International Journal of Molecular Sciences

MDPI

Review

Immunobiology of Atherosclerosis: A Complex Net of Interactions

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Received: 2 October 2019; Accepted: 22 October 2019; Published: 24 October 2019

Abstract: Cardiovascular disease is the leading cause of mortality worldwide, and atherosclerosis the principal factor underlying cardiovascular events. Atherosclerosis is a chronic inflammatory disease characterized by endothelial dysfunction, intimal lipid deposition, smooth muscle cell proliferation, cell apoptosis and necrosis, and local and systemic inflammation, involving key contributions to from innate and adaptive immunity. The balance between proatherogenic inflammatory and atheroprotective anti-inflammatory responses is modulated by a complex network of interactions among vascular components and immune cells, including monocytes, macrophages, dendritic cells, and T, B, and foam cells; these interactions modulate the further progression and stability of the atherosclerotic lesion. In this review, we take a global perspective on existing knowledge about the pathogenesis of immune responses in the atherosclerotic microenvironment and the interplay between the major innate and adaptive immune factors in atherosclerosis. Studies such as this are the basis for the development of new therapies against atherosclerosis

Keywords: atherosclerosis; monocyte; foam cell; macrophage; monocyte-derived dendritic cell; T-cell; B-cell; conventional dendritic cell; plasmacytoid dendritic cell; regulatory dendritic cell

1. Immune system

The immune system is divided into two main branches, the innate and adaptive responses Figure 1. Innate immunity is enacted by cells of the myeloid lineage characterized by their capacity to produce a rapid and nonspecific response as a first line of defense. Innate immune cells can sense pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) through their expression of pattern recognition receptors (PRRs), such as toll-like receptors (TLRs). Innate immune cells mediate host defense responses and inflammation by producing cytokines and chemokines, activating the complement cascade and phagocytosis, or presenting antigens to activate the adaptive immune response. Prominent cells of the innate immune system include neutrophils, macrophages, and dendritic cells (DCs). The adaptive response occurs later and depends on the presentation of antigens by antigen presenting cells (APCs) and the cytokine milieu generated by the innate response. The adaptive response is specific and relies on $CD4^+$ and $CD8^+$ T cell activation and the production of antibodies by B cells. Natural killer T cells (NKT cells) and γδ T

cells are cytotoxic T lymphocytes at the interface between innate and adaptive immunity. Abundant evidence indicates that innate and adaptive immunity both play important roles in the onset and progression of atherosclerosis [1–3]. For example, *Csf1*$^{-/-}$ mice, which lack macrophage colony stimulating factor (M-CSF, also known as CSF1) are less prone to developing atherosclerosis [4]. Moreover, mice lacking B and T cells (*Rag1*$^{-/-}$ or *Rag2*$^{-/-}$ mice lacking recombination-activating genes 1 or 2 or mice carrying the severe combined immunodeficiency (SCID) mutation) are resistant to atherosclerosis in the presence of mild hypercholesterolemia [5–10].

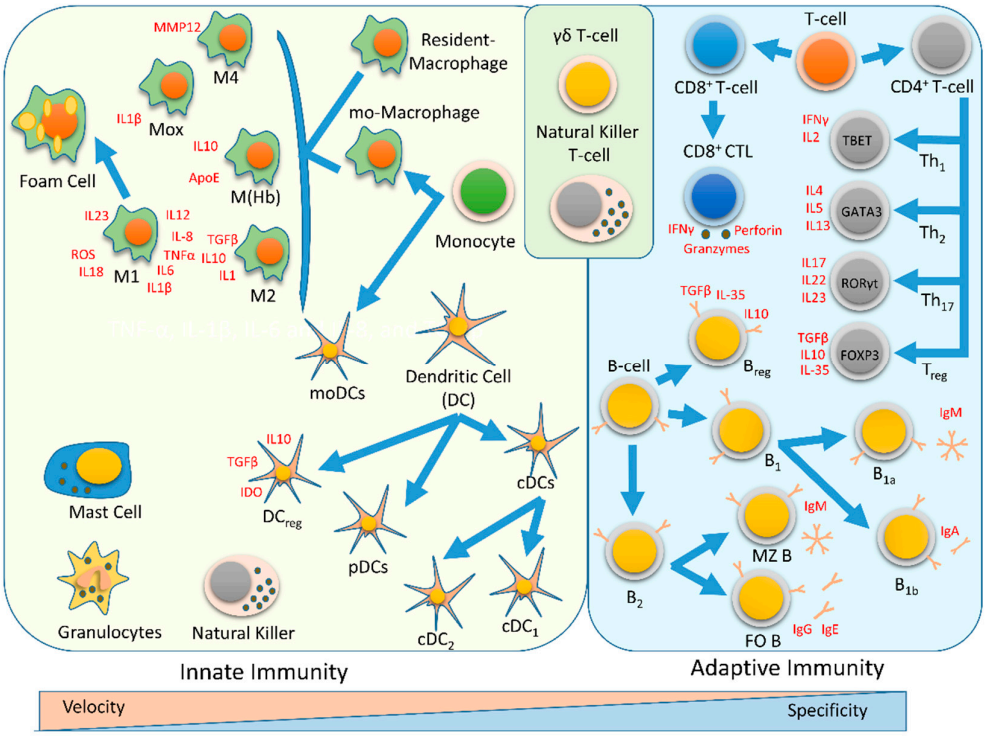

Figure 1. The innate and adaptive immune system in atherosclerosis. The immune system is divided into two main branches: innate and adaptive immunity. Innate immunity is mediated by monocytes, macrophages, dendritic cells, granulocytes, mast cells, and natural killer cells, and is characterized by the capacity of these cells to produce a rapid and nonspecific response as a first line of defense. Innate immune cells mediate host defense responses and inflammation by releasing cytokines and chemokines, activating the complement cascade and phagocytosis, and activating the adaptive immune response via antigen presentation. The adaptive immune response occurs later and depends on the presentation of antigens by antigen presenting cells (APCs) and the cytokine milieu generated by the innate response. The adaptive response is specific and relies on CD4^{+} and CD8^{+} T cell activation and antibody production by B cells. Natural killer T (NKT) cells and γδ T cells are cytotoxic T lymphocytes at the interface between innate and adaptive immunity. Abundant evidence points to a role of innate and adaptive immunity in the onset and progression of atherosclerosis. Several immune cell types play a proatherogenic role, including Th1 cells, M1 macrophages, and some B cells. In contrast, Tregs, Bregs, and DCregs have atheroprotective effects. DC, dendritic cell; moDC, monocyte-derived DC; mo-Macrophage, monocyte-derived macrophage; pDC, plasmacytoid DC; cDC, conventional DC; FO B, follicular B cell; MZ B, marginal zone B cell; Breg regulatory B cell; Treg, regulatory T cell.

2. Atherosclerosis's Epidemiology

Atherosclerosis is the leading cause of coronary artery disease, morbidity, and mortality worldwide [11,12]. Almost all individuals have atherosclerotic plaques [13], and even when lipids have been reduced to nominally safe levels and plaque development has been arrested, there is still

a high probability of sudden thrombotic events leading to myocardial infarction or stroke [14]. Atherosclerosis is characterized by systemic inflammation, and high levels of C-reactive protein (CRP), a circulating predictor of inflammation [15], are found in patients, so it has been proposed as a biomarker of atherosclerosis [16]. Atherosclerosis is a silent disease until increased intimal thickening eventually either diminishes or blocks blood flow, inducing ischemia in downstream tissues, or triggering thrombosis after atherosclerotic plaque rupture [17,18], resulting in myocardial infarction (MI) or stroke [19].

3. Atherosclerosis's Pathophysiology

Atherosclerosis is a chronic inflammatory disease of large and medium-sized arteries [20], characterized by endothelial dysfunction and the accumulation of low-density lipoproteins (LDL), immune cells, and necrotic debris in the subendothelial space, resulting in the formation of an atherosclerotic plaque [21–24]. LDL deposition is more likely in regions with turbulent flow and low shear stress [25] sensed by the vascular endothelium [26]. Turbulent flow modulates endothelial transcriptional and post-transcriptional programs, priming the endothelium for later cytokine activation [27]. Lipid accumulation also stimulates vascular smooth muscle cells (VSMC) and endothelial cells to generate inflammatory mediators and cytokines [28,29], contributing to the initial steps of the atherosclerotic process [30,31]. These changes increase endothelial damage and impair endothelial healing [32]. Endothelial cell activation induces the expression of leukocyte adhesion molecules, such as endothelial-selectin (E-selectin), P-selectin, and the glycoproteins intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). This is followed by the production of chemokines, such as monocyte chemoattractant protein-1 (MCP-1), which stimulates monocyte migration and infiltration through its receptor C-C chemokine receptor 2 (CCR2). Similarly, interleukin (IL)-8 and fractalkine promote cell migration through C–X–C chemokine receptor type 2 (CXCR2) expressed on leukocytes [27,33,34]. Infiltrating monocytes mature into macrophages in response to macrophage colony-stimulating factor (M-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) [35]. LDLs are modified by oxidation (oxLDL), enzymatic processing, desialylation and aggregation [36]. Macrophages differentiate into foam cells after recognizing and internalizing oxLDLs via an array of scavenger receptors, including scavenger receptor class A (SR-A), CD36, lectin-like oxidized LDL receptor-1 (LOX-1), scavenger receptor for phosphatidylserine and oxidized lipoprotein (SR-PSOX), and scavenger receptor class B type 1 (SR-B1). Moreover, oxLDLs, acting as DAMPs, stimulate TLRs in macrophages, aggravating inflammation in the plaque. Cholesterol efflux from macrophages is regulated by ATP binding cassette transporter A1 (ABCA1) [37]. Therefore, macrophages in the plaque show abnormal lipid metabolism with reduced cholesterol efflux, increased cell death, and reduced efferocytosis, leading to an inflammatory state [11] Figure 2.

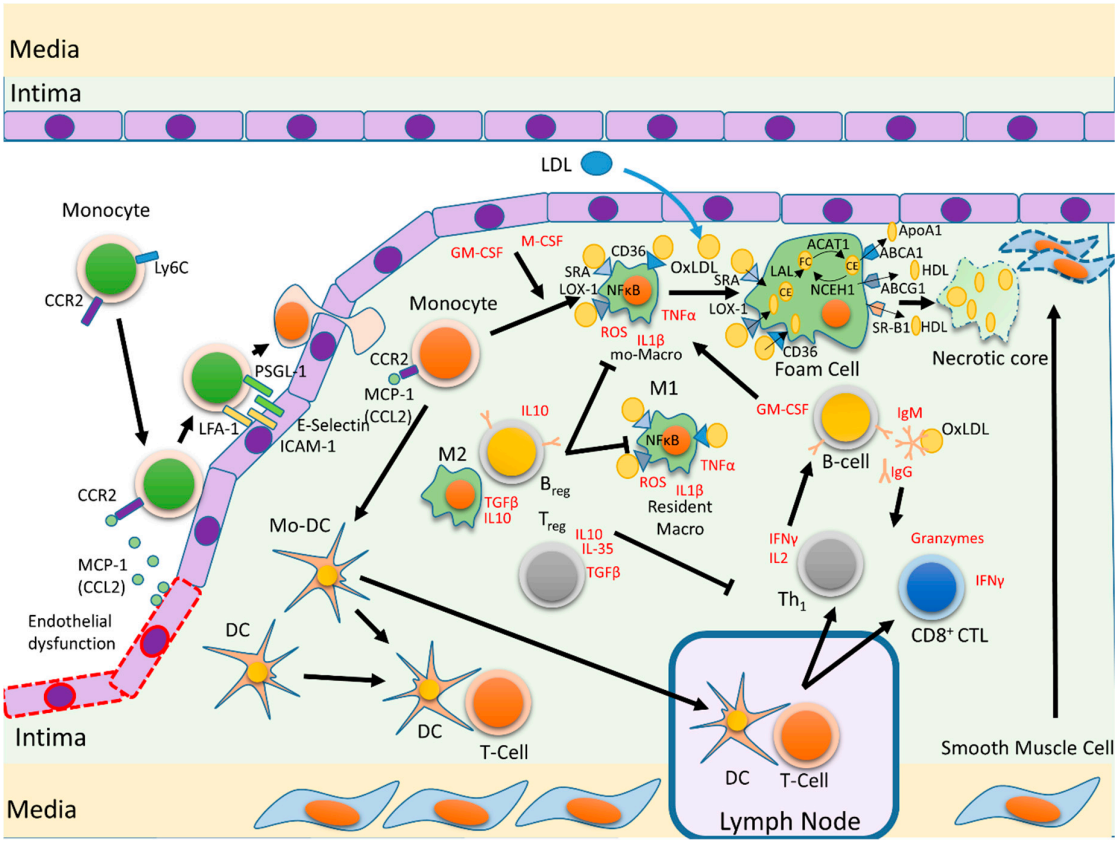

Figure 2. Pathogenesis of atherosclerosis. Atherosclerosis is a chronic inflammatory disease characterized by endothelial dysfunction and accumulation of low-density lipoproteins (LDLs), immune cells, and necrotic debris in the subendothelial space. Endothelial activation triggers the expression of leukocyte adhesion molecules, such as E and P-selectins, the glycoproteins ICAM-1 and VCAM-1, and the chemokine MCP-1, which signals via CCR2 to stimulate migration and infiltration of inflammatory monocytes. LDL deposition promotes the release of M-CSF and GM-CSF, which facilitates the maturation of infiltrating monocytes into macrophages or dendritic cells. LDLs give rise to modified-LDLs (especially oxLDL) that are recognized by macrophage scavenger receptors, such as CD36, LOX-1, and SR-A. These scavenger receptors activate NFκB signaling in macrophages, enhancing the release of proinflammatory cytokines, such as IL1β and TNFα, and leading to the generation of foam cells. Foam cells uptake ox-LDL, and LAL converts cholesterol esters (CE) into free cholesterol (FC) and free fatty acids. FC can be converted into CE by ACAT1 and ACAT2. NCEH1 transforms CE into FC. FC can be transported outside the foam cell by ABCA1, ABCG1, and SR-B1. APCs, such as DCs, process intraplaque oxLDLs and stimulate the adaptive immune response by presenting oxLDL-derived antigens in atheromatous plaques and in secondary lymphoid organs. M1 macrophages, Th1 cells, and some B cell subtypes promote atherosclerosis by the production of proinflammatory cytokines and chemokines, among other mechanisms. In contrast, Bregs, Tregs, M2 macrophages, and tolerogenic DCs suppress inflammation, reducing plaque size and stabilizing atheosclerotic lesions through several mechanisms. Plaque development is also promoted by the differentiation of smooth muscle cells to a proliferating phenotype.

OxLDLs also function as immune antigens [38]. DCs and other APCs process intraplaque oxLDLs and stimulate the adaptive immune response by presenting oxLDL-derived antigens in atheromatous plaques and in secondary lymphoid organs [39–42]. Consequently, $CD4^+$ and $CD8^+$ T cells are present in the plaque almost as early as monocytes [43] and play essential roles in its development [39,44]. The inflammatory response in the atherosclerotic lesion is also modified by infiltrating B cell subsets [42].

After these initial steps, plaques progress to advanced lesions, composed of lipid droplets, foam cells, macrophages, and lymphocytes [45–47]. These cells produce a plethora of cytokines and mediators with important roles in atherosclerotic progression [45–47]. Smooth muscle cell growth [48] and the production of collagens, matrix metalloproteinases (MMPs), fibronectin, and elastin also contribute to plaque development [20,49,50]. Among other cell types, macrophages can stimulate production of MMPs that destabilize the plaque by stimulating the production of proinflammatory cytokines [51,52]. Moreover, in advanced plaques, smooth muscle cells, macrophages, and foam cells undergo apoptosis and necrosis, leading to the formation of the necrotic core [53]. Local inflammation in the intima stimulates inflammation in other vessel layers by systemic inflammation in other organs, including adipose tissue and the liver [54,55].

4. Innate Immunity

4.1. Monocytes

The mononuclear phagocytic system consists of circulating monocytes, monocyte-derived DCs and macrophages, resident macrophages, and DCs [56]. These cells participate in scavenging, inflammation, and anti-pathogen defenses, both in the direct response to foreign agents and in shaping each diverse phase of the inflammatory response [57]. Circulating monocytes, which originate in the bone marrow, are generally found in blood, bone marrow, and the spleen in healthy animals [58]. Circulating monocytes and resident vascular macrophages are the first leukocytes to be recruited to the early atheromatous plaque [59]. Local inflammation is initiated by damaged endothelial cells, which release MCP-1 (also known as C–C motif chemokine ligand 2 (CCL2)). MCP-1 interacts with C–C chemokine receptors (CCR)2 and CCR4 expressed on circulating monocytes, recruiting them to the lesion [60–63]. Monocyte recruitment also depends on other cytokines and chemokines, including IL-8, CCL3, CCL4, and CCL5 [64–66].

Several monocyte subsets are recruited to the atheromatous plaque, with the most common subset in mice being lymphocyte antigen 6 complex high ($Ly6C^{hi}$) monocytes [67]. In humans, the most prevalent monocytes in the plaque are $CD14^{+}CD16^{-}$ cells, known as classical monocytes [68,69]. $CD14^{+}CD16^{-}$ and $Ly6C^{hi}$ monocytes both express CCR2[69]. $CD14^{+}CD16^{-}$ monocytes have a proinflammatory phenotype [70], and their number is increased in hypercholesterolemic conditions [71]. Human atherosclerotic plaques also contain $CD14^{+}CD16^{hi}$ monocytes (nonclassical) and $CD14^{hi}CD16^{+}$ monocytes (intermediate). Activated $CD14^{hi}CD16^{+}$ monocytes produce large amounts of proinflammatory molecules, such as tumor necrosis factor (TNF) α [72], and have been implicated in atherosclerotic progression [70]. Recruited monocytes are an important systemic source for renewal of tissue macrophages and DCs [73,74], but they are not the only source of plaque monocytes, which can also originate from a local proliferation of monocytes and resident macrophages [75] that maintain their capacity to mature and reach a phagocytic phenotype. Apart from their role as macrophage and DC precursors in atherosclerotic plaques, monocytes can trigger and modulate T-cell responses [76,77], regulate angiogenesis, and exert effector functions as accessory cells in atherogenesis [78]. Increased numbers of circulating proinflammatory monocytes have been found in mouse models of atherosclerosis, such as $ApoE^{-/-}$ mice [79]. Similarly, a high number of intermediate $CD14^{hi}CD16^{+}$ circulating monocytes seems to be related to increased atherosclerotic risk in unstable angina patients [80], and upregulation of TLR-4 on intermediate $CD14^{hi}CD16^{+}$ monocytes is associated with coronary plaque vulnerability in patients with angina pectoris [80,81].

In mice, circulating monocytes are recruited to the subendothelial space by P and E-selectin-mediated tethering and rolling and ICAM1 and VCAM1-mediated adhesion [34]. Knockdown of VCAM-1 [82] or its inhibition with the antioxidant AGI-1067 [83] results in reduced atherosclerosis in $LDLR^{-/-}$ mice.

Monocyte migration to the subendothelial space depends on signaling via CCR2, CCR5, and CX3C-chemokine receptor 1 (CX3CR1). A blockade of these receptors decreases monocyte recruitment and reduces atheromatous plaque size in $ApoE^{-/-}$ mice [60]. Monocyte recruitment and subsequent atherosclerosis in $ApoE^{-/-}$ mice are also reduced by inhibiting the chemoattractants CCL2,

CXCR1, CCR5, and M-CSF, either by pharmacological blockade [60] or genetic inactivation [4,84]. Migrated monocytes differentiate into macrophages that contribute to inflammation and plaque development [79]. In the course of hematopoiesis, the differentiation of monocytes into macrophages is triggered by M-CSF and GM-CSF [85]. Circulating monocytes differentiate in response to stimuli such as inflammation and infection, with inflammation playing an essential role in atherosclerotic development [86].

4.2. Macrophages

The early stages of atherosclerosis are characterized by the formation of fatty streaks, and these early lesions contain many macrophages [44]. Macrophages in atherosclerotic plaques maintain local inflammation by producing reactive oxygen species (ROS) and secreting inflammatory cytokines and chemokines, including TNF-α, IL-1β, IL-6, IL-8, and TGF-β, which promote chemotaxis of B and T-cells and macrophages toward the plaque [87]. Intraplaque macrophages have a reduced migratory capacity, acting instead to maintain inflammation and support plaque progression [36,88,89]. Monocytes enter into the arterial intima and differentiate to macrophages [90] but proliferation of artery wall macrophages has been associated with increased plaque development in advanced atherosclerotic lesions [91,92]. Macrophages in lesions internalize and accumulate lipoproteins, converting to foam cells filled with lipid droplets. The accumulation of foam cells drives plaque growth [93]. All phases of atherosclerosis are characterized by macrophage apoptosis and necrosis, which lead to the formation of the necrotic core in progressing plaques [94]. This exacerbates the accumulation of inflammatory cells and impairs the removal of dead cells (efferocytosis), further increasing plaque size and instability [95–97].

Macrophages are highly plastic, a property that allows them to hone responses to the specific microenvironment [98–100] [101]. Moreover, plaque composition and macrophage polarization are interdependent, each influencing the each other [102]. Differentiation of recruited monocytes into macrophages in the plaque is determined by several factors, including the local microenvironment [103], macrophage metabolic state [104,105], gut microbiota-derived metabolites [106], and genetic and epigenetic factors [107].

The classical classification of macrophages envisions two phenotypes, M1 and M2 [108–110]. Monocytes give rise to M1 or M2 macrophages in response to exposure to GM-CSF or M-CSF, respectively [111–115], and the predominance of M1 or M2 macrophages in atherosclerotic lesions has been proposed to reflect local M-CSF and GM-CSF concentrations [116]. Complete M1 macrophage differentiation is achieved after exposure to Th1 cytokines, including TNFα and interferon (IFN)-γ, produced upon lipopolysaccharide recognition by TLR or lipoproteins [117].

M1 macrophages are considered proinflammatory cells due to their capacity to secrete abundant proinflammatory factors, such as TNF-α, IL-1α, IL-1β, IL-6, IL-12, IL-18, IL-13, and IL-23, and the chemokines CXCL9, CXCL10, and CXCL11. Proinflammatory macrophages also produce ROS and nitric oxide (NO) [36,118–120].

M2 (or alternatively polarized) macrophages can be further divided into four different subsets, M2a, M2b, M2c, and M2d, depending on the activating stimulus [98,99,121,122]. The M2a subset is induced by exposure to the Th2 cytokines IL-4 and IL-13 and expresses high levels of the mannose receptor (CD206) and IL-1 receptor agonist (IL1RN). These cells secrete the anti-inflammatory cytokines IL-10, IL-1, and TGF-β and profibrotic factors, such as fibronectin, that contribute to tissue remodeling [99,121,122]. M2b macrophages are induced by immune complexes, TLR agonists, and IL-1 receptor agonist [99,121,122]. M2c macrophages are induced by glucocorticoids, TGFβ, and IL-10 and produce the anti-inflammatory molecules pentraxin-3 (PTX3), TGFβ, IL-10, and Mer receptor kinase (METK). M2c macrophages are responsible for the removal of apoptotic cells [121,123]. M2d macrophages differentiate in response to TLR signaling via the adenosine A2A receptor; these cells produce large amounts of IL-10 and vascular endothelial growth factor (VEGF) and promote angiogenesis in tumors and atherosclerotic plaques [99,122,124]. M2 macrophages, with the exception of the M2b subset, produce large quantities of anti-inflammatory cytokines, such as IL-10 [125].

Atherosclerotic lesions also contain other macrophage phenotypes. Mox macrophages are inflammatory cells that lack CD163 expression and show reduced phagocytic and chemotactic abilities and an elevated capacity for TLR-2-dependent production of IL-1β and cyclooxygenase-2 (COX-2) in an oxLDL-rich microenvironment [126]. Mox macrophages account for almost a third of the total macrophage content of advanced atherosclerotic plaques in mice [120,127] and play an antioxidant role dependent on their overexpression of Nrf2-related genes, such as *heme oxygenase-1* (*HMOX-1*), *sulforedoxin-1*, and *thioredoxin reductase* [127] [126,128]. Mox macrophages were initially described only in mouse models of atherosclerosis [127] [129] but have since been identified in humans [130].

Blood vessel injury releases erythrocytes and iron-holding pigments, which can be phagocytosed by macrophages [131,132]. Human atherosclerotic plaques in which neovascularization takes place contain iron deposits that can trigger the differentiation of M(Hb) macrophages [133] (also known as Mhem [134]). M(Hb) macrophages express the scavenger receptor cysteine-rich type-1 protein M130 (CD163) and macrophage mannose receptor 1 (MMR, known as CD206) [135], along with heme-dependent activating transcription factor 1 (ATF1) which induces expression of heme oxygenase 1 and liver X receptor β (LXR-β). The expression of the LXR-β-dependent genes *LXR-α* and *ABCA1* by this macrophage subtype increases cholesterol efflux [133,136], and M(Hb) macrophages have an antiatherogenic role related to their low lipid-loading capacity and anti-inflammatory properties, mediated through the production of IL-10 and apolipoprotein E [137] [133,138].

M4 macrophages are produced by stimulation with the chemokine C–X–C motif chemokine 4 (CXCL4) [139,140] and play a proatherogenic role through the production of MMP12 and the promotion of plaque instability [141] [120]. M4 macrophages have a lower capacity for phagocytosis than M1 and M2 macrophages [142] and limit the generation of Mhem macrophages [127]. Another intraplaque macrophage subtype is the IL-17A-stimulated macrophage [143].

Macrophages play decisive roles at all stages of atherosclerotic lesion progression [89,144], and intraplaque macrophage subtypes are heterogeneous [145]. Both M1 and M2 macrophages are found in atherosclerotic lesions [120,146,147], with M1 macrophages found in the lesion shoulder, which is the least stable region of the plaque, while both M1 and M2 macrophages are found in the fibrous cap, close to the necrotic core [120,148–150]. The production of proinflammatory factors by M1 macrophages results in inflammatory cell recruitment, accelerated plaque development [151], and increased necrotic core formation and plaque vulnerability, leading to thrombotic events [152]. In contrast, M2 macrophages play an anti-inflammatory and atheroprotective role through the inhibition of cell recruitment and tissue remodeling [153]. M2 macrophages also reduce foam cell formation [150] and increase plaque stability [154]. The proinflammatory and anti-inflammatory intraplaque macrophage content can, thus, serve as an index of plaque progression/instability or regression.

LDLs induce proinflammatory macrophage polarization by increasing the production of TNFα and IL-6 and reducing the expression of the anti-inflammatory M2 markers CD206 and CD200R [155]. Modified LDLs promote a stronger proinflammatory phenotype in macrophages upon recognition by TLRs and scavenger receptors like CD36 [156]. OxLDLs also promote a switch in macrophage phenotype from M2 to M1 [157].

Some studies suggest that atherosclerosis's development might be influenced by macrophage polarization in non-arterial tissues, as described in the epicardial adipose tissue of patients with coronary artery disease [158,159].

4.3. Foam Cells

Accumulation of lipoproteins in the arterial intima is a key element in the onset and development of atherosclerosis [160]. Lipoproteins with a diameter below 70 nm include high density lipoproteins (HDL), LDL, intermediate-density lipoproteins (IDL), most very low-density lipoproteins (VLDL), and some chylomicrons, and these biochemical assemblies can cross the endothelium from the blood and enter the arterial intima [161,162], where they are modified by

oxidizing agents, proteases, and lipases [163–165], generating oxLDLs, acetylatedLDLs, etc. Modification of LDLs also induces their aggregation [165]. These aggregated and modified LDLs can be internalized by VSMCs, DCs, and especially by macrophages, triggering their conversion to foam cells [160,166].

Lipid metabolism in macrophages depends on cholesterol uptake, esterification, and efflux. An imbalance among these processes results in the formation of lipid-dense macrophages, called foam cells [167], and most foam cells are derived from macrophages with a disproportionate influx of modified LDLs and cholesterol esters [168,169]. However, a small fraction of foam cells originate from VSMCs and endothelial cells [170,171]. Monocytes are also important in foam cell formation [172,173]. Macrophages internalize modified or native LDLs after binding by scavenger receptors; eight proteins able to bind modified lipoproteins have been described in macrophages [174–176], the best described being SR-A1, CD36, and LOX-1. Scavenger receptors can be modulated by MEKK-2 [177], MAP kinase [177,178], and STA [179]. Macrophages generate cholesterol esters through the action of acyl-coenzyme A: cholesterol acyltransferases (ACATs) [180]. Lipoprotein uptake and cholesterol ester generation are balanced in homeostatic conditions by the hydrolysis of cholesterol esters to free fatty acids and of cholesterol by neutral cholesteryl ester hydrolase 1 (NCEH1) and lysosomal acid lipase (LAL) [181,182]. Cholesterol efflux is mediated by ABCA1, ATP-binding cassette sub-family G member-1 (ABCG1), and scavenger receptor SR-B1 [183]. In disease conditions, this balance is disrupted by the increased macrophage expression of LOX-1 induced by proinflammatory cytokines and by the high levels of oxLDL [181], accompanied by decreased expression of ABCA1 and ABCG1 [184]. These changes result in the intracellular accumulation of cholesterol and the generation of foam cells. Foam cells have less proinflammatory capacity than M1 macrophages in response to the M1-polarizing factors LPS and IFN-γ. In contrast, foam cells develop an anti-inflammatory response similar to M2 macrophages in response to the M2-polarizing signal IL-4 [185]. Indeed, foam cell accumulation in M1-polarizing plaques results in attenuation of macrophage-associated inflammation.

Increased LOX-1 expression in atherosclerosis is also observed in endothelial cells [186], leading to PKC activation. Subsequent activation of RhoA/Rho kinase and protein phosphatase 1 regulatory subunit 14A (PPP1R14A) leads to occludin phosphorylation [187] and cytoskeketal rearrangement [188], respectively. LOX-1 overexpression reduces the expression of the desmosome components desmoglein 1 (DSG1) and desmocollin 2 (DSC2), downregulating desmosomal intercellular contacts [186,189]. Through these mechanisms, atherosclerosis-induced LOX-1 overexpression impairs intercellular interactions, promotes endothelial permeability to oxLDL and its access to the subendothelial space, and enhances foam cell formation [171].

OxLDL and other modified LDLs are internalized by altered phagocytosis [120]. SR-A1 exists in three isoforms. The full-length SR-A1 and shorter SR-A1.1 isoforms are encoded by the *MSR-1* gene and participate in oxLDL recognition and internalization, whereas the lipid-transport-dysfunctional SR-A1.2 isoform acts as an inhibitor of the other two isoforms [190,191]. SR-A1 and SR-A1.1 have high affinity for acetylated LDL and oxLDL [192]. The knockout of *SR-A1* in ApoE$^{-/-}$ and LDLR$^{-/-}$ mice inhibits foam cell formation and reduces atherosclerosis [193,194]. A similar reduction in atherosclerosis is observed in MSR-1$^{-/-}$, ApoE$^{-/-}$ [195], and MSR-1$^{-/-}$ LDLR$^{-/-}$ mice [196,197]. Total or macrophage-specific deletion of SR-As results in fewer atherosclerotic lesions [197]. SR-A1 expression is upregulated by proinflammatory cytokines via NFκB [198] and is downregulated by polyphenols via inhibition of peroxisome proliferator-activated receptor γ (PPARγ) and by curcumin via calpain-associated ubiquitination and degradation [199].

