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Macrophages in Vascular Inflammation – From Atherosclerosis to Vasculitis

Tsuyoshi Shirai[1], **Marc Hilhorst**[1], **David G. Harrison**[2], **Jörg J. Goronzy**[1], and **Cornelia M. Weyand**[1]

[1]Division of Immunology and Rheumatology, Department of Medicine, Stanford University School of Medicine

[2]Division of Clinical Pharmacology, Department of Medicine, Vanderbilt University School of Medicine

Abstract

The spectrum of vascular inflammatory disease ranges from atherosclerosis and hypertension, widespread conditions affecting large proportions of the population, to the vasculitides, rare syndromes leading to fast and irreversible organ failure. Atherosclerosis progresses over decades, inevitably proceeding through multiple phases of disease and causes its major complications when the vessel wall lesion ruptures, giving rise to lumen-occlusive atherothrombosis. Vasculitides of medium and large arteries progress rapidly, causing tissue ischemia through lumen-occlusive intimal hyperplasia. In both disease entities, macrophages play a decisive role in pathogenesis, but function in the context of other immune cells that direct their differentiation and their functional commitments. In atherosclerosis, macrophages are involved in the removal of lipids and tissue debris and make a critical contribution to tissue damage and wall remodeling. In several of the vasculitides, macrophages contribute to granuloma formation, a microstructural platform optimizing macrophage-T cell interactions, antigen containment and inflammatory amplification. By virtue of their versatility and plasticity, macrophages are able to promote a series of pathogenic functions, ranging from the release of cytokines and enzymes, the production of reactive oxygen species, presentation of antigen and secretion of tissue remodeling factors. However, as short-lived cells that lack memory, macrophages are also amendable to reprogramming, making them promising targets for anti-inflammatory interventions.

Keywords

cytokine; efferocytosis; giant cell; macrophage polarization; reactive oxygen species

Address correspondence to: C. M. Weyand, M.D., Division of Immunology and Rheumatology, Department of Medicine, Stanford University School of Medicine, CCSR Building Room 2225, Mail Code 5166, 269 Campus Drive West, Stanford, CA 94305-5166, USA; Tel. 650- 723-9027, Fax. 650- 721-1251, cweyand@stanford.edu.

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1. Introduction

Macrophages are resident phagocytic cells, which are critically involved in host defense by regulating protective inflammatory responses as well as tissue repair and healing. More recent evidence places macrophages at the center of steady-state tissue homeostasis, dealing with waste products and tissue regeneration. Macrophages are equipped with pattern recognition receptors (PRRs), which interact with pathogen-associated molecular patterns, enabling them to efficiently phagocytose pathogens and infected cells as well as secrete defense-relevant mediators and inflammatory cytokines (1, 2). Macrophages have further roles as antigen-presenting cells, effectively bridging innate and adaptive immunity. In an elegant feed-forward loop, the activation of antigen-specific T cells results in the amplification of macrophage response (1).

Macrophages are located in all organs to detect, ingest and process debris, dead cells and foreign materials and are numerous in chronically inflamed, nonhealing lesions, such as the atherosclerotic plaque. Macrophages are now recognized as key players in the pathogenesis of atherosclerosis, contributing to all stages of the disease process (3). At the same time, macrophages are critical components in vasculitides, aggressive inflammatory diseases that occur within and around blood vessels and lead to severe vascular damage and tissue ischemia. In several of the vasculitic syndromes, granuloma formation can occur, with highly activated macrophages and surrounding T cells forming complex lymphoid microstructures. How the microenvironment of the vascular wall affects macrophage differentiation and activation is not understood. Similarly, how macrophages shape inflammatory responses that occur in the vasculature is only partially known. Vascular inflammatory disease forms a spectrum, with smoldering, slowly progressive inflammatory wall damage typical for atherosclerosis, which progresses slowly over decades. Vasculitides, which lead to life-threatening complications within days to weeks, represent the other end of the spectrum. Highly inflammatory, tissue-destructive macrophages participate in the entire spectrum of vessel wall inflammatory disease. Vascular disease remains one of the major killers in the Western world, absorbing much of the health care costs spent on chronic disease. Insights gained from one disease condition on the spectrum of vascular inflammatory disease may have major impact on understanding how abnormal immuno-inflammation can be regulated. In this article, we have reviewed the current knowledge on how macrophages can misfunction and miscommunicate to threaten vascular integrity and blood supply to dependent organ systems.

2. Recruitment of macrophage to vascular inflammatory lesions

Macrophages represent a major component of vessel wall infiltrates, where they may form granulomatous arrangements (Table 1). It is well known that macrophages can live in healthy tissues for extended time periods, and multiple subsets of tissue-residing macrophages have been identified, such as microglia, dermal macrophages, and splenic marginal zone and metallophilic macrophages (4). In contrast with such resident macrophages in which primitive yolk-sac derived macrophages can be a precursor, inflammatory conditions recruit circulating monocytes and develop them into macrophages (4, 5). In mice, splenic hematopoietic stem and progenitor cells that originate from bone

marrow niches can be an extramedullary myelopoietic source of monocytes, which are then available for recruitment to inflammatory sites, including atherosclerotic lesions (6).

