

NLRP3 INFLAMMASOME ACTIVATION AND NEUTROPHIL EXTRACELLULAR TRAPS (NETS) IN CARDIOVASCULAR DISEASE: MECHANISMS LINKING INFLAMMATION, THROMBOSIS, AND VASCULAR INJURY

Isabelly Assmann Bueno

João Pedro Diniz Freire¹ Ricardo de Alvares Goulart¹ Enzo Pereira de Lima¹ Marcelo Dib Bechara¹
Sandra M. Barbalho^{1 2}

RESUMO

Introduction: Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide and are increasingly recognized as complex disorders driven by chronic low-grade inflammation and immune- metabolic dysregulation. Beyond traditional risk factors, such as dyslipidemia and hypertension, growing evidence highlights the central role of innate immune activation in the initiation and progression of vascular injury. In this context, the NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome has emerged as a critical intracellular sensor of metabolic stress signals, including oxidized lipids, cholesterol crystals, and reactive oxygen species (ROS). Its activation leads to the maturation and release of pro-inflammatory cytokines, amplifying vascular inflammation. In parallel, neutrophil extracellular traps (NETs), composed of chromatin fibers and granular proteins, have been implicated in endothelial dysfunction, thrombosis, and plaque destabilization. The interaction between these pathways represents a novel mechanistic link connecting inflammation, oxidative stress, and thrombotic events in CVD. **Objective:** The aim of this review is to investigate the role of NLRP3 inflammasome activation and NET formation in the pathophysiology of cardiovascular diseases, focusing on their contribution to inflammation, endothelial dysfunction, and thrombosis.

Methods: This narrative review was based on a structured search in PubMed/MEDLINE and Web of Science (2021-2026). The keywords included “NLRP3 inflammasome,” “neutrophil extracellular traps”, NETs,” “atherosclerosis,” and “cardiovascular disease.” Relevant original studies and reviews were selected, and data were qualitatively synthesized. **Results:** Activation of the NLRP3 inflammasome is primarily driven by metabolic and oxidative stress signals that promote mitochondrial dysfunction and increased ROS production, leading to caspase-1 activation and subsequent release of Interleukin (IL)-1 β and IL-18. These cytokines amplify endothelial activation, leukocyte recruitment, and vascular inflammation, contributing to plaque progression and instability. Concurrently, NETs released by activated neutrophils act as pro-thrombotic and pro-inflammatory structures, facilitating platelet adhesion, coagulation cascade activation, and endothelial damage. Importantly, recent evidence suggests a bidirectional crosstalk between NETs and NLRP3 signaling, in which NET-derived components can further activate the inflammasome, while NLRP3 activation enhances neutrophil priming and NETosis. This self-amplifying loop promotes persistent inflammation and atherothrombosis. Additionally, these processes are closely linked to redox imbalance and impaired nitric oxide bioavailability, further exacerbating vascular dysfunction. Understanding these integrated pathways provides new insights into residual inflammatory risk and identifies potential molecular targets for therapeutic intervention..

Conclusion: The interaction between NLRP3 inflammasome and NETs represents a critical axis in cardiovascular pathology, integrating inflammation, oxidative stress, and thrombosis. Targeting these pathways may offer novel therapeutic strategies to reduce residual cardiovascular risk.

Palavras-chave: NLRP3 Inflammasome NETs Atherosclerosis Cardiovascular Disease Inflammation Thrombosis Oxidative Stress.