CD36 is a member of the B family of scavenger receptors [200,201]. OxLDL-dependent CD36 production regulates inflammation through the induction of the TLR4/TLR6 complex assembly, NFκB activation, and chemokine release [202]. Accordingly, CD36 deficiency in macrophages diminishes cytokine production [203]. CD36 inhibition reduces oxLDL content in the arterial wall [204–207].

In macrophages, CD36 levels can be upregulated by curcumin-induced expression of nuclear factor (erythroid-derived 2)-like 2 (NFE2L2) [208], whereas in monocytes, CD36 is increased by LPS

via upregulation of AP-1 transcription factors [209] and by palmitate [210]. CD36 can be inhibited by ceramides in monocytes [211] and by plant antioxidant in macrophages [212–214]. *CD36* knockout in ApoE$^{-/-}$ mice protects against atherosclerotic lesion development only in males [215]. In contrast, CD36$^{-/-}$-ApoE$^{-/-}$ females show a relative increase in the number of atherosclerotic lesions [216].

LOX-1 is highly expressed in atherosclerotic plaques in humans [217] and in macrophages during atherosclerosis [181], accounting for 40% of oxLDL internalization [218]. LOX-1 is induced in macrophages by proinflammatory cytokines [181], oxLDL [219], LPS [220], advanced glycation end-products [209], and ROS [221]. In mouse models of atherosclerosis, *LOX-1* knockout decreases disease and inflammation, whereas LOX-1 overexpression has the opposite effect [220–223].

The accumulation of cholesterol esters in macrophages leads to the generation of foam cells. The transformation of cholesterol to cholesterol esters is catalyzed by acetyl-CoA acetyltransferase (ACAT1) [180], and the reverse process is mediated by NCEH [181,182].

Atherosclerosis in LDLR$^{-/-}$ mice is aggravated by macrophage-restricted depletion of ACAT1 [224]. In contrast, systemic ACAT1 deficiency ApoE$^{-/-}$ and LDL$^{-/-}$ mice does not affect atherosclerosis, but these mice develop dermal xanthomas and form cholesterol deposits in the brain [225]. Pharmacological inhibition of ACAT1 increases plaque formation in mouse and rabbit models of atherosclerosis [226]. ACAT1 activity or expression can be modulated by several molecules, such as the non-specific inhibitor F-1394 [227], the intestinal hormone Ghrelin via PPARγ [228], protein kinase A (PKA) via incretin hormones [229], dipeptidylpeptidase 4 (DDP4) via the incretin hormone glucagon-like peptide-1 (GLP-1) [230], insulin via CCAAT/enhancer-binding protein α (C/EBPα) and extracellular signal-regulated kinase (Erk), p38MAP kinase, Jnk [231], and leptin via janus-activated kinase 2 (Jak2)/phosphatidylinositide 3-kinase (PI3K) [232].

NCEH hydrolyzes cholesterol esters to release free cholesterol [182] that can be exported from the cell. In mouse models, NCEH inhibition increases atherosclerosis [233], whereas NCEH overexpression diminishes the lesion's necrotic core [234]. NCEH overproduction in macrophages also reduces cholesterol esters [235]. The NCEH1 isoform accelerates atherosclerosis in ApoE$^{-/-}$ mice [236]. NCEH and NCEH1 inhibit foam cell generation [237,238].

Cholesterol efflux is mediated by the transporters ABCA1 and ABCG2 and the scavenger receptor SR-B1, and by passive membrane diffusion with simultaneous genetic disruption of ABCA1; and SR-B1 potentiates foam cell formation but has no effect on lesion development [239]. In LDLR$^{-/-}$ mice, ABCA1 overexpression in the liver leads to the accumulation of proatherogenic LDL and enlarged aortic atherosclerotic lesions [240].

The effect of ABCG1 deletion is antiatherogenic [241] or moderately proatherogenic [242], depending on the study. SR-B1 overexpression has an atheroprotective effect, whereas its deletion produces a proatherogenic phenotype, demonstrating the antiatherogenic role of SR-B1 [243].

ABCA1 is regulated by transcription factor liver X receptor α (LXRα) [244], the flavonoid quercetin via the PPARγ/LXRα pathway [245], proteasome inhibition [246], and ApoA-1 [247]. Foam cell formation is reduced by ABCA1 upregulation by C–X–C motif chemokine 5 (CXCL5) [248], as well as cAMP, sterols, and PPARγ agonists [249]. ABCA1 expression is negatively regulated by unsaturated free fatty acids via PKCδ-dependent phosphorylation [250,251] and by IL-12 and IL-18 via activation of the zinc finger protein ZNF202 [252]. Macrophage ABCA1 and ABCG1 can be upregulated by the monoterpenoid cineol [253] and by olive-oil [254]. ABCA1 and ABCG1 levels are increased by the gut microbiota metabolite—protocatechuic acid (PCA), acting via miR-10b [255]. ABCG1 and SR-B1 levels are increased by caffeic and ferulic acids [256]. LXRα and SR-BI are enhanced by resveratrol and 13-hyroxy linoleic acid via PPARγ [257,258]. ABCA1, ABCG1, and SR-B1 are reduced via LXRα by the metalloproteinase pappalysin-1 (PAPPA), which hydrolyzes insulin-like growth factor-binding proteins (IGFBP) [259].

The accumulation of cholesterol crystals provokes the production of pro-inflammatory cytokines by M1 macrophages via the caspase-1-activating NLRP3 inflammasome [260]. Moreover, cholesterol esters induce the M1 phenotype by activating TLR4 and inducing the NF-κβ pathway [261]. A major product of cholesterol ester oxidation, 9-oxononanoyl-cholesterol, increases the release of TGF-β and

promotes the generation of anti-inflammatory macrophages [262]. In addition, conjugated linoleic acid promotes M2 polarization by augmenting IL-10 production [44,263]

4.4. Dendritic Cells

DCs link the innate and adaptive immune systems by presenting antigens to T cells. Immature DCs patrol tissues under physiological conditions. Upon activation, maturing DCs increase the expression of MHC class II (MHCII) and the costimulatory molecules CD80, CD86, and CD83 [264,265] and migrate to draining lymph nodes, where they stimulate the adaptive immune response by priming T cells and secreting cytokines [266]. Key features of DCs include stellate morphology, high expression of MHCII, and the capacity to take up, process, and present antigens, such as those derived from apolipoproteins [267].

Several DC subsets derive from a specific precursor population of common dendritic progenitors (CDP). CDPs give rise to plasmacytoid DCs (pDCs) in bone marrow or generate pre-DCs that circulate in blood and give rise to classical DCs (cDCs) in lymphoid and non-lymphoid organs. cDCs can be classified as cDC1 and cDC2 [265,268–271]. pDCs and cDCs are induced by the growth factor fms-like tyrosine kinase 3 ligand (Flt3L) [41]. DCs can also originate from circulating monocytes after their migration to tissues, where they differentiate to macrophages or monocyte-derived DCs through the action of M-CSF or GM-CSF, respectively; these monocyte-derived DCs are considered part of the mononuclear phagocyte system (MPS) [272,273]. Monocyte-derived DCs express CD11c and MHCII, and these markers have been widely used in studies of the role of DCs in atherosclerosis; however, some monocytes and macrophages also express these markers [274]. Following the nomenclature used by other authors [41], herein we refer to $CD11c^+MHCII^+$ DCs as APCs, and use pDC and cDC for more specific DC populations.

During atherosclerosis, endothelial cells enter a state of chronic activation [275], leading to the recruitment of monocytes into the subendothelial intima. Conditions in the intraplaque microenvironment trigger the generation of monocyte-derived DCs. The role of these DCs in atherosclerosis is unclear. A proatherogenic role in the early phases of atherosclerosis has been proposed, [276] as has as an atheroprotective function [88].

$CD11c^+MHCII^+F4/80^-$ APCs have been detected in atherosclerosis-prone areas of the mouse aorta before lesions develop [277,278]. $CD11c^+$ APCs migrate from atherosclerotic plaque upon blockade of CCL19 and CCL21, in a process dependent on CCL7 [279,280]. $CD11c^+MCHII^+$ DCs have been found in atheromatous plaques in mice [281–283] containing Flt3-dependent $CD103^+$ and $CD11b^+$ $CD172a^+$ cDCs [281,282] and monocyte-derived $CD11b^+$ DCs, both of which are M-CSF-dependent [281] and CD64-expressing [282]. In the early stages of plaque formation, $CD11c^+$ APCs can take up lipids and contribute to foam cell formation [276]. DCs in advanced atherosclerotic lesions show the activation of markers, including the costimulatory molecules CD83 and CD86 and cytokines [74,284].

Antigen presentation by DCs has been described in secondary lymphoid organs and in the atheromatous plaque [41,285]. Isolated aortic $CD11c^+MHCII^+$ APCs induce T cell proliferation in vitro [278,286] and stimulate T cell production of TNF-α and IFN-γ [287]. The importance of antigen presentation by APCs in atherosclerosis has been revealed by several studies. In *LDLR*$^{-/-}$ mice, abrogation of the invariant chain of CD74, a protein involved in MHCII-peptide complex formation [288], reduces T cell activation and atherosclerosis; however, in *ApoE*$^{-/-}$ mice, the inability to present antigens on MHCII increases atherosclerosis by reducing the pool of atheroprotective Tregs and increasing proatherogenic $CD8^+$ T cells [289]. The reason for this discrepancy is unknown, but an atheroprotective role of antigen presentation via MHCII is supported by the finding that TLR-activated $CD11c^+$ DCs promote Treg development and function in association with increased atherosclerosis [290]. Additionally, a cDC-specific loss of MHCII causes colitis and reduced Treg activation [291,292]. Atherosclerosis is also affected by the modulation of other key molecules in DCs' function. Lack of TGFβ type II receptor signaling in $CD11c^+$ APCs promotes atherosclerosis in *ApoE*$^{-/-}$ mice [293]. Loss of (HIF)-1α in $CD11c^+$ APCs in *LDLR*$^{-/-}$ mice increases proatherogenic T cell infiltration and the expansion of atherogenic Th1 cells [294]. The ablation of MyD88, a TLR adaptor, in $CD11c^+$ APCs produces a reduction in Tregs [290]. Abrogation of the mechanosensitive Kruppel-

like factor 2 (KLF2) in CD11c$^+$ APCs promotes surface localization of the costimulatory molecules CD40 and CD86 and increased T cell proliferation and apoptosis. After *Klf2*$^{-/-}$ bone marrow transplant to *LDLR*$^{-/-}$ mice, the absence of KLF2 increases the number of DCs in lesions, enhances T cell activation and cytokine production, and increases atherosclerotic lesions' size [295]. APCs also mediate tolerogenic responses by reducing effector T cell functions and enhancing Treg functions [296,297]. In *LDLR*$^{-/-}$ mice, oxLDL-loaded, bone–marrow-derived DCs reduce atherosclerotic lesion size by inhibiting the Th1 response [298], while ApoB100-loaded, bone–marrow-derived DCs achieve the same effect by increasing Treg responses [299].

4.4.1. cDCs

Investigation of the role of cDCs in atherosclerosis has yielded conflicting results. Atherosclerotic plaque size is unaffected in *LDLR*$^{-/-}$ mice, reconstituted with bone marrow depleted of cDCs by the insertion of diphtheria toxin receptor (DTR) into the cDC-specific Zbtb46 locus [300]. However, CD103$^+$ DC depletion in *LDLR*$^{-/-}$*Flt3*$^{-/-}$ mice shows the depletion of aortic Tregs and increased atherosclerosis [301]. Plaque size is unaffected in LDLR$^{-/-}$ mice reconstituted with Baft3$^{-/-}$ bone marrow [302] and in *LDLR*$^{-/-}$*Batf3*$^{-/-}$ mice [303]. However, experiments in *ApoE*$^{-/-}$ *Batf3*$^{-/-}$ mice support a proatherogenic role and elevated Th1 stimulation capacity for Batf3-dependent DCs [304]. These disparities likely reflect the different mouse models used. A proatherogenic function has been described for DNGR1$^+$ CD8α^+/CD103$^+$ DCs [305].

4.4.2. pDCs

Depletion of pDCs in atherosclerotic mouse models has been achieved using a number of antibodies against bone marrow stromal cell antigen 2 (BST2), resulting in enhanced atherosclerosis in *LDLR*$^{-/-}$ mice [306] and reduced atherosclerosis in ApoE$^{-/-}$ mice [307,308]. Injection of diphtheria toxin (DT) to deplete pDCs in LDLR$^{-/-}$ mice, reconstituted with γ-irradiated BDCA2-DTR bone marrow, results in increased atherosclerosis [309]. In contrast, atherosclerosis is unaffected in DT-treated *ApoE*$^{-/-}$ BDCA2-DTR mice [310].

An atheroprotective effect was found upon CD11c-specific deletion of the transcription factor E2-2/Tcf4 in pDCs or impairment of MHCII antigen presentation in pDCs [311], indicating a proatherogenic role of pDCs in MHCII-dependent antigen presentation via T cell responses in atherosclerosis.

Human studies suggest a correlation between low circulating levels of cDCs and pDCs and peripheral artery disease [312], and DC accumulation [313] and activation [314] is associated with plaque vulnerability.

4.4.3. Regulatory DCs

Regulatory DCs can present antigens but express low levels of costimulatory molecules and proinflammatory cytokines, while expressing higher levels of anti-inflammatory cytokines; moreover, regulatory DCs are refractory to maturation signals [315,316]. Regulatory DCs promote immune tolerance by reducing the expression of costimulatory molecules, increasing the expression of inhibitory molecules, such as indoleamine 2,3-dioxygenase (IDO), inhibiting the production of the proinflammatory cytokines IL-12 and TNFα, and promoting the induction of the anti-inflammatory cytokines IL10 and TGFβ [317]. Regulatory DCs mediate depletion and anergy of proinflammatory effector T cells [318,319] and the generation and expansion of atheroprotective Tregs [320].

Self-antigen recognition plays an important role in the chronic inflammation associated with atherosclerosis [321]. The accumulation of native LDLs, oxLDLs, and apolipoprotein B100 (ApoB100) in the vessel wall attracts immune cells and triggers chronic inflammation. The loading of DCs with oxLDL and ApoB100 diminishes the generation of proinflammatory cytokines and promotes the production of Tregs [298,299].

DC tolerance is generated by anti-inflammatory molecules, such as IL-10 and TGFβ, and immunosuppressive enzymes, such as IDO [322]. Adoptive transfer of oxLDL-loaded DCs

exacerbates atherosclerosis [309,323], while intravenous transfer of tolerogenic ApoB100-loaded and IL10-treated DCs attenuates atherosclerosis in hypercholesterolemic LDLR$^{-/-}$ mice expressing human ApoB100 [299].

Apoptotic cells are removed through efferocytosis, and the impairment of this process in atherosclerotic plaques increases inflammation. Intravenous administration of oxLDL-induced apoptotic DCs to LDLR$^{-/-}$ mice reduces atherosclerosis and increases plaque stability by increasing CD103^{+} tolerogenic DC and Treg numbers and reducing the numbers of Ly6C^{hi} monocytes and the level of circulating CCL12 [324]. Further studies are needed to determine the role of tolerogenic DCs in atherosclerosis's onset and development.

5. Adaptive Immunity

Adaptive immunity is a highly precise and lifelong immune response that plays essential roles in distinguishing foreign from self-antigens. Adaptive immunity is mainly mediated by T and B cells, which precisely recognize antigens through the specific receptors expressed on their surfaces, the T-cell receptor (TCR) and B-cell receptor (BCR) [325].

T cells are classified according to membrane and intracellular markers. They express the $\alpha\beta$ or $\gamma\delta$ TCR, CD3, and one of the coreceptors CD4 or CD8. The TCR-CD3 complex recognizes antigens presented in the context of major histocompatibility complex molecules (MHC or human leukocyte antigen (HLA) in humans) by an APC [325].

B cells produce antibodies, act as APCs, and release cytokines. B cells are categorized according to the expression of the cell-lineage marker CD19 and a variety of surface and intracellular proteins; the distinct BCRs they express; and their production of antibodies and cytokines [325].

APCs are able to present antigens to cognate naïve CD4^{+} and CD8^{+} T cells [326]. These antigens include non-self-antigens and self-antigens, including ox-LDLs and heat shock protein 60 (HSP 60) [327]. Upon activation, CD4^{+} T cells proliferate and differentiate into specialized effector T helper (Th) cells, whereas activated CD8^{+} T cells proliferate and differentiate into CD8^{+} cytotoxic T lymphocytes (CTL) [328]. Naïve CD4^{+} T cells can differentiate into various cell subsets, including effector T cells (T helper 1 (Th1), Th2, and Th17) and regulatory T cells (Treg) [329]. T-cell differentiation into varied Th subsets depends on the type of antigen encountered, the TCR signal intensity, and the local cytokine milieu [330–332]. These factors mediate Th polarization in atherosclerotic lesions [333].

5.1. CD4^{+} T Cell

Th phenotypes are classified by the differential expression of surface molecules, transcription factors, and effector cytokines [332]. Th1 cells are characterized by the release of large amounts of IFN-γ and IL-2 and the expression of the master transcription factor T-bet. Th2 cells produce IL-4, IL-5, and IL-13 and express the master transcription factor GATA-3. Th17 produce the cytokine IL-17 and express the transcription factor RORγt [334]. Tregs are defined by the expression of the transcription factor forkhead box 3 (Foxp3) and the extracellular marker CD25.

Although macrophages account for most inflammatory cells in atherosclerotic lesions, T and B cells play an essential role in atherosclerotic plaque development through by their capacity to control immune responses during disease onset and progression [335,336]. Atherosclerotic plaques have been found to contain CD4^{+} and CD8^{+} T cells, B cells, NKT cells, and follicular helper T cells [2,87,337–339]. T cells account for 10% of all cells in human plaques, with 70% of them being CD4^{+} T cells and most of the remaining 30% being CD8^{+} T cells [46]. The most abundant CD4^{+} T cells in the plaque are Th1 cells, but Th2, Treg, and Th17 cells have also be found, as have TCR$\gamma\delta^{+}$ T cells and NKT cells [340–343].

Global CD4^{+} T cell abrogation in ApoE$^{-/-}$ mice confers atheroprotection [344,345], whereas plaque size is increased by adoptive transfer of CD4^{+} T cells from ApoE$^{-/-}$ mice or modified-LDL-reactive CD4^{+} T cells [8]. However, the total abrogation of CD4^{+} T cells results in the absence of proinflammatory and anti-inflammatory cell populations with opposite influences on atherosclerosis.

5.1.1. Th1

Th1 cells play a proatherogenic role in atherosclerosis [45,327,333,346–348]. OxLDLs increase antigen presentation by DCs through HSP60, enhancing T-bet expression, Th1 polarization, and IFN-γ production [349]. Moreover, activated macrophages in atherosclerotic lesions produce IL-12 and IL-18, which also induce Th1 polarization and IFN-γ production [349]. The IL-12–IL-18–T-bet–IFN-γ pathway is a powerful proinflammatory stimulus that promotes and accelerates lesion development, and atherosclerosis is reduced by disruption of the IL12 gene in ApoE$^{-/-}$ mice [350] or by functional blockade of IL-12 with anti-IL-12 antibodies [351], accompanied by increased plaque stability, as indicated by augmented collagen levels. Atherosclerosis in ApoE$^{-/-}$ mice is also reduced and plaques are stabilized by IL-18 blockade with an IL-18 binding protein [352] or by genetic deletion [349].

The Th1 lineage-specific transcription factor T-bet, a member of the of the T box family, promotes Th1 differentiation [353] by binding to the IFN-γ promoter, stimulating IFN-γ production [354]. T-bet deficiency slows atherosclerosis development and increases production of the atheroprotective Th2 cytokines IL-4, IL-5, and IL-10, and IgM antibodies [346]. T-bet also promotes atheroprotection in cooperation with Foxp3 by increasing Treg activity [355].

Th1 cells produce high levels of IFN-γ [333]. IFN-γ promotes plaque development, as shown in ApoE$^{-/-}$ mice by the proatherogenic effect of recombinant IFN-γ injection [356] and the atheroprotective effect of *Ifng* gene knockout [357]. IFN-γ stimulates the IFN-γ cell surface receptor complex (IFN-γR), activating janus kinases (JAK) and recruiting and activating STAT1 (signal transducer and activator of transcription 1), which translocates to the nucleus and stimulates the transcription of IFN-γ target genes, such as *MCP-1* and *ICAM-1* [358]. Inhibition of STAT1's activity in LDLR$^{-/-}$ mice is atheroprotective, confirming the importance of the IFN-γ–JAK–STAT1 pathway during lesion progression [179,359]. IFN-γ modulates the recruitment of immune cells by inducing endothelial cell expression of ICAM-1 and VCAM-1 [360,361] and by promoting foam cell formation through the modulation of key genes involved in cholesterol metabolism, including ABCA1 and ACAT1 [362], and SR-A and SR-SPOX [363–365]. IFN-γ also stimulates CCR5 production in atherosclerosis [343,366].

The proatherogenic effect of Th1 cells in atherosclerosis appears to involve an important role for the chemokine receptor CCR5, a well-known HIV-1 co-receptor, through the T cell recruiting action and other effects of its ligands: macrophage inflammatory protein 1α (MIP-1α, CCL3), MIP-1β (CCL4), and RANTES (regulated on activation normal T cell expressed and secreted, CCL5) [348]. The naturally-occurring human variant CCR5delta32 downregulates *CCR5* gene function. The CCR5delta32 allele has been linked to protection against coronary artery disease [367,368] and heart disease [369] and a lower risk of myocardial infarction [370,371]. However, this protective effect has not been observed in other studies in diverse populations [372–376]. Mouse studies show that CCL5 receptor antagonism [90,377–379] and genetic depletion [65,366,380–383] exacerbate atherosclerosis. The CCR5 blocking antibody maraviroc has been used in HIV patients to block viral entry to CD4 T cells. CCR5 blockade with this antibody also reduces atherosclerosis in mouse models and HIV patients [384,385]. Deletion of CCL5 in ApoE$^{-/-}$ mice reduces atherosclerosis in a CCR5-dependent-manner [386], and in [44AANA47]-RANTES, which prevents CCL5 ligation with glycosaminoglycans, reduces atherosclerosis, and increases plaque stability in LDLR$^{-/-}$ mice [387]. In addition, disruption of TGF-β signaling in CD4^{+} T cells of ApoE$^{-/-}$ mice promotes atherosclerosis by enhancing the Th1 response [388].

5.1.2. Th2

Th2 differentiation is triggered by IL-4 via STAT6-induced GATA-3 expression [389]. Th2 cells are characterized by the production of IL-4, IL-5, and IL-13 and the promotion of B cell-mediated responses. The role of Th2 cells in atherosclerosis remains controversial [327,333]. An atheroprotective role is supported by the association of elevated numbers of circulating Th2 cells with less severe atherosclerosis and a lower risk of acute myocardial infarction in women [390]. Moreover, Th2 cells counteract the proatherogenic effects of IFN-γ-producing Th1. The Th2 cytokines IL-5 and IL-3 appear to be atheroprotective [391–393] through their capacity to augment collagen deposition,

diminish monocyte recruitment, and potentiate M2 polarization [393,394]. ApoB vaccination promotes Th2 responses that reduce atherosclerosis [395]. However, experimental manipulation of the signature Th2 cytokine IL-4, which inhibits Th1 responses [350,396], has produced conflicting results. Adoptive transfer of IL-4$^{-/-}$ bone marrow to LDLR$^{-/-}$ mice significantly reduces atherosclerosis [396], but similar studies in IL4$^{-/-}$ plus *ApoE*$^{-/-}$ or *LDLR*$^{-/-}$ double knockouts showed no effect on atherosclerotic plaque development, and IL-4 administration provided no protection against atherosclerosis [397]. Moreover, IL-4 increases a macrophage's expression of the proatherogenic molecules CD36 [398] and SR-A [399], and of VCAM-1 [400,401], MMP1 [402], and MCP1 [403].

Recent studies suggest that indirect modulation of the Th2 response is atheroprotective. *MHCII*$^{-/-}$*ApoE*$^{-/-}$ double knockout mice show aggravated atherosclerosis and reduced levels of Th2 cytokines in plasma [289]. Similarly, CCL1$^{-/-}$ApoE$^{-/-}$ mice show increased atherosclerosis and an elevated splenocytic Th1:Th2 ratio [404], whereas IL-12p35$^{-/-}$ApoE$^{-/-}$ mice show reduced atherosclerosis and a reduced Th1:Th2 ratio [405]. Notably, these three mouse models all show a significant atheroprotective role of Tregs. In contrast, the Th2 response appears to aggravate atherosclerosis in an asthmatic ApoE$^{-/-}$ mouse model [406].

5.1.3. Th17

Th17 cells have a role in the protection against extracellular pathogens [407]. Th17 differentiation is induced by IL-6 and TGF-β, which mediate the activation of STAT3 and the production of the Th17 signature transcription factor retinoic acid-related orphan receptor γT (ROR γT). Th17 cells and their signature cytokines have been linked to autoimmune diseases [408] and to atherosclerosis [409–413].

Th17 cells are found in human atherosclerotic plaques [414] but appear to have proatherogenic and antiatherogenic properties [409,410], possibly depending on animal model or methodological approach used and reflecting specific responses of Th17 cells to environmental cues [413]. The pathogenic action of Th17 cells in atherosclerosis depends on their capacity to produce proinflammatory factors, such as IL-6, IFN-γ, and GM-CSF [415,416], and some pathogenic Th17 cells are derived from Tregs that lose FOXP3 expression and immunosuppressive properties [417].

Th17 polarization is triggered by several cytokines [410]. IL-23 enhances pathogenic and proinflammatory effects of Th17 cells in humans [418–420], and IL-23 blockade impedes Th17 cell production of IFN-γ and GM-CSF [421]. Pathogenic Th17 cells are also potentiated by IL-1β and TGF-β3 [422] and are differentiated into atheroprotective IL-10-producing cells by TGF-β1 in the intestine [423].

Th17 cytokines play an important role in atherosclerosis. Th17 cells secrete IL-17A, IL-17F, IL-22, and IL-23 [424–426,427]. IL17 stimulates the NF-κB, ERK1/2, CCAAT/enhancer-binding protein β (C/EBPβ), and C/EBPδ signaling pathways [428]. This induces the production of proinflammatory cytokines, including TNFα, IL-1β [429,430], IFN-γ [431], IL-6, IL-8 [432], and GM-CSF [433] in various target cells, such as endothelial cells, smooth muscle cells, macrophages, and Th1 cells [428].

IL-17A can be produced not only by Th17 cells but also by CD8^{+} T cells, γδ T cells, invariant natural killer T cells (iNKT), NKT cells, natural Th17 cells, lymphoid tissue inducer (LTi) cells, group 3 innate lymphoid (ILC3) cells, macrophages, neutrophils, and mast cells [432]. The role of IL-17A in atherosclerosis appears to be complex, with both proatherogenic and antiatherogenic roles reported [14,414,429,434,435]. A proatherogenic role is supported by the capacity of IL-17A to induce VSMC production of proinflammatory factors, such as IL-6, CXCL8, and CXCL10[436], whereas an anti-inflammatory role is suggested by its ability to inhibit the action of VCAM-1 and adhesion molecules on fibroblasts and VSMCs [437] and by its capacity decrease the production of proatherogenic IFN-γ [438].

Several studies have reported that genetic abrogation of *IL-17A* or its receptor in atherogenic mouse models reduces atherosclerotic lesions and plaque vulnerability, supporting a proatherogenic role for IL-17 [429,439–442]. Another study showed that antibody blockade of IL-17A in ApoE$^{-/-}$ mice reduces plaque vulnerability [429]. However, another study indicated that IL17A is atheroprotective and favors plaque stability in LDLR$^{-/-}$ mice [435]. VSMC-dependent release of IL-17C plays a

proatherogenic role by promoting the recruitment of proinflammatory IL-17A-expressing Th17 cells to atherosclerotic plaques [443].

IL-22 is a member of the IL-10 family produced by Th17, Th22, cells, γδ T cells, NKT cells, and ILCs [444–446] that has been linked to proinflammatory and anti-inflammatory roles [447,448] [412,449,450]. IL-22 has been detected in atherosclerotic lesions [451] and reduces cholesterol efflux from macrophages by reducing the expression of the cholesterol efflux transporter ABCG1 [452] and promotes the production of MMP-9 and the proinflammatory cytokines IL-1β, IL-6, and TNFα [412]. IL-22$^{-/-}$ApoE$^{-/-}$ mice show reduced plaque size and increased VSMC integrity [453]. Intriguingly, IL-23 and IL-22 reduce atherosclerosis by repressing proatherogenic microbiota [454].

5.1.4. Tregs

Tregs suppress a wide range of immune cells, including CD4^{+} and CD8^{+} T cells, B cells, and NKT cells and drive DCs and macrophages toward a more tolerogenic phenotype.

Most Tregs express the master regulator of Treg development and function FOXP3, which is used as a marker for their identification. Natural Tregs (nTreg), which are generated in the thymus, mainly mediate tolerance to self-antigens through the expression of IL-10 and TGF-β [333]. nTregs are positive for the markers FOXP3^{+}CD4^{+}CD25^{+} [455,456]. Inducible Tregs (iTregs) are prominently implicated in pathogen tolerance and are generated from naïve T cells in the periphery [457]. iTregs may or may not express FOXP3 and present a variety of phenotypes, including Foxp3^{+}Tregs; IL-10-producing T regulatory type 1 (Tr1) cells, which lack FOXP3 and CD25 expression [458]; and TGF-β-producing T helper type 3 (Th3) cells. Th3 cells intervene in oral tolerance [459], express CD25 and Foxp3, and mediate suppression of Th1 and Th2 proliferation primarily by the release of TGF-β, but not IL-10 [456,460].

Treg cell generation and function is promoted by CD11c^{+}CD103^{+} DCs [290] and signaling from IL-10 and TGF-β [461]. Tregs play an important role in the suppression of immune responses, self-tolerance, and homeostasis [462] by regulating the immune balance.

Tregs exert their immunoregulatory and suppressive activity through several mechanisms [463–465]. One prominent mechanism is contact-dependent cell-mediated inhibition, and Tregs express suppressive surface molecules, such as T-lymphocyte–associated antigen-4 (CTLA-4) and programmed cell death-1 (PD-1). CTLA-4 downregulates APC function and T cell activation by diminishing CD80 and CD86 expression in the APC and by blocking the co-stimulatory interaction between CD80/CD86 in the APC and CD28 in the T cell [466]. Tregs can mediate effector cell eradication by the production of granzyme B [467] or by the generation of the tumor necrosis factor-related apoptosis inducing ligand (TRAIL)/death receptor 5 (DR5) and galectin-1, which promote effector T cell apoptosis [468,469]. Tregs also secrete the immunosuppressive cytokines TGF-β, IL-10, and IL-35 [463].

FOXP3 expression and Treg generation and function are induced by TGF-β [470]. TGF-β reduces plaque size and increases plaque stability by inhibiting the recruitment and activation of proinflammatory cells and by increasing VSMC numbers and promoting collagen accumulation [388]. In ApoE$^{-/-}$ mice, disruption of TGF-β signaling enhances atherosclerosis, whereas TGF-β overexpression reduces atherosclerotic lesion vulnerability and atherosclerosis [388].