The current paradigm holds that macrophages differentiate from monocytes once they transition from the circulation into tissue. The steps that regulate monocyte entry into the specialized tissue site of the arterial wall are independent of the source of the cells and depend on the upregulation of molecules that mediate the arrest of circulating monocytes by the leukocyte adhesion cascade on activated endothelial cells (ECs) (7, 8). As for the recruitment of macrophages into vascular inflammatory sites, two pathways with opposing directions are suspected to be relevant; the “inside-out” pathway, taking inflammatory cells from the main endothelial lumen into the wall in a radial pattern (9), and the “outside-in” pathway, in which inflammatory cells enter through the microvessels at the backside of the vascular wall and penetrate towards the macrolumen (10). An important aspect of this discussion is, of course, the size of the affected blood vessel, which dictates the absence or presence of wall microvessels. Determined by body size, human medium and large vessels (including coronary arteries) have such a diameter that the vessel wall requires a separate microvascular support system to secure oxygen and nutrient supply to the vessel; the vasa vasorum system. In contrast, the radius of mouse blood vessels is so small, and the wall thickness is so low, that oxygen and nutrients can easily diffuse into the wall tissues. This fundamental difference between man and mice provides a considerable challenge in translating pathogenic studies from one species to the other.

a. The “Inside-out” model—In the “inside-out” model, injured ECs express surface adhesion molecules and inflammatory mediators that participate in monocyte homing to the endothelium and eventual transmigration into the media (10). This step includes: (a) monocyte influx from the circulating blood because of the activation of ECs and elevation of chemotactic factors; (b) differentiation and activation of macrophages according to the microenvironment in the inflammatory region; and (c) retention of macrophages and amplification of the inflammation (11). Several chemokine receptors (CCR) as well as adhesion molecules expressed on the surface of monocytes have been implicated in facilitating the accumulation of macrophages (12). In atherosclerosis, three major CCR-chemokine pairs are considered to be involved in monocyte transmigration including CCR2-monocyte chemotactic protein 1 (MCP-1), CX3C-chemokine receptor 1 (CX3CR1)-CX3C-chemokine ligand 1 (CX3CL1), and CCR5-CCL5 (13). Genetic depletion of these three pairs led to 90% reduction of atherosclerosis in ApoE−/− mice (14). In addition, monocyte recruitment in the atherosclerotic plaque is enhanced by modified LDL (7). In experimental hypertension, CCR2-mediated responses are reported to be critical to the process of macrophage recruitment (15). Details of these chemokine systems in macrophages have been described in previous reviews (7, 16). Another notable molecule is sphingosine-1-phosphate (S1P), which is a bioactive lipid. Human macrophages express the relevant receptors, S1PR1-4 (17). Among S1PRs, S1PR2 inhibits macrophage migration, and depletion of S1PR2 enhances macrophage recruitment *in vivo* (18). Conversely, S1PR3 mediates chemotactic effects and promotes macrophage recruitment in atherosclerosis in ApoE−/− mice (19).

b. The "Outside-in" model—The "outside-in" model suggests that vascular inflammation starts from the adventitia and progresses toward the inner direction (10). It has been reported that the adventitial vasa vasorum undergoes marked expansion in atherosclerosis and vasculitis (20–22). Moreover, increased vasa vasorum neovascularization and macrophage presence in early atherosclerotic lesions before plaque neovascularization have been shown (23–25). Also, hypertension is accompanied by infiltration of the adventitia and perivascular adipose tissue by macrophages and other inflammatory immune cells (26). In giant cell arteritis (GCA), the entry of macrophages is in the vasa vasorum, and the prominent characteristic of GCA is that they migrate into an adventitial-intimal direction through tissue space (27). In this vasculitic syndrome, macrophages positioned in the adventitia produce proinflammatory cytokines, while collagenase-producing macrophages accumulate at the intima-media border of the inflamed vessel (28). It has been proposed that adventitial cells recruit macrophages and lymphocytes by altering the matrix and the redox status expression of adhesion molecules (10). Considerable uncertainty remains as to the specifics of adventitial cells that participate in the establishment and the regulation of inflammatory lesions. Notably, human arteries contain a population of endogenous dendritic cells (DCs), which have been named vascular DCs and which reside at the adventitia-media border (29). In the model system of GCA, such vascular DCs have been implicated in providing initial signals to recruit inflammatory cells, activate T cells, and trap inflammatory responses in the vessel wall (30–32). Remarkably, adventitial DCs in human arteries express a vessel-specific pattern of PRRs, imposing artery-specific recognition abilities on different arterial beds (29).

The retention of macrophages in the tissue niche is an indispensable element for continuation of inflammation. According to *in vivo* experiment using ApoE−/− mice, the chemokine receptor CCR7 is induced in foam cells during atherosclerosis regression, and lesion size and foam cell content are preserved when CCR7 function is abrogated (33). The signals that guide macrophages to exit inflammatory lesions, either by reverse transmigration through the endothelium to the lumen or by migrating through the media to adventitial lymphatics, remain to be determined (7).

3. Macrophage polarization

When activated with different environmental signals, macrophages make a commitment to polarize into distinct functional subpopulations (34). Such macrophage subsets are broadly classified into classically activated macrophage or M1, and alternatively activated macrophage or M2. The M1 differentiation program is defined by responses to the proinflammatory cytokine interferon (IFN)-γ and by the activation of Toll-like receptors (TLRs), such as TLR4 (35). M2 macrophages are further subdivided into M2a (induced by interleukin (IL)-4 or IL-13), M2b (induced by immune complexes in combination with IL-1β or lipopolysaccharide), and M2c (induced by IL-10, transforming growth factor (TGF)-β, or glucocorticoids) (35). M1 macrophages contribute to Th1 responses, and mediate inflammatory and tissue disruptive reactions (34). M2 macrophages manifest Th2-associated effector functions, and are considered anti-inflammatory or tissue repairing cells; expressing IL-10, scavenger receptors (SRs), and mannose receptors (11, 34).

