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Macrophage Functions in Atherosclerosis

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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 sub-endothelial space. Repeated failure of innate immune responses to clear sub-intimal low-density lipoprotein (LDL), results in the deposition of lipid-laden macrophages or foam cells. Foam cells secrete pro-inflammatory mediators that facilitate lipoprotein retention and maintain vascular inflammation.[1] Advancement of lesion is depicted 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 debri, leading to the formation of necrotic core which further enhances inflammation and atherogenesis.[2]

Accumulating indirect evidence implicate that anti-atherogenic 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 al[3] show that macrophage deficiency of ABCA1/G1 enhances lipid accumulation in macrophages, atherosclerosis and lesion inflammation. Authors also observed that macrophage foam cells in spleen facilitate monocytosis which is inhibited by ABCA1/G1 and high levels of HDL. Studies by Ramirez et al[4] 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 lesional macrophages and mechanisms of accumulation of

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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 human and mice[6]. Murine Ly6C^{high} 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 Ly6C^{high} monocytes recruited in the intima.[7,8] The Ly6C^{low} "patrolling" monocytes do not express CCR2 and are similar to CD14^{dim} CD16^{+} "patrolling" monocytes in humans. The Ly6C^{low} 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 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 towards pro-inflammatory M1 phenotype in NF-κB dependent manner. Nur 77 therefore could be a potential target for modulating inflammation in atherosclerotic plaque.

Mitochondrial oxidation in lesional cells is well documented in experimental animals and humans.[11, 12] However, it is not clear if mitochondrial oxidative stress is causally involved in the pathogenesis of atherosclerosis and if so, what are the underling mechanisms? Recently, Wang et al[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^{high} cells in the lesions. Mechanistic studies showed that mitochondrial oxidative stress augments monocyte infiltration through the activation of IKKβ-RelA(NF-κB) which enhances the expression of monocyte chemotactic protein-1. Lingrel et al[14] observed that myeloid cells specific deficiency of the zinc finger transcription factor, kruppel like factor 2 (KLF2), augments atherosclerosis and enhances the recruitment of neutrophils and macrophages to atherosclerotic lesions due to their increased adhesion to endothelial cells. This was accompanied by increased oxidative stress in the lesion. These recent findings complement earlier studies which showed that global hemizygous deficiency of KLF2 exacerbates atherosclerosis in hypercholesterolemic mice.[15]

Rapamycin complex 1 (mTORC1) inhibitor, rapamycin, has also been suggested to reduce inflammation and prevents atherosclerosis.[16] Recent studies by Ai et al[17] show that ablation of Raptor gene in macrophages decreases mTOR activity, atherosclerosis, macrophage accumulation and chemokine gene expression in atherosclerotic lesions. *In vitro* studies showed that upon treatment of macrophages with minimally oxidized LDL, mTORC1 activity enhanced the induction of chemokines by increasing IL6 signaling. Driscoll et al[18] reported that in mice, deficiency of transmembrane protease ADAM17 augments macrophage dependent efferocytosis which enhances anti-inflammatory response.

Folco et al[19] have probed the association between hypoxia, prevalent in atherosclerotic plaques, and inflammation. Their studies show that exposure of lipopolysaccharide-primed human macrophage to moderate level of hypoxia impedes the autophagic degradation resulting in increased intracellular accumulation of IL-1β, induction of NLRP3 and

activation of inflammasome, and augmented caspase-1 activity. In human carotid artery lesions, IL-1β co-localized with macrophage rich regions that express activated caspase 1 and the markers of hypoxia - hypoxia-inducible factor 1α and hexokinase-2.

Recent studies have also suggested that influenced by the microenvironment, lesional macrophages proliferate in atherosclerotic lesions.[20] Sayin et al[21] observed that deficiency of Zinc finger protein 148 (Zfp 148) enhances p53 activity and prevents atherosclerosis by blocking the proliferation of lesional macrophages.

Although monocyte derived macrophages play a key role in atherosclerosis, vascular smooth muscle cells (SMC) can also migrate from tunica media to the intima, where they engulf lipoproteins to form foam cells.[22] Using linear tracing experiments, Feil et al[23] showed that in atherosclerosis, SMC can undergo clonal expansion and transdifferentiate into macrophage like cells. Authors claim that these SMC- derived macrophages are major the component of advanced lesions. Moreover, since these cells no longer express the markers of SMC such as α-smooth muscle actin, it is plausible that previous immunostaining studies underestimated the abundance of SMC-derived macrophages in atherosclerotic plaques.

Stem progenitor cells (SPC) have been suggested to be another source of SMC and monocyte/macrophages in atherosclerotic lesion formation and progression.[24-26] In atherosclerotic lesions, SPC can either be recruited from the bone marrow via blood circulation or from the vessel wall. Recent studies by Xiao et al[25] 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 SPC 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 SPC diminished their ability to migrate through the endothelium or extracellular matrix; or into the arterial lesions.

Together, recent studies reinforce that macrophages play a central role in all stages of atherosclerosis and targeted inhibition of lesional macrophage inflammation could be beneficial in atheroprotection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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