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Long-term activation of the innate immune system in atherosclerosis

Anette Christ[a,b], Siroon Bekkering[d], Eicke Latz[a,b,c,**,1], Niels P. Riksen[d,*,1]

[a] Institute of Innate Immunity, University Hospitals Bonn, University of Bonn, Bonn, Germany
[b] Department of Infectious Diseases and Immunology, UMass Medical School, Worcester, MA, USA
[c] German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany
[d] Department of Internal Medicine, Radboud University Medical Center, Nijmegen, The Netherlands

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ABSTRACT

Efforts to reverse the pathologic consequences of vulnerable plaques are often stymied by the complex treatment resistant pro-inflammatory environment within the plaque. This suggests that pro-atherogenic stimuli, such as LDL cholesterol and high fat diets may impart longer lived signals on (innate) immune cells that persist even after reversing the pro-atherogenic stimuli. Recently, a series of studies challenged the traditional immunological paradigm that innate immune cells cannot display memory characteristics. Epigenetic reprogramming in these myeloid cell subsets, after exposure to certain stimuli, has been shown to alter the expression of genes upon re-exposure. This phenomenon has been termed trained innate immunity or innate immune memory. The changed responses of 'trained' innate immune cells can confer nonspecific protection against secondary infections, suggesting that innate immune memory has likely evolved as an ancient mechanism to protect against pathogens. However, dysregulated processes of immunological imprinting mediated by trained innate immunity may also be detrimental under certain conditions as the resulting exaggerated immune responses could contribute to autoimmune and inflammatory diseases, such as atherosclerosis. Pro-atherogenic stimuli most likely cause epigenetic modifications that persist for prolonged time periods even after the initial stimulus has been removed. In this review we discuss the concept of trained innate immunity in the context of a hyperlipidemic environment and atherosclerosis. According to this idea the epigenome of myeloid (progenitor) cells is presumably modified for prolonged periods of time, which, in turn, could evoke a condition of continuous immune cell over-activation.

Contents

* Corresponding author at: Radboud University Medical Center, Dept. Internal Medicine 463, Geert Grooteplein Zuid 8, 6525 GA Nijmegen, The Netherlands.
** Corresponding author at: Institute of Innate Immunity, University Hospitals Bonn, University of Bonn, Sigmund-Freud-Str. 25, 53127 Bonn, Germany.
E-mail addresses: Eicke.Latz@uni-bonn.de (E. Latz), Niels.Riksen@radboudumc.nl (N.P. Riksen).
[1] These authors equally contributed to this work.

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1. Atherosclerosis, a persistent inflammatory disease

Cardiovascular diseases (CVD), including stroke, and myocardial infarction, are the leading cause of mortality worldwide and together are responsible for approximately 17 million deaths per year [1]. The vast majority of cardiovascular events are caused by the rupture or erosion of atherosclerotic plaques in the arterial wall and the subsequent formation of an occluding thrombus. Traditionally, atherosclerosis is regarded as a disease of the developed Western Society, driven by the major classical risk factors dyslipoproteinemia, hypertension, diabetes, obesity, smoking, and a sedentary lifestyle. Interestingly, however, the development of atherosclerosis is not restricted to patients with a Western lifestyle. In a recent study, CT-scanning revealed signs of atherosclerosis in a third of mummies from several ancient populations, even in non-smoking populations that had an almost entirely marine diet [2]. These observations fit the paradigm shift in the early nineties that atherosclerosis is more than simply a vascular cholesterol storage disease, and that chronic low-grade vascular inflammation triggered by the deposited material could contribute to atherogenesis [3]. The inflammatory nature of atherosclerotic plaques was already recognized in the nineteenth century by Virchow [4], who wrote: "In some, particularly violent cases the softening manifests itself even in the arteries not as the consequence of a really fatty process, but as a direct product of inflammation".

In the last ten years, several novel non-traditional risk factors for atherosclerosis have been identified that are all associated with activation of the immune system. These include chronic inflammatory diseases such as rheumatoid arthritis, gout, psoriatic arthritis, and ankylosing spondylitis, as well as infections with bacteria or viruses, such as *Chlamydia pneumonia*, *Porphyromonas gingivalis* and *human immunodeficiency virus* (HIV) [5]. In addition, acute cardiovascular events occur more frequently in the weeks following an acute infection, such as pneumonia [6]. Recently, also cardiovascular events itself, such as myocardial infarction [7] or stroke were described to drive subsequent acceleration of atherosclerosis throughout the vascular system [8]. Finally, recent experimental evidence indicates that changes in diet and in dietary composition are able to directly influence lymphoid organs, thus profoundly and continuously influencing immune responses and the development of inflammatory and autoimmune diseases [9].

