

Microenviromental factors controlling macrophage polarization in atherosclerosis

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Abstract

Macrophages are critical for the initiation and perpetuation of intravascular inflammation through their ability to produce an array of cytokines and chemokines, to generate reactive oxygen species, and to process and present antigens to CD4⁺ T cells. Macrophages constitute a heterogeneous population of cells that are distinctly activated by various microenvironmental signals; however, the mechanisms contributing to the generation of distinct macrophage phenotypes in the context of atherosclerosis remain unclear. This review summarizes the well-characterized factors that govern macrophage polarization toward a specific phenotype and function. Understanding the microenvironmental factors that control macrophage polarization and the precise roles of distinct macrophage subsets could provide the basis for novel treatment strategies aimed at limiting the progression of atherosclerosis.

Introduction

Atherosclerosis and associated cardiovascular disease (acute myocardial infarction and stroke) are the leading causes of death in developed countries, and it has been estimated that by 2020 these disorders will be the main healthcare and socio-economic problem world-wide, in part due to progressive societal aging. It is wellestablished that progression from early lesion to vulnerable plaque involves the participation of numerous cellular and molecular inflammatory components. The most prominent immune cells that invade lesions are monocyte-derived macrophages (representing up to 60% of atheroma plaque mass) and T-lymphocytes. Both cell types produce a wide array of soluble inflammatory mediators (cytokines, chemokines) that are critical for disease initiation and progression. For this reason, atherosclerosis is now regarded not simply as a lipid metabolism disorder, but also as a chronic inflammatory disease, and macrophages play a central role in the atherogenic process as modulators of both lipid metabolism and immune responses [1,2]

Macrophages, the mature form of peripheral blood monocytes within tissues, are specialized phagocytic cells involved in multiple processes, both in homeostatic conditions and during the immune response induced by tissue damage or exposure to pathogen [3,4]. Macrophages acquire specialized phenotypes in response to signals from the local microenvironment that polarize them toward a specific activation state. Activation with IFNy, alone or in combination with pathogen-derived signals such as LPS, leads to classical-activated macrophages, also known as M1 cells, which participate in proinflammatory type 1 immune responses. Exposure to other immune signals results in profoundly different phenotypes. These include 'alternatively-activated' macrophages induced by IL-4 or L-13, which are associated with type 2 immune responses, and a spectrum of macrophage phenotypes related to anti-inflammatory, angiogenic, and tissue-repair properties, induced by stimuli including TGFB, immune complexes, glucocorticoids, and IL-10 [4-6]. Tissue-infiltrating monocytes are simultaneously exposed to differentiating and activating factors. Macrophages generated after monocyte stimulation with GM-CSF (granulocyte-macrophage colony-stimulating factor) are considered pro-inflammatory M1 macrophages, whereas monocytes differentiated and activated with M-CSF (Macrophage colonystimulating factor) acquire an anti-inflammatory phenotype and are denominated M2 macrophages. However, several authors consider that under homeostatic conditions, M-CSF differentiates monocytes into resident macrophages, which subsequently acquire the M1 or M2 phenotype in response to activation stimuli [7,8]. These two hypotheses might not be mutually exclusive: under steady-state conditions, monocytes infiltrate all tissues and differentiate into resident macrophages. Subsequently, in response to activation stimuli, these macrophages will acquire a specific differentiated phenotype. In addition, all immune responses involve recruitment of circulating blood monocytes, and these monocytes will be exposed simultaneously to differentiation and activation signals, resulting in their maturation into macrophages with a specific phenotype.

Roles of macrophages in atherosclerosis

Recent work suggests that different stages in the progression of atherosclerotic disease are associated with the presence of distinct macrophage subtypes [9,10].

The initial lesion: In both humans and experimental animals, hypercholesterolemia leads to the accumulation of plasma lipoproteins in the extracellular matrix of the vessel wall, where they undergo oxidation [11]. These deposits of oxidized lipoproteins, called fatty streaks, are very abundant in early atherosclerotic lesions, and are rich in lipid droplets, apoptotic cells and tissue debris. Endothelial cells neighbouring fatty streaks become dysfunctional, and it has been proposed that the prevalence of M2 macrophages in early atherosclerotic lesions is a reparative mechanism that limits disease progression in the initial stages. TGFB released by M2 macrophages inhibits the recruitment of inflammatory cells, and this is associated with a significant atheroprotective effect [12]. M2 macrophages also have an immunosuppressive action through the release of IL-10, which inhibits the secretion of inflammatory cytokines such as IFNy from other macrophages and from T-cells [13]. M2 macrophages are also atheroprotective through their capacity to reduce inflammation

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by clearing apoptotic cells and tissue debris, a process known as efferocytosis [14].

