VASCULAR INFLAMMATION IN ATHEROSCLEROSIS: THE MECHANISMS OF THE NLRP3 INFLAMMASOME IN THE GENESIS OF ATHEROSCLEROTIC PLAQUE INSTABILITY

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Abstract: Introduction: Atherosclerosis is a chronic inflammatory disease characterized by lipid accumulation and inflammatory cell infiltration within the arterial wall, representing the leading cause of cardiovascular diseases worldwide. Recent evidence has demonstrated that the NLRP3 inflammasome plays a central role in the inflammatory response responsible for atherosclerosis progression and atherosclerotic plaque instability. Objective: To analyze the mechanisms by which the NLRP3 inflammasome contributes to vascular inflammation and the development of unstable atherosclerotic plaques, as well as to discuss its potential as a therapeutic target. Methods: This is a descriptive, exploratory, qualitative narrative literature review conducted using PubMed/ MEDLINE, Scopus, Web of Science, and the Virtual Health Library (VHL). Controlled descriptors related to atherosclerosis, the NLRP3 inflammasome, and vascular inflammation were employed. After applying the eligibility criteria, 20 studies were included in the qualitative analysis. Results and discussion: The selected studies demonstrated that activation of the NLRP3 inflammasome by cholesterol crystals, reactive oxygen species, and other danger signals promotes caspase-1 activation and the release of IL-1β and IL-18, amplifying vascular inflammation. This process contributes to foam cell formation, extracellular matrix degradation, fibrous cap thinning, and plaque instability. Furthermore, experimental and clinical evidence indicates that anti-inflammatory therapies targeting the NLRP3 pathway reduce cardiovascular events, highlighting the translational potential of this therapeutic strategy. Conclusion: The NLRP3 inflammasome is a key mediator of atherosclerosis progression and plaque instability, representing both a promising biomarker and a potential therapeutic target for preventing cardiovascular complications. Further studies are needed to optimize diagnostic and therapeutic approaches aimed at modulating vascular inflammation.

Keywords: Atherosclerosis; Inflammation; NLRP3 Inflammasome.

INTRODUCTION

Atherosclerosis is a chronic inflammatory disease of the arterial wall characterized by the progressive accumulation of lipids, inflammatory cells, and fibrous tissue in the vascular intima, culminating in the formation of atherosclerotic plaques that can progress to luminal stenosis, rupture, and thrombosis. It is the main pathophysiological basis of ischemic cardiovascular diseases, including acute myocardial infarction and stroke, responsible for high morbidity and mortality worldwide. In addition to the classic risk factors, such as dyslipidemia, hypertension, diabetes mellitus, and smoking, recent studies show that immunoinflammatory mechanisms play a central role in both the initiation and progression of atherosclerotic disease (HERRINGTON et al., 2016).

In recent decades, the NLRP3 (NOD-like receptor family pyrin domain containing 3) inflammasome has emerged as one of the main regulators of the inflammatory response involved in atherogenesis. This multiprotein complex is activated by several danger signals present in the vascular microenvironment, including cholesterol crystals, reactive oxygen species, and products derived from injured cells, promoting the activation of caspase-1 and the subsequent maturation of the pro-inflammatory cytokines interleukin-1β (IL-1β) and interleukin-18 (IL-18). The amplification of this inflammatory cascade favors the recruitment of immune cells, intensifies endothelial dysfunction, and perpetuates inflammation of the arterial wall (DUEWELL et al., 2010; GREBE; HOSS; LATZ, 2018).

Persistent activation of the NLRP3 inflammasome is closely related to the evolution of atherosclerotic plaques to a vulnerable phenotype. The continuous production of inflammatory mediators stimulates macrophage infiltration, foamy cell formation, extracellular matrix degradation by metalloproteinases, and vascular smooth muscle cell apoptosis, culminating in the thinning of the fibrous cap and increased susceptibility to plaque rupture. These events are fundamental mechanisms for the triggering of acute coronary syndromes, reinforcing the role of inflammation as a determining element of atherosclerotic instability (BALDRIGHI; MALLAT; LI, 2017).