IL-10 plays a protective role in atherosclerosis by inhibiting Th1 differentiation and decreasing T cell and macrophage accumulation and by diminishing the production of proinflammatory cytokines [471,472]. In ApoE$^{-/-}$ mice, Tr1 cells, among other cell types, reduce inflammation and plaque lesions by producing IL-10 and reducing the generation of IFN-γ [473].

IL-35, a member of the IL-12 cytokine family, binds to IL-35R and stimulates STAT1 and STAT4 in T cells and endothelial cells [474–477] and STAT1 [478] in B cells [475,479–482]. IL-35 suppresses Th1 and Th17 cell proliferation and function while promoting Treg and regulatory B cell activity [477,482]. IL-35 is found in atherosclerotic lesions [483,484], and its circulating level is reduced in stable angina pectoris patients [484]. Treatment with IL35 reduces atherosclerosis in ApoE$^{-/-}$ mice [485].

Nevertheless, the role of IL-35 is complicated by its sharing of subunits with other IL-12 family members, including subunit IL-12A with IL-12 and subunit EBI3 with IL-27. EBI3 deficiency in LDLR$^{-/-}$ mice reduces atherosclerosis [486], although other studies indicate a proatherogenic role for IL-27 [486,487]. Therefore, further studies are needed to define the role of IL-35 and IL-27 in atherosclerosis.

Tregs mediate immunosuppression by disruption metabolism. Tregs deplete IL-2 from the media [488] and express CD39 and CD73, which then hydrolyze extracellular ATP to produce pericellular adenosine [489,490]. This adenosine activates the adenosine A2A receptor, which potentiates Tregs and inhibits effector T cell functions [491].

Tregs are found in atherosclerotic lesions [492]. ApoE$^{-/-}$ mice fed a hypercholesterolemic diet have fewer Tregs and more atherosclerosis than counterparts fed a normal diet [493]. Atherosclerosis has been linked to a variety of Treg phenotypes [463,494]. Several studies demonstrate a protective role for Treg subsets [463,494,495]. For example, disruption of CD4^{+}CD25^{+} Tregs with anti CD25 antibodies in ApoE$^{-/-}$ mice accelerates the development of atherosclerosis lesions and increases plaque vulnerability [496]. Atherosclerosis is also increased in LDLR$^{-/-}$ mice reconstituted with bone marrow depleted of FOXP3^{+} Tregs using a DT-based procedure [497,498]. Conversely, atherosclerosis is prevented by inducing Tregs with anti CD3 [499,500] and IL-2/anti-IL2 [501] or both monoclonal antibodies [502]. Protection against atherosclerosis is also achieved by reducing the effector T cell to Treg ratio with anti-CD3 monoclonal antibodies [503] or by exposure to ultraviolet B [504].

We recently reported that atherosclerosis is increased in ApoE$^{-/-}$ mice upon inhibition of Treg recruitment in early atherosclerotic plaques by the genetic disruption of *CCL1*, while a similar effect is observed in LDLR$^{-/-}$ mice upon monoclonal antibody blockade of the CCL1-receptor CCR8, suggesting the importance of Treg recruitment in atherosclerosis development [404].

Impairment of Treg function may contribute to the acceleration of atherosclerosis. Tregs from ApoE$^{-/-}$ mice have lower inhibitory Treg function than C57BL/6 mice, similar to the impaired Treg function observed in acute coronary syndrome patients [505]. Similarly, CCL-1 genetic disruption reduces Treg inhibitory capacity in ApoE$^{-/-}$ mice fed a high-fat diet [404].

The importance of Treg abundance and the effector T cell to Treg ratio in atherosclerosis is also supported by human studies. This is suggested by to the impaired Treg function observed in acute coronary syndrome patients [505] and the low abundance of peripheral Treg in patients with acute coronary syndrome or stable angina [506–509] and the higher effector T cell to Treg ratio observed in patients with coronary artery disease than in healthy individuals [510]. Treg numbers in patients with non-ST segment elevation acute coronary syndrome are reduced by apoptosis promoted by oxLDLs [506,509].

These data highlight the importance of the abundance and function of several Treg subsets and Treg-related cytokines in the development of atherosclerosis.

5.2. CD8 T Cells

CD8 T cells play a prominent role in the defense against intracellular pathogens. These T cells recognize antigen via the TCR in the context of ubiquitously expressed MHC class I molecules (MHC-I; HLA-A, B, or C in humans). Upon antigen recognition, naïve CD8^{+} T cells are activated, proliferate, and differentiate into CD8^{+} CTLs [511]. CD8 T cells play effector functions through the release of proinflammatory cytokines [511], such as TNF-α, which can induce apoptosis, and IFN-γ, which promotes MHC-I upregulation and further promotes the inflammatory response. CD8 T cells promote Fas receptor mediated-apoptosis of the target cell through the expression of Fas ligand and target cell lysis through the release of granzymes and perforin [512].

Some studies show no effect or a protective effect of CD8 T cells in atherosclerosis, whereas others report a proatherogenic effect [513]. A neutral or protective action is supported by unaltered atherosclerosis in ApoE$^{-/-}$ mice lacking antigen peptide transporter 1-(TAP1)-dependent MHC-I antigen presentation, despite the low number of CD8^{+} T cells in these animals [514]. Moreover, atherosclerosis in ApoE$^{-/-}$ mice is also unaffected by genetic disruption of CD8a [344]. However, increased plaque development was reported in a MHC-I deficient mouse model with reduced CD8^{+} T cell numbers [515], and the adoptive transfer of CD8^{+} T cells from p210 peptide of ApoB100-

immunized mice slows plaque formation in recipients while expanding CD8 T cells [516], suggesting an antiatherogenic role for at least some $CD8^+$ T cells. Indeed, atherosclerosis can be reduced by the cytolytic action of $CD8^+$ T-cells on proatherogenic DCs [327] and follicular Th cells [517]. Moreover, the plaque microenvironment might potentiate a protective action of CD8 T cells by inducing expression of the ectonucleotidase CD39, which mediates decreased IFN-γ and TNF-α production in CD8 T cells [518].

Other studies support a proatherogenic role of CD8 T cells, as suggested by the increase in $CD8^+$ T cell number as the lesion progresses toward more advanced stages [519], and the increased production of IFN-γ by $CD28^+CD8^+$ T cells in major artery-draining lymph nodes in hypercholesterolemic $ApoE^{-/-}$ mice [520]. Furthermore, CD8 T cell stimulation by the injection of an anti-CD137 antibody increases inflammation and plaque development [521], and CD8 T cell depletion in $LDLR^{-/-}$ mice reduces plaque formation by impeding monocyte hematopoiesis due to the decrease in systemic CD8 T-cell dependent IFN-γ [522]. $CD8^+$ T cells have been reported to promote atherosclerosis through the induction of apoptosis in macrophages, endothelial cells, and smooth muscle cells, leading to necrotic core formation and increased inflammation [522]. A proatherogenic role is further suggested by the ability of $CD8^+$ T cells to promote monocyte recruitment and augment lesion instability [513]. Overall, these studies, thus, suggest that different CD8 T cells subsets may play opposing roles in atherosclerosis [513].

5.3. B-Cells

B-cells play critical roles in innate and adaptive immunity through their capacity to produce antibodies and secrete cytokines. B cells are characterized by the expression of membrane-bound immunoglobulins, known as B cell receptor (BCRs), with exclusive epitope-binding sites. BCRs, each one unique to a single B cell clone, bind antigens and are generated by the recombination of variable (V), diversity (D), and joining (J) genes by the product of recombinase activation gene (RAG) [523,524]. The mature BCR and the subsequently produced antibodies are composed of duplicated copies of the recombined heavy and light immunoglobulin polypeptides. The BCR forms a complex with several other membrane proteins, including the B cell receptor CD22, receptor-type tyrosine protein phosphatase C (PTPRC, also known as B220 and CD45), and B-lymphocyte antigen CD19. BCR stimulation induces NF-κB, PI3K, and MAPK signaling, which play essential roles in B cell development, differentiation, and activation [525]. After activation, B cells proliferate and differentiate toward a plasma cell phenotype [525]. Differences in the Fc region define five major types of antibody: IgA, IgD, IgE, IgG, and IgM. Some of these can be divided into different subtypes [525].

B cells can be subclassified as B1 and B2 cells [526,527]. B1 cells derive from fetal hematopoietic stem cells and produce natural antibodies independently of Th signals, without infection or immunization [528,529]. B1 cells circulate systemically and also guard mucosal surfaces, where they generate immediate protection via antigen capture and opsonization of entering bacteria [530]. Like plasma cells, antibody-secreting B1 cells reside in the spleen and bone marrow in large numbers [530]. In mice, B1 cells are further classified as CD5-expressing B1a cells and B1b cells [531]. B1a cells produce spontaneous T cell-independent, long-lasting, unmutated IgM [532], whereas B1b cells produce IgA [533,534].

B2 cells derive from bone-marrow precursors, which, after several maturation steps in the bone marrow and the secondary lymphoid organs, differentiate into marginal zone (MZ) B cells and follicular (FO) B cells [526,527]. MZ B cells are found in the splenic marginal sinus and respond to blood-borne pathogens in a T cell-independent manner by differentiating toward antibody-secreting plasma cells [535]. FO B cells are found in the periphery and are activated by antigens and Th cells before undergoing the germinal center reactions (class-switch recombination and somatic hypermutation) to generate switched Igs and BCRs that more precisely react with the target antigen. At the germinal center, with the help of follicular DCs and follicular helper T cells, FO B cells undergo an affinity maturation and selection procedure for antigens and then give rise to antibody-precise, antibody-generating, long-lived plasma cells or memory B cells [532,536]. These plasma cells and

memory B cells govern antibody-mediated immune responses. B cells also regulate T cell and macrophage differentiation and modulate inflammatory responses through the secretion of specific cytokines [537–539]. Regulatory B cells (Bregs) play immunosuppressive roles through the release of IL-10, TGFβ, and IL-35 [479,540–542].

B cells can play protective and pathogenic roles in atherosclerosis. An atheroprotective role is supported by the increased atherosclerosis in ApoE$^{-/-}$ mice after splenectomy, which reduces B cells' numbers; this effect is attenuated by the adoptive transfer of splenic B cells [543]. Moreover, atherosclerosis is increased after the reconstitution of bone marrow-depleted LDLR$^{-/-}$ mice with bone marrow from B cell-deficient mice (μMT$^{-/-}$ mice) [544], and this effect is also reversed by the adoptive transfer of splenic B cells [545]. Immunization studies have confirmed the antiatherogenic role of B cell-derived antibodies [532], and atherosclerosis is reduced upon immunization with malondialdehyde modified LDL (MDA-LDL) [546] or other oxLDLs [547].

A proatherogenic action of B cells is revealed in ApoE$^{-/-}$ and LDLR$^{-/-}$ mice upon depletion of B2 cells with antibodies to CD20, the receptor for the B-cell survival regulator B cell activating factor receptor (BAFFR) or by genetic disruption of BAFFR [548–553]

The different B cell subclasses appear to make distinct contributions to the B cell-mediated modulation of atherosclerosis [42,532]. B1a cells produce natural IgM antibodies against oxLDL and antigens derived from apoptotic cells, blocking macrophage oxLDL uptake and foam-cell generation and stimulating apoptotic cell removal from atherosclerotic plaques [554,555]. Experiments in splenectomized ApoE$^{-/-}$ mice show that this atheroprotective effect is mediated by TLR4 and MYD88 [556]. The role of B1b cells in atherosclerosis is not fully understood; however, adoptive transfer of B1b cells to Rag1$^{-/-}$/ApoE$^{-/-}$ mice reduces atherosclerosis [557].

Atheroprotective B1 responses appear to depend on the control of the adaptive germinal center by B Cell Fcγ Receptor IIb [558]. The studies cited above suggest a proatherogenic action of B2 cells [548–552]. Bregs exert immunosuppressive functions by secreting the cytokines IL-10 and TGFβ [559–561], and IL-10 disruption promotes inflammatory cell infiltration and cytokine generation and enhances atherosclerosis in mice [471,543]. An atheroprotective role of Bregs is supported by increased IL-10 production and Treg induction after the transfer of CTB-p210-pulsed Bregs [562] or CD21hiCD23hiCD24hi Bregs [563]. However, another study found no protective effect of Bregs [548]. Further experiments are, therefore, needed to clarify this role.

6. Discussion

Emerging evidence indicates that LDLs stimulate both innate and adaptive immunity in atherosclerosis. Atherosclerosis is aggravated by proinflammatory responses mediated by macrophages, Th1 cells, and B2 cells. The action of proinflammatory immune-system components is reduced by regulatory cells, such as Tregs, Bregs, M2 macrophages, and tolerogenic DCs. Regulatory-cell–mediated approaches, thus, have great potential for future therapies. However, recent findings indicate that these immunosuppressive responses can become dysfunctional due to microenvironmental factors that convert protective functions into proatherogenic responses. Several immune cells, including CD8 T cells, B1 cells, Th2 cells, Th17 cells, and some DC subsets appear to play both a protective and a proatherogenic role in the onset and progression of atherosclerosis depending on other factors, or their true function remains unresolved. Further research is, therefore, need to elucidate the specific function of these cells in human atherosclerotic disease and develop therapeutic strategies that stimulate their protective actions.

Some studies in mice indicate that the inhibition of inflammatory processes in advanced atherosclerotic lesions allows atheroprotective immune responses to promote plaque regression. In humans, the CANTOS trial of the anti-IL-1β blocking antibody canakinumab in patients with a history of myocardial infarction and elevated serum hsCRP (high-sensitivity C-reactive protein) demonstrates that inflammation is a direct cause of the onset and development of atherosclerosis [564]. This clinical trial also highlights the importance of inflammation as a target for future treatments to reduce atherosclerosis. However, low dose methotrexate (MTX) treatment—included in the CIRT study [565] and aimed to reduce inflammation and cardiovascular risk in patients with

previous myocardial infarction or multivessel coronary disease who have indirect evidence of inflammatory risk, by additionally having either type 2 diabetes or the metabolic syndrome [566]—fails to reduce cardiovascular events. Contrasting with anti-IL-1β blocking antibody canakinumab treatment, MTX did not result in lower IL-1β, IL-6, or hsCRP levels than placebo. This may due to the fact that MTX function and molecular targets are different from the canakinumab, affecting less relevant pathogenic pathways in atherosclerosis. Moreover, CANTOS and CIRT trials also differ in the population of study [567]. Nevertheless, it is important to weigh the potential dangers of this type of anti-inflammatory therapy; risks include aggravating or potentiating undesired effects, such as infection and cancer. In the CANTOS trial, canakinumab increased the incidence of fatal infection and sepsis [564] and in the CIRT study, a slight increase in skin tumors was observed over time in the MTX treated population [565]. Further studies are needed to determine the importance for the essential inflammatory responses of many potential therapeutic targets in the prevention and treatment of atherosclerosis.

Acknowledgments: The authors thank S. Bartlett for English editing and F. Sanchez-Madrid for critical reading of the manuscript. B.H.F. and R.G.B. contributed equally to this manuscript.

Funding: The authors' research is supported by grants from the Instituto de Salud Carlos III (ISCIII) (PI17/01395; CPII16/00022) and EuroCellNet COST Action CA15214 with co-funding from the European Regional Development Fund (ERDF), "A way to build Europe," and the Miguel Servet Program. The CNIC is supported by the ISCIII, the Ministerio de Ciencia, Innovación y Universidades (MCNU), and the Pro CNIC Foundation and is a Severo Ochoa Center of Excellence (SEV-2015-0505). J.M.G.-G. is supported by the ISCIII Miguel Servet Program, i+12 and Universidad Autónoma de Madrid (UAM); R.G.B. and B.S. by i+12 and ISCIII and B.H.F. by i+12, UAM and FPU programs from the MCNU.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Shimada, K. Immune System and Atherosclerotic Disease: Heterogeneity of Leukocyte Subsets Participating in the Pathogenesis of Atherosclerosis. *Circ. J.* **2009**, *73*, 994–1001.
2. Hansson, G.K.; Hermansson, A. The Immune System in Atherosclerosis. *Nat. Immunol.* **2011**, *12*, 204–212.
3. Ammirati, E.; Moroni, F.; Magnoni, M.; Camici, P.G. The Role of T and B Cells in Human Atherosclerosis and Atherothrombosis. *Clin. Exp. Immunol.* **2015**, *179*, 173–187.
4. Smith, J.D.; Trogan, E.; Ginsberg, M.; Grigaux, C.; Tian, J.; Miyata, M. Decreased Atherosclerosis in Mice Deficient in Both Macrophage Colony-Stimulating Factor (op) and Apolipoprotein E. *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 8264–8268.
5. Song, L.; Leung, C.; Schindler, C. Lymphocytes are Important in Early Atherosclerosis. *J. Clin. Investig.* **2001**, *108*, 251–259.
6. Reardon, C.A.; Blachowicz, L.; Lukens, J.; Nissenbaum, M.; Getz, G.S. Genetic Background Selectively Influences Innominate Artery Atherosclerosis: Immune System Deficiency as a Probe. *Arterioscler. Thromb. Vasc. Biol.* **2003**, *23*, 1449–1454.
7. Dansky, H.M.; Charlton, S.A.; Harper, M.M.; Smith, J.D. T and B Lymphocytes Play a Minor Role in Atherosclerotic Plaque Formation in the Apolipoprotein E-Deficient Mouse. *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 4642–4646.
8. Zhou, X.; Nicoletti, A.; Elhage, R.; Hansson, G.K. Transfer of CD4(+) T Cells Aggravates Atherosclerosis in Immunodeficient Apolipoprotein E knockout Mice. *Circulation* **2000**, *102*, 2919–2922.
9. Reardon, C.A.; Blachowicz, L.; White, T.; Cabana, V.; Wang, Y.; Lukens, J.; Bluestone, J.; Getz, G.S. Effect of Immune Deficiency on Lipoproteins and Atherosclerosis in Male Apolipoprotein E-Deficient Mice. *Arterioscler. Thromb. Vasc. Biol.* **2001**, *21*, 1011–1016.
10. Daugherty, A.; Pure, E.; Delfel-Butteiger, D.; Chen, S.; Leferovich, J.; Roselaar, S.E.; Rader, D.J. The Effects of Total Lymphocyte Deficiency on the Extent of Atherosclerosis in Apolipoprotein E-/-mice. *J. Clin. Investig.* **1997**, *100*, 1575–1580.
11. Libby, P.; Lichtman, A.H.; Hansson, G.K. Immune Effector Mechanisms Implicated in Atherosclerosis: From Mice to Humans. *Immunity* **2013**, *38*, 1092–1104.

12. Disease, G.B.D.; Injury, I.; Prevalence, C. Global, Regional and National Incidence, Prevalence, and Years Lived with Disability for 354 Diseases and Injuries for 195 Countries and Territories, 1990–2017: A Systematic Analysis for the Global Burden of Disease Study 2017. *Lancet* **2018**, *392*, 1789–1858.
13. Berenson, G.S.; Srinivasan, S.R.; Bao, W.; Newman, W.P., 3rd; Tracy, R.E.; Wattigney, W.A. Association between Multiple Cardiovascular Risk Factors and Atherosclerosis in Children and Young Adults. The Bogalusa Heart Study. *N. Engl. J. Med.* **1998**, *338*, 1650–1656.
14. Hansson, G.K.; Libby, P.; Tabas, I. Inflammation and Plaque Vulnerability. *J. Intern. Med.* **2015**, *278*, 483–493.
15. Pepys, M.B.; Hirschfield, G.M. C-Reactive Protein: A Critical Update. *J. Clin. Investig.* **2003**, *111*, 1805–1812.
16. Xu, M.M.; Murphy, P.A.; Vella, A.T. Activated T-Effector seeds: Cultivating Atherosclerotic Plaque through Alternative Activation. *Am. J. Physiol. Heart Circ. Physiol.* **2019**, *316*, H1354–H1365.
17. Boren, J.; Olin, K.; Lee, I.; Chait, A.; Wight, T.N.; Innerarity, T.L. Identification of the Principal Proteoglycan-Binding Site in LDL. A Single-Point Mutation in Apo-B100 Severely Affects Proteoglycan Interaction without Affecting LDL Receptor Binding. *J. Clin. Investig.* **1998**, *101*, 2658–2664.
18. Kwon, G.P.; Schroeder, J.L.; Amar, M.J.; Remaley, A.T.; Balaban, R.S. Contribution of Macromolecular Structure to the Retention of Low-Density Lipoprotein at Arterial Branch Points. *Circulation* **2008**, *117*, 2919–2927.
19. Benjamin, E.J.; Blaha, M.J.; Chiuve, S.E.; Cushman, M.; Das, S.R.; Deo, R.; de Ferranti, S.D.; Floyd, J.; Fornage, M.; Gillespie, C.; et al. Heart Disease and Stroke Statistics-2017 Update: A Report from the American Heart Association. *Circulation* **2017**, *135*, e146–e603.
20. Ross, R. Atherosclerosis–An Inflammatory Disease. *N. Engl. J. Med.* **1999**, *340*, 115–126.
21. Hansson, G.K. Inflammation, Atherosclerosis, and Coronary Artery Disease. *N. Engl. J. Med.* **2005**, *352*, 1685–1695.
22. Back, M.; Hansson, G.K. Anti-Inflammatory Therapies for Atherosclerosis. *Nat. Rev. Cardiol.* **2015**, *12*, 199–211.
23. Galkina, E.; Ley, K. Immune and Inflammatory Mechanisms of Atherosclerosis (*). *Annu. Rev. Immunol.* **2009**, *27*, 165–197.
24. Tanaka, S.; Matsumoto, T.; Matsubara, Y.; Harada, Y.; Kyuragi, R.; Koga, J.I.; Egashira, K.; Nakashima, Y.; Yonemitsu, Y.; Maehara, Y. BubR1 Insufficiency Results in Decreased Macrophage Proliferation and Attenuated Atherogenesis in Apolipoprotein E-Deficient Mice. *J. Am. Heart Assoc.* **2016**, *5*, e004081.
25. Chatzizisis, Y.S.; Coskun, A.U.; Jonas, M.; Edelman, E.R.; Feldman, C.L.; Stone, P.H. Role of Endothelial Shear Stress in the Natural History of Coronary Atherosclerosis and Vascular Remodeling: Molecular, Cellular and Vascular Behavior. *J. Am. Coll. Cardiol.* **2007**, *49*, 2379–2393.
26. Dai, G.; Kaazempur-Mofrad, M.R.; Natarajan, S.; Zhang, Y.; Vaughn, S.; Blackman, B.R.; Kamm, R.D.; Garcia-Cardena, G.; Gimbrone, M.A., Jr. Distinct Endothelial Phenotypes Evoked by Arterial Waveforms Derived from Atherosclerosis-Susceptible and -Resistant Regions of Human Vasculature. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 14871–14876.
27. Gimbrone, M.A., Jr.; Garcia-Cardena, G. Endothelial Cell Dysfunction and the Pathobiology of Atherosclerosis. *Circ. Res.* **2016**, *118*, 620–636.
28. Lipton, B.A.; Parthasarathy, S.; Ord, V.A.; Clinton, S.K.; Libby, P.; Rosenfeld, M.E. Components of the Protein Fraction of Oxidized Low Density Lipoprotein Stimulate Interleukin-1 Alpha Production by Rabbit Arterial Macrophage-Derived foam Cells. *J. Lipid. Res.* **1995**, *36*, 2232–2242.
29. Kranzhofer, R.; Schmidt, J.; Pfeiffer, C.A.; Hagl, S.; Libby, P.; Kubler, W. Angiotensin Induces Inflammatory Activation of Human Vascular Smooth Muscle Cells. *Arterioscler. Thromb. Vasc. Biol.* **1999**, *19*, 1623–1629.
30. Libby, P.; Ordovas, J.M.; Auger, K.R.; Robbins, A.H.; Birinyi, L.K.; Dinarello, C.A. Endotoxin and Tumor Necrosis Factor Induce Interleukin-1 Gene Expression in Adult Human Vascular Endothelial Cells. *Am. J. Pathol.* **1986**, *124*, 179–185.
31. Libby, P.; Ridker, P.M.; Maseri, A. Inflammation and Atherosclerosis. *Circulation* **2002**, *105*, 1135–1143.
32. Mannarino, E.; Pirro, M. Endothelial Injury and Repair: A Novel Theory for Atherosclerosis. *Angiology* **2008**, *59*, 69S–72S.
33. Clinton, S.K.; Underwood, R.; Hayes, L.; Sherman, M.L.; Kufe, D.W.; Libby, P. Macrophage Colony-Stimulating Factor Gene Expression in Vascular Cells and in Experimental and Human Atherosclerosis. *Am. J. Pathol.* **1992**, *140*, 301–316.

34. Galkina, E.; Ley, K. Vascular Adhesion Molecules in Atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* **2007**, *27*, 2292–2301.
35. Libby, P.; Ridker, P.M.; Hansson, G.K.; Leducq Transatlantic Network on Atherothrombosis. Inflammation in Atherosclerosis: From Pathophysiology to Practice. *J. Am. Coll. Cardiol.* **2009**, *54*, 2129–2138.
36. Bobryshev, Y.V.; Ivanova, E.A.; Chistiakov, D.A.; Nikiforov, N.G.; Orekhov, A.N. Macrophages and Their Role in Atherosclerosis: Pathophysiology and Transcriptome Analysis. *Biomed. Res. Int.* **2016**, *2016*, 9582430.
37. Allahverdian, S.; Pannu, P.S.; Francis, G.A. Contribution of Monocyte-Derived Macrophages and Smooth Muscle Cells to Arterial Foam Cell Formation. *Cardiovasc. Res.* **2012**, *95*, 165–172.
38. Binder, C.J.; Papac-Milicevic, N.; Witztum, J.L. Innate Sensing of Oxidation-Specific Epitopes in Health and Disease. *Nat. Rev. Immunol.* **2016**, *16*, 485–497.
39. Song, M.; Xu, S.; Zhong, A.; Zhang, J. Crosstalk between Macrophage and T Cell in Atherosclerosis: Potential Therapeutic Targets for Cardiovascular Diseases. *Clin. Immunol.* **2019**, *202*, 11–17.
40. Worbs, T.; Hammerschmidt, S.I.; Forster, R. Dendritic Cell Migration in Health and Disease. *Nat. Rev. Immunol.* **2017**, *17*, 30–48.
41. Gil-Pulido, J.; Zernecke, A. Antigen-Presenting Dendritic Cells in Atherosclerosis. *Eur. J. Pharmacol.* **2017**, *816*, 25–31.
42. Sage, A.P.; Tsiantoulas, D.; Binder, C.J.; Mallat, Z. The Role of B Cells in Atherosclerosis. *Nat. Rev. Cardiol.* **2019**, *16*, 180–196.
43. Hansson, G.K.; Libby, P.; Schonbeck, U.; Yan, Z.Q. Innate and Adaptive Immunity in the Pathogenesis of Atherosclerosis. *Circ. Res.* **2002**, *91*, 281–291.
44. Abdolmaleki, F.; Gheibi Hayat, S.M.; Bianconi, V.; Johnston, T.P.; Sahebkar, A. Atherosclerosis and Immunity: A Perspective. *Trends Cardiovasc. Med.* **2019**, *29*, 363–371.
45. Frostegard, J.; Ulfgren, A.K.; Nyberg, P.; Hedin, U.; Swedenborg, J.; Andersson, U.; Hansson, G.K. Cytokine Expression in Advanced Human Atherosclerotic Plaques: Dominance of Pro-Inflammatory (Th1) and Macrophage-Stimulating Cytokines. *Atherosclerosis* **1999**, *145*, 33–43.
46. Jonasson, L.; Holm, J.; Skalli, O.; Bondjers, G.; Hansson, G.K. Regional Accumulations of T Cells, Macrophages and Smooth Muscle Cells in the Human Atherosclerotic Plaque. *Arteriosclerosis* **1986**, *6*, 131–138.
47. Kovanen, P.T.; Kaartinen, M.; Paavonen, T. Infiltrates of Activated Mast Cells at the Site of Coronary Atheromatous Erosion or Rupture in Myocardial Infarction. *Circulation* **1995**, *92*, 1084–1088.
48. Obikane, H.; Abiko, Y.; Ueno, H.; Kusumi, Y.; Esumi, M.; Mitsumata, M. Effect of Endothelial Cell Proliferation on Atherogenesis: A Role of p21(Sdi/Cip/Waf1) in Monocyte Adhesion to Endothelial Cells. *Atherosclerosis* **2010**, *212*, 116–122.
49. Libby, P.; Okamoto, Y.; Rocha, V.Z.; Folco, E. Inflammation in Atherosclerosis: Transition from Theory to Practice. *Circ. J.* **2010**, *74*, 213–220.
50. Verma, S.; Wang, C.H.; Li, S.H.; Dumont, A.S.; Fedak, P.W.; Badiwala, M.V.; Dhillon, B.; Weisel, R.D.; Li, R.K.; Mickle, D.A.; et al. A Self-Fulfilling Prophecy: C-Reactive Protein Attenuates Nitric Oxide Production and Inhibits Angiogenesis. *Circulation* **2002**, *106*, 913–919.
51. Quillard, T.; Tesmenitsky, Y.; Croce, K.; Travers, R.; Shvartz, E.; Koskinas, K.C.; Sukhova, G.K.; Aikawa, E.; Aikawa, M.; Libby, P. Selective Inhibition of Matrix Metalloproteinase-13 Increases Collagen Content of Established Mouse Atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* **2011**, *31*, 2464–2472.
52. Schneider, F.; Sukhova, G.K.; Aikawa, M.; Canner, J.; Gerdes, N.; Tang, S.M.; Shi, G.P.; Apte, S.S.; Libby, P. Matrix-Metalloproteinase-14 Deficiency in Bone-Marrow-Derived Cells Promotes Collagen Accumulation in Mouse Atherosclerotic Plaques. *Circulation* **2008**, *117*, 931–939.
53. Geng, Y.J.; Wu, Q.; Muszynski, M.; Hansson, G.K.; Libby, P. Apoptosis of Vascular Smooth Muscle Cells Induced by In Vitro Stimulation with Interferon-Gamma, Tumor Necrosis Factor-Alpha and Interleukin-1 Beta. *Arterioscler. Thromb. Vasc. Biol.* **1996**, *16*, 19–27.
54. Houtkamp, M.A.; de Boer, O.J.; van der Loos, C.M.; van der Wal, A.C.; Becker, A.E. Adventitial Infiltrates Associated with Advanced Atherosclerotic Plaques: Structural Organization Suggests Generation of Local Humoral Immune Responses. *J. Pathol.* **2001**, *193*, 263–269.
55. Moos, M.P.; John, N.; Grabner, R.; Nossmann, S.; Gunther, B.; Vollandt, R.; Funk, C.D.; Kaiser, B.; Habenicht, A.J. The Lamina Adventitia is the Major Site of Immune Cell Accumulation in Standard Chow-fed Apolipoprotein E-Deficient mice. *Arterioscler. Thromb. Vasc. Biol.* **2005**, *25*, 2386–2391.
56. Taylor, P.R.; Gordon, S. Monocyte Heterogeneity and Innate Immunity. *Immunity* **2003**, *19*, 2–4.