a. Molecular mechanisms of macrophage polarization—Macrophage polarization is regulated by a broad range of contributors, including signaling molecules and transcription factors (reviewed in detail previously) (36, 37). IFN-γ skews macrophage function toward the M1 program via signal transducer and activator of transcription (STAT)1. TLR4 signaling leads to activation of nuclear factor (NF)-κB and interferon regulatory factor (IRF)-3. Activation of NF-κB results in the production of inflammatory mediators, and production of IFN-β through IRF-3 induces IRF-5 and following transcription of cytokines (IL-12, IL-23, tumor necrosis factor (TNF)-α), which contribute to Th1 and Th17 responses (36, 38). IL-4 and IL-13 skew macrophage function toward the M2a program via STAT6, which in turn activates transcription of genes such as Krüppel-like factor (KLF)4, peroxisome proliferator-activated receptor (PPAR)γ, and PPARδ that are associated with M2 macrophage activation (39–44). Importantly, STAT signaling pathway is strictly controlled by suppressor of cytokine signaling; M2a stimuli induce cytokine signaling 1 which inhibit STAT1 (45). Similarly, NF-κB activation is regulated by the KLF family; KLF2 and KLF4 inhibit its activity whereas KLF6 acts cooperatively (36, 46, 47). Interestingly, NF-κB activation itself induce anti-inflammatory genes, which are involved in the resolution of inflammation (48).

b. Polarized macrophages in vascular inflammation—Polarized macrophages contribute to both, atherosclerotic disease and vasculitides and provide a wide spectrum of disease relevant functions (Table 2). In terms of polarization, atherosclerotic lesions contain both M1 and M2 macrophages (49). The phenotype of macrophages in the inflammatory region is not always consistent, rather, they can polarize into different subtypes according to their microenvironmental changes (7). Khallou-Laschet et al. have evaluated the phenotype of macrophages in ApoE−/− mice (50). In these experiments, early atherosclerotic lesions contain mainly M2 macrophages, while more progressed lesions are dominantly infiltrated by M1 macrophages, indicating that the macrophages are polarized according to surrounding inflammation. Stoger et al. have investigated human atherosclerosis, and have demonstrated a prominent and continued presence of both M1 and M2 macrophages during human atherosclerotic plaque development (51). In the plaque shoulders, which are important predilection sites for plaque rupture, M1 macrophages exist as the major subset, while fibrous cap regions have no significant differences in subsets. The authors also found that adventitial macrophages near atherosclerotic lesions are selectively polarized towards the M2 phenotype. Adventitial M2 macrophages outnumber their M1 counterparts by 2- to 3-fold (51). In the late phases of atherosclerosis, M1 macrophages facilitate the formation of the necrotic core and plaque destabilization, which bring about thrombotic events (52, 53). The role of M2 macrophages in atherosclerosis is still controversial. However, the finding that deletion of the transcription factors NR4A1 and KLF4, both of which promote M2 macrophage polarization and inhibit M1 macrophage polarization, results in acceleration of atherosclerosis suggests that pathways that promote M2 polarization of macrophages are primarily protective (7).

Inflammatory responses in vasculitis are much more pronounced than those observed in atherosclerosis. The clinical correlate is a strong acute phase response in vasculitis, whereas

inflammation-induced acute phase responses in atherosclerotic disease (e.g. elevation of C-reactive protein) are subtle (54, 55).

GCA lesions have features of a Th1 response, and both M1 (inducible nitric oxide synthase (iNOS)-positive) and M2 (CD163-positive) macrophages are present in vasculitic temporal arteries (56, 57). Ciccia et al. have proposed that IL-33 is involved in the M2 polarization, because Th2 cytokines (except for IL-33) are not detected in inflamed temporal arteries (56). In pulmonary hypertension, pulmonary arteries of humans, calves, and rats contain increased numbers of CD163-positive cells, particularly in the adventitia (58). Aortic aneurysmal segments, induced by continuous Angiotensin II infusion of ApoE−/− mice, exhibit accumulation of M2 macrophages in regions of medial disruption, predominantly in the adventitia (59).

Ohlsson et al. have reported that serum from AAV patients with anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) induces a macrophage subtype mainly resembling M2c (60). The relevance of this finding is difficult to assess as insufficient data are available to which extent macrophages in AAV patients are biased towards any of the functional subspecializations. In many other clinical conditions characterized by vascular inflammation, detailed analyses of macrophages in the blood vessel lesions and in the circulation are lacking, deeming any effort to define common macrophage-centric abnormalities premature (Table 1).

4. Pathogenic functions of macrophages in vascular inflammation

Pathogenic roles of macrophages in vascular inflammation range from secretion of soluble factors, such as cytokines, growth factors and enzymes, to the production of reactive oxygen species (ROS) (Table 2). Related to their phagocytic capabilities, macrophages can participate in debris removal and efferocytosis and evidence has been presented that they can mediate cytotoxic functions. Finally, macrophages are key players in regulating T cells, through antigen presentation, expression of costimulatory ligands and the release of mediators that modulate lymphocyte function (Figure 1). Especially in atherosclerosis, macrophages ingest the deposited normal and modified lipoproteins, transforming them into cholesterol-laden foam cells. Foam cells persist in plaques and promote disease progression through several mechanisms (7). Also, oxidized cholesterol esters have numerous proinflammatory effects on macrophages, some of them mediated by TLR4 signaling (61).