At the same time, recent advances have directed efforts towards the development of therapeutic strategies capable of selectively modulating the NLRP3 inflammasome and its inflammatory mediators. The pharmacological inhibition of this pathway demonstrates potential to reduce the progression of atherosclerosis and minimize cardiovascular events, consolidating the inflammasome as an important therapeutic target in cardiovascular medicine. Although several molecular mechanisms have already been described, there are still gaps regarding the integration between NLRP3 activation, vascular inflammation, and the processes responsible for atherosclerotic plaque instability, justifying the need for updated reviews on the subject (JABBOUR; KUMAR; HASSAN, 2023; KATSIMARDOS; PAPAIOANNOU; KARAMITSOS, 2025).

In this context, the present study aims to analyze the mechanisms by which the NLRP3 inflammasome contributes to vascular inflammation and to the genesis of atherosclerotic plaque instability. As specific objectives, we seek to describe the main mechanisms of activation of the NLRP3 inflammasome in atherosclerosis, to understand its interaction with the inflammatory pathways involved in the progression of the disease and to discuss the therapeutic perspectives related to the modulation of this molecular pathway. Thus, the following guiding question is established: how does the activation of the NLRP3 inflammasome participate in vascular inflammation and contribute to the development of atherosclerotic plaque instability, favoring the occurrence of acute cardiovascular events?

MATERIAL AND METHODS

The present study consists of a narrative review of the literature, of a descriptive, exploratory and qualitative nature, developed with the objective of gathering and analyzing the main scientific evidence about the role of the NLRP3 inflammasome in vascular inflammation and in the genesis of atherosclerotic plaque instability.

The bibliographic search was carried out between June and July 2026, using the PubMed/

MEDLINE, Scopus, Web of Science, and Virtual Health Library (VHL) databases, as they concentrate high-impact journals in the area of biomedical and cardiovascular sciences. To elaborate the search strategy, controlled descriptors from the Medical Subject Headings (MeSH) and Health Sciences Descriptors (DeCS) vocabularies were used, combined by Boolean operators (AND and OR). The main terms used were: "Atherosclerosis", "NLRP3 Inflammasome", "Vascular Inflammation", "Atherosclerotic Plaque", "Plaque Instability", "Inflammation", "Interleukin-1 beta", "Cholesterol Crystals", "Macrophages" and "Cardiovascular Diseases", as well as their counterparts in Portuguese.

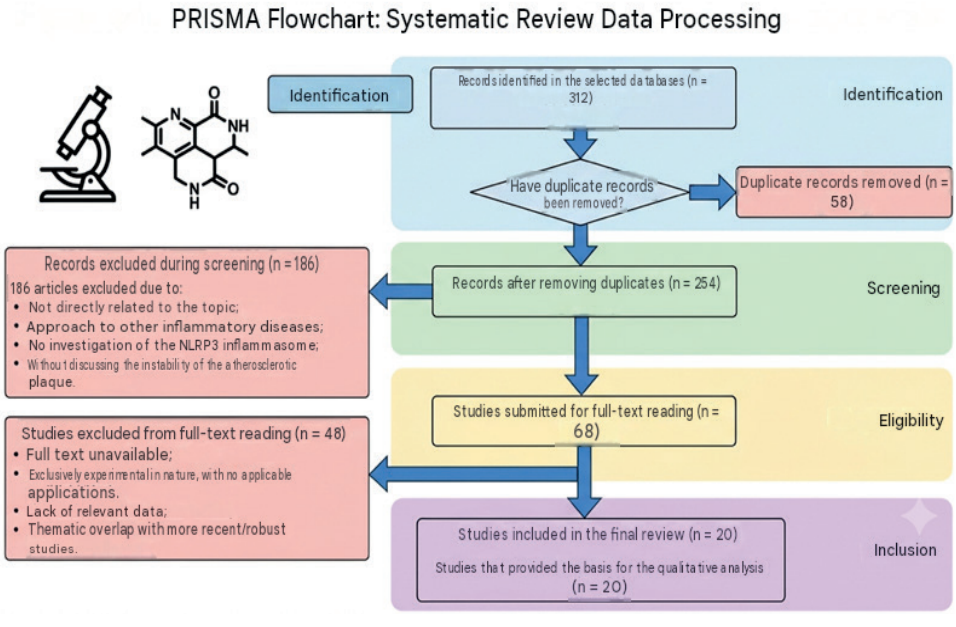
Original articles, systematic reviews, meta-analyses, clinical trials, experimental studies, and narrative reviews published in Portuguese or English, between 2015 and 2026, available in full, and that directly addressed the participation of the NLRP3 inflammasome in the inflammatory mechanisms of atherosclerosis, in the progression of atherosclerotic plaque, or in therapeutic strategies related to the modulation of this molecular pathway, were considered eligible. Duplicate studies, conference abstracts, letters to the editor, editorials, book chapters, dissertations, theses, and papers that did not have a direct relationship with the proposed theme were excluded.