57. van Furth, R.; Cohn, Z.A. The Origin and Kinetics of Mononuclear Phagocytes. *J. Exp. Med.* **1968**, *128*, 415–435.
58. Italiani, P.; Boraschi, D. From Monocytes to M1/M2 Macrophages: Phenotypical vs. Functional Differentiation. *Front. Immunol.* **2014**, *5*, 514.
59. Camici, P.G.; Rimoldi, O.E.; Gaemperli, O.; Libby, P. Non-Invasive Anatomic and Functional Imaging of Vascular Inflammation and Unstable Plaque. *Eur. Heart J.* **2012**, *33*, 1309–1317.
60. Combadiere, C.; Potteaux, S.; Rodero, M.; Simon, T.; Pezard, A.; Esposito, B.; Merval, R.; Proudfoot, A.; Tedgui, A.; Mallat, Z. Combined Inhibition of CCL2, CX3CR1 and CCR5 Abrogates Ly6C(hi) and Ly6C(lo) Monocytosis and Almost Abolishes Atherosclerosis in Hypercholesterolemic Mice. *Circulation* **2008**, *117*, 1649–1657.
61. Takeya, M.; Yoshimura, T.; Leonard, E.J.; Takahashi, K. Detection of Monocyte Chemoattractant Protein-1 in Human Atherosclerotic Lesions by an Anti-Monocyte Chemoattractant Protein-1 Monoclonal Antibody. *Hum. Pathol.* **1993**, *24*, 534–539.
62. Yla-Herttuala, S.; Lipton, B.A.; Rosenfeld, M.E.; Sarkioja, T.; Yoshimura, T.; Leonard, E.J.; Witztum, J.L.; Steinberg, D. Expression of Monocyte Chemoattractant Protein 1 in Macrophage-Rich Areas of Human and Rabbit Atherosclerotic Lesions. *Proc. Natl. Acad. Sci. USA* **1991**, *88*, 5252–5256.
63. Lin, J.; Kakkar, V.; Lu, X. Impact of MCP-1 in Atherosclerosis. *Curr. Pharm. Des.* **2014**, *20*, 4580–4588.
64. Boisvert, W.A.; Rose, D.M.; Johnson, K.A.; Fuentes, M.E.; Lira, S.A.; Curtiss, L.K.; Terkeltaub, R.A. Up-Regulated Expression of the CXCR2 Ligand KC/GRO-Alpha in Atherosclerotic Lesions Plays a Central Role in Macrophage Accumulation and Lesion Progression. *Am. J. Pathol.* **2006**, *168*, 1385–1395.
65. Zernecke, A.; Liehn, E.A.; Gao, J.L.; Kuziel, W.A.; Murphy, P.M.; Weber, C. Deficiency in CCR5 but not CCR1 Protects Against Neointima Formation in Atherosclerosis-Prone Mice: Involvement of IL-10. *Blood* **2006**, *107*, 4240–4243.
66. Koenen, R.R.; von Hundelshausen, P.; Nesmelova, I.V.; Zernecke, A.; Liehn, E.A.; Sarabi, A.; Kramp, B.K.; Piccinini, A.M.; Paludan, S.R.; Kowalska, M.A.; et al. Disrupting Functional Interactions between Platelet Chemokines Inhibits Atherosclerosis in Hyperlipidemic Mice. *Nat. Med.* **2009**, *15*, 97–103.
67. Moroni, F.; Ammirati, E.; Norata, G.D.; Magnoni, M.; Camici, P.G. The Role of Monocytes and Macrophages in Human Atherosclerosis, Plaque Neoangiogenesis and Atherothrombosis. *Mediat. Inflamm.* **2019**, *2019*, 7434376.
68. Ziegler-Heitbrock, L. The CD14+ CD16+ Blood Monocytes: Their Role in Infection and Inflammation. *J. Leukoc. Biol.* **2007**, *81*, 584–592.
69. Ziegler-Heitbrock, L.; Ancuta, P.; Crowe, S.; Dalod, M.; Grau, V.; Hart, D.N.; Leenen, P.J.; Liu, Y.J.; MacPherson, G.; Randolph, G.J.; et al. Nomenclature of Monocytes and Dendritic Cells in Blood. *Blood* **2010**, *116*, e74–80.
70. Rogacev, K.S.; Cremers, B.; Zawada, A.M.; Seiler, S.; Binder, N.; Ege, P.; Grosse-Dunker, G.; Heisel, I.; Hornof, F.; Jeken, J.; et al. CD14++CD16+ Monocytes Independently Predict Cardiovascular Events: A Cohort Study of 951 Patients Referred for Elective Coronary Angiography. *J. Am. Coll. Cardiol.* **2012**, *60*, 1512–1520.
71. Sala, F.; Cutuli, L.; Grigore, L.; Pirillo, A.; Chiesa, G.; Catapano, A.L.; Norata, G.D. Prevalence of Classical CD14++/CD16- but not of Intermediate CD14++/CD16+ Monocytes in Hypoalphalipoproteinemia. *Int. J. Cardiol.* **2013**, *168*, 2886–2889.
72. Belge, K.U.; Dayyani, F.; Horelt, A.; Siedlar, M.; Frankenberger, M.; Frankenberger, B.; Espevik, T.; Ziegler-Heitbrock, L. The Proinflammatory CD14+CD16+DR++ Monocytes are a Major Source of TNF. *J. Immunol.* **2002**, *168*, 3536–3542.
73. Boltjes, A.; van Wijk, F. Human Dendritic Cell Functional Specialization in Steady-State and Inflammation. *Front. Immunol.* **2014**, *5*, 131.
74. Liu, K.; Victora, G.D.; Schwickert, T.A.; Guermonprez, P.; Meredith, M.M.; Yao, K.; Chu, F.F.; Randolph, G.J.; Rudensky, A.Y.; Nussenzweig, M. In Vivo Analysis of Dendritic Cell Development and Homeostasis. *Science* **2009**, *324*, 392–397.
75. Zhao, C.; Zhang, H.; Wong, W.C.; Sem, X.; Han, H.; Ong, S.M.; Tan, Y.C.; Yeap, W.H.; Gan, C.S.; Ng, K.Q.; et al. Identification of Novel Functional Differences in Monocyte Subsets Using Proteomic and Transcriptomic Methods. *J. Proteome Res.* **2009**, *8*, 4028–4038.

76. Evans, H.G.; Gullick, N.J.; Kelly, S.; Pitzalis, C.; Lord, G.M.; Kirkham, B.W.; Taams, L.S. In Vivo Activated Monocytes from the Site of Inflammation in Humans Specifically Promote Th17 Responses. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 6232–6237.
77. Serbina, N.V.; Jia, T.; Hohl, T.M.; Pamer, E.G. Monocyte-Mediated Defense against Microbial Pathogens. *Annu. Rev. Immunol.* **2008**, *26*, 421–452.
78. Avraham-Davidi, I.; Yona, S.; Grunewald, M.; Landsman, L.; Cochain, C.; Silvestre, J.S.; Mizrahi, H.; Faroja, M.; Strauss-Ayali, D.; Mack, M.; et al. On-Site Education of VEGF-Recruited Monocytes Improves Their Performance as Angiogenic and Arteriogenic Accessory Cells. *J. Exp. Med.* **2013**, *210*, 2611–2625.
79. Swirski, F.K.; Libby, P.; Aikawa, E.; Alcaide, P.; Luscinskas, F.W.; Weissleder, R.; Pittet, M.J. Ly-6Chi Monocytes Dominate Hypercholesterolemia-Associated Monocytosis and Give Rise to Macrophages in Atheromata. *J. Clin. Investig.* **2007**, *117*, 195–205.
80. Justo-Junior, A.S.; Villarejos, L.M.; Lima, X.T.V.; Nadruz, W., Jr.; Sposito, A.C.; Mamoni, R.L.; Abdalla, R.; Fernandes, J.L.; Oliveira, R.T.D.; Blotta, M. Monocytes of Patients with Unstable Angina Express High Levels of Chemokine and Pattern-Recognition Receptors. *Cytokine* **2019**, *113*, 61–67.
81. Ozaki, Y.; Imanishi, T.; Hosokawa, S.; Nishiguchi, T.; Taruya, A.; Tanimoto, T.; Kuroi, A.; Yamano, T.; Matsuo, Y.; Ino, Y.; et al. Association of Toll-Like Receptor 4 on Human Monocyte Subsets and Vulnerability Characteristics of Coronary Plaque as Assessed by 64-Slice Multidetector Computed Tomography. *Circ. J.* **2017**, *81*, 837–845.
82. Cybulsky, M.I.; Iiyama, K.; Li, H.; Zhu, S.; Chen, M.; Iiyama, M.; Davis, V.; Gutierrez-Ramos, J.C.; Connelly, P.W.; Milstone, D.S. A Major Role for VCAM-1, but not ICAM-1, in Early Atherosclerosis. *J. Clin. Investig.* **2001**, *107*, 1255–1262.
83. Sundell, C.L.; Somers, P.K.; Meng, C.Q.; Hoong, L.K.; Suen, K.L.; Hill, R.R.; Landers, L.K.; Chapman, A.; Butteiger, D.; Jones, M.; et al. AGI-1067: A Multifunctional Phenolic Antioxidant, Lipid Modulator, Anti-Inflammatory and Antiatherosclerotic Agent. *J. Pharmacol. Exp. Ther.* **2003**, *305*, 1116–1123.
84. Qiao, J.H.; Tripathi, J.; Mishra, N.K.; Cai, Y.; Tripathi, S.; Wang, X.P.; Imes, S.; Fishbein, M.C.; Clinton, S.K.; Libby, P.; et al. Role of Macrophage Colony-Stimulating Factor in Atherosclerosis: Studies of Osteopetrotic Mice. *Am. J. Pathol.* **1997**, *150*, 1687–1699.
85. Nicola, N.A.; Metcalf, D. Specificity of Action of Colony-Stimulating Factors in the Differentiation of Granulocytes and Macrophages. *Ciba Found. Symp.* **1986**, *118*, 7–28.
86. Woollard, K.J.; Geissmann, F. Monocytes in Atherosclerosis: Subsets and Functions. *Nat. Rev. Cardiol.* **2010**, *7*, 77–86.
87. Zhou, X.; Hansson, G.K. Detection of B Cells and Proinflammatory Cytokines in Atherosclerotic Plaques of Hypercholesterolaemic Apolipoprotein E Knockout Mice. *Scand. J. Immunol.* **1999**, *50*, 25–30.
88. Randolph, G.J. Mechanisms that Regulate Macrophage Burden in Atherosclerosis. *Circ. Res.* **2014**, *114*, 1757–1771.
89. Moore, K.J.; Sheedy, F.J.; Fisher, E.A. Macrophages in Atherosclerosis: A Dynamic Balance. *Nat. Rev. Immunol.* **2013**, *13*, 709–721.
90. Tacke, F.; Alvarez, D.; Kaplan, T.J.; Jakubzick, C.; Spanbroek, R.; Llodra, J.; Garin, A.; Liu, J.; Mack, M.; van Rooijen, N.; et al. Monocyte Subsets Differentially Employ CCR2, CCR5, and CX3CR1 to Accumulate within Atherosclerotic Plaques. *J. Clin. Investig.* **2007**, *117*, 185–194.
91. Robbins, C.S.; Hilgendorf, I.; Weber, G.F.; Theurl, I.; Iwamoto, Y.; Figueiredo, J.L.; Gorbatov, R.; Sukhova, G.K.; Gerhardt, L.M.; Smyth, D.; et al. Local Proliferation Dominates Lesional Macrophage Accumulation in Atherosclerosis. *Nat. Med.* **2013**, *19*, 1166–1172.
92. Li, Q.; Park, K.; Xia, Y.; Matsumoto, M.; Qi, W.; Fu, J.; Yokomizo, H.; Khamaisi, M.; Wang, X.; Rask-Madsen, C.; et al. Regulation of Macrophage Apoptosis and Atherosclerosis by Lipid-Induced PKCdelta Isoform Activation. *Circ. Res.* **2017**, *121*, 1153–1167.
93. Shashkin, P.; Dragulev, B.; Ley, K. Macrophage Differentiation to Foam Cells. *Curr. Pharm. Des.* **2005**, *11*, 3061–3072.
94. Seimon, T.; Tabas, I. Mechanisms and Consequences of Macrophage Apoptosis in Atherosclerosis. *J. Lipid. Res.* **2009**, *50* (Suppl.), S382–S387.
95. Tajbakhsh, A.; Rezaee, M.; Kovanen, P.T.; Sahebkar, A. Efferocytosis in Atherosclerotic Lesions: Malfunctioning Regulatory Pathways and Control Mechanisms. *Pharmacol. Ther.* **2018**, *188*, 12–25.
96. Thorp, E.; Subramanian, M.; Tabas, I. The Role of Macrophages and Dendritic Cells in the Clearance of Apoptotic Cells in Advanced Atherosclerosis. *Eur. J. Immunol.* **2011**, *41*, 2515–2518.

97. Thorp, E.; Tabas, I. Mechanisms and Consequences of Efferocytosis in Advanced Atherosclerosis. *J. Leukoc. Biol.* **2009**, *86*, 1089–1095.
98. Murray, P.J.; Allen, J.E.; Biswas, S.K.; Fisher, E.A.; Gilroy, D.W.; Goerdt, S.; Gordon, S.; Hamilton, J.A.; Ivashkiv, L.B.; Lawrence, T.; et al. Macrophage Activation and Polarization: Nomenclature and Experimental Guidelines. *Immunity* **2014**, *41*, 14–20.
99. Martinez, F.O.; Sica, A.; Mantovani, A.; Locati, M. Macrophage Activation and Polarization. *Front. Biosci.* **2008**, *13*, 453–461.
100. Porcheray, F.; Viaud, S.; Rimaniol, A.C.; Leone, C.; Samah, B.; Dereuddre-Bosquet, N.; Dormont, D.; Gras, G. Macrophage Activation Switching: An Asset for the Resolution of Inflammation. *Clin. Exp. Immunol.* **2005**, *142*, 481–489.
101. Lee, S.; Huen, S.; Nishio, H.; Nishio, S.; Lee, H.K.; Choi, B.S.; Ruhrberg, C.; Cantley, L.G. Distinct Macrophage Phenotypes Contribute to Kidney Injury and Repair. *J. Am. Soc. Nephrol.* **2011**, *22*, 317–326.
102. Feig, J.E.; Rong, J.X.; Shamir, R.; Sanson, M.; Vengrenyuk, Y.; Liu, J.; Rayner, K.; Moore, K.; Garabedian, M.; Fisher, E.A. HDL Promotes Rapid Atherosclerosis Regression in Mice and Alters Inflammatory Properties of Plaque Monocyte-Derived Cells. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 7166–7171.
103. Lavin, Y.; Winter, D.; Blecher-Gonen, R.; David, E.; Keren-Shaul, H.; Merad, M.; Jung, S.; Amit, I. Tissue-Resident Macrophage Enhancer Landscapes are Shaped by the Local Microenvironment. *Cell* **2014**, *159*, 1312–1326.
104. Van den Bossche, J.; O'Neill, L.A.; Menon, D. Macrophage Immunometabolism: Where Are We (Going)? *Trends Immunol.* **2017**, *38*, 395–406.
105. Joseph, P.; Tawakol, A. Imaging Atherosclerosis with Positron Emission Tomography. *Eur. Heart J.* **2016**, *37*, 2974–2980.
106. Wang, Z.; Klipfell, E.; Bennett, B.J.; Koeth, R.; Levison, B.S.; Dugar, B.; Feldstein, A.E.; Britt, E.B.; Fu, X.; Chung, Y.M.; et al. Gut Flora Metabolism of Phosphatidylcholine Promotes Cardiovascular Disease. *Nature* **2011**, *472*, 57–63.
107. Phan, A.T.; Goldrath, A.W.; Glass, C.K. Metabolic and Epigenetic Coordination of T Cell and Macrophage Immunity. *Immunity* **2017**, *46*, 714–729.
108. Martinez, F.O.; Gordon, S.; Locati, M.; Mantovani, A. Transcriptional Profiling of the Human Monocyte-to-Macrophage Differentiation and Polarization: New Molecules and Patterns of Gene Expression. *J. Immunol.* **2006**, *177*, 7303–7311.
109. Shapouri-Moghaddam, A.; Mohammadian, S.; Vazini, H.; Taghadosi, M.; Esmaeili, S.A.; Mardani, F.; Seifi, B.; Mohammadi, A.; Afshari, J.T.; Sahebkar, A. Macrophage Plasticity, Polarization and Function in Health and Disease. *J. Cell. Physiol.* **2018**, *233*, 6425–6440.
110. Shortman, K.; Liu, Y.J. Mouse and Human Dendritic Cell Subtypes. *Nat. Rev. Immunol.* **2002**, *2*, 151–161.
111. Waldo, S.W.; Li, Y.; Buono, C.; Zhao, B.; Billings, E.M.; Chang, J.; Kruth, H.S. Heterogeneity of Human Macrophages in Culture and in Atherosclerotic Plaques. *Am. J. Pathol.* **2008**, *172*, 1112–1126.
112. Hoeve, M.A.; Savage, N.D.; de Boer, T.; Langenberg, D.M.; de Waal Malefyt, R.; Ottenhoff, T.H.; Verreck, F.A. Divergent Effects of IL-12 and IL-23 on the Production of IL-17 by Human T Cells. *Eur. J. Immunol.* **2006**, *36*, 661–670.
113. Brocheriou, I.; Maouche, S.; Durand, H.; Braunersreuther, V.; Le Naour, G.; Gratchev, A.; Koskas, F.; Mach, F.; Kzhyshkowska, J.; Ninio, E. Antagonistic Regulation of Macrophage Phenotype by M-CSF and GM-CSF: Implication in Atherosclerosis. *Atherosclerosis* **2011**, *214*, 316–324.
114. Burgess, A.W.; Metcalf, D. The Nature and Action of Granulocyte-Macrophage Colony Stimulating Factors. *Blood* **1980**, *56*, 947–958.
115. Gasson, J.C. Molecular Physiology of Granulocyte-Macrophage Colony-Stimulating Factor. *Blood* **1991**, *77*, 1131–1145.
116. Plenz, G.; Koenig, C.; Severs, N.J.; Robenek, H. Smooth Muscle Cells Express Granulocyte-Macrophage Colony-Stimulating Factor in the Undiseased and Atherosclerotic Human Coronary Artery. *Arterioscler. Thromb. Vasc. Biol.* **1997**, *17*, 2489–2499.
117. Lacave-Lapalun, J.V.; Benderitter, M.; Linard, C. Flagellin or Lipopolysaccharide Treatment Modified Macrophage Populations after Colorectal Radiation of Rats. *J. Pharmacol. Exp. Ther.* **2013**, *346*, 75–85.
118. Verreck, F.A.; de Boer, T.; Langenberg, D.M.; Hoeve, M.A.; Kramer, M.; Vaisberg, E.; Kastelein, R.; Kolk, A.; de Waal-Malefyt, R.; Ottenhoff, T.H. Human IL-23-Producing Type 1 Macrophages Promote but IL-10-

Producing Type 2 Macrophages Subvert Immunity to (myco)Bacteria. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 4560–4565.
119. Mosser, D.M. The Many Faces of Macrophage Activation. *J. Leukoc. Biol.* **2003**, *73*, 209–212.
120. Chistiakov, D.A.; Bobryshev, Y.V.; Nikiforov, N.G.; Elizova, N.V.; Sobenin, I.A.; Orekhov, A.N. Macrophage Phenotypic Plasticity in Atherosclerosis: The Associated Features and the Peculiarities of the Expression of Inflammatory Genes. *Int. J. Cardiol.* **2015**, *184*, 436–445.
121. Zizzo, G.; Hilliard, B.A.; Monestier, M.; Cohen, P.L. Efficient Clearance of Early Apoptotic Cells by Human Macrophages Requires M2c Polarization and MerTK Induction. *J. Immunol.* **2012**, *189*, 3508–3520.
122. Chistiakov, D.A.; Bobryshev, Y.V.; Orekhov, A.N. Changes in Transcriptome of Macrophages in Atherosclerosis. *J. Cell. Mol. Med.* **2015**, *19*, 1163–1173.
123. Mantovani, A.; Sica, A.; Sozzani, S.; Allavena, P.; Vecchi, A.; Locati, M. The Chemokine System in Diverse Forms of Macrophage Activation and Polarization. *Trends Immunol.* **2004**, *25*, 677–686.
124. Ferrante, C.J.; Pinhal-Enfield, G.; Elson, G.; Cronstein, B.N.; Hasko, G.; Outram, S.; Leibovich, S.J. The Adenosine-Dependent Angiogenic Switch of Macrophages to an M2-like Phenotype is Independent of Interleukin-4 Receptor Alpha (IL-4Ralpha) Signaling. *Inflammation* **2013**, *36*, 921–931.
125. Anderson, C.F.; Gerber, J.S.; Mosser, D.M. Modulating Macrophage Function with IgG Immune Complexes. *J. Endotoxin Res.* **2002**, *8*, 477–481.
126. Kadl, A.; Sharma, P.R.; Chen, W.; Agrawal, R.; Meher, A.K.; Rudraiah, S.; Grubbs, N.; Sharma, R.; Leitinger, N. Oxidized Phospholipid-Induced Inflammation is Mediated by Toll-Like Receptor 2. *Free Radic. Biol. Med.* **2011**, *51*, 1903–1909.
127. Kadl, A.; Meher, A.K.; Sharma, P.R.; Lee, M.Y.; Doran, A.C.; Johnstone, S.R.; Elliott, M.R.; Gruber, F.; Han, J.; Chen, W.; et al. Identification of a Novel Macrophage Phenotype that Develops in Response to Atherogenic Phospholipids via Nrf2. *Circ. Res.* **2010**, *107*, 737–746.
128. Marques, L.; Negre-Salvayre, A.; Costa, L.; Canonne-Hergaux, F. Iron Gene Expression Profile in Atherogenic Mox Macrophages. *Biochim. Biophys. Acta* **2016**, *1862*, 1137–1146.
129. Liberale, L.; Dallegri, F.; Montecucco, F.; Carbone, F. Pathophysiological Relevance of Macrophage Subsets in Atherogenesis. *Thromb. Haemost.* **2017**, *117*, 7–18.
130. Gill, N.; Leng, Y.; Romero, R.; Xu, Y.; Panaitescu, B.; Miller, D.; Arif, A.; Mumuni, S.; Qureshi, F.; Hsu, C.D.; et al. The Immunophenotype of Decidual Macrophages in Acute Atherosis. *Am. J. Reprod. Immunol.* **2019,** *81*, e13098.
131. Kockx, M.M.; Cromheeke, K.M.; Knaapen, M.W.; Bosmans, J.M.; De Meyer, G.R.; Herman, A.G.; Bult, H. Phagocytosis and Macrophage Activation Associated with Hemorrhagic Microvessels in Human Atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* **2003**, *23*, 440–446.
132. Ganz, T. Macrophages and Systemic Iron Homeostasis. *J. Innate Immun.* **2012**, *4*, 446–453.
133. Boyle, J.J.; Johns, M.; Kampfer, T.; Nguyen, A.T.; Game, L.; Schaer, D.J.; Mason, J.C.; Haskard, D.O. Activating Transcription Factor 1 Directs Mhem Atheroprotective Macrophages through Coordinated Iron Handling and Foam Cell Protection. *Circ. Res.* **2012**, *110*, 20–33.
134. Habib, A.; Finn, A.V. The Role of Iron Metabolism as a Mediator of Macrophage Inflammation and Lipid Handling in Atherosclerosis. *Front. Pharmacol.* **2014**, *5*, 195.
135. Nielsen, M.J.; Moller, H.J.; Moestrup, S.K. Hemoglobin and Heme Scavenger Receptors. *Antioxid. Redox Signal.* **2010**, *12*, 261–273.
136. Wan, X.; Huo, Y.; Johns, M.; Piper, E.; Mason, J.C.; Carling, D.; Haskard, D.O.; Boyle, J.J. 5′-AMP-Activated Protein Kinase-Activating Transcription Factor 1 Cascade Modulates Human Monocyte-Derived Macrophages to Atheroprotective Functions in Response to Heme or Metformin. *Arterioscler. Thromb. Vasc. Biol.* **2013**, *33*, 2470–2480.
137. Boyle, J.J. Heme and Haemoglobin Direct Macrophage Mhem Phenotype and Counter Foam Cell Formation in Areas of Intraplaque Haemorrhage. *Curr. Opin. Lipidol.* **2012**, *23*, 453–461.
138. Boyle, J.J.; Harrington, H.A.; Piper, E.; Elderfield, K.; Stark, J.; Landis, R.C.; Haskard, D.O. Coronary Intraplaque Hemorrhage Evokes a Novel Atheroprotective Macrophage Phenotype. *Am. J. Pathol.* **2009**, *174*, 1097–1108.
139. Pitsilos, S.; Hunt, J.; Mohler, E.R.; Prabhakar, A.M.; Poncz, M.; Dawicki, J.; Khalapyan, T.Z.; Wolfe, M.L.; Fairman, R.; Mitchell, M.; et al. Platelet Factor 4 Localization in Carotid Atherosclerotic Plaques: Correlation with Clinical Parameters. *Thromb. Haemost.* **2003**, *90*, 1112–1120.

140. Gleissner, C.A.; Ley, K. CXCL4 in Atherosclerosis: Possible Roles in Monocyte Arrest and Macrophage Foam Cell Formation. *Thromb. Haemost.* **2007**, *98*, 917–918.
141. Chinetti-Gbaguidi, G.; Colin, S.; Staels, B. Macrophage Subsets in Atherosclerosis. *Nat. Rev. Cardiol.* **2015**, *12*, 10–17.
142. Gleissner, C.A.; Shaked, I.; Little, K.M.; Ley, K. CXC Chemokine Ligand 4 Induces a Unique Transcriptome in Monocyte-Derived Macrophages. *J. Immunol.* **2010**, *184*, 4810–4818.
143. Erbel, C.; Okuyucu, D.; Akhavanpoor, M.; Zhao, L.; Wangler, S.; Hakimi, M.; Doesch, A.; Dengler, T.J.; Katus, H.A.; Gleissner, C.A. A Human Ex Vivo Atherosclerotic Plaque Model to Study Lesion Biology. *J. Vis. Exp.* **2014**, *87*, doi:10.3791/50542.
144. Moore, K.J.; Tabas, I. Macrophages in the Pathogenesis of Atherosclerosis. *Cell* **2011**, *145*, 341–355.
145. De Paoli, F.; Staels, B.; Chinetti-Gbaguidi, G. Macrophage Phenotypes and Their Modulation in Atherosclerosis. *Circ. J.* **2014**, *78*, 1775–1781.
146. Cochain, C.; Zernecke, A. Macrophages and Immune Cells in Atherosclerosis: Recent Advances and Novel Concepts. *Basic Res. Cardiol.* **2015**, *110*, 34.
147. Bouhlel, M.A.; Derudas, B.; Rigamonti, E.; Dievart, R.; Brozek, J.; Haulon, S.; Zawadzki, C.; Jude, B.; Torpier, G.; Marx, N.; et al. PPARgamma Activation Primes Human Monocytes into Alternative M2 Macrophages with Anti-Inflammatory Properties. *Cell Metab.* **2007**, *6*, 137–143.
148. Gleissner, C.A.; Shaked, I.; Erbel, C.; Bockler, D.; Katus, H.A.; Ley, K. CXCL4 Downregulates the Atheroprotective Hemoglobin Receptor CD163 in Human Macrophages. *Circ. Res.* **2010**, *106*, 203–211.
149. Stoger, J.L.; Gijbels, M.J.; van der Velden, S.; Manca, M.; van der Loos, C.M.; Biessen, E.A.; Daemen, M.J.; Lutgens, E.; de Winther, M.P. Distribution of Macrophage Polarization Markers in Human Atherosclerosis. *Atherosclerosis* **2012**, *225*, 461–468.
150. Chinetti-Gbaguidi, G.; Baron, M.; Bouhlel, M.A.; Vanhoutte, J.; Copin, C.; Sebti, Y.; Derudas, B.; Mayi, T.; Bories, G.; Tailleux, A.; et al. Human Atherosclerotic Plaque Alternative Macrophages Display Low Cholesterol Handling but High Phagocytosis Because of Distinct Activities of the PPARgamma and LXRalpha Pathways. *Circ. Res.* **2011**, *108*, 985–995.
151. Pirro, M.; Schillaci, G.; Savarese, G.; Gemelli, F.; Mannarino, M.R.; Siepi, D.; Bagaglia, F.; Mannarino, E. Attenuation of inflammation with short-term dietary intervention is associated with a reduction of arterial stiffness in subjects with hypercholesterolaemia. *Eur. J. Cardiovasc. Prev. Rehabil.* **2004**, *11*, 497–502.
152. Morris, D.L.; Singer, K.; Lumeng, C.N. Adipose tissue macrophages: Phenotypic plasticity and diversity in lean and obese states. *Curr. Opin. Clin. Nutr. Metab. Care* **2011**, *14*, 341–346.
153. Llodra, J.; Angeli, V.; Liu, J.; Trogan, E.; Fisher, E.A.; Randolph, G.J. Emigration of monocyte-derived cells from atherosclerotic lesions characterizes regressive, but not progressive, plaques. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11779–11784.
154. Shioi, A.; Ikari, Y. Plaque Calcification During Atherosclerosis Progression and Regression. *J. Atheroscler. Thromb.* **2018**, *25*, 294–303.
155. Al-Sharea, A.; Lee, M.K.; Moore, X.L.; Fang, L.; Sviridov, D.; Chin-Dusting, J.; Andrews, K.L.; Murphy, A.J. Native LDL promotes differentiation of human monocytes to macrophages with an inflammatory phenotype. *Thromb Haemost* **2016**, *115*, 762–772.
156. Jiang, Y.; Wang, M.; Huang, K.; Zhang, Z.; Shao, N.; Zhang, Y.; Wang, W.; Wang, S. Oxidized low-density lipoprotein induces secretion of interleukin-1beta by macrophages via reactive oxygen species-dependent NLRP3 inflammasome activation. *Biochem Biophys Res Commun* **2012**, *425*, 121–126.
157. van Tits, L.J.; Stienstra, R.; van Lent, P.L.; Netea, M.G.; Joosten, L.A.; Stalenhoef, A.F. Oxidized LDL enhances pro-inflammatory responses of alternatively activated M2 macrophages: A crucial role for Kruppel-like factor 2. *Atherosclerosis* **2011**, *214*, 345–349.
158. Hirata, Y.; Tabata, M.; Kurobe, H.; Motoki, T.; Akaike, M.; Nishio, C.; Higashida, M.; Mikasa, H.; Nakaya, Y.; Takanashi, S.; et al. Coronary atherosclerosis is associated with macrophage polarization in epicardial adipose tissue. *J. Am. Coll. Cardiol.* **2011**, *58*, 248–255.
159. Hirata, Y.; Kurobe, H.; Akaike, M.; Chikugo, F.; Hori, T.; Bando, Y.; Nishio, C.; Higashida, M.; Nakaya, Y.; Kitagawa, T.; et al. Enhanced inflammation in epicardial fat in patients with coronary artery disease. *Int. Heart J.* **2011**, *52*, 139–142.
160. Back, M.; Yurdagul, A., Jr.; Tabas, I.; Oorni, K.; Kovanen, P.T. Inflammation and its resolution in atherosclerosis: Mediators and therapeutic opportunities. *Nat. Rev. Cardiol.* **2019**, *16*, 389–406.

