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# Macrophages in atherosclerosis; the good, the bad and the foamy?

Atherosclerosis is a chronic inflammatory condition in which arteries are narrowed due to the deposition of plaque material to the artery walls. This narrowing can give rise to other cardiovascular events like thrombosis or a stroke. One of the risk factors for this disease are high levels of cholesterol in the blood due to unhealthy eating behavior or caused by a genetic background that causes stress in the artery walls. Macrophages, a specific type of immune cells, can take up this cholesterol and hereby become lipid-laden cells with a foamy appearance. These foamy macrophages contribute to all stages of the disease. For long it has been thought that foamy macrophages are the main contributors to the chronic inflammatory responses in plaques.

Kim and colleagues now show that foamy plaque macrophages are less inflammatory than their non-foamy counterparts (*Circulation Research, 2018*). This reduced level of inflammation in foamy macrophages had been suggested before by Spann and colleagues (*Cell, 2012*). They uncovered a desmosterol-mediated activation of LXR and subsequent reduction of inflammatory responses in foam cells, but also suggested that there was another parallel mechanism involved that still had to be researched.

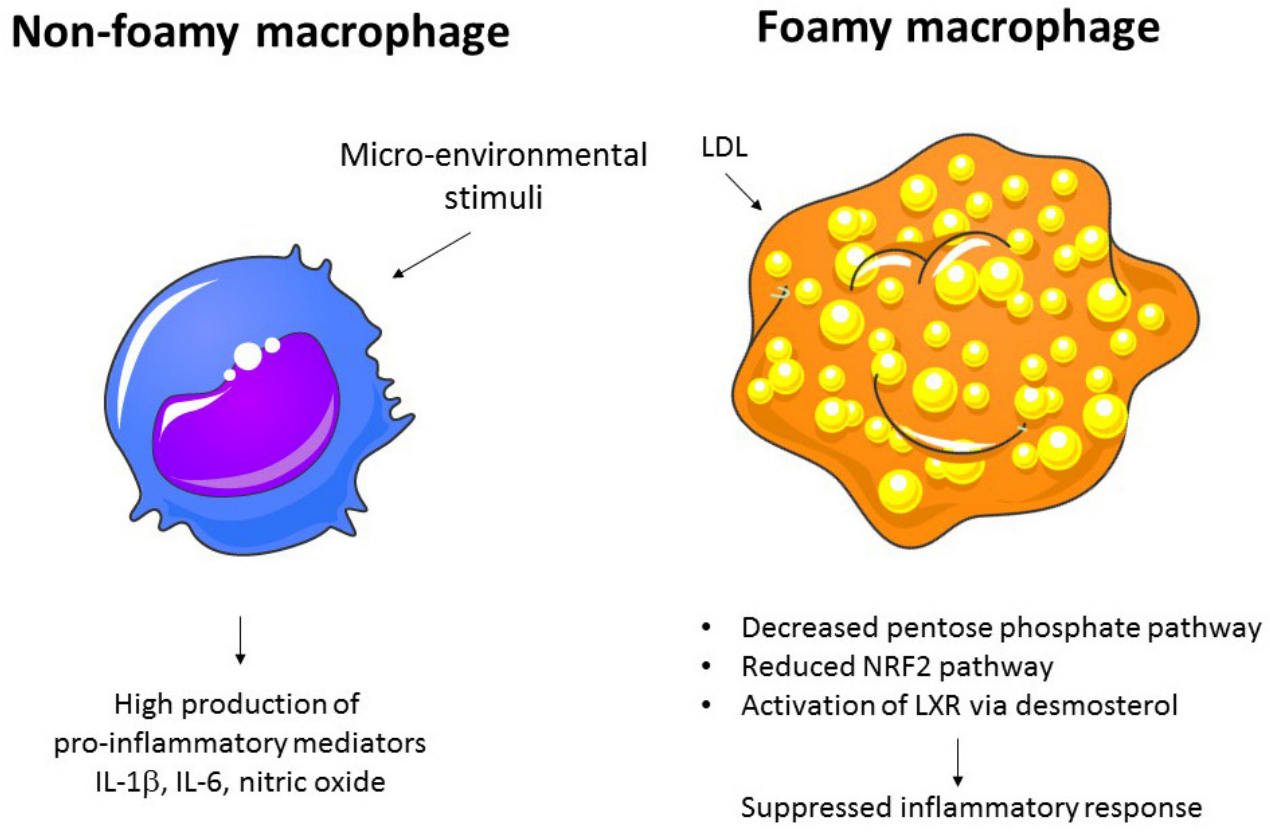


Fig. 1. Non-foamy rather than foamy macrophages are the cells that drive inflammation in atherosclerotic plaques. Metabolic rewiring in foamy macrophages suppressed inflammatory responses via distinct mechanisms.