The selection process of the studies was carried out in successive stages. Initially, the records were identified in the databases and duplicates were removed. Next, the titles and abstracts were read to assess the thematic relevance, and studies that did not meet the previously established eligibility criteria were excluded. Potentially relevant articles were submitted to the full text reading, allowing the confirmation of eligibility and the composition of the final review sample.

In the search process, 312 records were identified in the selected databases. After the removal of 58 duplicate studies, 254 publications remained for screening by titles and abstracts. At this stage, 186 articles were excluded because they were not directly related to the topic, addressed other inflammatory diseases, did not investigate the NLRP3 inflammasome, or did not discuss mechanisms of atherosclerotic plaque instability. Thus, 68 studies were submitted to reading in full. Of these, 48 publications were excluded because they did not meet the eligibility criteria, including unavailability of the full text, exclusively experimental character with no applicability to the purpose of the review,

absence of relevant data, or thematic overlap with more recent and robust studies. At the end of the selection process, 20 articles made up the final sample of the review and supported the qualitative analysis of the scientific evidence. This process is illustrated in Figure 1 below.

Figure 1: Processing of the selected studies.



Source: authors, 2026

After selection, the included studies were submitted to a systematic process of information extraction and organization. For each publication, the following were recorded: authors, year of publication, country of origin, methodological design, study objective, population characteristics or experimental model, main molecular mechanisms investigated, inflammatory biomarkers evaluated, NLRP3 inflammasome activation pathways, main results and conclusions related to vascular inflammation, atherosclerosis progression, and plaque instability.

The processing of the evidence occurred through qualitative and interpretative analysis, using thematic analysis technique. Initially, the studies were grouped according to their axes of investigation,

including: NLRP3 inflammasome activation mechanisms; participation of the IL-1β/IL-18 pathway in the inflammatory response; role of cholesterol crystals and macrophages in atherogenesis; vascular remodeling and atherosclerotic plaque instability; and therapeutic perspectives aimed at inhibiting the inflammasome. Subsequently, a critical comparison of the findings was carried out, identifying convergences, divergences and gaps in knowledge, allowing an integrated synthesis of the available evidence.

As this is a research based exclusively on secondary data from published scientific literature, without direct involvement of human beings or use of identifiable information, this study does not require consideration by the Research Ethics Committee, according to the guidelines of Resolution No. 510, of April 7, 2016, of the National Health Council.