Plaque growth: Defective efferocytosis and the accumulation of inflammatory signals, including modified LDLs, correlates with atherosclerosis progression, possibly due to increased secondary necrosis and recruitment of inflammatory cells. The accumulation of M1 macrophages in the damaged vessel wall has been shown to contribute to plaque expansion [9]. In general, M1-produced proinflammatory markers are elevated in patients with unstable angina and myocardial infarction, with high levels predicting a poor outcome. Factors released by M1 macrophages include cytokines IL-6, IL-7 and IL-8, the soluble CD40 ligand (CD40L), C-reactive protein (CRP) and pentraxin-3 [15,16]. Atherosclerotic macrophages also secrete TNFa, which contributes to scavenger receptor downregulation [17]. In addition to activating other inflammatory cells, most of the inflammatory molecules produced by M1 macrophages contribute to the differentiation of newly-recruited monocytes to the M1 phenotype, increasing the inflammatory reaction through a feedback loop. M1 macrophages also release vasoactive molecules such as nitric oxide, endothelins, and eicosanoids [18]. Reactive oxygen species generated by M1 macrophages induce lipoprotein oxidation, with significant cytotoxic consequences [19].

Pro-M1 Factors in Atherosclerosis

The macrophage-differentiating stimulus: GM-CSF

Human macrophages can be obtained in vitro by culturing CD14⁺ peripheral blood monocytes in the presence of GM-CSF. This cytokine is considered a differentiating and activating molecule and is needed for the survival of monocytes in vitro. Macrophages obtained by culture of monocytes in the presence of GM-CSF have adherent 'fried egg' morphology and are characterized by considerable expression of the inflammatory cytokines IL-1 β , IL-18, IL-6, and TNF α and high expression of IL-23 and IL-12 [20].

Under basal conditions, endothelial cells, smooth muscle cells and macrophages express little GM-CSF in vivo, but expression is increased upon exposure to pro-atherosclerotic stimuli such as inflammatory cytokines or oxLDL [17,21]. However, GM-CSF⁺ macrophages (CD68⁺ CD14⁻ according to Waldo et al.) seem to constitute only a minor fraction of atherosclerotic macrophages, and indeed GM-CSF is not always detected in human atherosclerotic lesions [22].

Th1 cytokines: IFNγ

IFN γ is the most important Th1 cytokine inducing the acquisition of an M1 macrophage phenotype. These macrophages are effectors in type I immune responses, pathogen killing and anti-tumor defense [6,23].

IFN γ mRNA is highly expressed in atherosclerotic lesions and correlates with plaque progression [24]. IFN γ -stimulated macrophages have a pro-atherogenic phenotype characterized by production of the inflammatory cytokines IL-12, IL23 and IL-1 β . Although IFN γ -activated human and murine atherosclerotic macrophages show reduced expression of CD36 and SR-A receptors, they contribute to abnormal cholesterol homeostasis by reducing cholesterol efflux, accumulating cholesterol esters and forming foam cells as a result ofincreased ACAT-1 activity and reduced expression of 27-hydroxylase and the ABCA1 cholesterol transporter [25].

Inflammatory molecules: TNFa, CD40L and C-reactive protein (CRP)

In addition to their priary role in inflammation, most inflammatory

cytokines produced by M1 macrophages also help maintain the proinflammatory phenotype (of newly recruited monocytes). TNF α released by inflammatory atherosclerotic macrophages contribute to atherosclerotic inflammation [26], and TNF α production also modulates macrophage phenotype: macrophages stimulated with TNF α display an M1 phenotype by downregulating scavenger receptor expression and foam cell formation. Moreover, TNF α has been shown to induce stronger activation of NF- κ B in the presence of IFN γ , and this NF-kB activation is accomplished via increased production of reactive oxygen species and induction of inducible nitric oxide synthase (iNOS) to produce nitric oxide (NO) [27].