Although it is now well established that inflammation plays an essential role in the initiation, progression, and destabilization of atherosclerotic plaques, the mechanisms that drive the persistent non-resolving inflammation in the vessel wall remain incompletely understood. Macrophages are the most abundant inflammatory cells present in atherosclerotic plaques. Cells of the adaptive immune system such as T and B lymphocytes are also present, but in lower numbers. Evidence is rapidly accumulating that innate immune cells can adopt a persistent pro-inflammatory phenotype after brief exposure to a variety of stimuli, a phenomenon that has been termed 'trained innate immunity' [10].

In this review, we discuss the concept that trained immunity contributes to the development of atherosclerosis, both in the setting of traditional cardiovascular risk factors, and in the setting of non-traditional risk factors, such as acute and chronic infections, and non-infectious chronic inflammatory disorders. In addition, it might well be that elevated dietary fats and consequently an alteration of the gut microbiota, impact immune homeostasis (dysbalance between inflammatory and tolerogenic processes), thus inducing a long-term epigenetic reprogramming of innate immune cells.

2. The innate immune system and atherosclerosis

Within atherosclerotic plaques, macrophages are the most abundant subset of leukocytes. Arterial resident macrophages are derived from embryonic CX3CR1^{+} precursors and from bone marrow-derived monocytes that colonize the tissue immediately after birth [11,12]. During atherogenesis, arterial plaque macrophages are sustained by local proliferation, but also by recruitment of Ly6C^{high} monocytes [13]. Monocytes and macrophages are critically promoting the initiation, progression, and destabilization of atherosclerotic plaques by several mechanisms [14,15]. In the early stages of atherosclerosis, macrophages contribute to the clearance of reactive lesional oxidized low-density lipoprotein (oxLDL) particles through scavenger receptor A (SR-A) and CD36 mediated uptake. In later stages, macrophages are impaired in their phagocytic functionality due to intracellular accumulation and defective efflux of oxLDL. Foam cell macrophages undergo apoptosis due to cellular stress and inflammatory responses, a process, which ultimately contributes to the formation of the pro-thrombotic necrotic core that characterizes mature atherosclerotic plaques. Damage Associated Molecular Patters (DAMPs), which accumulate in the atherosclerotic plaques, represent a source of endogenous danger ligands that can further activate macrophages by binding to specific Pattern Recognition Receptors (PRR), such as membrane-bound Toll Like Receptors (TLR), SR, and intracellular NOD-like receptors (NLRs) [16]. Multiple pro-inflammatory triggers could hence cause an inflammatory milieu in the plaque. In addition, even the phase transition of cholesterol can cause inflammation as cholesterol crystals can activate the Nlrp3 (NOD-, LRR- and pyrin domain-containing 3) inflammasome, triggering the secretion of pro-inflammatory IL-1β and IL-18 [17]. Finally, lesional macrophages contribute to the remodeling of atherosclerotic plaques into a rupture-prone unstable phenotype by the production of proteases, such as matrix metalloproteinases [18]. Overall, plaque macrophages display a marked phenotypic heterogeneity [19], which is dictated by the composition of the local DAMPs that are present in the specific environment during different stages of plaque development.

Several studies have shown that hypercholesterolemia considerably increases the number of circulating Ly6C^{high} pro-inflammatory monocytes in mice (or the CD14^{++}CD16^{-}/CD14^{++}CD16^{+} equivalent in humans), thereby accelerating atherosclerosis [20,21]. Additionally, an acute myocardial infarction, stroke or sepsis can accelerate subsequent atherosclerosis by inducing monocytosis [7,22]. Which factors are driving monocytosis in the context of a hypercholesterolemic environment remains to be fully resolved. Besides, although the adverse contribution of myeloid cells in atherosclerosis is generally accepted, it is still an open question why a strong pro-inflammatory response within the arterial wall fails to be resolved even after reducing potential inflammatory triggers. Recent studies have illuminated the mechanisms underlying the hypercholesterolemia-induced myelopoiesis and a shifting towards the pro-inflammatory Ly6C^{high} monocytes [23,24]. Hitherto, the debate has primarily focused on the link between cholesterol accumulation within the plaque macrophage and local ongoing inflammatory processes. However, myeloid priming and