RESULTS AND DISCUSSION

The analysis of the studies showed a consensus that atherosclerosis should be understood as a chronic inflammatory disease, in which the innate immune response plays a determining role from the formation of the fatty stretch mark to the rupture of the atherosclerotic plaque. In this context, the NLRP3 inflammasome stands out as one of the main mediators of vascular inflammation, functioning as an intracellular sensor capable of recognizing signs of damage and triggering the activation of caspase-1, culminating in the release of the pro-inflammatory cytokines IL-1β and IL-18. This process establishes a cycle of persistent inflammation that favors the progression of atherosclerotic lesion and vascular remodeling (SWANSON; DENG; TING, 2019; LIBBY, 2022; KATSIMARDOS; PAPAIOANNOU; KARAMITSOS, 2025).

Studies have shown that multiple stimuli participate in the activation of the NLRP3 inflammasome in the vascular environment. Cholesterol crystals, modified lipoproteins, reactive oxygen species, cell necrosis products, and mitochondrial alterations promote oligomerization of the inflammasomal complex, favoring an intense local inflammatory response. These mechanisms

represent a link between lipid metabolism and innate immunity, explaining why lipid accumulation alone is not sufficient to justify the evolution of atherosclerosis without the participation of inflammation (KUBO; TAKAHASHI, 2020; LIAQAT et al., 2020; SWANSON; DENG; TING, 2019).

Another recurring aspect among the publications refers to the participation of macrophages in the maintenance of vascular inflammation. After internalization of oxidized low-density lipoproteins (LDL-ox), these cells differentiate into foamy cells and start producing inflammatory mediators that perpetuate NLRP3 activation. At the same time, there is an increase in the expression of IL-1β, IL-18, and other cytokines capable of amplifying leukocyte recruitment and stimulating new inflammatory cells, favoring the expansion of atherosclerotic plaque and increasing its structural complexity (TAKAHASHI, 2017; LIBBY, 2021; LIBBY; BORÉN; HANSSON, 2021).

The stability of atherosclerotic plaque depends on the balance between repairing and inflammatory mechanisms. The studies analyzed demonstrate that persistent inflammasome activation promotes extracellular matrix degradation through the induction of metalloproteinases, apoptosis of vascular smooth muscle cells, and increase of the necrotic lipid nucleus. Consequently, there is thinning of the fibrous layer, reduction of the mechanical resistance of the plaque and greater predisposition to rupture, an event directly related to the development of acute myocardial infarction and ischemic stroke. These findings reinforce that the intensity of inflammation is a more relevant factor for plaque vulnerability than the isolated degree of arterial stenosis (LIBBY, 2022; SIANOS; KOUTROUBAKIS, 2023; KHAIR et al., 2024).

The systematic review conducted by Khair et al. (2024) consolidated evidence from experimental and clinical studies demonstrating a consistent association between higher NLRP3 inflammasome activity and progression of atherosclerosis, corroborating observations previously described by Takahashi (2017) and Kubo and Takahashi (2020). Taken together, these investigations indicate that individuals with greater activation of this pathway have a greater intensity of the vascular inflammatory response, greater formation of vulnerable plaques, and an increased risk of major cardiovascular events.

In recent years, the development of therapies targeting inflammation modulation has significantly modified the understanding of atherosclerosis treatment. Ridker (2016) proposed a change in the therapeutic paradigm by demonstrating that the selective reduction of inflammation, regardless of lipid levels, could represent an effective strategy for cardiovascular prevention. This hypothesis was later confirmed by the CANTOS study, in which IL-1β blockade by canakinumab significantly reduced the incidence of recurrent cardiovascular events, consolidating the clinical importance of the inflammatory pathway mediated by the NLRP3 inflammasome (RIDKER et al., 2017).

Similar results were observed with low-dose colchicine. The COLCOT clinical trial demonstrated a significant reduction in cardiovascular events after acute myocardial infarction in patients treated with colchicine, a drug that exerts an inhibitory effect on different components of the inflammatory response, including the activation of the NLRP3 inflammasome. These findings reinforce that pharmacological control of inflammation represents a complementary approach to traditional lipid-lowering therapy, expanding the therapeutic possibilities for patients with established atherosclerosis (TARDIF et al., 2019).

