interacts with ASC through pyrin domain to form NLRP3-ASC-pro-caspase-1 complex, which is called NLRP3 inflammasome (38, 39). Currently, there are three commonly accepted activation pathways of NLRP3 inflammasome corpuscles:

- Potassium outflow: Excessive ATP production can activate P2X7 receptors, which increase K⁺ outflow in cells; and pannexin-1 membrane channels, which are combined with P2X7 receptors, release stimulating factors intracellularly and further activate NLRP3 corpuscles (7).
- Lysosomal damage: Macrophages exhibit endocytotic processes that sequester cholesterol crystals and silicon and can break or damage lysosomes, after which the released protease substances activate the NLRP3 inflammasome body.
- Reactive oxygen species (ROS): When the body is injured, ROS levels generally increase, which will induce thioredoxin (TRX) to separate TRX from TXNIP, which subsequently activates the inflammasome body of NLRP3 (40). NLRP3-mediated inflammation activated by the above mechanism increases the secretion of downstream inflammasome factors, damages cells, and induces pyroptosis, which exacerbates inflammasome responses (41) (Fig. 1 and 2).

Energy metabolism disorder activates NLRP3 inflammasome corpuscles in heart failure

From the perspective of energy metabolism in HF, fatty acids and glycolysis as well as other energy metabolism pathways activate the NLRP3 inflammasome corpuscles through ATP and ROS (42). Saturated fatty acids, especially palmitic acid (PA), represent the most abundant fatty acid. When LPS is used to pretreat fibroblasts, it has been found that PA can induce the expression of both pro-interleukin (IL) 1 β and NLRP3 mRNA in fibroblasts, which are necessary for activating the inflammasome body of NLRP3 (43). IL-1 β is a cytokine from the IL-1 family. It has been found that pretreatment of mice with an IL-1 blocker retains systolic function and reduces contractions (44). In addition, *in vitro* studies have shown that IL-1 can affect myocardial diastolic pressure (45, 46).

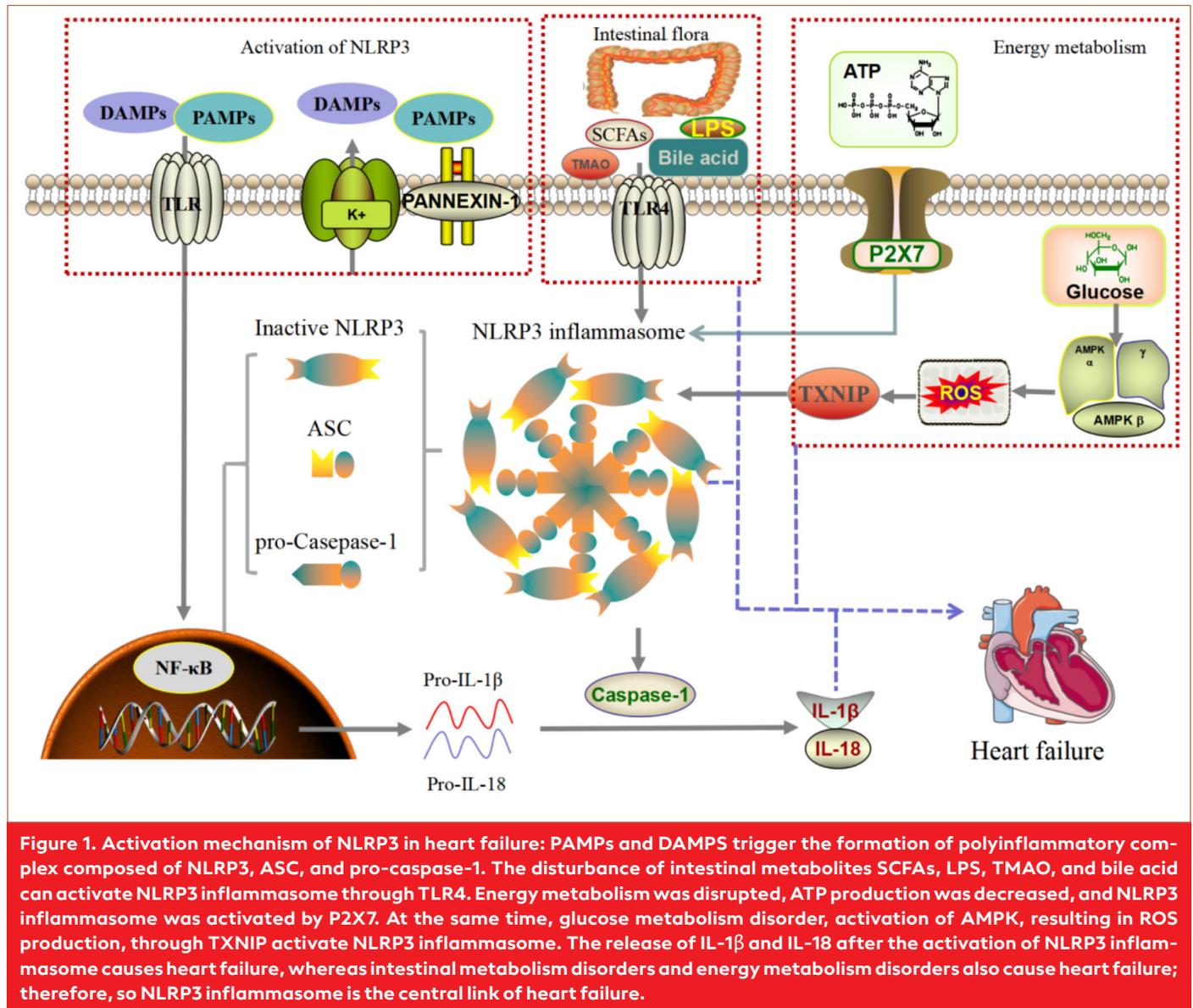
AMP-activated protein kinase (AMPK) can regulate glycolipid metabolism to improve HF via classical pathways of energy metabolism. Specifically, AMPK can inhibit activation of the NF- κ B pathway, activate the downstream NLRP3 inflammasome body, and participate in the regulation of inflammasome responses (47). This suggests that AMPK may affect HF by regulating the inflammasome corpuscles of NLRP3. ATP is the most direct energy source in an organism and can activate NLRP3 inflammasome corpuscles in cardiac fibroblasts (48). It is noteworthy that although ATP signaling can induce rapid activation of inflammasome cells in NLRP3 inflammasome, this may reflect the involvement of intermediate metabolites (49).

