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NEW NLRP3 INHIBITORS IN THE TREATMENT OF ATHEROSCLEROSIS AND HEART FAILURE WITH PRESERVED EJECTION FRACTION

Gaziyeva Anastasiya Ruslanovna
A Third-Year Student at Kimyo International
University in Tashkent, Uzbekistan, Tashkent city
E-mail: gazievan068@gmail.com

Yusupjanova Shaxzoda Abdujalolovna
A Third-Year Student at Kimyo International
University in Tashkent, Uzbekistan, Tashkent City
E-mail: nargiza9111094@mail.ru

Abstract
Low-grade chronic inflammation is considered a key pathogenic mechanism underlying atherosclerosis and heart failure with preserved ejection fraction (HFpEF). The NLRP3 inflammasome—a multiprotein complex of the innate immune system that activates caspase-1, leading to the production of interleukin-1β and interleukin-18, as well as the development of pyroptosis—plays a central role in the initiation and maintenance of the inflammatory response. This review summarizes current data on the role of NLRP3 in the pathogenesis of cardiovascular diseases, including its interaction with the NF-κB signaling pathway, mitochondrial dysfunction, and oxidative stress. Experimental and early clinical data on selective NLRP3 inhibitors (MCC950, CY-09, dapansutril/OLT1177, RRx-001) are analyzed. It is shown that targeted suppression of NLRP3 can reduce residual inflammatory risk and represents a promising direction for the pathogenetic treatment of atherosclerosis and HFpEF.

Keywords: NLRP3, inflammasome, atherosclerosis, HFpEF, inflammation, interleukin-1β, inhibitors.

Introduction

Atherosclerosis and heart failure remain the leading causes of mortality and disability worldwide [1,4]. In recent decades, there has been a significant reevaluation of their pathogenesis: alongside lipid metabolism disorders, hemodynamic factors, and ischemia, a key role has come to be attributed to chronic sterile inflammation [1,3].

This concept is particularly significant for heart failure with preserved ejection fraction (HFpEF), the prevalence of which is steadily increasing, while effective treatment options remain limited [5]. Current understanding links the development of HFpEF to systemic inflammation induced by comorbid conditions such as obesity, type 2 diabetes, and hypertension [2,5]. These factors lead to endothelial dysfunction, impaired microcirculation, and myocardial remodeling [3,9]. At the center of these processes is the NLRP3 inflammasome, which acts as an integrator of metabolic and stress signals and an initiator of the inflammatory cascade [1,3].

Molecular mechanisms of NLRP3 inflammasome activation. The NLRP3 inflammasome is an intracellular multiprotein complex consisting of the sensor protein NLRP3, the adapter molecule ASC, and the effector caspase-1 [1]. Its activation occurs in two stages. In the first stage, known as priming, innate immune receptors—including Toll-like receptors—are activated, leading to the activation of the transcription factor NF-κB and increased expression of inflammasome components, as well as inactive precursors of pro-inflammatory cytokines [1]. The second stage involves the direct activation of the complex under the influence of a wide range of stimuli, among which cholesterol crystals, reactive oxygen species, disruption of ion homeostasis, and mitochondrial dysfunction are of particular importance [3,4]. The latter is accompanied by the release of mitochondrial DNA and increased oxidative stress, which further stimulates NLRP3 activation [1,2]. The formed inflammasome complex leads to the activation of caspase-1, which mediates the proteolytic conversion of pro-interleukins-1β and -18 into their active forms and initiates pyroptosis via the cleavage of gasdermin D [1].