4-1. Secreted factors

a. Cytokine—M1 macrophages secrete an armamentarium of proinflammatory cytokines, including IL-1β, IL-6, IL-8, IL-12, IL-23, IL-27, and TNF-α (11). Such M1 macrophage cytokines have been implicated as critical amplifiers of inflammation in the pathogenesis of atherosclerosis, abdominal aortic aneurysms (AAA), GCA, Takayasu arteritis (TAK), Kawasaki disease (KD), and AAV (7, 28, 62–67).

Proinflammatory cytokines manifest their biological effects through a plethora of pathways. First, cytokines, especially TNF-α, restructure the intercellular junctions, which facilitate leukocyte transmigration (66). Cytokines activate ECs and induce endothelial expression of

integrin ligands, especially vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1, which lead to the recruitment of more inflammatory cells into the inflammatory lesions (7, 68, 69). In KD, it has been proposed that inflammatory cells recruited by macrophage cytokines damage the ECs and smooth muscle cells (SMCs), initiating complex inflammatory responses underlying vasculitis (64). Such mechanisms may have a role in many of the scenarios presenting as arterial wall inflammation.

M1-derived cytokines bring about endothelial dysfunction by down-regulation of endothelial NOS (eNOS) expression and promotion of oxidative stress through ROS and reactive nitrogen species production (70).

In advanced stages of atherosclerosis, proinflammatory cytokines promote cell apoptosis and matrix degradation, which result in destabilization of atherosclerotic plaques. Particularly IL-1β and TNF-α can induce SMC and macrophage apoptosis and promote Fas-Fas ligand killing (66, 67), inducing tissue injury and accelerating the need for wound healing.

IL-1β and TNF-α increase tissue procoagulant activity and suppress anticoagulant activity mediated by thrombomodulin-protein C (71). Proinflammatory cytokines modify the fibrinolytic properties of EC, by decreasing the production of tissue plasminogen activator and increasing the production of type I plasminogen activator inhibitor (72). Taken together, proinflammatory cytokines have ability to effectuate thrombus formation, which results in acute coronary syndromes, a clinically important complication of atherosclerosis.

Meanwhile, M2-derived cytokines such as TGF-β and IL-10 are considered to have anti-inflammatory effects by inhibiting inflammatory cell recruitment and suppressing the feed-forward loops of proinflammatory cytokine production, respectively (11, 73, 74). Curiously, there is the possibility that M2 macrophages also display proatherogenic functions, as IL-4 induces CD36 expression, which promotes the uptake of oxidized LDL (11).

b. Chemokines—A crucial function of macrophages lies in their ability to secrete chemokines, thus shaping the composition of the inflammatory infiltrate that forms in a tissue site. MCP-1 is highly expressed in atherosclerotic lesions and in the aneurysmal aortic wall, and is involved in both initiation and amplification of monocyte recruitment to the arterial wall layers (75, 76). Macrophage-derived chemokines may represent a major amplification system in vasculitis as well. Sera of patients with a history of KD induce expression of MCP-1, CCR2, and iNOS in THP-1 macrophages *in vitro*, suggesting feed-forward cycles of macrophage activation (77). In terms of possible signals inducing chemokine production, microRNA-155 has been shown to induce MCP-1 and enhance plaque formation through repressing Bcl6 (78), suggesting abnormalities in cell-internal regulation networks. M2 macrophages are potent producers of CCL18, which can recruit naïve T cells to the inflamed site, giving them a potentially disease-enhancing role (79).

c. Matrix metalloproteinases—Matrix metalloproteinases (MMPs) are a major product of macrophages, enabling myeloid cells to actively digest matrix, and their production is also influenced by proinflammatory and anti-inflammatory cytokines (66, 80).

MMPs have been consistently seen in the inflamed arterial wall and have been implicated to contribute to atherosclerosis, AAA, GCA, and KD (66, 80–85). Macrophages are thought to destabilize the atherosclerotic plaque via production and secretion of MMPs, which solubilize extracellular matrix and destroy the fibrous cap (82). The release of MMPs and apoptotic death of SMCs collectively result in the conversion of stable fibroatheromas into vulnerable thin cap fibroatheromas in atherosclerosis and progressive weakness of the aortic wall in AAA (81, 83). Even in GCA, activated macrophages in the intima-media junctions produced MMPs and ROS and played an important role in damaging the medial layer (85). iNOS and MMP9 have been placed at the site of vascular wall inflammation in KD (84).

d. Growth factors—A major pathogenic mechanism in vasculitis is the formation of intimal hyperplasia, occluding the vascular lumen and obstructing blood flow to dependent organs. Neither superficial breakdown of the endothelial layer nor superimposed thrombotic occlusions appear to be relevant in vasculitic tissue ischemia. Growth, migration and secretory activity of SMCs forming the hyperplastic intima depend on appropriate growth factors. Also, the expanding intimal layer needs to be supplied with oxygen and nutrients, necessitating the formation of neomicrovessels. Production of growth factors, such as platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), has been reported for GCA, TAK and KD (65, 86, 87). VEGF supports increased neovascularization, and PDGF promotes the migration of and expansion of SMCs in GCA and TA. Increased vascular permeability and dilation of coronary arteries, pathognomic events in KD, have been attributed to the excess production of VEGF and PDGF (64).

e. ROS—Oxidative stress is a pathological phenomenon resulting from the imbalance in the production of ROS and the ability of biological systems to detoxify the reactive intermediates. ROS production as a means of attacking pathogens is one of the most important mechanisms through which macrophages protect the host. Excess production of ROS, leading to the damage of membranes, proteins and DNA is believed to play a critical role in vascular disease and convincing evidence indicatess that oxidative stress contributes to atherosclerosis and GCA (85, 88–90). In macrophages, the NADPH oxidase Nox2 is one of the dominant sources of ROS generation and is a signifying product of M1 macrophages (91). Nox2 is by far not the sole source of ROS in macrophages, but Nox4, mitochondria, myeloperoxidase (MPO), xanthine oxidase, lipoxygenase, and the uncoupling of NOS all add to the production of ROS (92). ROS promotes macrophage recruitment and impairs efferocytosis in atherosclerotic plaques (93, 94). Oxidative modifications of LDL particles enhance the proinflammatory functions of lipids (95). In GCA, lipid peroxidation mediated by reactive oxygen intermediates is an important pathway of arterial wall damage (85, 89).

f. Other secreted factors—In pulmonary hypertension, Tian et al. have reported that leukotriene (LT) B4 derived by macrophages acts to injure the endothelium, with inhibition of LTB biosynthesis reversing pulmonary hypertension (96).

