BRUNO BUCHHOLZ

Role of Neutrophils in Vascular Inflammation and Hyperlipidemia. New Mechanisms

Osaka M, Deushi M, Aoyama J, Funakoshi T, Ishigami A, Yoshida M. High-Fat Diet Enhances Neutrophil Adhesion in LDLR-Null Mice Via Hypercitrullination of Histone H3. **JACC Basic Transl Sci. 2021;6(6):507-23. http://dx.doi.org10.1016/j.jacbts.2021.04.002.**

Excess fat intake can lead to hyperlipidemia, and both are risk factors for the development of atherosclerotic disease. Experimental and clinical evidence demonstrate that vascular inflammation is the main pathophysiological mechanism that causes atherosclerosis and is strongly associated with a high-fat diet (HFD) and dyslipidemia. Neutrophils are key players in acute inflammatory processes, associated with their activation and adhesion to the arterial vascular endothelium. Recent studies suggest that in HFD-induced vascular inflammation, neutrophil activation has a pivotal role in the machinery that links acute with chronic inflammation. However, the intimate mechanisms that produce neutrophil activation and their participation in the vascular atherosclerotic lesion are not fully known.

In this work, Osaka et al. studied the mechanisms producing neutrophil contribution to HFD-induced vascular inflammation in a genetically-modified mouse model not expressing the low-density lipoprotein receptor (LDLR-/-). Four weeks after being fed a HFD diet, LDLR-/- mice showed a significant increase of neutrophil adhesion to the femoral artery endothelium, studied by intravital microscopy. In turn, the HFD induces neutrophil histone H3 citrullination in LDLR-/- mice via induction of chemokine ligand 1 (CXCL1) in the blood. Citrullination, that is the conversion of arginine into citrulline, is mediated by peptidyl arginine deaminase 4 (PAD4), which results in chromatin decondensation. It is known that histone hypercitrullination is involved in neutrophil extracellular trap (NET) formation, an inflammation activating mechanism in antimicrobial defenses. Therefore, the authors assume that NET development could contribute to HFD-induced vascular inflammation in stages preceding atherosclerosis. Pemafibrate administration reduced total cholesterol and triglyceride increase by HFD, decreasing neutrophil adhesion and histone H3 citrullination through CXCL1 reduction. Histone citrullination inhibition reversed neutrophil adhesion both in in vitro and in vivo tests.

The study by Osaka et al. shows once again the importance of neutrophils in vascular inflammation induced by a HFD, even in stages prior to the development of lipid plaques. The authors convincingly report that the administration of an already available drug, as pemafibrate, not only decreases lipid levels, but also has vascular anti-inflammatory effects by reducing CXCL1 lipid induction and the consequent citrullination of neutrophil histones through PAD4. They consider that this pathway is a new mechanism that could facilitate the transition of acute to chronic inflammation in arterial atherosclerotic disease, with the limitation that the experimental model was only extended to a 4-week study, which is insufficient to develop lipid plaques.

Use of monoclonal anti-CXCL1 antibodies or antagonists of its CXCR2 receptor has demonstrated efficiency in reducing the inflammatory response in chronic diseases, as rheumatoid arthritis. This emphasizes the importance of Osaka et al.'s finding on the identification of CXCL1 specificity in neutrophil activation and endothelial adhesion in response to high fat intake, as an early mechanism that could lead to atherosclerotic plaque formation. Consequently, the histone citrullination pathway as a mechanism of neutrophil adhesion could open new opportunities of therapeutic research to prevent or delay atherosclerosis development.