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CD40 ligand (CD40L) is a 39-kd transmembrane member of the TNF family with a well-established role in atherosclerosis. High levels of CD40L have been detected in patients suffering from hypercholesterolemia, unstable angina, or acute myocardial infarction [28]. Binding of CD40L to CD40 promotes pro-inflammatory cytokine production, reduces NO bioavailability, and induces overexpression of adhesion molecules, in turn promoting leukocyte recruitment and atheroma formation [29]. In a recent study, Verreck et al. showed that treatment of GM-CSF-derived macrophages with CD40L induced the expression of IL-18, IL-6 and TNF α , suggesting a role for CD40L in the maintenance of the pro-inflammatory macrophage phenotype in atherosclerosis [30].

C-reactive protein (CRP) is considered a reliable predictor of adverse cardiovascular events [31]. Moreover, administration of human CRP to rats induces endothelial dysfunction and activation of NADPH oxidase, NF- κ B, matrix metalloproteinase-9, tissue factor activity, and release of the pro-inflammatory cytokines IL-1 and IL-6CRP (32). CRP has also recently been shown to promote the differentiation of human monocytes into M1 macrophages that release large amounts of the pro-inflammatory cytokines IL-12, IL-1 β , IL-6, TNF α and MCP-1 while upregulating expression of CCR2 [33].

Pro-M2 Factors in Atherosclerosis

The macrophage-differentiating stimulus: M-CSF

Stimulation of human CD14⁺ peripheral blood monocytes with M-CSF promotes monocyte survival and their differentiation into M2-like phagocytic macrophages that produce high levels of IL-10 [20]. M-CSF-derived macrophages are adherent, with a stretched, spindle-like morphology, and are better able than GM-CSF-derived cells to form foam cells. A phenotype favoring foam cell formation is supported by genetic profiling of M-CSF-differentiated primary mouse macrophages [8]. M-CSF upregulates enzymes involved in cholesterol biosynthesis and downregulates ATP-binding cassette transporter G1 (ABCG1), which is involved in cholesterol efflux. Moreover, in human monocyte-derived macrophages, oxLDL accumulation is higher in M-CSF-differentiated macrophages than in GM-CSF-differentiated cells, and correlates with the upregulation of CD36 and SR-A, membrane proteins involved in the uptake of modified lipids [8,22].

In mouse and human lesions, M-CSF is detected both in healthy arteries and atherosclerotic lesions, and in the latter is associated with macrophage and foam-cell content and correlates with plaque progression [8,21,22,34]. These data are consistent with a scenario in which M-CSF and GM-CSF both contribute to macrophage heterogeneity observed in plaques. Since M-CSF is constitutively expressed, macrophages infiltrating early lesions are likely to differentiate toward an M2-like phenotype. As the plaque progresses, oxLDL and other inflammatory stimuli could potentially increase the production of both M-CSF and GM-CSF, making the balance between the levels of these differentiation factors very important. Since high GM-CSF expression seems to be Specifically associated with advanced lesions, a high GM-CSF: M-CSF ratio may favour a phenotypic switch toward pro-inflammatory M1-like macrophages upon plaque progression, as observed by Khallou-Lashet et al. in moue lesions [9].

Th2 cytokines: IL-4

Macrophages primed by Th2-derived cytokines are referred to as alternative-activated macrophages or M2, and are further subdivided according to the polarizing cytokine and function. Macrophages primed by IL-4 or IL-13 are referred to as M2a and are characterized by high expression of Arginase-1 (Arg-1), chitinase 3-like 3 lectin (also known as Ym1), the transcription factor found in inflammatory zone 1 (FIZZ1) and mannose receptor (MMR). M2a macrophages are mainly involved in homeostasis, tissue repair, allergy and resistance to parasites [4,5].