161. Nordestgaard, B.G.; Wootton, R.; Lewis, B. Selective retention of VLDL, IDL, and LDL in the arterial intima of genetically hyperlipidemic rabbits in vivo. Molecular size as a determinant of fractional loss from the intima-inner media. *Arterioscler. Thromb. Vasc. Biol.* **1995**, *15*, 534–542.
162. Shaikh, M.; Wootton, R.; Nordestgaard, B.G.; Baskerville, P.; Lumley, J.S.; La Ville, A.E.; Quiney, J.; Lewis, B. Quantitative studies of transfer in vivo of low density, Sf 12-60, and Sf 60-400 lipoproteins between plasma and arterial intima in humans. *Arterioscler. Thromb.* **1991**, *11*, 569–577.
163. Boren, J.; Williams, K.J. The central role of arterial retention of cholesterol-rich apolipoprotein-B-containing lipoproteins in the pathogenesis of atherosclerosis: A triumph of simplicity. *Curr. Opin. Lipidol.* **2016**, *27*, 473–483.
164. Houde, M.; Van Eck, M. Escaping the atherogenic trap: Preventing LDL fusion and binding in the intima. *Atherosclerosis* **2018**, *275*, 376–378.
165. Oorni, K.; Pentikainen, M.O.; Ala-Korpela, M.; Kovanen, P.T. Aggregation, fusion, and vesicle formation of modified low density lipoprotein particles: Molecular mechanisms and effects on matrix interactions. *J. Lipid Res.* **2000**, *41*, 1703–1714.
166. Sheedy, F.J.; Grebe, A.; Rayner, K.J.; Kalantari, P.; Ramkhelawon, B.; Carpenter, S.B.; Becker, C.E.; Ediriweera, H.N.; Mullick, A.E.; Golenbock, D.T.; et al. CD36 coordinates NLRP3 inflammasome activation by facilitating intracellular nucleation of soluble ligands into particulate ligands in sterile inflammation. *Nat. Immunol.* **2013**, *14*, 812–820.
167. Maguire, E.M.; Pearce, S.W.A.; Xiao, Q. Foam cell formation: A new target for fighting atherosclerosis and cardiovascular disease. *Vascul. Pharmacol.* **2019**, *112*, 54–71.
168. Chistiakov, D.A.; Orekhov, A.N.; Bobryshev, Y.V. Endothelial Barrier and Its Abnormalities in Cardiovascular Disease. *Front. Physiol.* **2015**, *6*, 365.
169. Hutchins, P.M.; Heinecke, J.W. Cholesterol efflux capacity, macrophage reverse cholesterol transport and cardioprotective HDL. *Curr. Opin. Lipidol.* **2015**, *26*, 388–393.
170. Lao, K.H.; Zeng, L.; Xu, Q. Endothelial and smooth muscle cell transformation in atherosclerosis. *Curr. Opin. Lipidol.* **2015**, *26*, 449–456.
171. Chistiakov, D.A.; Melnichenko, A.A.; Myasoedova, V.A.; Grechko, A.V.; Orekhov, A.N. Mechanisms of foam cell formation in atherosclerosis. *J. Mol. Med.* **2017**, *95*, 1153–1165.
172. Bobryshev, Y.V. Monocyte recruitment and foam cell formation in atherosclerosis. *Micron* **2006**, *37*, 208–222.
173. Bekkering, S.; Quintin, J.; Joosten, L.A.; van der Meer, J.W.; Netea, M.G.; Riksen, N.P. Oxidized low-density lipoprotein induces long-term proinflammatory cytokine production and foam cell formation via epigenetic reprogramming of monocytes. *Arterioscler. Thromb. Vasc. Biol.* **2014**, *34*, 1731–1738.
174. Acton, S.L.; Scherer, P.E.; Lodish, H.F.; Krieger, M. Expression cloning of SR-BI, a CD36-related class B scavenger receptor. *J. Biol. Chem.* **1994**, *269*, 21003–21009.
175. Endemann, G.; Stanton, L.W.; Madden, K.S.; Bryant, C.M.; White, R.T.; Protter, A.A. CD36 is a receptor for oxidized low density lipoprotein. *J. Biol. Chem.* **1993**, *268*, 11811–11816.
176. Kodama, T.; Freeman, M.; Rohrer, L.; Zabrecky, J.; Matsudaira, P.; Krieger, M. Type I macrophage scavenger receptor contains alpha-helical and collagen-like coiled coils. *Nature* **1990**, *343*, 531–535.
177. Rahaman, S.O.; Lennon, D.J.; Febbraio, M.; Podrez, E.A.; Hazen, S.L.; Silverstein, R.L. A CD36-dependent signaling cascade is necessary for macrophage foam cell formation. *Cell Metab.* **2006**, *4*, 211–221.
178. Coller, S.P.; Paulnock, D.M. Signaling pathways initiated in macrophages after engagement of type A scavenger receptors. *J. Leukoc. Biol.* **2001**, *70*, 142–148.
179. Agrawal, S.; Febbraio, M.; Podrez, E.; Cathcart, M.K.; Stark, G.R.; Chisolm, G.M. Signal transducer and activator of transcription 1 is required for optimal foam cell formation and atherosclerotic lesion development. *Circulation* **2007**, *115*, 2939–2947.
180. Yu, X.H.; Fu, Y.C.; Zhang, D.W.; Yin, K.; Tang, C.K. Foam cells in atherosclerosis. *Clin. Chim. Acta* **2013**, *424*, 245–252.
181. Kume, N.; Moriwaki, H.; Kataoka, H.; Minami, M.; Murase, T.; Sawamura, T.; Masaki, T.; Kita, T. Inducible expression of LOX-1, a novel receptor for oxidized LDL, in macrophages and vascular smooth muscle cells. *Ann. N. Y. Acad. Sci.* **2000**, *902*, 323–327.
182. Ghosh, S. Early steps in reverse cholesterol transport: Cholesteryl ester hydrolase and other hydrolases. *Curr. Opin. Endocrinol. Diabetes Obes.* **2012**, *19*, 136–141.

183. Chistiakov, D.A.; Bobryshev, Y.V.; Orekhov, A.N. Macrophage-mediated cholesterol handling in atherosclerosis. *J. Cell. Mol. Med.* **2016**, *20*, 17–28.
184. Favari, E.; Chroni, A.; Tietge, U.J.; Zanotti, I.; Escola-Gil, J.C.; Bernini, F. Cholesterol efflux and reverse cholesterol transport. *Handb. Exp. Pharmacol.* **2015**, *224*, 181–206.
185. da Silva, R.F.; Lappalainen, J.; Lee-Rueckert, M.; Kovanen, P.T. Conversion of human M-CSF macrophages into foam cells reduces their proinflammatory responses to classical M1-polarizing activation. *Atherosclerosis* **2016**, *248*, 170–178.
186. Li, Y.B.; Zhang, Q.H.; Chen, Z.; He, Z.J.; Yi, G.H. Oxidized low-density lipoprotein attenuated desmoglein 1 and desmocollin 2 expression via LOX-1/Ca(2+)/PKC-beta signal in human umbilical vein endothelial cells. *Biochem. Biophys. Res. Commun.* **2015**, *468*, 380–386.
187. van Nieuw Amerongen, G.P.; Vermeer, M.A.; Negre-Aminou, P.; Lankelma, J.; Emeis, J.J.; van Hinsbergh, V.W. Simvastatin improves disturbed endothelial barrier function. *Circulation* **2000**, *102*, 2803–2809.
188. Kasa, A.; Csortos, C.; Verin, A.D. Cytoskeletal mechanisms regulating vascular endothelial barrier function in response to acute lung injury. *Tissue Barriers* **2015,** *3*, e974448.
189. Syed, S.E.; Trinnaman, B.; Martin, S.; Major, S.; Hutchinson, J.; Magee, A.I. Molecular interactions between desmosomal cadherins. *Biochem. J.* **2002**, *362*, 317–327.
190. Ben, J.; Zhu, X.; Zhang, H.; Chen, Q. Class A1 scavenger receptors in cardiovascular diseases. *Br. J. Pharmacol.* **2015**, *172*, 5523–5530.
191. Murphy, J.E.; Tedbury, P.R.; Homer-Vanniasinkam, S.; Walker, J.H.; Ponnambalam, S. Biochemistry and cell biology of mammalian scavenger receptors. *Atherosclerosis* **2005**, *182*, 1–15.
192. Moore, K.J.; Freeman, M.W. Scavenger receptors in atherosclerosis: Beyond lipid uptake. *Arterioscler. Thromb. Vasc. Biol.* **2006**, *26*, 1702–1711.
193. Makinen, P.I.; Lappalainen, J.P.; Heinonen, S.E.; Leppanen, P.; Lahteenvuo, M.T.; Aarnio, J.V.; Heikkila, J.; Turunen, M.P.; Yla-Herttuala, S. Silencing of either SR-A or CD36 reduces atherosclerosis in hyperlipidaemic mice and reveals reciprocal upregulation of these receptors. *Cardiovasc. Res.* **2010**, *88*, 530–538.
194. Dai, X.Y.; Cai, Y.; Mao, D.D.; Qi, Y.F.; Tang, C.; Xu, Q.; Zhu, Y.; Xu, M.J.; Wang, X. Increased stability of phosphatase and tensin homolog by intermedin leading to scavenger receptor A inhibition of macrophages reduces atherosclerosis in apolipoprotein E-deficient mice. *J. Mol. Cell. Cardiol.* **2012**, *53*, 509–520.
195. Suzuki, H.; Kurihara, Y.; Takeya, M.; Kamada, N.; Kataoka, M.; Jishage, K.; Ueda, O.; Sakaguchi, H.; Higashi, T.; Suzuki, T.; et al. A role for macrophage scavenger receptors in atherosclerosis and susceptibility to infection. *Nature* **1997**, *386*, 292–296.
196. Sakaguchi, H.; Takeya, M.; Suzuki, H.; Hakamata, H.; Kodama, T.; Horiuchi, S.; Gordon, S.; van der Laan, L.J.; Kraal, G.; Ishibashi, S.; et al. Role of macrophage scavenger receptors in diet-induced atherosclerosis in mice. *Lab. Investig.* **1998**, *78*, 423–434.
197. Babaev, V.R.; Gleaves, L.A.; Carter, K.J.; Suzuki, H.; Kodama, T.; Fazio, S.; Linton, M.F. Reduced atherosclerotic lesions in mice deficient for total or macrophage-specific expression of scavenger receptor-A. *Arterioscler. Thromb. Vasc. Biol.* **2000**, *20*, 2593–2599.
198. Hashizume, M.; Mihara, M. Blockade of IL-6 and TNF-alpha inhibited oxLDL-induced production of MCP-1 via scavenger receptor induction. *Eur. J. Pharmacol.* **2012**, *689*, 249–254.
199. Zhao, J.F.; Ching, L.C.; Huang, Y.C.; Chen, C.Y.; Chiang, A.N.; Kou, Y.R.; Shyue, S.K.; Lee, T.S. Molecular mechanism of curcumin on the suppression of cholesterol accumulation in macrophage foam cells and atherosclerosis. *Mol. Nutr. Food Res.* **2012**, *56*, 691–701.
200. Van Berkel, T.J.; Van Eck, M.; Herijgers, N.; Fluiter, K.; Nion, S. Scavenger receptor classes A and B. Their roles in atherogenesis and the metabolism of modified LDL and HDL. *Ann. N. Y. Acad. Sci.* **2000**, *902*, 113–126; discussion 126-7.
201. Pepino, M.Y.; Kuda, O.; Samovski, D.; Abumrad, N.A. Structure-function of CD36 and importance of fatty acid signal transduction in fat metabolism. *Annu. Rev. Nutr.* **2014**, *34*, 281–303.
202. Stewart, C.R.; Stuart, L.M.; Wilkinson, K.; van Gils, J.M.; Deng, J.; Halle, A.; Rayner, K.J.; Boyer, L.; Zhong, R.; Frazier, W.A.; et al. CD36 ligands promote sterile inflammation through assembly of a Toll-like receptor 4 and 6 heterodimer. *Nat. Immunol.* **2010**, *11*, 155–161.
203. Parsons, M.S.; Barrett, L.; Little, C.; Grant, M.D. Harnessing CD36 to rein in inflammation. *Endocr. Metab. Immune Disord. Drug Targets* **2008**, *8*, 184–191.

204. Hrboticky, N.; Draude, G.; Hapfelmeier, G.; Lorenz, R.; Weber, P.C. Lovastatin decreases the receptor-mediated degradation of acetylated and oxidized LDLs in human blood monocytes during the early stage of differentiation into macrophages. *Arterioscler. Thromb. Vasc. Biol.* **1999**, *19*, 1267–1275.
205. Fuhrman, B.; Koren, L.; Volkova, N.; Keidar, S.; Hayek, T.; Aviram, M. Atorvastatin therapy in hypercholesterolemic patients suppresses cellular uptake of oxidized-LDL by differentiating monocytes. *Atherosclerosis* **2002**, *164*, 179–185.
206. Geloen, A.; Helin, L.; Geeraert, B.; Malaud, E.; Holvoet, P.; Marguerie, G. CD36 inhibitors reduce postprandial hypertriglyceridemia and protect against diabetic dyslipidemia and atherosclerosis. *PLoS ONE* **2012,** 7, e37633.
207. Mansor, L.S.; Sousa Fialho, M.D.L.; Yea, G.; Coumans, W.A.; West, J.A.; Kerr, M.; Carr, C.A.; Luiken, J.; Glatz, J.F.C.; Evans, R.D.; et al. Inhibition of sarcolemmal FAT/CD36 by sulfo-N-succinimidyl oleate rapidly corrects metabolism and restores function in the diabetic heart following hypoxia/reoxygenation. *Cardiovasc. Res.* **2017**, *113*, 737–748.
208. Mimche, P.N.; Brady, L.M.; Keeton, S.; Fenne, D.S.; King, T.P.; Quicke, K.M.; Hudson, L.E.; Lamb, T.J. Expression of the Receptor Tyrosine Kinase EphB2 on Dendritic Cells Is Modulated by Toll-Like Receptor Ligation but Is Not Required for T Cell Activation. *PLoS ONE* **2015**, *10*, e0138835.
209. Li, L.; Sawamura, T.; Renier, G. Glucose enhances human macrophage LOX-1 expression: Role for LOX-1 in glucose-induced macrophage foam cell formation. *Circ. Res.* **2004**, *94*, 892–901.
210. Gao, D.; Pararasa, C.; Dunston, C.R.; Bailey, C.J.; Griffiths, H.R. Palmitate promotes monocyte atherogenicity via de novo ceramide synthesis. *Free Radic. Biol. Med.* **2012**, *53*, 796–806.
211. Li, X.Y.; Wang, C.; Xiang, X.R.; Chen, F.C.; Yang, C.M.; Wu, J. Porphyromonas gingivalis lipopolysaccharide increases lipid accumulation by affecting CD36 and ATP-binding cassette transporter A1 in macrophages. *Oncol. Rep.* **2013**, *30*, 1329–1336.
212. Choi, J.S.; Bae, J.Y.; Kim, D.S.; Li, J.; Kim, J.L.; Lee, Y.J.; Kang, Y.H. Dietary compound quercitrin dampens VEGF induction and PPARgamma activation in oxidized LDL-exposed murine macrophages: Association with scavenger receptor CD36. *J. Agric. Food Chem.* **2010**, *58*, 1333–1341.
213. Tang, F.T.; Cao, Y.; Wang, T.Q.; Wang, L.J.; Guo, J.; Zhou, X.S.; Xu, S.W.; Liu, W.H.; Liu, P.Q.; Huang, H.Q. Tanshinone IIA attenuates atherosclerosis in ApoE(-/-) mice through down-regulation of scavenger receptor expression. *Eur. J. Pharmacol.* **2011**, *650*, 275–284.
214. Granados-Principal, S.; Quiles, J.L.; Ramirez-Tortosa, C.L.; Ochoa-Herrera, J.; Perez-Lopez, P.; Pulido-Moran, M.; Ramirez-Tortosa, M.C. Squalene ameliorates atherosclerotic lesions through the reduction of CD36 scavenger receptor expression in macrophages. *Mol. Nutr. Food Res.* **2012**, *56*, 733–740.
215. Febbraio, M.; Podrez, E.A.; Smith, J.D.; Hajjar, D.P.; Hazen, S.L.; Hoff, H.F.; Sharma, K.; Silverstein, R.L. Targeted disruption of the class B scavenger receptor CD36 protects against atherosclerotic lesion development in mice. *J. Clin. Investig.* **2000**, *105*, 1049–1056.
216. Moore, K.J.; Kunjathoor, V.V.; Koehn, S.L.; Manning, J.J.; Tseng, A.A.; Silver, J.M.; McKee, M.; Freeman, M.W. Loss of receptor-mediated lipid uptake via scavenger receptor A or CD36 pathways does not ameliorate atherosclerosis in hyperlipidemic mice. *J. Clin. Investig.* **2005**, *115*, 2192–2201.
217. Kataoka, H.; Kume, N.; Miyamoto, S.; Minami, M.; Moriwaki, H.; Murase, T.; Sawamura, T.; Masaki, T.; Hashimoto, N.; Kita, T. Expression of lectinlike oxidized low-density lipoprotein receptor-1 in human atherosclerotic lesions. *Circulation* **1999**, *99*, 3110–3117.
218. Schaeffer, D.F.; Riazy, M.; Parhar, K.S.; Chen, J.H.; Duronio, V.; Sawamura, T.; Steinbrecher, U.P. LOX-1 augments oxLDL uptake by lysoPC-stimulated murine macrophages but is not required for oxLDL clearance from plasma. *J. Lipid Res.* **2009**, *50*, 1676–1684.
219. Pirillo, A.; Norata, G.D.; Catapano, A.L. LOX-1, OxLDL, and atherosclerosis. *Mediat. Inflamm.* **2013**, *2013*, 152786.
220. Inoue, K.; Arai, Y.; Kurihara, H.; Kita, T.; Sawamura, T. Overexpression of lectin-like oxidized low-density lipoprotein receptor-1 induces intramyocardial vasculopathy in apolipoprotein E-null mice. *Circ. Res.* **2005**, *97*, 176–184.
221. Ding, Z.; Liu, S.; Wang, X.; Deng, X.; Fan, Y.; Shahanawaz, J.; Shmookler Reis, R.J.; Varughese, K.I.; Sawamura, T.; Mehta, J.L. Cross-talk between LOX-1 and PCSK9 in vascular tissues. *Cardiovasc. Res.* **2015**, *107*, 556–567.

222. Ishino, S.; Mukai, T.; Kume, N.; Asano, D.; Ogawa, M.; Kuge, Y.; Minami, M.; Kita, T.; Shiomi, M.; Saji, H. Lectin-like oxidized LDL receptor-1 (LOX-1) expression is associated with atherosclerotic plaque instability--analysis in hypercholesterolemic rabbits. *Atherosclerosis* **2007**, *195*, 48–56.
223. Kuge, Y.; Kume, N.; Ishino, S.; Takai, N.; Ogawa, Y.; Mukai, T.; Minami, M.; Shiomi, M.; Saji, H. Prominent lectin-like oxidized low density lipoprotein (LDL) receptor-1 (LOX-1) expression in atherosclerotic lesions is associated with tissue factor expression and apoptosis in hypercholesterolemic rabbits. *Biol. Pharm. Bull.* **2008**, *31*, 1475–1482.
224. Fazio, S.; Major, A.S.; Swift, L.L.; Gleaves, L.A.; Accad, M.; Linton, M.F.; Farese, R.V., Jr. Increased atherosclerosis in LDL receptor-null mice lacking ACAT1 in macrophages. *J. Clin. Investig.* **2001**, *107*, 163–171.
225. Accad, M.; Smith, S.J.; Newland, D.L.; Sanan, D.A.; King, L.E., Jr.; Linton, M.F.; Fazio, S.; Farese, R.V., Jr., Massive xanthomatosis and altered composition of atherosclerotic lesions in hyperlipidemic mice lacking acyl CoA:cholesterol acyltransferase 1. *J. Clin. Investig.* **2000**, *105*, 711–719.
226. Perrey, S.; Legendre, C.; Matsuura, A.; Guffroy, C.; Binet, J.; Ohbayashi, S.; Tanaka, T.; Ortuno, J.C.; Matsukura, T.; Laugel, T.; et al. Preferential pharmacological inhibition of macrophage ACAT increases plaque formation in mouse and rabbit models of atherogenesis. *Atherosclerosis* **2001**, *155*, 359–370.
227. Chang, C.C.; Sakashita, N.; Ornvold, K.; Lee, O.; Chang, E.T.; Dong, R.; Lin, S.; Lee, C.Y.; Strom, S.C.; Kashyap, R.; et al. Immunological quantitation and localization of ACAT-1 and ACAT-2 in human liver and small intestine. *J. Biol. Chem.* **2000**, *275*, 28083–28092.
228. Cheng, B.; Wan, J.; Wang, Y.; Mei, C.; Liu, W.; Ke, L.; He, P. Ghrelin inhibits foam cell formation via simultaneously down-regulating the expression of acyl-coenzyme A:cholesterol acyltransferase 1 and up-regulating adenosine triphosphate-binding cassette transporter A1. *Cardiovasc. Pathol.* **2010**, *19*, e159–e166.
229. Nagashima, M.; Watanabe, T.; Terasaki, M.; Tomoyasu, M.; Nohtomi, K.; Kim-Kaneyama, J.; Miyazaki, A.; Hirano, T. Native incretins prevent the development of atherosclerotic lesions in apolipoprotein E knockout mice. *Diabetologia* **2011**, *54*, 2649–2659.
230. Darsalia, V.; Larsson, M.; Klein, T.; Patrone, C. The high need for trials assessing functional outcome after stroke rather than stroke prevention with GLP-1 agonists and DPP-4 inhibitors. *Cardiovasc. Diabetol.* **2018**, *17*, 32.
231. Ge, J.; Zhai, W.; Cheng, B.; He, P.; Qi, B.; Lu, H.; Zeng, Y.; Chen, X. Insulin induces human acyl-coenzyme A: Cholesterol acyltransferase1 gene expression via MAP kinases and CCAAT/enhancer-binding protein alpha. *J. Cell. Biochem.* **2013**, *114*, 2188–2198.
232. Hongo, S.; Watanabe, T.; Arita, S.; Kanome, T.; Kageyama, H.; Shioda, S.; Miyazaki, A. Leptin modulates ACAT1 expression and cholesterol efflux from human macrophages. *Am. J. Physiol. Endocrinol. Metab.* **2009,** 297, E474–E482.
233. Igarashi, M.; Osuga, J.; Isshiki, M.; Sekiya, M.; Okazaki, H.; Takase, S.; Takanashi, M.; Ohta, K.; Kumagai, M.; Nishi, M.; et al. Targeting of neutral cholesterol ester hydrolase to the endoplasmic reticulum via its N-terminal sequence. *J. Lipid Res.* **2010**, *51*, 274–285.
234. Zhao, B.; Song, J.; Chow, W.N.; St Clair, R.W.; Rudel, L.L.; Ghosh, S. Macrophage-specific transgenic expression of cholesteryl ester hydrolase significantly reduces atherosclerosis and lesion necrosis in Ldlr mice. *J. Clin. Investig.* **2007**, *117*, 2983–2992.
235. Igarashi, M.; Osuga, J.; Uozaki, H.; Sekiya, M.; Nagashima, S.; Takahashi, M.; Takase, S.; Takanashi, M.; Li, Y.; Ohta, K.; et al. The critical role of neutral cholesterol ester hydrolase 1 in cholesterol removal from human macrophages. *Circ. Res.* **2010**, *107*, 1387–1395.
236. Sekiya, M.; Osuga, J.; Nagashima, S.; Ohshiro, T.; Igarashi, M.; Okazaki, H.; Takahashi, M.; Tazoe, F.; Wada, T.; Ohta, K.; et al. Ablation of neutral cholesterol ester hydrolase 1 accelerates atherosclerosis. *Cell Metab.* **2009**, *10*, 219–228.
237. Sakai, K.; Igarashi, M.; Yamamuro, D.; Ohshiro, T.; Nagashima, S.; Takahashi, M.; Enkhtuvshin, B.; Sekiya, M.; Okazaki, H.; Osuga, J.; et al. Critical role of neutral cholesteryl ester hydrolase 1 in cholesteryl ester hydrolysis in murine macrophages. *J. Lipid Res.* **2014**, *55*, 2033–2040.
238. Sekiya, M.; Osuga, J.; Igarashi, M.; Okazaki, H.; Ishibashi, S. The role of neutral cholesterol ester hydrolysis in macrophage foam cells. *J. Atheroscler Thromb* **2011**, *18*, 359–364.
239. Zhao, Y.; Pennings, M.; Vrins, C.L.; Calpe-Berdiel, L.; Hoekstra, M.; Kruijt, J.K.; Ottenhoff, R.; Hildebrand, R.B.; van der Sluis, R.; Jessup, W.; et al. Hypocholesterolemia, foam cell accumulation, but no

atherosclerosis in mice lacking ABC-transporter A1 and scavenger receptor BI. *Atherosclerosis* **2011**, *218*, 314–322.

240. Joyce, C.W.; Wagner, E.M.; Basso, F.; Amar, M.J.; Freeman, L.A.; Shamburek, R.D.; Knapper, C.L.; Syed, J.; Wu, J.; Vaisman, B.L.; et al. ABCA1 overexpression in the liver of LDLr-KO mice leads to accumulation of pro-atherogenic lipoproteins and enhanced atherosclerosis. *J. Biol. Chem.* **2006**, *281*, 33053–33065.
241. Baldan, A.; Pei, L.; Lee, R.; Tarr, P.; Tangirala, R.K.; Weinstein, M.M.; Frank, J.; Li, A.C.; Tontonoz, P.; Edwards, P.A. Impaired development of atherosclerosis in hyperlipidemic Ldlr-/- and ApoE-/- mice transplanted with Abcg1-/- bone marrow. *Arterioscler. Thromb. Vasc. Biol.* **2006**, *26*, 2301–2307.
242. Meurs, I.; Lammers, B.; Zhao, Y.; Out, R.; Hildebrand, R.B.; Hoekstra, M.; Van Berkel, T.J.; Van Eck, M. The effect of ABCG1 deficiency on atherosclerotic lesion development in LDL receptor knockout mice depends on the stage of atherogenesis. *Atherosclerosis* **2012**, *221*, 41–47.
243. Zhang, W.; Yancey, P.G.; Su, Y.R.; Babaev, V.R.; Zhang, Y.; Fazio, S.; Linton, M.F. Inactivation of macrophage scavenger receptor class B type I promotes atherosclerotic lesion development in apolipoprotein E-deficient mice. *Circulation* **2003**, *108*, 2258–2263.
244. Bennett, D.J.; Cooke, A.J.; Edwards, A.S. Non-steroidal LXR agonists; an emerging therapeutic strategy for the treatment of atherosclerosis. *Recent Pat. Cardiovasc. Drug Discov.* **2006**, *1*, 21–46.
245. Lee, S.M.; Moon, J.; Cho, Y.; Chung, J.H.; Shin, M.J. Quercetin up-regulates expressions of peroxisome proliferator-activated receptor gamma, liver X receptor alpha, and ATP binding cassette transporter A1 genes and increases cholesterol efflux in human macrophage cell line. *Nutr. Res.* **2013**, *33*, 136–143.
246. Ogura, M.; Ayaori, M.; Terao, Y.; Hisada, T.; Iizuka, M.; Takiguchi, S.; Uto-Kondo, H.; Yakushiji, E.; Nakaya, K.; Sasaki, M.; et al. Proteasomal inhibition promotes ATP-binding cassette transporter A1 (ABCA1) and ABCG1 expression and cholesterol efflux from macrophages in vitro and in vivo. *Arterioscler. Thromb. Vasc. Biol.* **2011**, *31*, 1980–1987.
247. Tang, C.K.; Tang, G.H.; Yi, G.H.; Wang, Z.; Liu, L.S.; Wan, S.; Yuan, Z.H.; He, X.S.; Yang, J.H.; Ruan, C.G.; et al. Effect of apolipoprotein A-I on ATP binding cassette transporter A1 degradation and cholesterol efflux in THP-1 macrophage-derived foam cells. *Acta Biochim. Biophys. Sin. (Shanghai)* **2004**, *36*, 218–226.
248. Rousselle, A.; Qadri, F.; Leukel, L.; Yilmaz, R.; Fontaine, J.F.; Sihn, G.; Bader, M.; Ahluwalia, A.; Duchene, J. CXCL5 limits macrophage foam cell formation in atherosclerosis. *J. Clin. Investig.* **2013**, *123*, 1343–1347.
249. Santamarina-Fojo, S.; Remaley, A.T.; Neufeld, E.B.; Brewer, H.B., Jr. Regulation and intracellular trafficking of the ABCA1 transporter. *J. Lipid Res.* **2001**, *42*, 1339–1345.
250. Wang, Y.; Oram, J.F. Unsaturated fatty acids phosphorylate and destabilize ABCA1 through a protein kinase C delta pathway. *J. Lipid Res.* **2007**, *48*, 1062–1068.
251. Ku, C.S.; Park, Y.; Coleman, S.L.; Lee, J. Unsaturated fatty acids repress expression of ATP binding cassette transporter A1 and G1 in RAW 264.7 macrophages. *J. Nutr. Biochem.* **2012**, *23*, 1271–1276.
252. Yu, X.H.; Jiang, H.L.; Chen, W.J.; Yin, K.; Zhao, G.J.; Mo, Z.C.; Ouyang, X.P.; Lv, Y.C.; Jiang, Z.S.; Zhang, D.W.; et al. Interleukin-18 and interleukin-12 together downregulate ATP-binding cassette transporter A1 expression through the interleukin-18R/nuclear factor-kappaB signaling pathway in THP-1 macrophage-derived foam cells. *Circ. J.* **2012**, *76*, 1780–1791.
253. Jun, H.J.; Hoang, M.H.; Yeo, S.K.; Jia, Y.; Lee, S.J. Induction of ABCA1 and ABCG1 expression by the liver X receptor modulator cineole in macrophages. *Bioorg Med. Chem. Lett.* **2013**, *23*, 579–583.
254. Helal, O.; Berrougui, H.; Loued, S.; Khalil, A. Extra-virgin olive oil consumption improves the capacity of HDL to mediate cholesterol efflux and increases ABCA1 and ABCG1 expression in human macrophages. *Br. J. Nutr.* **2013**, *109*, 1844–1855.
255. Wang, D.; Xia, M.; Yan, X.; Li, D.; Wang, L.; Xu, Y.; Jin, T.; Ling, W. Gut microbiota metabolism of anthocyanin promotes reverse cholesterol transport in mice via repressing miRNA-10b. *Circ. Res.* **2012**, *111*, 967–981.
256. Uto-Kondo, H.; Ayaori, M.; Ogura, M.; Nakaya, K.; Ito, M.; Suzuki, A.; Takiguchi, S.; Yakushiji, E.; Terao, Y.; Ozasa, H.; et al. Coffee consumption enhances high-density lipoprotein-mediated cholesterol efflux in macrophages. *Circ. Res.* **2010**, *106*, 779–787.
257. Kammerer, I.; Ringseis, R.; Biemann, R.; Wen, G.; Eder, K. 13-hydroxy linoleic acid increases expression of the cholesterol transporters ABCA1, ABCG1 and SR-BI and stimulates apoA-I-dependent cholesterol efflux in RAW264.7 macrophages. *Lipids Health Dis.* **2011**, *10*, 222.