Energy metabolism of mitochondria: Mitochondria are important energy producing organelles that comprise the main energy sources of human cells and represent the common medium for activating NLRP3 inflammasome bodies by multiple channels (50). There is evidence that the assembly of mitochondrial DNA (mtDNA) by several mitochondrial-centered mechanisms in NLRP3 inflammasome corpuscles promotes the activation of inflammasome corpuscles (51). Mitochondrial damage induced by environmental or metabolic stress can induce mtDNA oxidation. Oxidized mtDNA can be released into the cytoplasm and combine with NLRP3 inflammasome, which leads to activation of inflammasome corpuscles and secretion of IL-1 β (52). In conclusion, mitochondria play an important role in the activation of NLRP3 inflammasome.

Disorder of intestinal flora metabolites in heart failure initiates NLRP3 inflammasome corpuscles

Trimethylamine can activate the inflammasome body of NLRP3 (53). Lipid metabolism of intestinal cells is also an important upstream signal for activating NLRP3 inflammasome corpuscles. Moon et al. (54) have demonstrated that mitochondrial uncoupling protein can stimulate macrophages to regulate the expression of caspase-1 by inducing fatty acid synthesis. Other studies have shown that decreased fatty acid synthesis can lead to decreased activity of the NLRP3 inflammasome body in macrophages and can significantly increase the survival rate of mice (55).

The mechanism of SCFAs in protecting dysfunction of the intestinal barrier is complex. Acetic acid, propionic acid,



and butyric acid are the main SCFAs near the large intestine in both humans and rodents. SCFAs can act as histone deacetylase (HDAC) inhibitor to affect the inflammasome body of NLRP3. Feng et al. (56) and other studies have shown that SCFAs inhibit the activation of NLRP3 inflammasome bodies and protect the function of the intestinal barrier. The same conclusion is obtained in dB/db mice. Yuan et al. (57) have suggested that SCFA may target the formation and activation of inflammasome corpuscles of NLRP3 to produce corresponding biological effects.

Bile acids are important mediators of intestinal microecology and NLRP3 activation. Bile acids do not activate NLRP3 inflammasome bodies under normal conditions. However, when bile acid deposits in the liver, NLRP3 inflammasome bodies are activated.

Similarly, whether dietary fiber supplementation improves intestinal inflammation also depends on changes in the axis of inflammasome corpuscles of microbial bile acid NLRP3

(58). Collectively, bile acid metabolism is related to activation of NLRP3 inflammasome.

NLRP3 INFLAMMASOME IS A KEY TARGET FOR HEART FAILURE TREATMENT

Targeted inhibition of assembly of the NLRP3 inflammasome body mitigates heart failure

Colchicine is a nonspecific inhibitor of NLRP3 inflammasome. Colchicine was initially thought to only inhibit microtubule polymerization and leukocyte exudation. As an anti-inflammasome drug, a large part of the efficacy of colchicine is related to inhibition of NLRP3 inflammasome (59). Colchicine alleviates pressure-overload HF in dogs (60) and rats (61, 62). *In vivo* and *in vitro* studies have shown that colchicine can effectively improve myocardial cell injury (63-65). Colchicine also increases calcium currents in rat cardiomyocytes (66, 67). All these results indicate that colchicine can be used to treat HF by inhibiting NLRP3. In one clinical trial, colchicine significantly reduced IL-6 concentrations compared with that of a placebo (63).