IL-4 has been shown in mice and humans to increase in vitro and in vivo macrophage 15-lipoxygenase, an M2 marker linked to increased foam-cell formation [35], and CD36 and SR-A, thereby allowing macrophages to take up more oxLDL and acLDL [36]. However, despite the a priori anti-inflammatory role of IL-4-primed macrophages, their role in atherosclerosis in vivo is still unclear. Atherosclerotic lesions consistently contain large amounts of IL-4, probably produced by neutrophils [37] or NKT cells [38], and elevated IL-4 levels are associated with atherosclerosis progression. A study in human atherosclerotic plaques, using MMR as a marker of IL-4-primed macrophages, showed that CD68+MMR+ cells in IL-4-rich areas of the lesion showed reduced lipid accumulation and were predominantly present in stable cell-rich areas of the plaque; in contrast, CD68+MMRcells were more lipid-filled and were found in areas surrounding the lipid-rich core. Moreover, the lipid phenotype of CD68+MMR+ plaque macrophages was confirmed by in vitro experiments showing reduced uptake of native and oxidized lipoproteins by human monocyte-derived macrophages primed with IL-4. Remarkably, these CD68+MMR+ cells also exhibited decreased expression of ABCA1 and apolipoprotein E (ApoE), thereby implying lower cholesterol efflux capacities [39].

Finally, IL-4 has been shown to upregulate the expression of metalloproteinases involved in matrix degradation and plaque release [6,40,41]. Therefore, despite the putative role of IL-4 in resolving M1-mediated inflammatory responses, IL-4-activated macrophages may also have a pro-atherogenic role.

Anti-inflammatory molecules: IL-10 and TGFβ

IL-10-primed macrophages are often called 'regulatory' or M2c, and act as safeguards that control and dampen immune responses through high production of IL-10 and TGF β [42]. In mouse macrophages, IL-10 increases foam-cell formation by upregulating CD36 and SR-A. These macrophages are less prone to apoptosis, and show increased cholesterol efflux mediated via PPAR γ -induced ABCA1 expression [43].

Frostegard et al. did not detect IL-10 in human lesions [21], while others were able to show IL-10 mRNA expression in a number of human atherosclerotic plaques [44]. Nonetheless most authorities agree that the atheroprotective role of IL-10-primed macrophages is mediated mainly by their anti-inflammatory properties [45].

Macrophages activated with TGF β are also included in the M2c class because they show the hallmark downregulation of pro-inflammatory cytokines, increased debris scavenging, and a pro-healing functional program [46]. Blocking antibodies against TGF β or treatment with soluble TGF β receptor II accelerates atherosclerosis, associated with a significant loss of collagen content [47].

Role of Apolipoprotein E and LDLs in Macrophage Polarization

Apolipoprotein E (ApoE) is a major protein component of verylow-density lipoproteins (VLDL) and high-density lipoproteins (HDL) and the ApoE knockout (ApoE-/-) mouse is the most widely usedatherosclerosis model. Elimination of ApoE in this model causes severe hypercholesterolemia leading to spontaneous development of atherosclerosis [48,49].

ApoE was recently shown to induce characteristics typical of alternative activation in mouse macrophages, reducing the steadystate production of M1 cytokines IL-12 and macrophage inflammatory protein-1 α while increasing the production of the M2 cytokines IL-1RA and GM-CSF in a concentration-dependent manner. These findings indicate that ApoE shifts the balance from a pro-inflammatory to an anti-inflammatory cytokine profile [50].

Macrophages stimulated with immunocomplexes are called M2b. Oxidized LDLs (OxLDLs) are major autoantigens that form immunocomplexes with anti-oxLDL antibodies present in atherosclerotic lesions. Macrophages can ingest these complexes via Fc- γ receptors, leading to their activation. Kadl and colleagues recently proposed the existence of a third polarized macrophage sub-type, specifically associated with the oxLDL-rich microenvironment of atherosclerosis. This sub-type, termed Mox, develops in response to atherogenic phospholipids via expression of the redox-regulated transcription factor Nrf2, and has a lower phagocytotic and chemotactic capacity than the conventional M1 and M2 macrophages [51].

Concluding Remarks

Macrophages are central to the initiation and progression of atherosclerosis. Different macrophage sub-types have recently been shown to be involved in different stages of the disease. The phenotype and activity of each macrophage subtype depend on the profile of factors present in the local microenviroment. Understanding how each cytokine influences macrophage phenotype is crucial for the development of anti-atherosclerosis therapies, and several current studies are characterizing these processes. Although characterization of the effects of individual cytokines is crucial, it must be remembered that in a living organism cells are exposed to multiple cytokines simultaneously. Future studies of the role of macrophages in atherosclerosis must therefore examine the effect of combined stimuli on the phenotype and function of these cells.

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