258. Voloshyna, I.; Hai, O.; Littlefield, M.J.; Carsons, S.; Reiss, A.B. Resveratrol mediates anti-atherogenic effects on cholesterol flux in human macrophages and endothelium via PPARgamma and adenosine. *Eur. J. Pharmacol.* **2013**, *698*, 299–309.
259. Tang, S.L.; Chen, W.J.; Yin, K.; Zhao, G.J.; Mo, Z.C.; Lv, Y.C.; Ouyang, X.P.; Yu, X.H.; Kuang, H.J.; Jiang, Z.S.; et al. PAPP-A negatively regulates ABCA1, ABCG1 and SR-B1 expression by inhibiting LXRalpha through the IGF-I-mediated signaling pathway. *Atherosclerosis* **2012**, *222*, 344–354.
260. Duewell, P.; Kono, H.; Rayner, K.J.; Sirois, C.M.; Vladimer, G.; Bauernfeind, F.G.; Abela, G.S.; Franchi, L.; Nunez, G.; Schnurr, M.; et al. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. *Nature* **2010**, *464*, 1357–1361.
261. Libby, P.; Aikawa, M.; Schonbeck, U. Cholesterol and atherosclerosis. *Biochim. Biophys. Acta* **2000**, *1529*, 299–309.
262. Sottero, B.; Gamba, P.; Longhi, M.; Robbesyn, F.; Abuja, P.M.; Schaur, R.J.; Poli, G.; Leonarduzzi, G. Expression and synthesis of TGFbeta1 is induced in macrophages by 9-oxononanoyl cholesterol, a major cholesteryl ester oxidation product. *Biofactors* **2005**, *24*, 209–216.
263. McCarthy, C.; Duffy, M.M.; Mooney, D.; James, W.G.; Griffin, M.D.; Fitzgerald, D.J.; Belton, O. IL-10 mediates the immunoregulatory response in conjugated linoleic acid-induced regression of atherosclerosis. *FASEB J.* **2013**, *27*, 499–510.
264. Banchereau, J.; Briere, F.; Caux, C.; Davoust, J.; Lebecque, S.; Liu, Y.J.; Pulendran, B.; Palucka, K. Immunobiology of dendritic cells. *Annu. Rev. Immunol.* **2000**, *18*, 767–811.
265. Zernecke, A. Dendritic cells in atherosclerosis: Evidence in mice and humans. *Arterioscler. Thromb. Vasc. Biol.* **2015**, *35*, 763–770.
266. Bousso, P. T-cell activation by dendritic cells in the lymph node: Lessons from the movies. *Nat. Rev. Immunol.* **2008**, *8*, 675–684.
267. Steinman, R.M. Decisions about dendritic cells: Past, present, and future. *Annu. Rev. Immunol.* **2012**, *30*, 1–22.
268. Schraml, B.U.; Reis e Sousa, C. Defining dendritic cells. *Curr. Opin. Immunol.* **2015**, *32*, 13–20.
269. Mildner, A.; Jung, S. Development and function of dendritic cell subsets. *Immunity* **2014**, *40*, 642–656.
270. Guilliams, M.; Dutertre, C.A.; Scott, C.L.; McGovern, N.; Sichien, D.; Chakarov, S.; Van Gassen, S.; Chen, J.; Poidinger, M.; De Prijck, S.; et al. Unsupervised High-Dimensional Analysis Aligns Dendritic Cells across Tissues and Species. *Immunity* **2016**, *45*, 669–684.
271. Dutertre, C.A.; Wang, L.F.; Ginhoux, F. Aligning bona fide dendritic cell populations across species. *Cell. Immunol.* **2014**, *291*, 3–10.
272. Greter, M.; Helft, J.; Chow, A.; Hashimoto, D.; Mortha, A.; Agudo-Cantero, J.; Bogunovic, M.; Gautier, E.L.; Miller, J.; Leboeuf, M.; et al. GM-CSF controls nonlymphoid tissue dendritic cell homeostasis but is dispensable for the differentiation of inflammatory dendritic cells. *Immunity* **2012**, *36*, 1031–1046.
273. Ushach, I.; Zlotnik, A. Biological role of granulocyte macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (M-CSF) on cells of the myeloid lineage. *J. Leukoc. Biol.* **2016**, *100*, 481–489.
274. Hume, D.A. Macrophages as APC and the dendritic cell myth. *J. Immunol.* **2008**, *181*, 5829–5835.
275. Jongstra-Bilen, J.; Haidari, M.; Zhu, S.N.; Chen, M.; Guha, D.; Cybulsky, M.I. Low-grade chronic inflammation in regions of the normal mouse arterial intima predisposed to atherosclerosis. *J. Exp. Med.* **2006**, *203*, 2073–2083.
276. Paulson, K.E.; Zhu, S.N.; Chen, M.; Nurmohamed, S.; Jongstra-Bilen, J.; Cybulsky, M.I. Resident intimal dendritic cells accumulate lipid and contribute to the initiation of atherosclerosis. *Circ. Res.* **2010**, *106*, 383–390.
277. Choi, J.H.; Cheong, C.; Dandamudi, D.B.; Park, C.G.; Rodriguez, A.; Mehandru, S.; Velinzon, K.; Jung, I.H.; Yoo, J.Y.; Oh, G.T.; et al. Flt3 signaling-dependent dendritic cells protect against atherosclerosis. *Immunity* **2011**, *35*, 819–831.
278. Choi, J.H.; Do, Y.; Cheong, C.; Koh, H.; Boscardin, S.B.; Oh, Y.S.; Bozzacco, L.; Trumpfheller, C.; Park, C.G.; Steinman, R.M. Identification of antigen-presenting dendritic cells in mouse aorta and cardiac valves. *J. Exp. Med.* **2009**, *206*, 497–505.
279. Roufaiel, M.; Gracey, E.; Siu, A.; Zhu, S.N.; Lau, A.; Ibrahim, H.; Althagafi, M.; Tai, K.; Hyduk, S.J.; Cybulsky, K.O.; et al. CCL19-CCR7-dependent reverse transendothelial migration of myeloid cells clears Chlamydia muridarum from the arterial intima. *Nat. Immunol.* **2016**, *17*, 1263–1272.

280. Trogan, E.; Feig, J.E.; Dogan, S.; Rothblat, G.H.; Angeli, V.; Tacke, F.; Randolph, G.J.; Fisher, E.A. Gene expression changes in foam cells and the role of chemokine receptor CCR7 during atherosclerosis regression in ApoE-deficient mice. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 3781–3786.
281. Ginhoux, F.; Jung, S. Monocytes and macrophages: Developmental pathways and tissue homeostasis. *Nat. Rev. Immunol.* **2014**, *14*, 392–404.
282. Rescigno, M.; Martino, M.; Sutherland, C.L.; Gold, M.R.; Ricciardi-Castagnoli, P. Dendritic cell survival and maturation are regulated by different signaling pathways. *J. Exp. Med.* **1998**, *188*, 2175–2180.
283. Pflicke, H.; Sixt, M. Preformed portals facilitate dendritic cell entry into afferent lymphatic vessels. *J. Exp. Med.* **2009**, *206*, 2925–2935.
284. Gonzalez, S.F.; Lukacs-Kornek, V.; Kuligowski, M.P.; Pitcher, L.A.; Degn, S.E.; Kim, Y.A.; Cloninger, M.J.; Martinez-Pomares, L.; Gordon, S.; Turley, S.J.; et al. Capture of influenza by medullary dendritic cells via SIGN-R1 is essential for humoral immunity in draining lymph nodes. *Nat. Immunol.* **2010**, *11*, 427–434.
285. MacRitchie, N.; Grassia, G.; Noonan, J.; Cole, J.E.; Hughes, C.E.; Schroeder, J.; Benson, R.A.; Cochain, C.; Zernecke, A.; Guzik, T.J.; et al. The aorta can act as a site of naive CD4+ T cell priming. *Cardiovasc Res.* **2019**, doi:10.1093/cvr/cvz102.
286. Weber, C.; Meiler, S.; Doring, Y.; Koch, M.; Drechsler, M.; Megens, R.T.; Rowinska, Z.; Bidzhekov, K.; Fecher, C.; Ribechini, E.; et al. CCL17-expressing dendritic cells drive atherosclerosis by restraining regulatory T cell homeostasis in mice. *J. Clin. Investig.* **2011**, *121*, 2898–2910.
287. Koltsova, E.K.; Garcia, Z.; Chodaczek, G.; Landau, M.; McArdle, S.; Scott, S.R.; von Vietinghoff, S.; Galkina, E.; Miller, Y.I.; Acton, S.T.; et al. Dynamic T cell-APC interactions sustain chronic inflammation in atherosclerosis. *J. Clin. Investig.* **2012**, *122*, 3114–3126.
288. Sun, J.; Hartvigsen, K.; Chou, M.Y.; Zhang, Y.; Sukhova, G.K.; Zhang, J.; Lopez-Ilasaca, M.; Diehl, C.J.; Yakov, N.; Harats, D.; et al. Deficiency of antigen-presenting cell invariant chain reduces atherosclerosis in mice. *Circulation* **2010**, *122*, 808–820.
289. Wigren, M.; Rattik, S.; Yao Mattisson, I.; Tomas, L.; Gronberg, C.; Soderberg, I.; Alm, R.; Sundius, L.; Ljungcrantz, I.; Bjorkbacka, H.; et al. Lack of Ability to Present Antigens on Major Histocompatibility Complex Class II Molecules Aggravates Atherosclerosis in ApoE(-/-) Mice. *Circulation* **2019**, *139*, 2554–2566.
290. Subramanian, M.; Thorp, E.; Hansson, G.K.; Tabas, I. Treg-mediated suppression of atherosclerosis requires MYD88 signaling in DCs. *J. Clin. Investig.* **2013**, *123*, 179–188.
291. Loschko, J.; Schreiber, H.A.; Rieke, G.J.; Esterhazy, D.; Meredith, M.M.; Pedicord, V.A.; Yao, K.H.; Caballero, S.; Pamer, E.G.; Mucida, D.; et al. Absence of MHC class II on cDCs results in microbial-dependent intestinal inflammation. *J. Exp. Med.* **2016**, *213*, 517–534.
292. Agouridis, A.P.; Elisaf, M.; Milionis, H.J. An overview of lipid abnormalities in patients with inflammatory bowel disease. *Ann. Gastroenterol.* **2011**, *24*, 181–187.
293. Lievens, D.; Habets, K.L.; Robertson, A.K.; Laouar, Y.; Winkels, H.; Rademakers, T.; Beckers, L.; Wijnands, E.; Boon, L.; Mosaheb, M.; et al. Abrogated transforming growth factor beta receptor II (TGFbetaRII) signalling in dendritic cells promotes immune reactivity of T cells resulting in enhanced atherosclerosis. *Eur. Heart J.* **2013**, *34*, 3717–3727.
294. Chaudhari, S.M.; Sluimer, J.C.; Koch, M.; Theelen, T.L.; Manthey, H.D.; Busch, M.; Caballero-Franco, C.; Vogel, F.; Cochain, C.; Pelisek, J.; et al. Deficiency of HIF1alpha in Antigen-Presenting Cells Aggravates Atherosclerosis and Type 1 T-Helper Cell Responses in Mice. *Arterioscler. Thromb. Vasc. Biol.* **2015**, *35*, 2316–2325.
295. Alberts-Grill, N.; Engelbertsen, D.; Bu, D.; Foks, A.; Grabie, N.; Herter, J.M.; Kuperwaser, F.; Chen, T.; Destefano, G.; Jarolim, P.; et al. Dendritic Cell KLF2 Expression Regulates T Cell Activation and Proatherogenic Immune Responses. *J. Immunol.* **2016**, *197*, 4651–4662.
296. Thomson, A.W.; Robbins, P.D. Tolerogenic dendritic cells for autoimmune disease and transplantation. *Ann. Rheum. Dis.* **2008**, *67* (Suppl. 3), iii90–iii96.
297. Mok, M.Y. Tolerogenic dendritic cells: Role and therapeutic implications in systemic lupus erythematosus. *Int. J. Rheum. Dis* **2015**, *18*, 250–259.
298. Habets, K.L.; van Puijvelde, G.H.; van Duivenvoorde, L.M.; van Wanrooij, E.J.; de Vos, P.; Tervaert, J.W.; van Berkel, T.J.; Toes, R.E.; Kuiper, J. Vaccination using oxidized low-density lipoprotein-pulsed dendritic cells reduces atherosclerosis in LDL receptor-deficient mice. *Cardiovasc. Res.* **2010**, *85*, 622–630.

299. Hermansson, A.; Johansson, D.K.; Ketelhuth, D.F.; Andersson, J.; Zhou, X.; Hansson, G.K. Immunotherapy with tolerogenic apolipoprotein B-100-loaded dendritic cells attenuates atherosclerosis in hypercholesterolemic mice. *Circulation* **2011**, *123*, 1083–1091.
300. Rombouts, M.; Cools, N.; Grootaert, M.O.; de Bakker, F.; Van Brussel, I.; Wouters, A.; De Meyer, G.R.; De Winter, B.Y.; Schrijvers, D.M. Long-Term Depletion of Conventional Dendritic Cells Cannot Be Maintained in an Atherosclerotic Zbtb46-DTR Mouse Model. *PLoS ONE* **2017**, *12*, e0169608.
301. McKenna, H.J.; Stocking, K.L.; Miller, R.E.; Brasel, K.; De Smedt, T.; Maraskovsky, E.; Maliszewski, C.R.; Lynch, D.H.; Smith, J.; Pulendran, B.; et al. Mice lacking flt3 ligand have deficient hematopoiesis affecting hematopoietic progenitor cells, dendritic cells, and natural killer cells. *Blood* **2000**, *95*, 3489–3497.
302. Legein, B.; Janssen, E.M.; Theelen, T.L.; Gijbels, M.J.; Walraven, J.; Klarquist, J.S.; Hennies, C.M.; Wouters, K.; Seijkens, T.T.; Wijnands, E.; et al. Ablation of CD8alpha(+) dendritic cell mediated cross-presentation does not impact atherosclerosis in hyperlipidemic mice. *Sci Rep.* **2015**, *5*, 15414.
303. Gil-Pulido, J.; Cochain, C.; Lippert, M.A.; Schneider, N.; Butt, E.; Amezaga, N.; Zernecke, A. Deletion of Batf3-dependent antigen-presenting cells does not affect atherosclerotic lesion formation in mice. *PLoS ONE* **2017**, *12*, e0181947.
304. Li, Y.; Liu, X.; Duan, W.; Tian, H.; Zhu, G.; He, H.; Yao, S.; Yi, S.; Song, W.; Tang, H. Batf3-dependent CD8alpha(+) Dendritic Cells Aggravates Atherosclerosis via Th1 Cell Induction and Enhanced CCL5 Expression in Plaque Macrophages. *EBioMedicine* **2017**, *18*, 188–198.
305. Haddad, Y.; Lahoute, C.; Clement, M.; Laurans, L.; Metghalchi, S.; Zeboudj, L.; Giraud, A.; Loyer, X.; Vandestienne, M.; Wain-Hobson, J.; et al.The Dendritic Cell Receptor DNGR-1 Promotes the Development of Atherosclerosis in Mice. *Circ. Res.* **2017**, *121*, 234–243.
306. Daissormont, I.T.; Christ, A.; Temmerman, L.; Sampedro Millares, S.; Seijkens, T.; Manca, M.; Rousch, M.; Poggi, M.; Boon, L.; van der Loos, C.; et al. Plasmacytoid dendritic cells protect against atherosclerosis by tuning T-cell proliferation and activity. *Circ. Res.* **2011**, *109*, 1387–1395.
307. Doring, Y.; Manthey, H.D.; Drechsler, M.; Lievens, D.; Megens, R.T.; Soehnlein, O.; Busch, M.; Manca, M.; Koenen, R.R.; Pelisek, J.; et al. Auto-antigenic protein-DNA complexes stimulate plasmacytoid dendritic cells to promote atherosclerosis. *Circulation* **2012**, *125*, 1673–1683.
308. Macritchie, N.; Grassia, G.; Sabir, S.R.; Maddaluno, M.; Welsh, P.; Sattar, N.; Ialenti, A.; Kurowska-Stolarska, M.; McInnes, I.B.; Brewer, J.M.; et al. Plasmacytoid dendritic cells play a key role in promoting atherosclerosis in apolipoprotein E-deficient mice. *Arterioscler. Thromb. Vasc. Biol.* **2012**, *32*, 2569–2579.
309. Yun, T.J.; Lee, J.S.; Machmach, K.; Shim, D.; Choi, J.; Wi, Y.J.; Jang, H.S.; Jung, I.H.; Kim, K.; Yoon, W.K.; et al. Indoleamine 2,3-Dioxygenase-Expressing Aortic Plasmacytoid Dendritic Cells Protect against Atherosclerosis by Induction of Regulatory T Cells. *Cell Metab.* **2016**, *23*, 852–866.
310. Mandl, M.; Drechsler, M.; Jansen, Y.; Neideck, C.; Noels, H.; Faussner, A.; Soehnlein, O.; Weber, C.; Doring, Y. Evaluation of the BDCA2-DTR Transgenic Mouse Model in Chronic and Acute Inflammation. *PLoS ONE* **2015**, *10*, e0134176.
311. Sage, A.P.; Murphy, D.; Maffia, P.; Masters, L.M.; Sabir, S.R.; Baker, L.L.; Cambrook, H.; Finigan, A.J.; Ait-Oufella, H.; Grassia, G.; et al. MHC Class II-restricted antigen presentation by plasmacytoid dendritic cells drives proatherogenic T cell immunity. *Circulation* **2014**, *130*, 1363–1373.
312. Kretzschmar, D.; Rohm, I.; Schaller, S.; Betge, S.; Pistulli, R.; Atiskova, Y.; Figulla, H.R.; Yilmaz, A. Decrease in circulating dendritic cell precursors in patients with peripheral artery disease. *Mediat. Inflamm.* **2015**, *2015*, 450957.
313. Van Vre, E.A.; Van Brussel, I.; Bosmans, J.M.; Vrints, C.J.; Bult, H. Dendritic cells in human atherosclerosis: From circulation to atherosclerotic plaques. *Mediat. Inflamm.* **2011**, *2011*, 941396.
314. Liu, A.; Ming, J.Y.; Fiskesund, R.; Ninio, E.; Karabina, S.A.; Bergmark, C.; Frostegard, A.G.; Frostegard, J. Induction of dendritic cell-mediated T-cell activation by modified but not native low-density lipoprotein in humans and inhibition by annexin a5: Involvement of heat shock proteins. *Arterioscler. Thromb. Vasc. Biol.* **2015**, *35*, 197–205.
315. Fehervari, Z.; Sakaguchi, S. Control of Foxp3+ CD25+CD4+ regulatory cell activation and function by dendritic cells. *Int. Immunol.* **2004**, *16*, 1769–1780.
316. Liu, J.; Cao, X. Regulatory dendritic cells in autoimmunity: A comprehensive review. *J. Autoimmun.* **2015**, *63*, 1–12.
317. Morelli, A.E.; Thomson, A.W. Tolerogenic dendritic cells and the quest for transplant tolerance. *Nat. Rev. Immunol.* **2007**, *7*, 610–621.

318. Chen, M.; Wang, Y.H.; Wang, Y.; Huang, L.; Sandoval, H.; Liu, Y.J.; Wang, J. Dendritic cell apoptosis in the maintenance of immune tolerance. *Science* **2006**, *311*, 1160–1164.
319. Selenko-Gebauer, N.; Majdic, O.; Szekeres, A.; Hofler, G.; Guthann, E.; Korthauer, U.; Zlabinger, G.; Steinberger, P.; Pickl, W.F.; Stockinger, H.; et al. B7-H1 (programmed death-1 ligand) on dendritic cells is involved in the induction and maintenance of T cell anergy. *J. Immunol.* **2003**, *170*, 3637–3644.
320. Darrasse-Jeze, G.; Deroubaix, S.; Mouquet, H.; Victora, G.D.; Eisenreich, T.; Yao, K.H.; Masilamani, R.F.; Dustin, M.L.; Rudensky, A.; Liu, K.; et al. Feedback control of regulatory T cell homeostasis by dendritic cells in vivo. *J. Exp. Med.* **2009**, *206*, 1853–1862.
321. Ye, Z.S.; Huang, R.C. Selectins modify dendritic cells during atherosclerosis. *Chronic Dis. Transl. Med.* **2018**, *4*, 205–210.
322. Torres-Aguilar, H.; Sanchez-Torres, C.; Jara, L.J.; Blank, M.; Shoenfeld, Y. IL-10/TGF-beta-treated dendritic cells, pulsed with insulin, specifically reduce the response to insulin of CD4+ effector/memory T cells from type 1 diabetic individuals. *J. Clin. Immunol.* **2010**, *30*, 659–668.
323. Hjerpe, C.; Johansson, D.; Hermansson, A.; Hansson, G.K.; Zhou, X. Dendritic cells pulsed with malondialdehyde modified low density lipoprotein aggravate atherosclerosis in Apoe(-/-) mice. *Atherosclerosis* **2010**, *209*, 436–441.
324. Frodermann, V.; van Puijvelde, G.H.; Wierts, L.; Lagraauw, H.M.; Foks, A.C.; van Santbrink, P.J.; Bot, I.; Kuiper, J.; de Jager, S.C. Oxidized low-density lipoprotein-induced apoptotic dendritic cells as a novel therapy for atherosclerosis. *J. Immunol.* **2015**, *194*, 2208–2218.
325. Ketelhuth, D.F.; Hansson, G.K. Adaptive Response of T and B Cells in Atherosclerosis. *Circ. Res.* **2016**, *118*, 668–678.
326. Bustos-Moran, E.; Blas-Rus, N.; Martin-Cofreces, N.B.; Sanchez-Madrid, F. Orchestrating Lymphocyte Polarity in Cognate Immune Cell-Cell Interactions. *Int. Rev. Cell Mol. Biol.* **2016**, *327*, 195–261.
327. Gronberg, C.; Nilsson, J.; Wigren, M. Recent advances on CD4(+) T cells in atherosclerosis and its implications for therapy. *Eur. J. Pharmacol.* **2017**, *816*, 58–66.
328. Kaech, S.M.; Wherry, E.J.; Ahmed, R. Effector and memory T-cell differentiation: Implications for vaccine development. *Nat. Rev. Immunol.* **2002**, *2*, 251–262.
329. Zhou, L.; Chong, M.M.; Littman, D.R. Plasticity of CD4+ T cell lineage differentiation. *Immunity* **2009**, *30*, 646–655.
330. Rocha-Perugini, V.; Gonzalez-Granado, J.M. Nuclear envelope lamin-A as a coordinator of T cell activation. *Nucleus* **2014**, *5*, 396–401.
331. van Panhuys, N.; Klauschen, F.; Germain, R.N. T-cell-receptor-dependent signal intensity dominantly controls CD4(+) T cell polarization In Vivo. *Immunity* **2014**, *41*, 63–74.
332. Zhu, J.; Yamane, H.; Paul, W.E. Differentiation of effector CD4 T cell populations (*). *Annu. Rev. Immunol.* **2010**, *28*, 445–489.
333. Tse, K.; Tse, H.; Sidney, J.; Sette, A.; Ley, K. T cells in atherosclerosis. *Int. Immunol.* **2013**, *25*, 615–622.
334. Zhu, J.; Paul, W.E. CD4 T cells: Fates, functions, and faults. *Blood* **2008**, *112*, 1557–1569.
335. Gounopoulos, P.; Merki, E.; Hansen, L.F.; Choi, S.H.; Tsimikas, S. Antibodies to oxidized low density lipoprotein: Epidemiological studies and potential clinical applications in cardiovascular disease. *Minerva Cardioangiol.* **2007**, *55*, 821–837.
336. Libby, P. Inflammation in atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* **2012**, *32*, 2045–2051.
337. Lahoute, C.; Herbin, O.; Mallat, Z.; Tedgui, A. Adaptive immunity in atherosclerosis: Mechanisms and future therapeutic targets. *Nat. Rev. Cardiol.* **2011**, *8*, 348–358.
338. Iborra, S.; Gonzalez-Granado, J.M. In Vitro Differentiation of Naive CD4(+) T Cells: A Tool for Understanding the Development of Atherosclerosis. *Methods Mol. Biol.* **2015**, *1339*, 177–189.
339. Aubry, M.C.; Riehle, D.L.; Edwards, W.D.; Maradit-Kremers, H.; Roger, V.L.; Sebo, T.J.; Gabriel, S.E. B-Lymphocytes in plaque and adventitia of coronary arteries in two patients with rheumatoid arthritis and coronary atherosclerosis: Preliminary observations. *Cardiovasc. Pathol.* **2004**, *13*, 233–236.
340. Ketelhuth, D.F.; Hansson, G.K. Cellular immunity, low-density lipoprotein and atherosclerosis: Break of tolerance in the artery wall. *Thromb. Haemost.* **2011**, *106*, 779–786.
341. Mallat, Z.; Taleb, S.; Ait-Oufella, H.; Tedgui, A. The role of adaptive T cell immunity in atherosclerosis. *J. Lipid Res.* **2009**, *50* (Suppl.), S364–S369.

342. Laurat, E.; Poirier, B.; Tupin, E.; Caligiuri, G.; Hansson, G.K.; Bariety, J.; Nicoletti, A. In vivo downregulation of T helper cell 1 immune responses reduces atherogenesis in apolipoprotein E-knockout mice. *Circulation* **2001**, *104*, 197–202.
343. Li, J.; McArdle, S.; Gholami, A.; Kimura, T.; Wolf, D.; Gerhardt, T.; Miller, J.; Weber, C.; Ley, K. CCR5+T-bet+FoxP3+ Effector CD4 T Cells Drive Atherosclerosis. *Circ. Res.* **2016**, *118*, 1540–1552.
344. Elhage, R.; Gourdy, P.; Brouchet, L.; Jawien, J.; Fouque, M.J.; Fievet, C.; Huc, X.; Barreira, Y.; Couloumiers, J.C.; Arnal, J.F.; et al. Deleting TCR alpha beta+ or CD4+ T lymphocytes leads to opposite effects on site-specific atherosclerosis in female apolipoprotein E-deficient mice. *Am. J. Pathol.* **2004**, *165*, 2013–2018.
345. Zhou, X.; Robertson, A.K.; Rudling, M.; Parini, P.; Hansson, G.K. Lesion development and response to immunization reveal a complex role for CD4 in atherosclerosis. *Circ. Res.* **2005**, *96*, 427–434.
346. Buono, C.; Binder, C.J.; Stavrakis, G.; Witztum, J.L.; Glimcher, L.H.; Lichtman, A.H. T-bet deficiency reduces atherosclerosis and alters plaque antigen-specific immune responses. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 1596–1601.
347. Buono, C.; Come, C.E.; Stavrakis, G.; Maguire, G.F.; Connelly, P.W.; Lichtman, A.H. Influence of interferon-gamma on the extent and phenotype of diet-induced atherosclerosis in the LDLR-deficient mouse. *Arterioscler. Thromb. Vasc. Biol.* **2003**, *23*, 454–460.
348. Jones, K.L.; Maguire, J.J.; Davenport, A.P. Chemokine receptor CCR5: From AIDS to atherosclerosis. *Br. J. Pharmacol.* **2011**, *162*, 1453–1469.
349. Elhage, R.; Jawien, J.; Rudling, M.; Ljunggren, H.G.; Takeda, K.; Akira, S.; Bayard, F.; Hansson, G.K. Reduced atherosclerosis in interleukin-18 deficient apolipoprotein E-knockout mice. *Cardiovasc. Res.* **2003**, *59*, 234–240.
350. Davenport, P.; Tipping, P.G. The role of interleukin-4 and interleukin-12 in the progression of atherosclerosis in apolipoprotein E-deficient mice. *Am. J. Pathol.* **2003**, *163*, 1117–1125.
351. Hauer, A.D.; Uyttenhove, C.; de Vos, P.; Stroobant, V.; Renauld, J.C.; van Berkel, T.J.; van Snick, J.; Kuiper, J. Blockade of interleukin-12 function by protein vaccination attenuates atherosclerosis. *Circulation* **2005**, *112*, 1054–1062.
352. Mallat, Z.; Corbaz, A.; Scoazec, A.; Graber, P.; Alouani, S.; Esposito, B.; Humbert, Y.; Chvatchko, Y.; Tedgui, A. Interleukin-18/interleukin-18 binding protein signaling modulates atherosclerotic lesion development and stability. *Circ. Res.* **2001,** 89, E41–E45.
353. Haybar, H.; Rezaeeyan, H.; Shahjahani, M.; Shirzad, R.; Saki, N. T-bet transcription factor in cardiovascular disease: Attenuation or inflammation factor? *J. Cell. Physiol.* **2019**, *234*, 7915–7922.
354. Oh, S.; Hwang, E.S. The role of protein modifications of T-bet in cytokine production and differentiation of T helper cells. *J. Immunol. Res.* **2014**, *2014*, 589672.
355. Yu, F.; Sharma, S.; Edwards, J.; Feigenbaum, L.; Zhu, J. Dynamic expression of transcription factors T-bet and GATA-3 by regulatory T cells maintains immunotolerance. *Nat. Immunol.* **2015**, *16*, 197–206.
356. Whitman, S.C.; Ravisankar, P.; Elam, H.; Daugherty, A. Exogenous interferon-gamma enhances atherosclerosis in apolipoprotein E-/- mice. *Am. J. Pathol.* **2000**, *157*, 1819–1824.
357. Gupta, S.; Pablo, A.M.; Jiang, X.; Wang, N.; Tall, A.R.; Schindler, C. IFN-gamma potentiates atherosclerosis in ApoE knock-out mice. *J. Clin. Investig.* **1997**, *99*, 2752–2761.
358. Moss, J.W.; Ramji, D.P. Interferon-gamma: Promising therapeutic target in atherosclerosis. *World J. Exp. Med.* **2015**, *5*, 154–159.
359. Lim, W.S.; Timmins, J.M.; Seimon, T.A.; Sadler, A.; Kolodgie, F.D.; Virmani, R.; Tabas, I. Signal transducer and activator of transcription-1 is critical for apoptosis in macrophages subjected to endoplasmic reticulum stress in vitro and in advanced atherosclerotic lesions in vivo. *Circulation* **2008**, *117*, 940–951.
360. Blankenberg, S.; Barbaux, S.; Tiret, L. Adhesion molecules and atherosclerosis. *Atherosclerosis* **2003**, *170*, 191–203.
361. Chung, H.K.; Lee, I.K.; Kang, H.; Suh, J.M.; Kim, H.; Park, K.C.; Kim, D.W.; Kim, Y.K.; Ro, H.K.; Shong, M. Statin inhibits interferon-gamma-induced expression of intercellular adhesion molecule-1 (ICAM-1) in vascular endothelial and smooth muscle cells. *Exp. Mol. Med.* **2002**, *34*, 451–461.
362. Harvey, E.J.; Ramji, D.P. Interferon-gamma and atherosclerosis: Pro- or anti-atherogenic? *Cardiovasc. Res.* **2005**, *67*, 11–20.
363. Canton, J.; Neculai, D.; Grinstein, S. Scavenger receptors in homeostasis and immunity. *Nat. Rev. Immunol.* **2013**, *13*, 621–634.