We now discovered such a mechanism and published those findings in *Cell Reports*. The main aim of our project was to study if and how systemic metabolic changes influence the macrophage's intracellular metabolism and function. Patients with familial hypercholesterolemia display systemic metabolic changes due to a genetic disorder in cholesterol metabolism. Therefore, these patients cope with high cholesterol levels and herewith with an increased risk for the development of cardiovascular diseases. In the past, researchers have studied those patients and extensive knowledge about their white blood cell gene expression profiles was available in a database. We used this database to get a first insight on how systemic changes in cholesterol metabolism can affect the metabolism of immune cells. Hence, we found that the function of the energetic motor, the mitochondria, was affected in the immune cells these patients. Next we aimed to study how systemic metabolic changes affect macrophage metabolism and function in more detail.

To investigate this, mice were fed either a normal fat diet or a high fat diet, after which the latter group had increased blood cholesterol levels. Their macrophages displayed a lipid-laden foamy appearance. We found that the lipid uptake by macrophages suppresses NRF2 and the pentose phosphate pathway, the latter being a key metabolic pathway that macrophages use to induce inflammatory responses. As a result, foamy macrophages are unable to induce an inflammatory response as strong as the non-foamy macrophages.

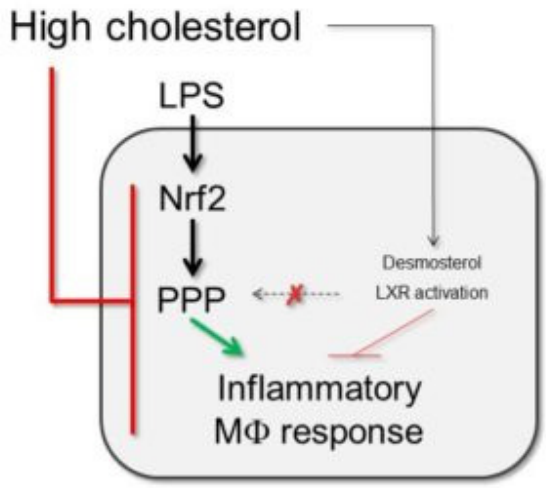


Fig. 2. Suppression of NRF2 and the Pentose Phosphate Pathway Reduces Inflammatory Macrophage Responses in a high cholesterol environment. LDL cholesterol uptake and foam cell formation suppresses NRF2 and the pentose phosphate pathway. Together with desmosterol-mediated activation of LXR, this suppresses the secretion of pro-inflammatory mediators such as IL-1β IL-6 and nitric oxide by foamy macrophages.

In our research, we provide a new mechanism for the observed reduced inflammatory phenotype that acts in parallel to the mechanism reported in 2012. Altogether, we and others demonstrate that foam cells are less inflammatory in atherosclerosis than one would expect. Therefore, extensive follow-up research will be needed to unravel the questions that emerge from those new and exciting findings and to be able to implement this new knowledge on the development of new treatments for atherosclerosis. Are macrophage foam cells

less detrimental than the dogma suggests? Or does their less inflammatory phenotype cover other properties that drive plaque instability and cardiovascular complications in distinct ways? Answering these questions, we will further unravel the path and the targets from cholesterol to macrophage to atherosclerosis.

This study was initiated by Jan Van den Bossche during his postdoc in the laboratory of Menno de Winther (Department of Medical Biochemistry, Amsterdam UMC, AMC) and was performed together with their PhD student Jeroen Baardman. Sanne Verberk helped to finalize the project during the start of her PhD in the new "Translational Macrophage Immunometabolism" research group of Van den Bossche at the department of Molecular Cell Biology and Immunology at VUmc.

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## Publication

A Defective Pentose Phosphate Pathway Reduces Inflammatory Macrophage Responses during Hypercholesterolemia.
Baardman J, Verberk SGS, Prange KHM, van Weeghel M, van der Velden S, Ryan DG, Wüst RCI, Neele AE, Speijer D, Denis SW, Witte ME, Houtkooper RH, O'neill LA, Knatko EV, Dinkova-Kostova AT, Lutgens E, de Winther MPJ, Van den Bossche J
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