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CRITICAL REVIEW

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An overview of the innate and adaptive immune system in atherosclerosis

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Abstract

Cardiovascular disease is the leading cause of death globally. Coronary artery disease (CAD) is a chronic inflammatory disease usually caused by atherosclerosis, in which the coronary arteries become narrowed by atheromatous plaque. Plaques in atherosclerosis are formed through the accumulation of lipids and various immune cells. Both adaptive and innate immune systems are involved in the pathogenesis of atherosclerosis and facilitate plaque formation and disease progression. Almost all immune system cells, including neu-

Abbreviations: APCs, antigen-presenting cells; ApoB100, apolipoprotein B100; APPs, acute-phase proteins; Arg1, arginase 1; Bcl6, B cell lymphoma 6; CAD, coronary artery disease; CRP, C-reactive protein; CVD, cardiovascular disease; DAMPs, damage-associated molecular patterns; DCs, dendritic cells; FKN, fractalkine; FOXP3, forkhead box P3; GM-CSF, granulocyte-macrophage colony-stimulating factor; HLA-DR, human leukocyte antigen; HSPs, heat-shock proteins; HSP60, heat shock protein 60; HSP70, heat shock protein 70; ICAM -1, intercellular adhesion molecule 1; ICOS, inducible T cell co-stimulator; ICOSL, inducible T cell co-stimulator ligand; IDO, indoleamine 2,3-dioxygenase; IFN, interferon; IFNγ, interferon-gamma; IL, interleukin; IL-17R, IL-17 receptor; iNKT, invariant NKT; IRF4, interferon regulatory factor 4; iTregs, induced Tregs; JAK1, Janus kinase 1; JAK3, Janus kinase 3; LGL, large granular lymphocytes; LPS, lipopolysaccharide; LXR, liver × receptor; MCP-1, monocyte chemoattractant protein-1; MerTK, Mer receptor kinase; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; MPO, myeloperoxidases; MR, mannose receptor; mDC, myeloid DC; NET, neutrophil extracellular traps; NK, natural killer; NKT, natural killer T; Nrf2, nuclear erythroid-2 related factor; nTregs, natural Tregs; ox-LDL, oxidized low-density lipoprotein; PCR, polymerase chain reaction; pDC, plasmacytoid DC; PECAM -1, platelets, endothelial cell adhesion molecule 1; PF4, platelet factor 4; PPARγ, peroxisome proliferator-activated receptor γ; PTX3, pentraxin-3; RNS, reactive nitrogen specie; ROS, reactive oxygen species; RORγt, retinoic acid-related orphan receptor gamma t; RUNX1, runt-related transcription factor 1; SMC, smooth muscle cells; STAT3, signal transducer and activator of transcription 3; STAT-4, signal transducer and activator of transcriptoion-4; STAT6, signal transducer and activator of transcription 6; TBX21, T-box transcription factor; TFH, T follicular helper; TGF-β, transforming growth factor beta; Th, T-helper; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-alpha; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; Tregs, regulatory T cells; VCAM3, vascular cell adhesion molecule 3; VEGF, vascular endothelial growth factor; VSMCs, vascular smooth muscle cells.

trophils, B cells, T cells monocytes, macrophages, foam cells, and dendritic cells (DCs), play a vital role in atherosclerotic plaque. Atherogenesis, the normal function of the endothelium, is initially disrupted and, then, cells of the immune system are recruited to the endothelium following increased expression of cell adhesion molecules. Accumulation of immune cells and lipids leads to the formation of a necrotic nucleus. As the disease progresses, smooth muscle cells form fibrous layers, whose rupture results in exposing the necrotic nucleus and thrombosis. Accordingly, the present review was conducted to determine the role of different cells in innate and adaptive immune systems in inhibition and progression of atherosclerosis.