4-2. Apoptosis

Apoptosis of macrophages is a noticeable feature of atherosclerosis at all stages; its pathogenic role in vasculitides has not been explored (97–100). It is considered in early

atherosclerotic lesions that an increase of macrophage apoptosis causes the attenuation of atherogenesis. On the other hand, impairment of removal for apoptotic macrophages in late stages of atherosclerosis results in the enlargement of the lipid core. Deposition of debris drives proinflammatory responses and furthers apoptotic signals for SMCs, ECs, and leukocytes within the plaques (100). Apoptosis of SMCs in plaque leads to thinning in the fibrous cap, considered an important prerequisite for plaque rupture (101).

Moreover, macrophages within atherosclerotic plaques express Fas-ligand, providing a partner for Fas expressing neighboring cells, and possibly mediating apoptosis of SMCs and ECs (102, 103). Interestingly, the lesional macrophages themselves are considered prone to undergo apoptosis through the Fas pathway (104). NO increases macrophage Fas-ligand and SMC Fas expression, promoting macrophage-induced SMC killing (67, 101). Oxidized lipids can also trigger apoptosis in endoplasmic reticulum-stressed macrophages by a mechanism involving both CD36 and TLR2 (98).

4-3. Phagocytosis and efferocytosis

Phagocytosis protects the arterial tissue from exposure to harmful proinflammatory deposits and immunogenic contents of dying cells, and further limits the overall inflammatory process by restricting lesion growth through postapoptotic necrosis (105). Removal of apoptotic cells, a constant source of proinflammatory signal, is an important tissue protective mechanism, and is called efferocytosis. Insufficient efferocytosis in clearing apoptotic cells from the lesions may function to amplify tissue damage and chronicity of inflammation. In atherosclerosis, M2 macrophages mainly conduct efferocytosis so as to eliminate apoptotic cells and their harmful effects (11, 99). Efferocytosis inhibits macrophages from producing the proinflammatory cytokines through the autocrine/paracrine secretion of TGF-β and IL-10 (11, 106, 107). In advanced experimental atherosclerosis, efferocytosis is typically impaired, and this leads to the assemblage of apoptotic cells which impair the resolution of inflammation (105).

The involvement of efferocytosis of macrophages for the pathogenicity of AAV has been proposed; yet exact mechanisms are still unclear (62). Harper et al. have described that neutrophils from AAV patients show an increased apoptotic rate, and ANCA opsonization of apoptotic neutrophils increases the uptake of neutrophils by macrophages and subsequent secretion of IL-1 and IL-8 (108). Other studies, however, have supported the notion that efferocytosis in AAV is impaired, rather than being hyperactive. van Rossum et al. have suggested a role for pentraxin 3 in delaying macrophage uptake of apoptotic neutrophils in AAV (109). In addition, proteinase 3 (PR3), an autoantigen recognized by ANCA, also seems to impair macrophage efferocytosis when PR3 is externalized during neutrophil apoptosis (110).

Macrophage PRRs, such as the scavenger receptors, CD36, and scavenger receptor-A are intimately involved in the process of apoptotic cell removal (111). Regulation of such PRRs on plaque-residing macrophages may, therefore, represent a critical event in plaque inflammation.

4-4. Giant cells

Fusion of macrophages leads to the formation of multinucleated giant cells, a hallmark of a granulomatous responses (112). Typically, granulomas are formed if the host fails to eliminate antigen. Granulomas display a unique architecture, with highly activated macrophages surrounding a core, that is sometimes necrotic, the most outer layer of the structures are often T cells and granuloma formation is a T cell-dependent mechanism. Giant cells are so typical for GCA that they are part of the disease's name. In GCA, multinucleated giant cells are often identified along the fragmented internal elastic lamina. They retain secretory activity and are an important source of VEGF (85). The precise mechanism leading to the formation of multinucleated giant cells are still unknown. A multitude of factors, including IL-4 and IL-13, granulocyte-macrophage colony-stimulating factor, IL-17A, IFN-γ and lectins have all been considered capable of promoting the formation of multinucleated giant cells (112).

4-5. Interaction with T cells

M1 and M2 macrophages are often understood as counterparts of Th1 and Th2 cells, respectively. M1 macrophages produce IL-12 and IL-23, which direct the differentiation and expansion of Th1 and Th17 cells (113). Conversely, the Th1 product IFN-γ primes macrophages to differentiate into M1 cells. Also, the Th2 cytokine, IL-4, provides critical differentiation signals for M2 cells. A macrophage-T cell partnership of pathogenic relevance is suspected in atherosclerosis, GCA, TAK, KD, anti-glomerular basement membrane disease, AAV, and thromboangiitis obliterans (TAO) (3, 27, 65, 114–119). In all these conditions, macrophages and T cells colocalize in the disease lesions, supporting the concept that a mutual dependence of both cell types initiates and sustains pathologic inflammation. While there is a growing body of evidence connecting T cells and macrophages, the molecular details and the specific cell populations participating in disease-relevant cross-talk are not understood.