364. Kzhyshkowska, J.; Neyen, C.; Gordon, S. Role of macrophage scavenger receptors in atherosclerosis. *Immunobiology* **2012**, *217*, 492–502.
365. Wuttge, D.M.; Zhou, X.; Sheikine, Y.; Wagsater, D.; Stemme, V.; Hedin, U.; Stemme, S.; Hansson, G.K.; Sirsjo, A. CXCL16/SR-PSOX is an interferon-gamma-regulated chemokine and scavenger receptor expressed in atherosclerotic lesions. *Arterioscler. Thromb. Vasc. Biol.* **2004**, *24*, 750–755.
366. Braunersreuther, V.; Zernecke, A.; Arnaud, C.; Liehn, E.A.; Steffens, S.; Shagdarsuren, E.; Bidzhekov, K.; Burger, F.; Pelli, G.; Luckow, B.; et al. Ccr5 but not Ccr1 deficiency reduces development of diet-induced atherosclerosis in mice. *Arterioscler. Thromb. Vasc. Biol.* **2007**, *27*, 373–379.
367. Afzal, A.R.; Kiechl, S.; Daryani, Y.P.; Weerasinghe, A.; Zhang, Y.; Reindl, M.; Mayr, A.; Weger, S.; Xu, Q.; Willeit, J. Common CCR5-del32 frameshift mutation associated with serum levels of inflammatory markers and cardiovascular disease risk in the Bruneck population. *Stroke* **2008**, *39*, 1972–1978.
368. Szalai, C.; Duba, J.; Prohaszka, Z.; Kalina, A.; Szabo, T.; Nagy, B.; Horvath, L.; Csaszar, A. Involvement of polymorphisms in the chemokine system in the susceptibility for coronary artery disease (CAD). Coincidence of elevated Lp(a) and MCP-1 -2518 G/G genotype in CAD patients. *Atherosclerosis* **2001**, *158*, 233–239.
369. Pai, J.K.; Kraft, P.; Cannuscio, C.C.; Manson, J.E.; Rexrode, K.M.; Albert, C.M.; Hunter, D.; Rimm, E.B. Polymorphisms in the CC-chemokine receptor-2 (CCR2) and -5 (CCR5) genes and risk of coronary heart disease among US women. *Atherosclerosis* **2006**, *186*, 132–139.
370. Balistreri, C.R.; Candore, G.; Caruso, M.; Incalcaterra, E.; Franceschi, C.; Caruso, C. Role of polymorphisms of CC-chemokine receptor-5 gene in acute myocardial infarction and biological implications for longevity. *Haematologica* **2008**, *93*, 637–638.
371. Gonzalez, P.; Alvarez, R.; Batalla, A.; Reguero, J.R.; Alvarez, V.; Astudillo, A.; Cubero, G.I.; Cortina, A.; Coto, E. Genetic variation at the chemokine receptors CCR5/CCR2 in myocardial infarction. *Genes Immun* **2001**, *2*, 191–195.
372. Sharda, S.; Gilmour, A.; Harris, V.; Singh, V.P.; Sinha, N.; Tewari, S.; Ramesh, V.; Agrawal, S.; Mastana, S. Chemokine receptor 5 (CCR5) deletion polymorphism in North Indian patients with coronary artery disease. *Int. J. Cardiol.* **2008**, *124*, 254–258.
373. Ghilardi, G.; Biondi, M.L.; Turri, O.; Pateri, F.; d'Eril, G.M.; Scorza, R. Genetic control of chemokines in severe human internal carotid artery stenosis. *Cytokine* **2008**, *41*, 24–28.
374. Apostolakis, S.; Baritaki, S.; Kochiadakis, G.E.; Igoumenidis, N.E.; Panutsopulos, D.; Spandidos, D.A. Effects of polymorphisms in chemokine ligands and receptors on susceptibility to coronary artery disease. *Thromb Res.* **2007**, *119*, 63–71.
375. Petrkova, J.; Cermakova, Z.; Lukl, J.; Petrek, M. CC chemokine receptor 5 (CCR5) deletion polymorphism does not protect Czech males against early myocardial infarction. *J. Intern. Med.* **2005**, *257*, 564–566.
376. Simeoni, E.; Winkelmann, B.R.; Hoffmann, M.M.; Fleury, S.; Ruiz, J.; Kappenberger, L.; Marz, W.; Vassalli, G. Association of RANTES G-403A gene polymorphism with increased risk of coronary arteriosclerosis. *Eur. Heart J.* **2004**, *25*, 1438–1446.
377. van Wanrooij, E.J.; Happe, H.; Hauer, A.D.; de Vos, P.; Imanishi, T.; Fujiwara, H.; van Berkel, T.J.; Kuiper, J. HIV entry inhibitor TAK-779 attenuates atherogenesis in low-density lipoprotein receptor-deficient mice. *Arterioscler. Thromb. Vasc. Biol.* **2005**, *25*, 2642–2647.
378. Veillard, N.R.; Kwak, B.; Pelli, G.; Mulhaupt, F.; James, R.W.; Proudfoot, A.E.; Mach, F. Antagonism of RANTES receptors reduces atherosclerotic plaque formation in mice. *Circ. Res.* **2004**, *94*, 253–261.
379. Schober, A.; Manka, D.; von Hundelshausen, P.; Huo, Y.; Hanrath, P.; Sarembock, I.J.; Ley, K.; Weber, C. Deposition of platelet RANTES triggering monocyte recruitment requires P-selectin and is involved in neointima formation after arterial injury. *Circulation* **2002**, *106*, 1523–1529.
380. Quinones, M.P.; Martinez, H.G.; Jimenez, F.; Estrada, C.A.; Dudley, M.; Willmon, O.; Kulkarni, H.; Reddick, R.L.; Fernandes, G.; Kuziel, W.A.; et al. CC chemokine receptor 5 influences late-stage atherosclerosis. *Atherosclerosis* **2007,** 195, e92–e103.
381. Potteaux, S.; Combadiere, C.; Esposito, B.; Lecureuil, C.; Ait-Oufella, H.; Merval, R.; Ardouin, P.; Tedgui, A.; Mallat, Z. Role of bone marrow-derived CC-chemokine receptor 5 in the development of atherosclerosis of low-density lipoprotein receptor knockout mice. *Arterioscler. Thromb. Vasc. Biol.* **2006**, *26*, 1858–1863.
382. Luckow, B.; Joergensen, J.; Chilla, S.; Li, J.P.; Henger, A.; Kiss, E.; Wieczorek, G.; Roth, L.; Hartmann, N.; Hoffmann, R.; et al. Reduced intragraft mRNA expression of matrix metalloproteinases Mmp3, Mmp12,

Mmp13 and Adam8, and diminished transplant arteriosclerosis in Ccr5-deficient mice. *Eur. J. Immunol.* **2004**, *34*, 2568–2578.
383. Kuziel, W.A.; Dawson, T.C.; Quinones, M.; Garavito, E.; Chenaux, G.; Ahuja, S.S.; Reddick, R.L.; Maeda, N. CCR5 deficiency is not protective in the early stages of atherogenesis in apoE knockout mice. *Atherosclerosis* **2003**, *167*, 25–32.
384. Piconi, S.; Pocaterra, D.; Rainone, V.; Cossu, M.; Masetti, M.; Rizzardini, G.; Clerici, M.; Trabattoni, D. Maraviroc Reduces Arterial Stiffness in PI-Treated HIV-infected Patients. *Sci. Rep.* **2016**, *6*, 28853.
385. Cipriani, S.; Francisci, D.; Mencarelli, A.; Renga, B.; Schiaroli, E.; D'Amore, C.; Baldelli, F.; Fiorucci, S. Efficacy of the CCR5 antagonist maraviroc in reducing early, ritonavir-induced atherogenesis and advanced plaque progression in mice. *Circulation* **2013**, *127*, 2114–2124.
386. Krohn, R.; Raffetseder, U.; Bot, I.; Zernecke, A.; Shagdarsuren, E.; Liehn, E.A.; van Santbrink, P.J.; Nelson, P.J.; Biessen, E.A.; Mertens, P.R.; et al. Y-box binding protein-1 controls CC chemokine ligand-5 (CCL5) expression in smooth muscle cells and contributes to neointima formation in atherosclerosis-prone mice. *Circulation* **2007**, *116*, 1812–1820.
387. Braunersreuther, V.; Steffens, S.; Arnaud, C.; Pelli, G.; Burger, F.; Proudfoot, A.; Mach, F. A novel RANTES antagonist prevents progression of established atherosclerotic lesions in mice. *Arterioscler. Thromb. Vasc. Biol.* **2008**, *28*, 1090–1096.
388. Robertson, A.K.; Rudling, M.; Zhou, X.; Gorelik, L.; Flavell, R.A.; Hansson, G.K. Disruption of TGF-beta signaling in T cells accelerates atherosclerosis. *J. Clin. Investig.* **2003**, *112*, 1342–1350.
389. Ho, I.C.; Tai, T.S.; Pai, S.Y. GATA3 and the T-cell lineage: Essential functions before and after T-helper-2-cell differentiation. *Nat. Rev. Immunol.* **2009**, *9*, 125–135.
390. Engelbertsen, D.; Andersson, L.; Ljungcrantz, I.; Wigren, M.; Hedblad, B.; Nilsson, J.; Bjorkbacka, H. T-helper 2 immunity is associated with reduced risk of myocardial infarction and stroke. *Arterioscler. Thromb. Vasc. Biol.* **2013**, *33*, 637–644.
391. Mantani, P.T.; Duner, P.; Bengtsson, E.; Alm, R.; Ljungcrantz, I.; Soderberg, I.; Sundius, L.; To, F.; Nilsson, J.; Bjorkbacka, H.; et al. IL-25 inhibits atherosclerosis development in apolipoprotein E deficient mice. *PLoS ONE* **2015**, *10*, e0117255.
392. Silveira, A.; McLeod, O.; Strawbridge, R.J.; Gertow, K.; Sennblad, B.; Baldassarre, D.; Veglia, F.; Deleskog, A.; Persson, J.; Leander, K.; et al. Plasma IL-5 concentration and subclinical carotid atherosclerosis. *Atherosclerosis* **2015**, *239*, 125–130.
393. Binder, C.J.; Hartvigsen, K.; Chang, M.K.; Miller, M.; Broide, D.; Palinski, W.; Curtiss, L.K.; Corr, M.; Witztum, J.L. IL-5 links adaptive and natural immunity specific for epitopes of oxidized LDL and protects from atherosclerosis. *J. Clin. Investig.* **2004**, *114*, 427–437.
394. Cardilo-Reis, L.; Gruber, S.; Schreier, S.M.; Drechsler, M.; Papac-Milicevic, N.; Weber, C.; Wagner, O.; Stangl, H.; Soehnlein, O.; Binder, C.J. Interleukin-13 protects from atherosclerosis and modulates plaque composition by skewing the macrophage phenotype. *EMBO Mol. Med.* **2012**, *4*, 1072–1086.
395. Engelbertsen, D.; Rattik, S.; Knutsson, A.; Bjorkbacka, H.; Bengtsson, E.; Nilsson, J. Induction of T helper 2 responses against human apolipoprotein B100 does not affect atherosclerosis in ApoE-/- mice. *Cardiovasc. Res.* **2014**, *103*, 304–312.
396. King, V.L.; Szilvassy, S.J.; Daugherty, A. Interleukin-4 deficiency decreases atherosclerotic lesion formation in a site-specific manner in female LDL receptor-/- mice. *Arterioscler. Thromb. Vasc. Biol.* **2002**, *22*, 456–461.
397. King, V.L.; Cassis, L.A.; Daugherty, A. Interleukin-4 does not influence development of hypercholesterolemia or angiotensin II-induced atherosclerotic lesions in mice. *Am. J. Pathol.* **2007**, *171*, 2040–2047.
398. Huang, J.T.; Welch, J.S.; Ricote, M.; Binder, C.J.; Willson, T.M.; Kelly, C.; Witztum, J.L.; Funk, C.D.; Conrad, D.; Glass, C.K. Interleukin-4-dependent production of PPAR-gamma ligands in macrophages by 12/15-lipoxygenase. *Nature* **1999**, *400*, 378–382.
399. Cornicelli, J.A.; Butteiger, D.; Rateri, D.L.; Welch, K.; Daugherty, A. Interleukin-4 augments acetylated LDL-induced cholesterol esterification in macrophages. *J. Lipid Res.* **2000**, *41*, 376–383.
400. Barks, J.L.; McQuillan, J.J.; Iademarco, M.F. TNF-alpha and IL-4 synergistically increase vascular cell adhesion molecule-1 expression in cultured vascular smooth muscle cells. *J. Immunol.* **1997**, *159*, 4532–4538.
401. Lee, Y.W.; Kuhn, H.; Hennig, B.; Neish, A.S.; Toborek, M. IL-4-induced oxidative stress upregulates VCAM-1 gene expression in human endothelial cells. *J. Mol. Cell. Cardiol.* **2001**, *33*, 83–94.

402. Sasaguri, T.; Arima, N.; Tanimoto, A.; Shimajiri, S.; Hamada, T.; Sasaguri, Y. A role for interleukin 4 in production of matrix metalloproteinase 1 by human aortic smooth muscle cells. *Atherosclerosis* **1998**, *138*, 247–253.
403. Walch, L.; Massade, L.; Dufilho, M.; Brunet, A.; Rendu, F. Pro-atherogenic effect of interleukin-4 in endothelial cells: Modulation of oxidative stress, nitric oxide and monocyte chemoattractant protein-1 expression. *Atherosclerosis* **2006**, *187*, 285–291.
404. Vila-Caballer, M.; Gonzalez-Granado, J.M.; Zorita, V.; Abu Nabah, Y.N.; Silvestre-Roig, C.; Del Monte-Monge, A.; Molina-Sanchez, P.; Ait-Oufella, H.; Andres-Manzano, M.J.; Sanz, M.J.; et al. Disruption of the CCL1-CCR8 axis inhibits vascular Treg recruitment and function and promotes atherosclerosis in mice. *J. Mol. Cell. Cardiol.* **2019**, *132*, 154–163.
405. Huang, Y.; Hu, H.; Liu, L.; Ye, J.; Wang, Z.; Que, B.; Liu, W.; Shi, Y.; Zeng, T.; Shi, L.; et al. Interleukin-12p35 Deficiency Reverses the Th1/Th2 Imbalance, Aggravates the Th17/Treg Imbalance, and Ameliorates Atherosclerosis in ApoE-/- Mice. *Mediat. Inflamm.* **2019**, *2019*, 3152040.
406. Gao, S.; Zhang, W.; Zhao, Q.; Zhou, J.; Wu, Y.; Liu, Y.; Yuan, Z.; Wang, L. Curcumin ameliorates atherosclerosis in apolipoprotein E deficient asthmatic mice by regulating the balance of Th2/Treg cells. *Phytomedicine* **2019**, *52*, 129–135.
407. Gaffen, S.L. Structure and signalling in the IL-17 receptor family. *Nat. Rev. Immunol.* **2009**, *9*, 556–567.
408. Selmi, C. Autoimmunity in 2018. *Clin. Rev. Allergy Immunol.* **2019**, *56*, 375–384.
409. Akhavanpoor, M.; Akhavanpoor, H.; Gleissner, C.A.; Wangler, S.; Doesch, A.O.; Katus, H.A.; Erbel, C. The Two Faces of Interleukin-17A in Atherosclerosis. *Curr. Drug Targets* **2017**, *18*, 863–873.
410. Allam, G.; Abdel-Moneim, A.; Gaber, A.M. The pleiotropic role of interleukin-17 in atherosclerosis. *Biomed. Pharmacother.* **2018**, *106*, 1412–1418.
411. Lu, X. The Impact of IL-17 in Atherosclerosis. *Curr. Med. Chem.* **2017**, *24*, 2345–2358.
412. Zheng, Y.; Li, T. Interleukin-22, a potent target for treatment of non-autoimmune diseases. *Hum. Vaccin. Immunother.* **2018**, *14*, 2811–2819.
413. Taleb, S.; Tedgui, A. IL-17 in atherosclerosis: The good and the bad. *Cardiovasc. Res.* **2018**, *114*, 7–9.
414. Smith, E.; Prasad, K.M.; Butcher, M.; Dobrian, A.; Kolls, J.K.; Ley, K.; Galkina, E. Blockade of interleukin-17A results in reduced atherosclerosis in apolipoprotein E-deficient mice. *Circulation* **2010**, *121*, 1746–1755.
415. El-Behi, M.; Ciric, B.; Dai, H.; Yan, Y.; Cullimore, M.; Safavi, F.; Zhang, G.X.; Dittel, B.N.; Rostami, A. The encephalitogenicity of T(H)17 cells is dependent on IL-1- and IL-23-induced production of the cytokine GM-CSF. *Nat. Immunol.* **2011**, *12*, 568–575.
416. Ogura, H.; Murakami, M.; Okuyama, Y.; Tsuruoka, M.; Kitabayashi, C.; Kanamoto, M.; Nishihara, M.; Iwakura, Y.; Hirano, T. Interleukin-17 promotes autoimmunity by triggering a positive-feedback loop via interleukin-6 induction. *Immunity* **2008**, *29*, 628–636.
417. Weaver, C.T.; Hatton, R.D. Interplay between the TH17 and TReg cell lineages: A (co-)evolutionary perspective. *Nat. Rev. Immunol.* **2009**, *9*, 883–889.
418. Zuniga, L.A.; Jain, R.; Haines, C.; Cua, D.J. Th17 cell development: From the cradle to the grave. *Immunol. Rev.* **2013**, *252*, 78–88.
419. Krausgruber, T.; Schiering, C.; Adelmann, K.; Harrison, O.J.; Chomka, A.; Pearson, C.; Ahern, P.P.; Shale, M.; Oukka, M.; Powrie, F. T-bet is a key modulator of IL-23-driven pathogenic CD4(+) T cell responses in the intestine. *Nat. Commun.* **2016**, *7*, 11627.
420. Abdel-Moneim, A.; Bakery, H.H.; Allam, G. The potential pathogenic role of IL-17/Th17 cells in both type 1 and type 2 diabetes mellitus. *Biomed. Pharmacother.* **2018**, *101*, 287–292.
421. Hirota, K.; Duarte, J.H.; Veldhoen, M.; Hornsby, E.; Li, Y.; Cua, D.J.; Ahlfors, H.; Wilhelm, C.; Tolaini, M.; Menzel, U.; et al. Fate mapping of IL-17-producing T cells in inflammatory responses. *Nat. Immunol.* **2011**, *12*, 255–263.
422. Lee, Y.; Awasthi, A.; Yosef, N.; Quintana, F.J.; Xiao, S.; Peters, A.; Wu, C.; Kleinewietfeld, M.; Kunder, S.; Hafler, D.A.; et al. Induction and molecular signature of pathogenic TH17 cells. *Nat. Immunol.* **2012**, *13*, 991–999.
423. Gagliani, N.; Amezcua Vesely, M.C.; Iseppon, A.; Brockmann, L.; Xu, H.; Palm, N.W.; de Zoete, M.R.; Licona-Limon, P.; Paiva, R.S.; Ching, T.; et al. Th17 cells transdifferentiate into regulatory T cells during resolution of inflammation. *Nature* **2015**, *523*, 221–225.
424. Korn, T.; Bettelli, E.; Oukka, M.; Kuchroo, V.K. IL-17 and Th17 Cells. *Annu Rev. Immunol* **2009**, *27*, 485–517.

425. Liuzzo, G.; Trotta, F.; Pedicino, D. Interleukin-17 in atherosclerosis and cardiovascular disease: The good, the bad, and the unknown. *Eur. Heart J.* **2013**, *34*, 556–559.
426. Yao, Z.; Painter, S.L.; Fanslow, W.C.; Ulrich, D.; Macduff, B.M.; Spriggs, M.K.; Armitage, R.J. Human IL-17: A novel cytokine derived from T cells. *J. Immunol.* **1995**, *155*, 5483–5486.
427. Harrington, L.E.; Hatton, R.D.; Mangan, P.R.; Turner, H.; Murphy, T.L.; Murphy, K.M.; Weaver, C.T. Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. *Nat. Immunol.* **2005**, *6*, 1123–1132.
428. Butcher, M.; Galkina, E. Current views on the functions of interleukin-17A-producing cells in atherosclerosis. *Thromb. Haemost.* **2011**, *106*, 787–795.
429. Erbel, C.; Chen, L.; Bea, F.; Wangler, S.; Celik, S.; Lasitschka, F.; Wang, Y.; Bockler, D.; Katus, H.A.; Dengler, T.J. Inhibition of IL-17A attenuates atherosclerotic lesion development in apoE-deficient mice. *J. Immunol.* **2009**, *183*, 8167–8175.
430. Jovanovic, D.V.; Di Battista, J.A.; Martel-Pelletier, J.; Jolicoeur, F.C.; He, Y.; Zhang, M.; Mineau, F.; Pelletier, J.P. IL-17 stimulates the production and expression of proinflammatory cytokines, IL-beta and TNF-alpha, by human macrophages. *J. Immunol.* **1998**, *160*, 3513–3521.
431. Madhur, M.S.; Funt, S.A.; Li, L.; Vinh, A.; Chen, W.; Lob, H.E.; Iwakura, Y.; Blinder, Y.; Rahman, A.; Quyyumi, A.A.; et al. Role of interleukin 17 in inflammation, atherosclerosis, and vascular function in apolipoprotein e-deficient mice. *Arterioscler. Thromb. Vasc. Biol.* **2011**, *31*, 1565–1572.
432. Beringer, A.; Noack, M.; Miossec, P. IL-17 in Chronic Inflammation: From Discovery to Targeting. *Trends Mol. Med.* **2016**, *22*, 230–241.
433. Ley, K.; Smith, E.; Stark, M.A. IL-17A-producing neutrophil-regulatory Tn lymphocytes. *Immunol. Res.* **2006**, *34*, 229–242.
434. Taleb, S.; Romain, M.; Ramkhelawon, B.; Uyttenhove, C.; Pasterkamp, G.; Herbin, O.; Esposito, B.; Perez, N.; Yasukawa, H.; Van Snick, J.; et al. Loss of SOCS3 expression in T cells reveals a regulatory role for interleukin-17 in atherosclerosis. *J. Exp. Med.* **2009**, *206*, 2067–2077.
435. Gistera, A.; Robertson, A.K.; Andersson, J.; Ketelhuth, D.F.; Ovchinnikova, O.; Nilsson, S.K.; Lundberg, A.M.; Li, M.O.; Flavell, R.A.; Hansson, G.K. Transforming growth factor-beta signaling in T cells promotes stabilization of atherosclerotic plaques through an interleukin-17-dependent pathway. *Sci. Transl. Med.* **2013**, *5*, 196ra100.
436. Zhu, F.; Wang, Q.; Guo, C.; Wang, X.; Cao, X.; Shi, Y.; Gao, F.; Ma, C.; Zhang, L. IL-17 induces apoptosis of vascular endothelial cells: A potential mechanism for human acute coronary syndrome. *Clin. Immunol.* **2011**, *141*, 152–160.
437. Madhur, M.S.; Lob, H.E.; McCann, L.A.; Iwakura, Y.; Blinder, Y.; Guzik, T.J.; Harrison, D.G. Interleukin 17 promotes angiotensin II-induced hypertension and vascular dysfunction. *Hypertension* **2010**, *55*, 500–507.
438. Danzaki, K.; Matsui, Y.; Ikesue, M.; Ohta, D.; Ito, K.; Kanayama, M.; Kurotaki, D.; Morimoto, J.; Iwakura, Y.; Yagita, H.; et al. Interleukin-17A deficiency accelerates unstable atherosclerotic plaque formation in apolipoprotein E-deficient mice. *Arterioscler. Thromb. Vasc. Biol.* **2012**, *32*, 273–280.
439. van Es, T.; van Puijvelde, G.H.; Ramos, O.H.; Segers, F.M.; Joosten, L.A.; van den Berg, W.B.; Michon, I.M.; de Vos, P.; van Berkel, T.J.; Kuiper, J. Attenuated atherosclerosis upon IL-17R signaling disruption in LDLr deficient mice. *Biochem. Biophys. Res. Commun.* **2009**, *388*, 261–265.
440. Butcher, M.J.; Gjurich, B.N.; Phillips, T.; Galkina, E.V. The IL-17A/IL-17RA axis plays a proatherogenic role via the regulation of aortic myeloid cell recruitment. *Circ. Res.* **2012**, *110*, 675–687.
441. Gao, Q.; Jiang, Y.; Ma, T.; Zhu, F.; Gao, F.; Zhang, P.; Guo, C.; Wang, Q.; Wang, X.; Ma, C.; et al. A critical function of Th17 proinflammatory cells in the development of atherosclerotic plaque in mice. *J. Immunol.* **2010**, *185*, 5820–5827.
442. Nordlohne, J.; von Vietinghoff, S. Interleukin 17A in atherosclerosis - Regulation and pathophysiologic effector function. *Cytokine* **2017**, *122*, 154089.
443. Butcher, M.J.; Waseem, T.C.; Galkina, E.V. Smooth Muscle Cell-Derived Interleukin-17C Plays an Atherogenic Role via the Recruitment of Proinflammatory Interleukin-17A+ T Cells to the Aorta. *Arterioscler. Thromb. Vasc. Biol.* **2016**, *36*, 1496–1506.
444. Sedda, S.; Marafini, I.; Figliuzzi, M.M.; Pallone, F.; Monteleone, G. An overview of the role of innate lymphoid cells in gut infections and inflammation. *Mediat. Inflamm.* **2014**, *2014*, 235460.
445. Kumar, P.; Thakar, M.S.; Ouyang, W.; Malarkannan, S. IL-22 from conventional NK cells is epithelial regenerative and inflammation protective during influenza infection. *Mucosal Immunol.* **2013**, *6*, 69–82.

446. Brockmann, L.; Giannou, A.D.; Gagliani, N.; Huber, S. Regulation of TH17 Cells and Associated Cytokines in Wound Healing, Tissue Regeneration, and Carcinogenesis. *Int. J. Mol. Sci.* **2017**, *18*, 1033.
447. Zenewicz, L.A.; Yancopoulos, G.D.; Valenzuela, D.M.; Murphy, A.J.; Karow, M.; Flavell, R.A. Interleukin-22 but not interleukin-17 provides protection to hepatocytes during acute liver inflammation. *Immunity* **2007**, *27*, 647–659.
448. Gong, F.; Wu, J.; Zhou, P.; Zhang, M.; Liu, J.; Liu, Y.; Lu, X.; Liu, Z. Interleukin-22 Might Act as a Double-Edged Sword in Type 2 Diabetes and Coronary Artery Disease. *Mediat. Inflamm* **2016**, *2016*, 8254797.
449. Eyerich, S.; Eyerich, K.; Pennino, D.; Carbone, T.; Nasorri, F.; Pallotta, S.; Cianfarani, F.; Odorisio, T.; Traidl-Hoffmann, C.; Behrendt, H.; et al. Th22 cells represent a distinct human T cell subset involved in epidermal immunity and remodeling. *J. Clin. Investig.* **2009**, *119*, 3573–3585.
450. Ouyang, W.; Rutz, S.; Crellin, N.K.; Valdez, P.A.; Hymowitz, S.G. Regulation and functions of the IL-10 family of cytokines in inflammation and disease. *Annu. Rev. Immunol.* **2011**, *29*, 71–109.
451. Xia, Q.; Xiang, X.; Patel, S.; Puranik, R.; Xie, Q.; Bao, S. Characterisation of IL-22 and interferon-gamma-inducible chemokines in human carotid plaque. *Int. J. Cardiol.* **2012**, *154*, 187–189.
452. Chellan, B.; Yan, L.; Sontag, T.J.; Reardon, C.A.; Hofmann Bowman, M.A. IL-22 is induced by S100/calgranulin and impairs cholesterol efflux in macrophages by downregulating ABCG1. *J. Lipid Res.* **2014**, *55*, 443–454.
453. Rattik, S.; Hultman, K.; Rauch, U.; Soderberg, I.; Sundius, L.; Ljungcrantz, I.; Hultgardh-Nilsson, A.; Wigren, M.; Bjorkbacka, H.; Fredrikson, G.N.; et al. IL-22 affects smooth muscle cell phenotype and plaque formation in apolipoprotein E knockout mice. *Atherosclerosis* **2015**, *242*, 506–514.
454. Fatkhullina, A.R.; Peshkova, I.O.; Dzutsev, A.; Aghayev, T.; McCulloch, J.A.; Thovarai, V.; Badger, J.H.; Vats, R.; Sundd, P.; Tang, H.Y.; et al. An Interleukin-23-Interleukin-22 Axis Regulates Intestinal Microbial Homeostasis to Protect from Diet-Induced Atherosclerosis. *Immunity* **2018**, *49*, 943–957.e9.
455. Sakaguchi, S.; Sakaguchi, N.; Asano, M.; Itoh, M.; Toda, M. Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. *J. Immunol.* **1995**, *155*, 1151–1164.
456. Apostolou, I.; von Boehmer, H. In vivo instruction of suppressor commitment in naive T cells. *J. Exp. Med.* **2004**, *199*, 1401–1408.
457. Ray, A.; Khare, A.; Krishnamoorthy, N.; Qi, Z.; Ray, P. Regulatory T cells in many flavors control asthma. *Mucosal Immunol.* **2010**, *3*, 216–229.
458. Roncarolo, M.G.; Bacchetta, R.; Bordignon, C.; Narula, S.; Levings, M.K. Type 1 T regulatory cells. *Immunol. Rev.* **2001**, *182*, 68–79.
459. Bocian, K.; Kiernozek, E.; Domagala-Kulawik, J.; Korczak-Kowalska, G.; Stelmaszczyk-Emmel, A.; Drela, N. Expanding Diversity and Common Goal of Regulatory T and B Cells. I: Origin, Phenotype, Mechanisms. *Arch. Immunol. Ther. Exp. (Warsz)* **2017**, *65*, 501–520.
460. Weiner, H.L. Induction and mechanism of action of transforming growth factor-beta-secreting Th3 regulatory cells. *Immunol. Rev.* **2001**, *182*, 207–214.
461. Chaudhry, A.; Samstein, R.M.; Treuting, P.; Liang, Y.; Pils, M.C.; Heinrich, J.M.; Jack, R.S.; Wunderlich, F.T.; Bruning, J.C.; Muller, W.; et al. Interleukin-10 signaling in regulatory T cells is required for suppression of Th17 cell-mediated inflammation. *Immunity* **2011**, *34*, 566–578.
462. Hori, S.; Nomura, T.; Sakaguchi, S. Control of regulatory T cell development by the transcription factor Foxp3. *Science* **2003**, *299*, 1057–1061.
463. Amin, H.Z.; Sasaki, N.; Hirata, K.I. Regulatory T Cell Immunity in Atherosclerosis. *Acta Med. Indones* **2017**, *49*, 63–68.
464. Arce-Sillas, A.; Alvarez-Luquin, D.D.; Tamaya-Dominguez, B.; Gomez-Fuentes, S.; Trejo-Garcia, A.; Melo-Salas, M.; Cardenas, G.; Rodriguez-Ramirez, J.; Adalid-Peralta, L. Regulatory T Cells: Molecular Actions on Effector Cells in Immune Regulation. *J. Immunol. Res.* **2016**, *2016*, 1720827.
465. Tselios, K.; Sarantopoulos, A.; Gkougkourelas, I.; Boura, P. T regulatory cells: A promising new target in atherosclerosis. *Crit. Rev. Immunol.* **2014**, *34*, 389–397.
466. Wing, K.; Onishi, Y.; Prieto-Martin, P.; Yamaguchi, T.; Miyara, M.; Fehervari, Z.; Nomura, T.; Sakaguchi, S. CTLA-4 control over Foxp3+ regulatory T cell function. *Science* **2008**, *322*, 271–275.
467. Gondek, D.C.; Lu, L.F.; Quezada, S.A.; Sakaguchi, S.; Noelle, R.J. Cutting edge: Contact-mediated suppression by CD4+CD25+ regulatory cells involves a granzyme B-dependent, perforin-independent mechanism. *J. Immunol.* **2005**, *174*, 1783–1786.