KEYWORDS

adaptive immune systems, atherosclerosis, innate immune system

1 | INTRODUCTION

Coronary artery diseases (CAD) are a complex clinical disease which have a variety of serious complications.[1] Plaques in atherosclerosis are formed through the accumulation of lipids and various types of immune cells.[2] Common symptoms of this disease include chest pain or discomfort as well as sudden manifestations of the disease comprising myocardial infarction and death.[3,4] Underlying mechanisms vary depending on the disease. Atherosclerosis is the main mechanism of CAD. Atherosclerosis can be caused by smoking, high blood pressure, high blood cholesterol, poor diet, obesity, the lack of exercise, and diabetes.[5] Atherosclerosis begins with dysfunction of endothelial cells, subendothelial deposition, and altered lipoproteins serving as damage-associated molecular patterns (DAMPs) that activate immune receptors, increase proliferation of immune cells, and induce vascular inflammation.[6] It is now established that atherosclerosis is a chronic inflammatory disease occurring in the arterial wall. The oxidation of low-density lipoprotein (LDL) in subendothelial plays a crucial role in atherosclerotic plaque formation. Oxidized LDL (ox-LDL) is taken up by endothelial cells, smooth muscle cells, and macrophages mainly through several receptors and activated other immune cells.[7] In response to endogenous altered structures (e.g., ox-LDL) stimulated both specific and innate immune responses.[8] The pathogenesis of atherosclerosis depends on the amount of lipids in the blood because lipid accumulation causes the absorption and activation of immune cells.[9] This study aims to describe the function of different cells of adaptive and innate immune systems in progression and suppression of atherosclerosis.

2 | THE ROLE OF INNATE IMMUNE SYSTEM IN ATHEROSCLEROSIS

In atherosclerosis, the expression of adhesion molecules (including vascular cell adhesion molecule 3 (VCAM3), intercellular adhesion molecule 1 (ICAM −1), and platelets endothelial cell adhesion molecule 1 (PECAM −1) increase on the surface of endothelial cells. The increased expression of these cells recruits immune system cells towards endothelial cells.[10] Various cells from the innate immune system are activated in response to extracellular signals, such as lipopolysaccharides, and intracellular signals, such as ox-LDL. These can lead to progression of atherosclerosis by producing inflammatory mediators.[11] In the following, we addressed the role of innate immune system cells in pathogenesis of atherosclerosis (Table 1).

2.1 | The role of macrophages in atherosclerosis

Macrophages, in a process known as phagocytosis, ingest microbes, cancer cells, foreign substances, cellular debris, and anything else not having the type of proteins specific to normal body cells on its surface.[12] Macrophages are originated from monocyte cells and located in various body tissues.[13] During the course of atherosclerosis, macrophages located under the endothelium vessels take up ox-LDL, and cholesterol derived from ox-LDL is accumulated in these cells. The accumulated cholesterol is pumped from macrophages by the process of cholesterol efflux. If there is a defect in this process, macrophages are transformed into foam cells.[14–16] One way to form atherosclerotic plaque is necrosis of macrophages and

TABLE 1 The role of innate immune cells in atherosclerosis

Innate immune cells	Function during atherosclerosis	Atheroprotective or pro-atherogenic	Ref
Macrophage	• Transformed into foam cells and form atherosclerotic plaque • Imbalance between macrophage: Atherosclerosis progress ○ Classic or M1 macrophages • Acute-phase proteins (APPs) leads to formation of M1 macrophages and progression of atherosclerotic plaque • Destruction of fibrous layer, plaque rupture, and eventually myocardial infarction through production of collagenase (MMP1) and stromelysin (MMP-10) ○ Alternative or M2 macrophages • M2 macrophages predominate in the early stages of atherosclerosis • May play an atheroprotective role • M2 macrophages are categorized into four subclasses, including M2a, M2b, M2c, and M2d ○ Other types of macrophages in atherosclerosis plaque include M4, Mox, M(Hb), and Mhem	Pro-atherogenic Atheroprotective and pro-atherogenic	14–19 25,27 21,32,36,46 47–58
Monocyte	• Two subgroups of mouse monocytes have been identified • $Gr1^{+}Ly6C^{high}CCR2^{+}CX3CR^{low}$(inflammatory) • $Gr1^{-}Ly6C^{low}CCR2^{-}CX3CR1^{high}$ • Ly-$6C^{high}$ monocytes is raised in the first days following acute myocardial infarction • Ly-$6C^{low}$ monocytes is raised following acute myocardial infarction and can boost wound healing and regeneration of blood vessels • $Ly6C^{low}$ and $Ly6C^{high}$ monocytes become macrophages M2 and M1, respectively • Monocyte subtypes may play a vital role in inhibition and progression of atherosclerosis ○ Monocytes in the humans are classified into three subgroups including • Non-classical ($CD14^{+}$ $CD16^{++}$) • Intermediate ($CD14^{++}$ $CD16^{+}$) • Classical ($CD14^{++}$ $CD16^{-}$) • $CD14^{+}CD16^{high}$ monocytes promote atherosclerosis by the increased production of TNF-α	Pro-atherogenic	63–66 71,72 73–79
Neutrophil	• Elevated cholesterol levels: Increase release of neutrophils and size of atherosclerotic plaque • Direct relationship between the number of peripheral neutrophils and size of the atherosclerotic lesion • Inflammatory activity in atherosclerotic plaques via secretion of various mediators ○ Pentraxin 3, ROS, neutrophil elastases, MPO, leukotriene B4, neutrophil extracellular traps (NET), connexin, IFN-γ, and MMPs	Pro-atherogenic	89,91,105