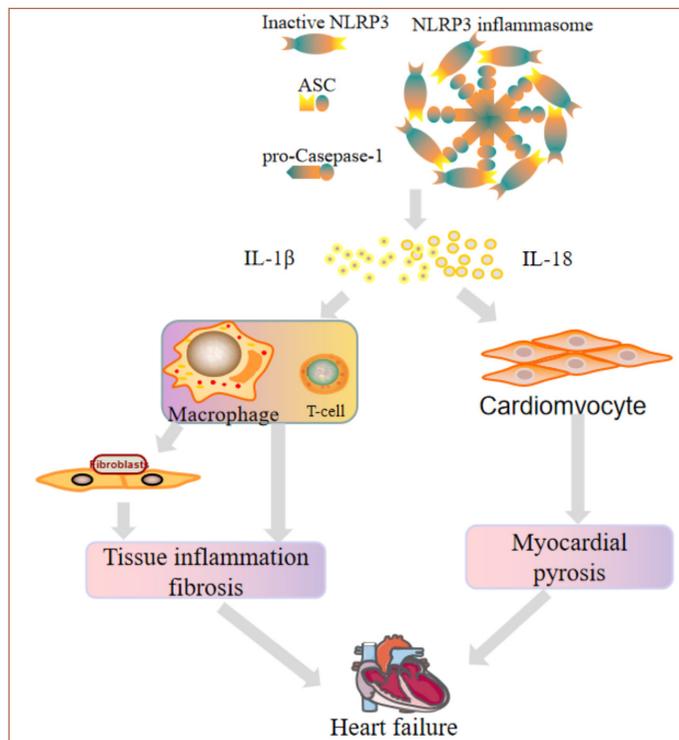


Figure 2. Heart failure caused by NLRP3 inflammasome corpuscle activation. Inflammatory factors produced by NLRP3 trigger cardiac inflammation by recruiting macrophages and subsequent T cells, leading to fibrosis, adverse cardiac remodeling, and heart failure. It can also induce cardiomyocytes scorch death and finally promote myocarditis and remodeling.

MCC950 selectively inhibits NLRP3 inflammasome (68, 69). Mcc950 can prevent diseases associated with NLRP3 inflammasome (70), such as hypertension (71) and CVD (72). Another NLRP3 inflammasome inhibitor, cy-09, can also prevent NLRP3 related diseases (73).

In HF, ASC methylation is increased, expression levels of ASC protein and mRNA are decreased, and the expression of IL-1 β is decreased (74). ASC methylation is a potential mechanism to reduce inflammation and ameliorate HF (75). Caspase-1 protein has been demonstrated to be significantly up-regulated in mice with HF, and deletion of endogenous caspase-1 can mitigate the development of HF after myocardial infarction (76). The application of ice/caspase-1 inhibitors has indicated that caspase-1 may be a therapeutic target for preventing the progression of cardiac remodeling in HF (77). Triptolide (TP) attenuates isoproterenol (ISO)-induced cardiac hypertrophy in mice (78). In addition, low dose TP can block NLRP3 inflammasome to improve myocardial fibrosis (79).

Inhibition of NLRP3 inflammasome release-effector factor mitigates heart failure

IL-1 β is an important effector of NLRP3 activation. By treating mice with recombinant IL-1 β , contractile myocardial damage can be reproduced in vivo. If a single injection of IL-1 β causes myocardial contractile dysfunction, repeated injections of IL-1 β will produce reversible non-ischemic

cardiomyopathy. Anakinra is an IL-1 blocker. A clinical follow-up of anakinra in patients with HF has shown that the incidence of adverse remodeling and HF tends to decrease after three months (80). In clinical trials on canakinumab, inhibition of IL-1 expression can reduce the incidence of CVD (81, 82).

IL-18 is another important effector of NLRP3 activation. In patients with HF, IL-18 is released from the plasma by p38 MAPK, which leads to myocardial systolic dysfunction. Blocking IL-18 with a neutralizing antibody to IL-18bp or via genetic manipulation can prevent the development of myocardial systolic dysfunction caused by IL-1 β (83). These findings suggest that blockade of IL-18 may improve myocardial systolic function in patients with HF. Atorvastatin can reduce the expression of NLRP3 inflammasome, IL-1 β , and IL-18. The effect of rosuvastatin, however, is unclear. Furthermore, statins can inhibit endothelial dysfunction (84) and ischemic reperfusion injury. However, further research is needed to confirm this finding (85).

CONCLUSION

HF is accompanied by energy metabolism disorder and intestinal microflora metabolite disorder, which can activate NLRP3 inflammasome and further aggravate the process of HF. Energy metabolism disorder and intestinal microflora metabolite disorder interact with each other, and a large number of relevant studies have reported that regulating NLRP3 inflammasome can ameliorate HF. Therefore, we propose NLRP3-inflammasome centered comprehensive prevention and treatment of HF. Future studies to determine validation of this perspective may provide new directions for the treatment of HF.

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