Particularly, IFN-γ exerts various biological effects that are predicted to either promote lesion development or destabilize established lesions in atherosclerosis (3). These effects include stimulation of proinflammatory cytokine and chemokine secretion, and production of ROS and MMPs by macrophages (111). IFN-γ is recognized as a critical factor in GCA, with the vascular lesions having typical features of Th1 lesions (27). IFN-γ–producing T cells are surrounded by highly activated macrophages, and interaction of these two types of cells leads to the formation of the granulomas predominantly in the medial layer of the vascular wall.

As for the participation of Th17 in vascular inflammation, Gan et al. examined experimental murine anti-MPO-induced glomerulonephritis, and found IL-17A secreted by Th17 cells promoted the recruitment of pathogenic macrophages to the inflammatory region in response to MPO as an autoantigen (115). Smith et al. have shown a similar effect of IL-17A on recruitment of macrophages in ApoE−/− mice (114).

In a model of KD using Rag1−/− mice, T cells are required for the development of the arteritis, and the interaction of macrophages and DCs with T cells is necessary for the

pathologic manifestations of coronary arteritis (116). Macrophages are common effectors for both CD4 and CD8 T cell-dependent injury in anti-glomerular basement membrane disease (119) and macrophage depletion diminishes the recruitment of T cells to the kidney and provides renal protection (120, 121). Activation of macrophages in the intima in the association with T cells have a key role in thromboangiitis obliterans (117, 118).

5. Macrophages as diagnostic tools

Positron emission tomography (PET) imaging using [18F] fluorodeoxyglucose (FDG) has been applied for the vascular inflammation with the goal to identify high-risk plaques and quantify the disease burden in vasculitides (122, 123). [18F]FDG PET imaging is founded on the excessive demand of glucose in inflammatory cells, particularly macrophages in vascular inflammation. Activated M1 macrophages undergo a switch to glycolysis, which increases the uptake of radiolabeled glucose accumulation (124). PET imaging in combination with contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) visualizes FDG uptake in carotid plaques and FDG accumulation is associated with inflammation of atherosclerotic plaques related to macrophage infiltration (125, 126). Because cellular studies in human macrophages have indicated higher metabolic fluorodeoxymannose (FDM) uptake and mannose receptors are upregulated in high-risk plaques in humans, Tahara et al. have utilized radiolabeled mannose, [^{18}F]FDM, to demonstrate superior imaging characteristics for atherosclerosis (122). As for vasculitis, PET may be useful for large vessel vasculitis (123), but CT and MRI based imaging approaches can provide important information on wall structure and blood pooling (54).

However, PET imaging is not a specific procedure to detect macrophages. Ultrasmall superparamagnetic particles of iron oxide (USPIO) that enable visualization of macrophages residing in the plaques using MRI promise a functionally more relevant approach (127, 128). Furthermore, new macrophage-targeted agents have been developed to delineate the disease in terms of biological processes, which are undetectable when using traditional morphological imaging techniques (129). The application of these imaging modalities to vasculitides might lead to further understanding of how macrophages exhibit their pathogenicity.

6. Macrophages as therapeutic targets

Considering the central position of macrophages in the pathogenic events underlying vascular inflammatory disease, macrophages emerge as a promising therapeutic target to selectively suppress damaging immunity in the blood vessel wall (Table 3). Macrophages themselves can be depleted by using pharmacological agents such as mammalian target of rapamycin inhibitors (130). However, depletion of macrophages can have both harmful effects of worsening diseases as well as beneficial effects in decreasing the inflammatory activities in experimental hyperlipidemia (131).

Because the effects of macrophage-depleting reagents are nonspecific, more precise targets need to be identified, with the ultimate goal to eliminate pathogenic macrophages in a highly selective fashion. Macrophage-centric interventions can be divided into two major

categories: reducing macrophage recruitment/retention and suppression of proinflammatory capabilities.

6-1. Reducing macrophage recruitment/retention

The adjustment of macrophage recruitment is a fascinating therapeutic approach not only for the treatment itself, but also for the prevention of vascular inflammation (132). In this regard, inhibitors of VCAM-1 synthesis and modulators for the chemokine system, such as the vascular protectant succinobucol (AGI-1067) and a selective inhibitor of VCAM-1 synthesis in ECs (CAM741), have been explored (11). Although such interventions have attenuated atherosclerosis development in animal models, their therapeutic effects on human atherosclerosis are not confirmed yet (133). As a drug, a dexamethasone prodrug can effectively impair macrophage infiltration although its mechanism is not fully understood (134). In addition, Notch1, tumor necrosis factor receptor-associated factor 1, and thrombospondin-1 are reported to be involved in the recruitment of macrophages and might provide elegant options to target macrophage-dependent pathology (63, 135, 136). However, therapeutic strategies targeting macrophage recruitment also need to accommodate their potential harmful side resulting from the disruption of housekeeping functions of macrophages in vascular tissues. Therefore, the timing of intervention seems to be crucial even in regard to inhibiting macrophage recruitment (7).

6-2. Suppression of proinflammatory capabilities

Manipulating factors that inhibit M1 macrophage polarization or promote M2 macrophage polarization has been proposed as a potential therapeutic strategy. Specifically, boosting M2 macrophages could have beneficial effects in accelerating wound healing and stabilizing the vessel wall. A possible approach could be to deliver IL-4 or macrophage colony-stimulating factor to the site-of-interest and facilitate localized induction of M2 macrophages although the resident macrophages, but not recruited macrophages, might be preferentially targeted (7, 137).