In addition to the direct inhibition of the inflammasome, new molecular strategies have been investigated. Recent studies highlight the regulatory role of microRNAs, long non-coding RNAs, and epigenetic mechanisms in modulating NLRP3 expression, opening perspectives for more specific therapies with a lower risk of systemic immunosuppression. Ryan, O'Neill, and Freeman (2024) demonstrate that epigenetic modifications directly influence the intensity of the inflammatory response, while Zhang et al. (2023) describe the therapeutic potential of non-coding RNAs as regulators of inflammasome activation, configuring one of the main lines of translational research today.

Despite the advances obtained, important challenges persist for the clinical incorporation of these strategies. The heterogeneity of the inflammatory response among individuals, the multiplicity of pathways involved in NLRP3 activation, and the need for biomarkers capable of identifying patients with greater therapeutic benefit still limit the routine application of these interventions. Recent reviews highlight that the future of atherosclerosis treatment should involve personalized approaches,

integrating inflammatory markers, genetic profiling, and molecular characteristics of atherosclerotic plaque to target specific therapies and increase clinical efficacy (SIANOS; KOUTROUBAKIS, 2023; KATSIMARDOS; PAPAIOANNOU; KARAMITSOS, 2025).

Taken together, the analyzed evidence demonstrates that the NLRP3 inflammasome is one of the main elements responsible for the connection between lipid metabolism, innate immunity and vascular inflammation. Its participation in the activation of pro-inflammatory cytokines, cell recruitment, vascular remodeling, and atherosclerotic plaque destabilization consolidates it as an important biomarker and therapeutic target for the prevention of cardiovascular events. The integration of knowledge from experimental studies, systematic reviews, and clinical trials indicates that the therapeutic direction of this pathway represents one of the most promising prospects for translational cardiology in the coming decades (LIBBY, 2021; LIBBY; BORÉN; HANSSON, 2021; KHAIR et al., 2024; KATSIMARDOS; PAPAIOANNOU; KARAMITSOS, 2025).

FINAL CONSIDERATIONS

The present review showed that the NLRP3 inflammasome plays a central role in the pathophysiology of atherosclerosis, acting as an important link between lipid metabolism, innate immunity and vascular inflammation. The persistent activation of this complex promotes the production of pro-inflammatory cytokines, intensifies the local immune response, and favors processes such as the formation of foamy cells, degradation of the extracellular matrix, apoptosis of smooth muscle cells, and thinning of the fibrous cap, events that culminate in atherosclerotic plaque instability and increase the risk of acute cardiovascular events.

The studies analyzed also demonstrated that the understanding of atherosclerosis goes beyond the traditional concept of disease resulting exclusively from lipid accumulation, consolidating inflammation as a determining component for both the progression and vulnerability of plaques. In this scenario, the NLRP3 inflammasome pathway emerges as one of the main targets for innovative

therapeutic interventions, supported by evidence from experimental studies, systematic reviews, and clinical trials that demonstrate benefits of modulation of the inflammatory response in reducing cardiovascular events.

Although important advances have been achieved, challenges remain related to the identification of biomarkers capable of selecting patients with greater inflammatory activity, understanding the interactions between the different regulatory mechanisms of the inflammasome, and developing more specific, effective, and safe therapies. In addition, the influence of genetic, epigenetic, and non-coding RNA factors represents a promising field for future investigations.

Thus, it is concluded that the NLRP3 inflammasome is a fundamental component in the genesis of atherosclerotic plaque instability, representing not only an important marker of vascular inflammatory activity, but also a potential therapeutic target for the prevention of cardiovascular complications. It is expected that new clinical and translational research will contribute to the development of personalized treatment strategies, capable of integrating inflammation control with conventional therapies, promoting better clinical outcomes and reducing the high burden of atherosclerotic diseases in the population.

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