The role of NLRP3 in the pathogenesis of atherosclerosis. Atherosclerosis is currently regarded as a chronic inflammatory disease of the vascular wall [3,4,9]. One of the key triggers for NLRP3 activation in atherosclerotic plaques is cholesterol crystals, which are engulfed by macrophages and cause damage to lysosomes, thereby initiating an inflammatory response [3]. Inflammasome activation leads to the release of interleukin-1β, which enhances the recruitment of inflammatory cells and plaque progression. Experimental studies have shown that genetic or pharmacological suppression of NLRP3 is accompanied by a reduction in the size of atherosclerotic plaques, a decrease in inflammatory infiltration, and an increase in their stability [1,3]. The clinical significance of this pathway was confirmed in the CANTOS study, in which inhibition of interleukin-1β with canakinumab led to a reduction in the incidence of cardiovascular events regardless of lipid levels [1]. These data formed the basis for the concept of residual inflammatory risk, reflecting

the contribution of inflammation to disease progression even with optimal lipid-lowering therapy.

The Role of NLRP3 in Heart Failure with Preserved Ejection Fraction. The pathogenesis of HFpEF is multifactorial and closely linked to systemic inflammation [5]. Activation of NLRP3 contributes to the development of diastolic dysfunction, myocardial fibrosis, and endothelial dysfunction [5]. Pro-inflammatory cytokines, particularly interleukin-1β, alter the mechanical properties of cardiomyocytes by acting on the titin protein, leading to increased myocardial stiffness and impaired relaxation [1,5]. In addition, inflammatory mediators stimulate the activation of fibroblasts and their transformation into myofibroblasts, accompanied by excessive collagen synthesis [2]. Inflammation of the endothelium of coronary microvessels also plays an important role, leading to a decrease in nitric oxide bioavailability and impaired myocardial perfusion [2,3]. Metabolic abnormalities characteristic of patients with HFpEF, including hyperglycemia and lipotoxicity, enhance NLRP3 activation through mechanisms of oxidative stress and mitochondrial dysfunction, forming a vicious pathological cycle [2,4].

Pharmacological inhibition of NLRP3. The development of selective NLRP3 inhibitors represents one of the most promising areas of modern cardiovascular pharmacology. The first extensively studied inhibitor, MCC950, demonstrated high efficacy in experimental models by inhibiting inflammasome assembly and reducing interleukin-1β production. However, its further clinical development was limited by identified idiosyncratic hepatotoxicity [6]. Another promising compound is CY-09, which binds to the ATP-binding domain of NLRP3, preventing its activation [3]. Preclinical studies have shown that CY-09 is capable of reducing inflammation and slowing the progression of atherosclerosis. Of particular interest is dapansutril (OLT1177)—an oral selective NLRP3 inhibitor that suppresses inflammasome activation, leading to a subsequent reduction in caspase-1 activity [2]. The drug has demonstrated a favorable safety profile in clinical trials for inflammatory diseases and is currently being studied in patients with cardiovascular conditions, including HFpEF. The compound RRx-001, originally developed for oncology, also exhibits the ability to inhibit NLRP3 through redox modulation and covalent protein modification [2]. The availability of clinical data on its safety makes it a promising candidate for repositioning in cardiology.

Clinical implications. Targeted inhibition of NLRP3 opens up new possibilities for reducing residual inflammatory risk in patients with cardiovascular disease [1,2]. Unlike traditional approaches, which are primarily aimed at correcting lipid and hemodynamic abnormalities, NLRP3 inhibitors act on the fundamental mechanisms

of inflammation. Their use as part of combination therapy alongside statins, renin-angiotensin-aldosterone system inhibitors, and sodium-glucose cotransporter 2 inhibitors appears promising [9]. Stratification of patients based on levels of inflammatory biomarkers may play a special role, enabling the implementation of personalized medicine principles [2]. At the same time, questions regarding the safety of long-term suppression of innate immunity remain unresolved, particularly regarding the risk of infectious complications, which necessitates large-scale randomized trials.

Conclusion

The NLRP3 inflammasome plays a key role in the pathogenesis of atherosclerosis and heart failure with preserved ejection fraction, linking metabolic abnormalities, inflammation, and structural tissue remodeling. Selective NLRP3 inhibitors represent a promising class of drugs capable of targeting the fundamental mechanisms of the disease and reducing residual inflammatory risk [1,2,3,5]. The results of ongoing clinical trials will determine their place in modern cardiology and the possibility of widespread use in clinical practice.

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