The clinical trial, Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS), is evaluating the efficacy of IL-1β inhibition in reducing cardiovascular events based on the inflammation hypothesis of atherosclerosis in humans (138). In regard to manipulating ROS production, enhancing an endogenous antioxidant such as glutathione, which prevents oxidative damage, may prove to be more effective in managing human cardiovascular disease (92, 139). Antioxidant strategies in atherosclerosis have proven disappointing in numerous large clinical trials.

Current efforts to reset efferocytotic activity in the atherosclerotic plaque have focused on maintaining levels of efferocytosis using substances such as IL-10 or liver X receptor (LXR) agonists (7). It has been predicted that increasing lipid efflux using LXR agonists or inhibition of microRNA-33 may favorably affect disease-sustaining macrophages (140, 141).

Progress in rectifying macrophage function in vascular inflammation depends on a much better understanding of the factors that control the activities of these cells. An unanswered question is whether the primary abnormalities lay within the pathogenic macrophages

themselves or whether the cells are actually normal, but are swayed towards excess inflammatory behavior through microenvironmental cues. A recent study has broadened the view of how the tissue microenvironment can shape the function of immune cells, biasing them towards disease-inducing functional activities. Piggott et al. have reported that disruption of Notch signaling effectively suppressed both T cell and macrophage functions in inflamed human arteries (142). This study suggested that immunostromal communications are relevant in guiding innate and adaptive immune responses in the arterial wall and that such communication pathways are potential therapeutic targets. The uniqueness of the tissue site, being accessible through adventitial vasa vasorum, offers opportunities for developing new molecular approaches in treating inflammatory disease. Bringing together the study of atherosclerosis and vasculitides creates new opportunities to learn from the aggressive inflammatory abnormalities in rare vasculitic conditions and apply new knowledge to the huge patient base that is affected by the inflammatory condition of atherosclerosis. A combination of molecular finesse and technical breakthroughs that permit selective delivery of reagents to the arterial wall will pave the way to test nanoparticles, reconstituted lipoproteins, siRNAs, and small molecule inhibitors to reeducate inflammatory macrophages that have settled in the wall layers of arteries (7, 143, 144).

7. Conclusion

Macrophages are powerful innate immune cells protecting the host from infection and malignancy and are equally sophisticated when it comes to supporting chronic inflammatory lesions. Macrophages are key drivers of vascular inflammation, a spectrum of diseases that ranges from aggressive, life-threatening vasculitis to slowly progressive atherosclerosis. Vasculitides of small blood vessels, e.g AAV, as well as vasculitides of medium and large vessels, such as GCA and TAK, critically depend on pathogenic macrophages. Macrophages occupy the atherosclerotic plaque, at times transforming into the typical lipid-laden foam cells. Macrophages cause tissue damage through a multiplicity of functions, all connected to their inherit ability to rapidly attract other immune cells, release large amounts of tissue-injurious mediators and phagocytose waste and dead cells. Due to their specialization in inflammatory amplification mechanisms, M1 cells are considered the most likely candidates for causing vessel wall inflammation. It is equally possible that a loss of protective macrophage function leaves the host susceptible to nonhealing inflammation and disorganized vessel wall remodeling. To which extent pathogenic macrophages result from faulty microenvironmental signals versus cell indigenous abnormalities is insufficiently understood. Answering this question is critical to develop appropriate therapeutic strategies. The importance of host age, particularly in atherosclerosis, suggests that vascular wall aging is a critical component of disease. Equally important must be determinants imposed by the tissue environment, as all vasculitides and atherosclerosis share the stringency in tissue tropism, meaning that they almost exclusively occur in an anatomically defined part of the vascular tree. Immune cell aging fundamentally changes the functionality of innate and adaptive immune cells. How the tissue aging process affects the propensity to attract and retain inflammatory cells in the vessel wall is unexplored. Exploiting the phagocytic ability of macrophages to load them with specific cargo will provide new avenues for immunomodulatory therapy in restricted tissue sites.

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Review criteria

We searched PubMed for the search terms “ANCA associated vasculitis”, “atherosclerosis”, “giant cell arteritis”, “Kawasaki disease”, “macrophage”, “Takayasu arteritis”, “vascular inflammation”, and “vasculitis”. Publications from the past 10 years were analyzed for pathogenic studies. If appropriate to support scientific concepts, older publications were included. Case reports were not included, unless providing unique insights into pathogenic pathways. The date of the last search was 03 July 2014.

