Macrophage Functions in Atherosclerosis

Iris Zeller, Sanjay Srivastava

Atherosclerosis is a chronic inflammatory disease of the arterial wall instigated by the excessive accumulation of lipoproteins; monocyte recruitment and their differentiation into macrophages in the subendothelial space. Repeated failure of innate immune responses to clear subintimal low-density lipoprotein (LDL), results in the deposition of lipid-laden macrophages or foam cells. Foam cells secrete proinflammatory mediators that facilitate lipoprotein retention and maintain vascular inflammation.1 Advancement of lesion is characterized by the apoptosis of these macrophages in the lipid core. Macrophage apoptosis plays a dual role in atherosclerosis. In early fatty streaks lesions, efferocytosis removes apoptotic cells and prevents lesion development, whereas in the advanced lesions, efferocytosis is not efficient to clear the apoptotic debris, leading to the formation of necrotic core which further enhances inflammation and atherogenesis.2

Accumulating indirect evidence suggests that the antiatherogenic role of high density lipoprotein (HDL) could at least in part, be due to its ability to stimulate cholesterol efflux from macrophages by ATP-binding cassette transporter A1 and G1 (ABCA1 and ABCG1). Complementing this notion, recent studies by Westerterp et al3 show that macrophage deficiency of ABCA1/G1 enhances lipid accumulation in macrophages, atherosclerosis and lesion inflammation. These authors observed that macrophage foam cells in spleen facilitate monocyteosis which is inhibited by ABCA1/G1 and high levels of HDL. Studies by Ramirez et al4 demonstrate that activation of liver X receptor (LXR) augments the transcription of microRNA 144 (miR144) and inhibition of miR144 in macrophages upregulates ABCA1 expression and cholesterol efflux. In vivo, supplementation of mice with miR144 suppresses ABCA1 expression in the liver and reduces plasma HDL levels. Silencing of miR144 enhances ABCA1 expression and plasma HDL concentration. Activation of nuclear receptor farnesoid X receptor (FXR) also increases the expression of miR144 in the liver, which in turn downregulates ABCA1 protein and decreases plasma HDL.5 Conversely, silencing of miR144 in mice upregulates hepatic ABCA1 and increases plasma HDL levels. Together, these studies provide further evidence that ABCA1 is a critical regulator of cholesterol efflux and miR144 could be a potential therapeutic target for increasing the circulating levels of HDL.

Although, it is well recognized that macrophages play a critical role in all stages of atherosclerosis, sources of lesion macrophages and mechanisms of accumulation of macrophages in atherosclerotic lesions have been a matter of debate. Monocytes are widely recognized as critical players in chronic inflammatory disease like atherosclerosis. At least two distinct monocyte subsets with differential migratory properties have been characterized in humans and mice.6 Murine Ly6Chigh monocytes express high levels of CCR2, are inflammatory and functionally similar to CD16 CD14+ monocytes in humans. In hypercholesterolemic mice, macrophages in early lesions are predominantly derived from Ly6Chigh monocytes recruited in the intima.7,8 The Ly6Clow “patrolling” monocytes do not express CCR2 and are similar to CD14dim CD16+ “patrolling” monocytes in humans. The Ly6Clow monocytes patrol the vasculature and are recruited in atherosclerotic lesions less frequently. Orphan receptor Nur 77 has been suggested to be a critical regulator of differentiation and survival of Ly6C low monocytes.9 Recent studies show that the absence of Nur 77 in hematopoietic cells enhances atherosclerosis in western diet-fed LDLR-KO mice.10 Deficiency of Nur 77 in monocytes and macrophages increased TLR4 signaling and polarization of macrophages toward proinflammatory M1 phenotype in NF-κB dependent manner. Nur 77 therefore could be a potential target for modulating inflammation in atherosclerotic plaque.

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Mitochondrial oxidation in lesional cells is well documented in experimental animals and humans.\textsuperscript{11,12} However, it is unclear whether mitochondrial oxidative stress is causally involved in the pathogenesis of atherosclerosis and if so, what are the underlying mechanisms? Recently, Wang et al\textsuperscript{13} reported that mitochondria targeted expression of catalase in macrophages suppresses mitochondrial oxidative stress in lesional macrophages, decreases atherosclerosis and prevents the recruitment of Ly6C\textsuperscript{hi} cells in the lesions. Mechanistic studies showed that mitochondrial oxidative stress augments monocite infiltration through the activation of IKKβ-RelA(NF-kB) which enhances the expression of monocite chemotactic protein-1. Lingrel et al\textsuperscript{14} observed that deficiency of hypoxia-hypoxia-inducible factor 1 colocalized with macrophage carotid artery lesions, IL-1β inflammasome, and augmented caspase-1 activity. In human studies by Xiao et al\textsuperscript{15} show that matrix metalloproteinase 8 (MMP8) plays a pivotal role in SMC migration and recruitment to atherosclerotic plaque. Authors showed that deficiency of MMP8 in apoE-KO mice decreases the abundance of SMC in atherosclerotic lesions; apoE-KO/MMP8-KO mice transplanted with MMP8 deficient SMC displayed smaller lesions than ApoE-KO/MMP8-KO mice which received SMC from wild type mice; and deficiency of MMP8 in SMC diminished their ability to migrate through the endothelium or extra-cellular matrix; or into the arterial lesions.

Together, recent work reinforces the idea that macrophages play a central role in all stages of atherosclerosis and targeted inhibition of lesional macrophage inflammation could be beneficial in protecting against atherosclerotic lesion formation.

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