468. Garin, M.I.; Chu, C.C.; Golshayan, D.; Cernuda-Morollon, E.; Wait, R.; Lechler, R.I. Galectin-1: A key effector of regulation mediated by CD4+CD25+ T cells. *Blood* **2007**, *109*, 2058–2065.
469. Ren, X.; Ye, F.; Jiang, Z.; Chu, Y.; Xiong, S.; Wang, Y. Involvement of cellular death in TRAIL/DR5-dependent suppression induced by CD4(+)CD25(+) regulatory T cells. *Cell Death Differ.* **2007**, *14*, 2076–2084.
470. Li, M.O.; Flavell, R.A. TGF-beta: A master of all T cell trades. *Cell* **2008**, *134*, 392–404.
471. Mallat, Z.; Besnard, S.; Duriez, M.; Deleuze, V.; Emmanuel, F.; Bureau, M.F.; Soubrier, F.; Esposito, B.; Duez, H.; Fievet, C.; et al. Protective role of interleukin-10 in atherosclerosis. *Circ. Res.* **1999**, *85*, e17–e24.
472. Potteaux, S.; Esposito, B.; van Oostrom, O.; Brun, V.; Ardouin, P.; Groux, H.; Tedgui, A.; Mallat, Z. Leukocyte-derived interleukin 10 is required for protection against atherosclerosis in low-density lipoprotein receptor knockout mice. *Arterioscler. Thromb. Vasc. Biol.* **2004**, *24*, 1474–1478.
473. Mallat, Z.; Gojova, A.; Brun, V.; Esposito, B.; Fournier, N.; Cottrez, F.; Tedgui, A.; Groux, H. Induction of a regulatory T cell type 1 response reduces the development of atherosclerosis in apolipoprotein E-knockout mice. *Circulation* **2003**, *108*, 1232–1237.
474. Sawant, D.V.; Hamilton, K.; Vignali, D.A. Interleukin-35: Expanding Its Job Profile. *J. Interferon Cytokine Res.* **2015**, *35*, 499–512.
475. Collison, L.W.; Delgoffe, G.M.; Guy, C.S.; Vignali, K.M.; Chaturvedi, V.; Fairweather, D.; Satoskar, A.R.; Garcia, K.C.; Hunter, C.A.; Drake, C.G.; et al. The composition and signaling of the IL-35 receptor are unconventional. *Nat. Immunol.* **2012**, *13*, 290–299.
476. Sha, X.; Meng, S.; Li, X.; Xi, H.; Maddaloni, M.; Pascual, D.W.; Shan, H.; Jiang, X.; Wang, H.; Yang, X.F. Interleukin-35 Inhibits Endothelial Cell Activation by Suppressing MAPK-AP-1 Pathway. *J. Biol. Chem.* **2015**, *290*, 19307–19318.
477. Li, X.; Fang, P.; Yang, W.Y.; Wang, H.; Yang, X. IL-35, as a newly proposed homeostasis-associated molecular pattern, plays three major functions including anti-inflammatory initiator, effector, and blocker in cardiovascular diseases. *Cytokine* **2017**, *122*, 154076.
478. Vignali, D.A.; Kuchroo, V.K. IL-12 family cytokines: Immunological playmakers. *Nat. Immunol.* **2012**, *13*, 722–728.
479. Wang, R.X.; Yu, C.R.; Dambuza, I.M.; Mahdi, R.M.; Dolinska, M.B.; Sergeev, Y.V.; Wingfield, P.T.; Kim, S.H.; Egwuagu, C.E. Interleukin-35 induces regulatory B cells that suppress autoimmune disease. *Nat. Med.* **2014**, *20*, 633–641.
480. Collison, L.W.; Vignali, D.A. Interleukin-35: Odd one out or part of the family? *Immunol. Rev.* **2008**, *226*, 248–262.
481. Collison, L.W.; Workman, C.J.; Kuo, T.T.; Boyd, K.; Wang, Y.; Vignali, K.M.; Cross, R.; Sehy, D.; Blumberg, R.S.; Vignali, D.A. The inhibitory cytokine IL-35 contributes to regulatory T-cell function. *Nature* **2007**, *450*, 566–569.
482. Olson, B.M.; Sullivan, J.A.; Burlingham, W.J. Interleukin 35: A key mediator of suppression and the propagation of infectious tolerance. *Front. Immunol.* **2013**, *4*, 315.
483. Kempe, S.; Heinz, P.; Kokai, E.; Devergne, O.; Marx, N.; Wirth, T. Epstein-barr virus-induced gene-3 is expressed in human atheroma plaques. *Am. J. Pathol.* **2009**, *175*, 440–447.
484. Lin, Y.; Huang, Y.; Lu, Z.; Luo, C.; Shi, Y.; Zeng, Q.; Cao, Y.; Liu, L.; Wang, X.; Ji, Q. Decreased plasma IL-35 levels are related to the left ventricular ejection fraction in coronary artery diseases. *PLoS ONE* **2012,** 7, e52490.
485. Tao, L.; Zhu, J.; Chen, Y.; Wang, Q.; Pan, Y.; Yu, Q.; Zhou, B.; Zhu, H. IL-35 improves Treg-mediated immune suppression in atherosclerotic mice. *Exp. Ther. Med.* **2016**, *12*, 2469–2476.
486. Hirase, T.; Hara, H.; Miyazaki, Y.; Ide, N.; Nishimoto-Hazuku, A.; Fujimoto, H.; Saris, C.J.; Yoshida, H.; Node, K. Interleukin 27 inhibits atherosclerosis via immunoregulation of macrophages in mice. *Am. J. Physiol. Heart Circ. Physiol.* **2013**, *305*, H420–H429.
487. Koltsova, E.K.; Kim, G.; Lloyd, K.M.; Saris, C.J.; von Vietinghoff, S.; Kronenberg, M.; Ley, K. Interleukin-27 receptor limits atherosclerosis in Ldlr-/- mice. *Circ. Res.* **2012**, *111*, 1274–1285.
488. Pandiyan, P.; Zheng, L.; Ishihara, S.; Reed, J.; Lenardo, M.J. CD4+CD25+Foxp3+ regulatory T cells induce cytokine deprivation-mediated apoptosis of effector CD4+ T cells. *Nat. Immunol.* **2007**, *8*, 1353–1362.
489. Kobie, J.J.; Shah, P.R.; Yang, L.; Rebhahn, J.A.; Fowell, D.J.; Mosmann, T.R. T regulatory and primed uncommitted CD4 T cells express CD73, which suppresses effector CD4 T cells by converting 5′-adenosine monophosphate to adenosine. *J. Immunol.* **2006**, *177*, 6780–6786.

490. Borsellino, G.; Kleinewietfeld, M.; Di Mitri, D.; Sternjak, A.; Diamantini, A.; Giometto, R.; Hopner, S.; Centonze, D.; Bernardi, G.; Dell'Acqua, M.L.; et al. Expression of ectonucleotidase CD39 by Foxp3+ Treg cells: Hydrolysis of extracellular ATP and immune suppression. *Blood* **2007**, *110*, 1225–1232.
491. Zarek, P.E.; Huang, C.T.; Lutz, E.R.; Kowalski, J.; Horton, M.R.; Linden, J.; Drake, C.G.; Powell, J.D. A2A receptor signaling promotes peripheral tolerance by inducing T-cell anergy and the generation of adaptive regulatory T cells. *Blood* **2008**, *111*, 251–259.
492. de Boer, O.J.; van der Meer, J.J.; Teeling, P.; van der Loos, C.M.; van der Wal, A.C. Low numbers of FOXP3 positive regulatory T cells are present in all developmental stages of human atherosclerotic lesions. *PLoS ONE* **2007**, 2, e779.
493. Wang, Z.; Mao, S.; Zhan, Z.; Yu, K.; He, C.; Wang, C. Effect of hyperlipidemia on Foxp3 expression in apolipoprotein E-knockout mice. *J. Cardiovasc. Med. (Hagerstown)* **2014**, *15*, 273–279.
494. Ou, H.X.; Guo, B.B.; Liu, Q.; Li, Y.K.; Yang, Z.; Feng, W.J.; Mo, Z.C. Regulatory T cells as a new therapeutic target for atherosclerosis. *Acta Pharmacol. Sin.* **2018**, *39*, 1249–1258.
495. Sasaki, N.; Yamashita, T.; Kasahara, K.; Takeda, M.; Hirata, K. Regulatory T cells and tolerogenic dendritic cells as critical immune modulators in atherogenesis. *Curr. Pharm Des.* **2015**, *21*, 1107–1117.
496. Ait-Oufella, H.; Salomon, B.L.; Potteaux, S.; Robertson, A.K.; Gourdy, P.; Zoll, J.; Merval, R.; Esposito, B.; Cohen, J.L.; Fisson, S.; et al. Natural regulatory T cells control the development of atherosclerosis in mice. *Nat. Med.* **2006**, *12*, 178–180.
497. Lahl, K.; Loddenkemper, C.; Drouin, C.; Freyer, J.; Arnason, J.; Eberl, G.; Hamann, A.; Wagner, H.; Huehn, J.; Sparwasser, T. Selective depletion of Foxp3+ regulatory T cells induces a scurfy-like disease. *J. Exp. Med.* **2007**, *204*, 57–63.
498. Klingenberg, R.; Gerdes, N.; Badeau, R.M.; Gistera, A.; Strodthoff, D.; Ketelhuth, D.F.; Lundberg, A.M.; Rudling, M.; Nilsson, S.K.; Olivecrona, G.; et al. Depletion of FOXP3+ regulatory T cells promotes hypercholesterolemia and atherosclerosis. *J. Clin. Investig.* **2013**, *123*, 1323–1334.
499. Steffens, S.; Burger, F.; Pelli, G.; Dean, Y.; Elson, G.; Kosco-Vilbois, M.; Chatenoud, L.; Mach, F. Short-term treatment with anti-CD3 antibody reduces the development and progression of atherosclerosis in mice. *Circulation* **2006**, *114*, 1977–1984.
500. Sasaki, N.; Yamashita, T.; Takeda, M.; Shinohara, M.; Nakajima, K.; Tawa, H.; Usui, T.; Hirata, K. Oral anti-CD3 antibody treatment induces regulatory T cells and inhibits the development of atherosclerosis in mice. *Circulation* **2009**, *120*, 1996–2005.
501. Dinh, T.N.; Kyaw, T.S.; Kanellakis, P.; To, K.; Tipping, P.; Toh, B.H.; Bobik, A.; Agrotis, A. Cytokine therapy with interleukin-2/anti-interleukin-2 monoclonal antibody complexes expands CD4+CD25+Foxp3+ regulatory T cells and attenuates development and progression of atherosclerosis. *Circulation* **2012**, *126*, 1256–1266.
502. Kasahara, K.; Sasaki, N.; Yamashita, T.; Kita, T.; Yodoi, K.; Sasaki, Y.; Takeda, M.; Hirata, K. CD3 antibody and IL-2 complex combination therapy inhibits atherosclerosis by augmenting a regulatory immune response. *J. Am. Heart Assoc.* **2014,** 3, e000719.
503. Kita, T.; Yamashita, T.; Sasaki, N.; Kasahara, K.; Sasaki, Y.; Yodoi, K.; Takeda, M.; Nakajima, K.; Hirata, K. Regression of atherosclerosis with anti-CD3 antibody via augmenting a regulatory T-cell response in mice. *Cardiovasc. Res.* **2014**, *102*, 107–117.
504. Sasaki, N.; Yamashita, T.; Kasahara, K.; Fukunaga, A.; Yamaguchi, T.; Emoto, T.; Yodoi, K.; Matsumoto, T.; Nakajima, K.; Kita, T.; et al. UVB Exposure Prevents Atherosclerosis by Regulating Immunoinflammatory Responses. *Arterioscler. Thromb. Vasc. Biol.* **2017**, *37*, 66–74.
505. Zhu, Z.F.; Meng, K.; Zhong, Y.C.; Qi, L.; Mao, X.B.; Yu, K.W.; Zhang, W.; Zhu, P.F.; Ren, Z.P.; Wu, B.W.; et al. Impaired circulating CD4+ LAP+ regulatory T cells in patients with acute coronary syndrome and its mechanistic study. *PLoS ONE* **2014**, *9*, e88775.
506. Zhang, W.C.; Wang, J.; Shu, Y.W.; Tang, T.T.; Zhu, Z.F.; Xia, N.; Nie, S.F.; Liu, J.; Zhou, S.F.; Li, J.J.; et al. Impaired thymic export and increased apoptosis account for regulatory T cell defects in patients with non-ST segment elevation acute coronary syndrome. *J. Biol. Chem.* **2012**, *287*, 34157–34166.
507. Wigren, M.; Bjorkbacka, H.; Andersson, L.; Ljungcrantz, I.; Fredrikson, G.N.; Persson, M.; Bryngelsson, C.; Hedblad, B.; Nilsson, J. Low levels of circulating CD4+FoxP3+ T cells are associated with an increased risk for development of myocardial infarction but not for stroke. *Arterioscler. Thromb. Vasc. Biol.* **2012**, *32*, 2000–2004.

508. Ammirati, E.; Cianflone, D.; Banfi, M.; Vecchio, V.; Palini, A.; De Metrio, M.; Marenzi, G.; Panciroli, C.; Tumminello, G.; Anzuini, A.; et al. Circulating CD4+CD25hiCD127lo regulatory T-Cell levels do not reflect the extent or severity of carotid and coronary atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* **2010**, *30*, 1832–1841.
509. Mor, A.; Luboshits, G.; Planer, D.; Keren, G.; George, J. Altered status of CD4(+)CD25(+) regulatory T cells in patients with acute coronary syndromes. *Eur Heart J.* **2006**, *27*, 2530–2537.
510. Emoto, T.; Sasaki, N.; Yamashita, T.; Kasahara, K.; Yodoi, K.; Sasaki, Y.; Matsumoto, T.; Mizoguchi, T.; Hirata, K. Regulatory/effector T-cell ratio is reduced in coronary artery disease. *Circ. J.* **2014**, *78*, 2935–2941.
511. Kalia, V.; Sarkar, S. Regulation of Effector and Memory CD8 T Cell Differentiation by IL-2-A Balancing Act. *Front. Immunol.* **2018**, *9*, 2987.
512. Andersen, M.H.; Schrama, D.; Thor Straten, P.; Becker, J.C. Cytotoxic T cells. *J. Invest. Dermatol.* **2006**, *126*, 32–41.
513. van Duijn, J.; Kuiper, J.; Slutter, B. The many faces of CD8+ T cells in atherosclerosis. *Curr. Opin. Lipidol.* **2018**, *29*, 411–416.
514. Kolbus, D.; Ljungcrantz, I.; Soderberg, I.; Alm, R.; Bjorkbacka, H.; Nilsson, J.; Fredrikson, G.N. TAP1-deficiency does not alter atherosclerosis development in Apoe-/- mice. *PLoS ONE* **2012**, *7*, e33932.
515. Fyfe, A.I.; Qiao, J.H.; Lusis, A.J. Immune-deficient mice develop typical atherosclerotic fatty streaks when fed an atherogenic diet. *J. Clin. Investig.* **1994**, *94*, 2516–2520.
516. Chyu, K.Y.; Zhao, X.; Dimayuga, P.C.; Zhou, J.; Li, X.; Yano, J.; Lio, W.M.; Chan, L.F.; Kirzner, J.; Trinidad, P.; et al. CD8+ T cells mediate the athero-protective effect of immunization with an ApoB-100 peptide. *PLoS ONE* **2012**, *7*, e30780.
517. Gewaltig, J.; Kummer, M.; Koella, C.; Cathomas, G.; Biedermann, B.C. Requirements for CD8 T-cell migration into the human arterial wall. *Hum. Pathol* **2008**, *39*, 1756–1762.
518. van Duijn, J.; van Elsas, M.; Benne, N.; Depuydt, M.; Wezel, A.; Smeets, H.; Bot, I.; Jiskoot, W.; Kuiper, J.; Slutter, B. CD39 identifies a microenvironment-specific anti-inflammatory CD8(+) T-cell population in atherosclerotic lesions. *Atherosclerosis* **2019**, *285*, 71–78.
519. Barquera, S.; Pedroza-Tobias, A.; Medina, C.; Hernandez-Barrera, L.; Bibbins-Domingo, K.; Lozano, R.; Moran, A.E. Global Overview of the Epidemiology of Atherosclerotic Cardiovascular Disease. *Arch. Med. Res.* **2015**, *46*, 328–338.
520. Kolbus, D.; Ramos, O.H.; Berg, K.E.; Persson, J.; Wigren, M.; Bjorkbacka, H.; Fredrikson, G.N.; Nilsson, J. CD8+ T cell activation predominate early immune responses to hypercholesterolemia in Apoe(-)(/)(-) mice. *BMC Immunol.* **2010**, *11*, 58.
521. Olofsson, P.S.; Soderstrom, L.A.; Wagsater, D.; Sheikine, Y.; Ocaya, P.; Lang, F.; Rabu, C.; Chen, L.; Rudling, M.; Aukrust, P.; et al. CD137 is expressed in human atherosclerosis and promotes development of plaque inflammation in hypercholesterolemic mice. *Circulation* **2008**, *117*, 1292–1301.
522. Kyaw, T.; Winship, A.; Tay, C.; Kanellakis, P.; Hosseini, H.; Cao, A.; Li, P.; Tipping, P.; Bobik, A.; Toh, B.H. Cytotoxic and proinflammatory CD8+ T lymphocytes promote development of vulnerable atherosclerotic plaques in apoE-deficient mice. *Circulation* **2013**, *127*, 1028–1039.
523. Schatz, D.G.; Ji, Y. Recombination centres and the orchestration of V(D)J recombination. *Nat. Rev. Immunol.* **2011**, *11*, 251–263.
524. Clark, M.R.; Mandal, M.; Ochiai, K.; Singh, H. Orchestrating B cell lymphopoiesis through interplay of IL-7 receptor and pre-B cell receptor signalling. *Nat. Rev. Immunol.* **2014**, *14*, 69–80.
525. Nimmerjahn, F.; Ravetch, J.V. Divergent immunoglobulin g subclass activity through selective Fc receptor binding. *Science* **2005**, *310*, 1510–1512.
526. Pillai, S.; Cariappa, A. The follicular versus marginal zone B lymphocyte cell fate decision. *Nat. Rev. Immunol* **2009**, *9*, 767–777.
527. Hardy, R.R.; Kincade, P.W.; Dorshkind, K. The protean nature of cells in the B lymphocyte lineage. *Immunity* **2007**, *26*, 703–714.
528. Hardy, R.R. B-1 B cells: Development, selection, natural autoantibody and leukemia. *Curr. Opin. Immunol.* **2006**, *18*, 547–555.
529. Baumgarth, N. B-1 Cell Heterogeneity and the Regulation of Natural and Antigen-Induced IgM Production. *Front. Immunol.* **2016**, *7*, 324.
530. Choi, Y.S.; Dieter, J.A.; Rothaeusler, K.; Luo, Z.; Baumgarth, N. B-1 cells in the bone marrow are a significant source of natural IgM. *Eur. J. Immunol.* **2012**, *42*, 120–129.

531. Berland, R.; Wortis, H.H. Origins and functions of B-1 cells with notes on the role of CD5. *Annu. Rev. Immunol.* **2002**, *20*, 253–300.
532. Srikakulapu, P.; McNamara, C.A. B cells and atherosclerosis. *Am. J. Physiol Heart Circ. Physiol.* **2017,** 312, H1060–H1067.
533. Roy, B.; Shukla, S.; Lyszkiewicz, M.; Krey, M.; Viegas, N.; Duber, S.; Weiss, S. Somatic hypermutation in peritoneal B1b cells. *Mol. Immunol.* **2009**, *46*, 1613–1619.
534. Roy, B.; Brennecke, A.M.; Agarwal, S.; Krey, M.; Duber, S.; Weiss, S. An intrinsic propensity of murine peritoneal B1b cells to switch to IgA in presence of TGF-beta and retinoic acid. *PLoS ONE* **2013**, *8*, e82121.
535. Vaughan, A.T.; Roghanian, A.; Cragg, M.S. B cells--masters of the immunoverse. *Int. J. Biochem. Cell Biol.* **2011**, *43*, 280–285.
536. Hamel, K.M.; Liarski, V.M.; Clark, M.R. Germinal center B-cells. *Autoimmunity* **2012**, *45*, 333–347.
537. Shen, P.; Fillatreau, S. Antibody-independent functions of B cells: A focus on cytokines. *Nat. Rev. Immunol.* **2015**, *15*, 441–451.
538. Lund, F.E. Cytokine-producing B lymphocytes-key regulators of immunity. *Curr. Opin. Immunol.* **2008**, *20*, 332–338.
539. Lund, F.E.; Garvy, B.A.; Randall, T.D.; Harris, D.P. Regulatory roles for cytokine-producing B cells in infection and autoimmune disease. *Curr. Dir. Autoimmun.* **2005**, *8*, 25–54.
540. Parekh, V.V.; Prasad, D.V.; Banerjee, P.P.; Joshi, B.N.; Kumar, A.; Mishra, G.C. B cells activated by lipopolysaccharide, but not by anti-Ig and anti-CD40 antibody, induce anergy in CD8+ T cells: Role of TGF-beta 1. *J. Immunol.* **2003**, *170*, 5897–5911.
541. Tian, J.; Zekzer, D.; Hanssen, L.; Lu, Y.; Olcott, A.; Kaufman, D.L. Lipopolysaccharide-activated B cells down-regulate Th1 immunity and prevent autoimmune diabetes in nonobese diabetic mice. *J. Immunol.* **2001**, *167*, 1081–1089.
542. Yanaba, K.; Bouaziz, J.D.; Haas, K.M.; Poe, J.C.; Fujimoto, M.; Tedder, T.F. A regulatory B cell subset with a unique CD1dhiCD5+ phenotype controls T cell-dependent inflammatory responses. *Immunity* **2008**, *28*, 639–650.
543. Caligiuri, G.; Nicoletti, A.; Poirier, B.; Hansson, G.K. Protective immunity against atherosclerosis carried by B cells of hypercholesterolemic mice. *J. Clin. Investig.* **2002**, *109*, 745–753.
544. Major, A.S.; Fazio, S.; Linton, M.F. B-lymphocyte deficiency increases atherosclerosis in LDL receptor-null mice. *Arterioscler. Thromb. Vasc. Biol.* **2002**, *22*, 1892–1898.
545. Doran, A.C.; Lipinski, M.J.; Oldham, S.N.; Garmey, J.C.; Campbell, K.A.; Skaflen, M.D.; Cutchins, A.; Lee, D.J.; Glover, D.K.; Kelly, K.A.; et al. B-cell aortic homing and atheroprotection depend on Id3. *Circ. Res.* **2012,** *110*, e1–e12.
546. Palinski, W.; Miller, E.; Witztum, J.L. Immunization of low density lipoprotein (LDL) receptor-deficient rabbits with homologous malondialdehyde-modified LDL reduces atherogenesis. *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 821–825.
547. Ameli, S.; Hultgardh-Nilsson, A.; Regnstrom, J.; Calara, F.; Yano, J.; Cercek, B.; Shah, P.K.; Nilsson, J. Effect of immunization with homologous LDL and oxidized LDL on early atherosclerosis in hypercholesterolemic rabbits. *Arterioscler. Thromb. Vasc. Biol.* **1996**, *16*, 1074–1079.
548. Sage, A.P.; Tsiantoulas, D.; Baker, L.; Harrison, J.; Masters, L.; Murphy, D.; Loinard, C.; Binder, C.J.; Mallat, Z. BAFF receptor deficiency reduces the development of atherosclerosis in mice--brief report. *Arterioscler. Thromb. Vasc. Biol.* **2012**, *32*, 1573–1576.
549. Kyaw, T.; Tay, C.; Khan, A.; Dumouchel, V.; Cao, A.; To, K.; Kehry, M.; Dunn, R.; Agrotis, A.; Tipping, P.; et al. Conventional B2 B cell depletion ameliorates whereas its adoptive transfer aggravates atherosclerosis. *J. Immunol.* **2010**, *185*, 4410–4419.
550. Kyaw, T.; Tay, C.; Hosseini, H.; Kanellakis, P.; Gadowski, T.; MacKay, F.; Tipping, P.; Bobik, A.; Toh, B.H. Depletion of B2 but not B1a B cells in BAFF receptor-deficient ApoE mice attenuates atherosclerosis by potently ameliorating arterial inflammation. *PLoS ONE* **2012**, *7*, e29371.
551. Kyaw, T.; Cui, P.; Tay, C.; Kanellakis, P.; Hosseini, H.; Liu, E.; Rolink, A.G.; Tipping, P.; Bobik, A.; Toh, B.H. BAFF receptor mAb treatment ameliorates development and progression of atherosclerosis in hyperlipidemic ApoE(-/-) mice. *PLoS ONE* **2013**, *8*, e60430.
552. Ait-Oufella, H.; Herbin, O.; Bouaziz, J.D.; Binder, C.J.; Uyttenhove, C.; Laurans, L.; Taleb, S.; Van Vre, E.; Esposito, B.; Vilar, J.; et al. B cell depletion reduces the development of atherosclerosis in mice. *J. Exp. Med.* **2010**, *207*, 1579–1587.

553. Tsiantoulas, D.; Sage, A.P.; Goderle, L.; Ozsvar-Kozma, M.; Murphy, D.; Porsch, F.; Pasterkamp, G.; Menche, J.; Schneider, P.; Mallat, Z.; et al. B Cell-Activating Factor Neutralization Aggravates Atherosclerosis. *Circulation* **2018**, *138*, 2263–2273.
554. Horkko, S.; Bird, D.A.; Miller, E.; Itabe, H.; Leitinger, N.; Subbanagounder, G.; Berliner, J.A.; Friedman, P.; Dennis, E.A.; Curtiss, L.K.; et al. Monoclonal autoantibodies specific for oxidized phospholipids or oxidized phospholipid-protein adducts inhibit macrophage uptake of oxidized low-density lipoproteins. *J. Clin. Investig.* **1999**, *103*, 117–128.
555. Lewis, M.J.; Malik, T.H.; Ehrenstein, M.R.; Boyle, J.J.; Botto, M.; Haskard, D.O. Immunoglobulin M is required for protection against atherosclerosis in low-density lipoprotein receptor-deficient mice. *Circulation* **2009**, *120*, 417–426.
556. Hosseini, H.; Li, Y.; Kanellakis, P.; Tay, C.; Cao, A.; Liu, E.; Peter, K.; Tipping, P.; Toh, B.H.; Bobik, A.; et al. Toll-Like Receptor (TLR)4 and MyD88 are Essential for Atheroprotection by Peritoneal B1a B Cells. *J. Am. Heart Assoc.* **2016**, *5*, e002947.
557. Rosenfeld, S.M.; Perry, H.M.; Gonen, A.; Prohaska, T.A.; Srikakulapu, P.; Grewal, S.; Das, D.; McSkimming, C.; Taylor, A.M.; Tsimikas, S.; et al. B-1b Cells Secrete Atheroprotective IgM and Attenuate Atherosclerosis. *Circ. Res.* **2015**, *117*, e28–e39.
558. Bagchi-Chakraborty, J.; Francis, A.; Bray, T.; Masters, L.; Tsiantoulas, D.; Nus, M.; Harrison, J.; Broekhuizen, M.; Leggat, J.; Clatworthy, M.R.; et al. B Cell Fcgamma Receptor IIb Modulates Atherosclerosis in Male and Female Mice by Controlling Adaptive Germinal Center and Innate B-1-Cell Responses. *Arterioscler. Thromb. Vasc. Biol.* **2019**, *39*, 1379–1389.
559. Mizoguchi, A.; Mizoguchi, E.; Takedatsu, H.; Blumberg, R.S.; Bhan, A.K. Chronic intestinal inflammatory condition generates IL-10-producing regulatory B cell subset characterized by CD1d upregulation. *Immunity* **2002**, *16*, 219–230.
560. Fillatreau, S.; Sweenie, C.H.; McGeachy, M.J.; Gray, D.; Anderton, S.M. B cells regulate autoimmunity by provision of IL-10. *Nat. Immunol.* **2002**, *3*, 944–950.
561. Mauri, C.; Gray, D.; Mushtaq, N.; Londei, M. Prevention of arthritis by interleukin 10-producing B cells. *J. Exp. Med.* **2003**, *197*, 489–501.
562. Rattik, S.; Mantani, P.T.; Yao Mattisson, I.; Ljungcrantz, I.; Sundius, L.; Bjorkbacka, H.; Terrinoni, M.; Lebens, M.; Holmgren, J.; Nilsson, J.; et al. B cells treated with CTB-p210 acquire a regulatory phenotype in vitro and reduce atherosclerosis in apolipoprotein E deficient mice. *Vascul. Pharmacol.* **2018**, *111*, 54–61.
563. Strom, A.C.; Cross, A.J.; Cole, J.E.; Blair, P.A.; Leib, C.; Goddard, M.E.; Rosser, E.C.; Park, I.; Hultgardh Nilsson, A.; Nilsson, J.; et al. B regulatory cells are increased in hypercholesterolaemic mice and protect from lesion development via IL-10. *Thromb. Haemost.* **2015**, *114*, 835–847.
564. Ridker, P.M.; Everett, B.M.; Thuren, T.; MacFadyen, J.G.; Chang, W.H.; Ballantyne, C.; Fonseca, F.; Nicolau, J.; Koenig, W.; Anker, S.D.; et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *N. Engl. J. Med.* **2017**, *377*, 1119–1131.
565. Ridker, P.M.; Everett, B.M.; Pradhan, A.; MacFadyen, J.G.; Solomon, D.H.; Zaharris, E.; Mam, V.; Hasan, A.; Rosenberg, Y.; Iturriaga, E.; et al. Investigators, C. Low-Dose Methotrexate for the Prevention of Atherosclerotic Events. *N. Engl. J. Med.* **2019**, *380*, 752–762.
566. Everett, B.M.; Pradhan, A.D.; Solomon, D.H.; Paynter, N.; Macfadyen, J.; Zaharris, E.; Gupta, M.; Clearfield, M.; Libby, P.; Hasan, A.A.; et al. Rationale and design of the Cardiovascular Inflammation Reduction Trial: A test of the inflammatory hypothesis of atherothrombosis. *Am. Heart J.* **2013**, *166*, 199–207.e15.
567. Palmer, R.D.; Vaccarezza, M. New Promises and Challenges on Inflammation and Atherosclerosis: Insights From CANTOS and CIRT Trials. *Front. Cardiovasc. Med.* **2019**, *6*, 90.