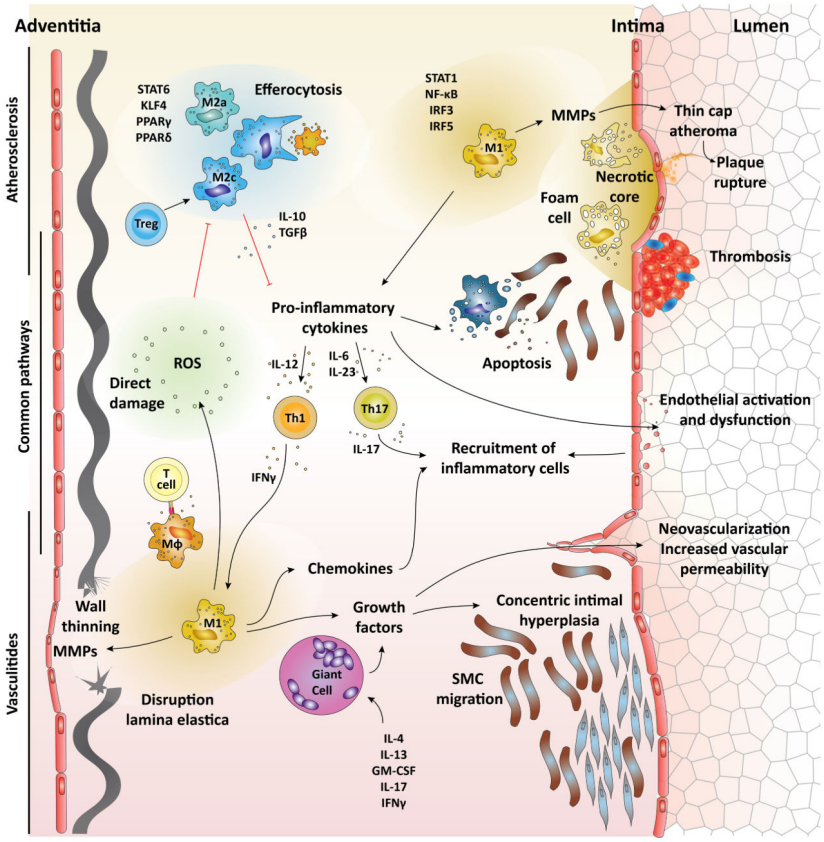

Figure 1.

Pathophysiology of macrophages in vascular inflammation. The major pathophysiology of macrophages in vascular inflammation is outlined. Th1 cytokine IFN-γ and stimulation of TLRs primes macrophages to polarize into M1 macrophages through STAT1, NF-κB, IRF3, and IRF5. Th2 cytokine IL-4 and IL-13 provide differentiation signals for M2a macrophages through STAT6, KLF4, PPARγ and PPARδ. Treg skew macrophages into M2c by IL-10. Proinflammatory cytokines secreted by M1 macrophages induce activation and dysfunction of the endothelium, SMC and macrophage apoptosis, thrombus formation, and differentiation of Th1 and Th17. Recruitment of inflammatory cells into the inflammatory lesions is augmented by the activated endothelium, chemokines, ROS, and IL-17. MMPs solubilize extracellular matrix, resulting in thin cap fibroatheroma and thinning of the wall. M1 macrophages and giant cells produce growth factors. Growth factors induce neovascularization and vascular hyperpermeability, and promote the migration and expansion of SMCs, which results in intimal hyperplasia. ROS directly damages the arterial wall, promotes macrophage recruitment, and impairs efferocytosis. Apoptosis of macrophages and SMCs is a prominent feature of atherosclerosis, and impairment of their clearance results in enlargement of the necrotic core. M2c and efferocytosis produce cytokines such as TGF-β and IL-10, which inhibit inflammatory cell recruitment and suppress the proinflammatory cytokine production, respectively.

Table 1

Vascular inflammation associated with macrophage

Disease	Vessel size	Localization of Macrophages	Granulomatous changes	Reference
Atherosclerosis		Intima Adventitia	Absent	(3, 7, 11, 12, 51, 92, 111, 132, 145)
Hypertension		Adventitia	Absent	(10, 15, 146)
Pulmonary hypertension		Adventitia	Absent	(58, 96)
Abdominal aortic aneurysm		Adventitia	Absent	(10, 59, 63, 75, 83)
Giant cell arteritis	Large and medium	Adventitia Media	Present	(27, 28, 56, 57, 85, 147)
Takayasu arteritis	Large and medium	Adventitia Media	Present	(65, 148)
Polyarteritis nodosa	Medium	Transmural	Absent	(62)
Kawasaki Disease	Medium	Coronary artery	Present	(64, 77, 84, 116)
ANCA-associated vasculitis	Small	Glomeruli	Present	(62, 108–110)
Anti-GBM disease	Small	Glomeruli	Absent	(149)
Cryoglobulinemic vasculitis	Small	Glomerular tuft	Absent	(150)
Primary angiitis of the central nervous system		Transmural	Present	(147)
Thromboangiitis Obliterans		Intima, Thrombi	Absent	(118, 151)

ANCA, anti-neutrophil cytoplasmic antibody; GBM, glomerular basement membrane.

Table 2

Macrophage polarization and vascular inflammation

	M1	M2
Atherosclerosis	Atherogenic	Atheroprotective and atherogenic
	Endothelial activation Chemotaxis of inflammatory cells Weakening of cap Oxidative stress Prothrombotic activity Enlargement of necrotic core ? antigen presentation	Uptake of oxidized lipoproteins Efferocytosis Production of IL-10 and TGF-β Promotion of neoangiogenesis
Vasculitis	Vasculitogenic	Vasculitogenic
	Granuloma formation Giant cell formation Endothelial activation Oxidative stress Digestion of elastic tissues Media thinning Intimal hyperplasia ? antigen presentation	Granuloma formation Giant cell formation Neoangiogenesis Intimal hyperplasia ? efferocytosis

Table 3

Therapeutic strategies targeting macrophage function

Depletion of macrophages	Clodronate Nitric oxide donors Mammalian target of rapamycin inhibitors Protein synthesis inhibitors Statins
Reduction of macrophage recruitment/retention	Prodrug of dexamethasone VCAM-1 inhibitors (e.g. AGI-1067, CAM741) Notch1 TRAF1 TSP-1
Suppression of proinflammatory capabilities	Induction of M2 (IL-4, M-CSF) IL-1β inhibition (e.g. Canakinumab) Prevention of oxidative damage (e.g. GSH) Resetting efferocytosis (e.g. IL-10, LXR agonists) Notch inhibitors