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Endoplasmic Reticulum Stress, Inflammation, Oxidative Stress and Neutrophil Extracellular Traps in Cardiovascular Diseases

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Abstract

The aim of this work is to summarize the understanding of the interrelated roles of endoplasmic reticulum (ER) stress, oxidative stress & inflammation in cardiovascular diseases. Insults interfering with ER function lead to the accumulation of unfolded & misfolded proteins in the ER. An excess of proteins folding in the ER is known as ER stress. This condition initiates the unfolded protein response (UPR). When the UPR fails to control the level of unfolded & misfolded proteins, ER-initiated apoptotic signalling is induced. Moreover, the role of the protective nuclear erythroid-related factor 2 (Nrf2)/antioxidant-related element (ARE) & the activation of the pro-inflammatory nuclear factor-kappa B (NF-kB) are analysed. Current literature data are presented, focusing on three topics of related pathologies: atherosclerotic plaque, coronary artery disease & diabetes. Moreover, current evidence suggests the likelihood of a link between venous thromboembolism (VTE) & atherosclerosis, although they have been traditionally considered as different pathological identities. The contribution of neutrophils to human atherogenesis has been underestimated, if compared to their contribution established in VTE. This is due to the major importance attributed to macrophages in the plaque destabilization. Nevertheless, recently, the role of neutrophils in atherogenesis deserves increasing attention. In particular, neutrophil extracellular traps (NETs) are net-like chromatin fibres which are released from dying neutrophils. The death of neutrophils with NETs formation is called NETosis. During activation, neutrophils produce Reactive Oxygen Species (ROS), through the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. The main function of NETs is trapping and killing pathogens. However, NETs formation has been observed in various chronic inflammatory diseases, autoimmune diseases, vasculitis, lung diseases, cancer and VTE. Recent studies suggest that NETs formation could contribute also to atherosclerosis progression. New data report the presence of NETs in the luminal portion of human atherosclerotic vessels and coronary specimens obtained from patients after acute myocardial infarction. Programmed death mechanisms in atherosclerosis such as apoptosis, efferocytosis and also NETosis, share common features & triggers. If defective, they can lead the cells to a switch from programmed death to necrosis, resulting in the release of pro-atherogenic factors, accumulation of cell debris and progression of the disease. This talk aims to analyse the emerging role of neutrophils focusing on NETosis and oxidative stress burden in orchestrating common mechanisms in atherosclerosis & thrombosis. Diverse clinical factors, including intestinal ischemia, contribute to acute lung injury (ALI), which has up to a 40% mortality rate. During the development of lung injury an immune response is elicited that exacerbates the lung insult. Neutrophils have been well studied in mediating the pulmonary insults through an assortment of mechanisms, such as release of granule contents and production of proinflammatory cytokines due to the overactivation of complement and cytokines. In this study, we found that enhanced endoplasmic reticulum (ER) stress was observed in infiltrated neutrophils in the early stage of an ALI mice model. In neutrophils, complement 5a (C5a) inspires strong ER stress through inositol-requiring kinase 1a and, to a less extent, the protein kinase R–like ER kinase signaling pathway. The granule release induced by C5a was ER stress mediated. Knowkdown of X-box–binding protein 1, a downstream signaling molecule of inositol-requiring kinase 1a, impaired granule release, based on myeloperoxidase production. Further analysis revealed that C5a induced ER stress by binding to C5a receptor in neutrophils. Using xbpf/f MRP8-cre mice in which X-box–binding protein 1 is deficient specifically in neutrophils and ER stress is deprived, we confirmed that ER stress in neutrophils was required for granule release in vivo and led to ALI, whereas dampening ER stress in neutrophils

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substantially alleviated ALI. Taken together, our results demonstrated that C5a receptor–mediated ER stress induced granule release in neutrophils, contributing to the development of ALI. This novel mechanism suggests a new potential therapeutic target in autophagy regulation for ALI. Neutrophil extracellular traps (NETs) are formed by decondensed chromatin, histones, and neutrophil granular proteins and have a role in entrapping microbial pathogens. NETs, however, have pro-thrombotic properties by stimulating fibrin deposition, and increased NET levels correlate with larger infarct size and predict major adverse cardiovascular (CV) events. NETs have been involved also in the pathogenesis of diabetes, as high glucose levels were found to induce NETosis. Accordingly, NETs have been described as drivers of diabetic complications, such as diabetic wound and diabetic retinopathy. Inflammasomes are macromolecular structures involved in the release of pro-inflammatory mediators, such as interleukin-1, which is a key mediator in CV diseases. A crosstalk between the inflammasome and NETs is known for some rheumatologic diseases, while this link is still under investigation and not completely understood in CV diseases. In this review, we summarized the most recent updates about the role of NETs in acute myocardial infarction and metabolic diseases and provided an overview on the relationship between NET and inflammasome activities in rheumatologic diseases, speculating a possible link between these two entities also in CV diseases.

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