TABLE 1 (Continued)

Innate immune cells	Function during atherosclerosis	Atheroprotective or pro-atherogenic	Ref
	• Neutrophils are also involved in development of atherosclerosis by secreting azurocidin, proteinase 3, and defensin.		
Mast cell	• Inactivation of mast cells by FcεR1: decrease the number of inflammatory cells like macrophages and T cells in atherosclerotic plaque • Activation of mast cells by TLR4 induces apoptosis in vascular smooth muscle cells of atherosclerotic plaques • Mast cells cause plaque instability and exposing of necrotic nucleus through secretion of various mediators: ○ Histamine, heparin, proteases (tryptase and chymase), and multiple cytokines (such as IL-6, IL-8, MCP1, TNF-α, and IFN-γ)	Pro-atherogenic	114,115,119,120,134
Natural killer cell	• NK cells are leading sources for production of IFN-γ: decrease in the IFN-γ levels significantly reduces atherosclerotic plaques in mice • Overall, the function of NK cells in atherosclerosis has not been identified	Has not been identified	139,140
Dendritic cells	• DCs have a pivotal role in both innate and adaptive immune systems • Decreased number of DCs reduces lipid accumulation and number of foam cells and ultimately reduces size of atherosclerotic plaques • Interactions of DCs with NK cells enhance production of IL-12 and IFN-γ: may have a role in formation and progression of atherosclerosis plaques • The interaction between mDC, pDC, and other immune cells activates other immune cells, rupture plaques, and eventually leads to atherosclerosis • Regulatory DCs interfere with anergy and depletion of inflammatory T cells and production and proliferation of atheroprotective Tregs	Atheroprotective and pro-atherogenic	139,145,158,165–168

cholesterol release in the environment.[17–19] Ox-LDL activates macrophages through toll-like receptor 4 (TLR4) and increases secretion of tumor necrosis factor-alpha (TNF-α) from them.[20] Macrophages have remarkable flexibility and change their phenotype in response to environmental alteration.[21,22] Overall, the imbalance between macrophage subsets seem to play an essential role in the progress of atherosclerosis.[23] Figure 1 shows the role of different resident macrophage subsets in the atherosclerotic lesion site.

2.1.1 | Classic or M1 macrophages

Classic or M1 macrophages are activated in response to interferon-gamma (IFN-γ) produced by Th1 lymphocytes. M1 macrophages produce low and high levels of interleukin (IL)-10 and IL-12, respectively.[24] This type of macrophages secrete factors, including inflammatory cytokines TNF-α and IL-1 beta (IL-1β), that increase the differentiation of naive T cells into Th1. Studies have shown that production of acute-phase proteins (APPs), such as C-

reactive protein (CRP), leads to formation of M1 macrophages and progression of atherosclerotic plaque.[25] According to in vitro investigations, ox-LDL elevates IL-8 expression in M1 macrophages.[26] Additionally, M1 macrophages in atherosclerotic plaque cause destruction of the fibrous layer and availability of necrotic nuclei through production of metalloproteinase (MMP). In the human beings, M1 macrophages cause destruction of fibrous layer, plaque rupture, and, eventually, myocardial infarction through production of collagenase (MMP1) and stromelysin-2 (MMP-10).[27]

2.1.2 | Alternative or M2 macrophages

M2 macrophages support the regulation/suppression of inflammatory responses and wound healing.[28] IL-13 and IL-4 cytokines produced by Th2 lymphocytes can induce the production of alternative or M2 macrophages.[29] M2 macrophages produce low and high levels of IL-12 and IL-10, respectively, and lead to the increased differentiation of naive T cell lymphocytes into Th2.[30,31] Although M2 macrophages predominate in the early stages of atherosclerosis, M1 macrophages become predominated as the disease progresses.[21] An increased number of M2 macrophages in the initial stages of atherosclerosis may play an atheroprotective role by creating small atherosclerotic lesions. In contrast, M1 macrophages are predominated with development of atherosclerosis, leading to plaque development by expressed NO synthase (iNOS).[32] Cholesterol efflux is impaired and accumulation of cytoplasmic lipids increases in M2 macrophages because of low expression of cholesterol efflux gene (LXR-a). However, M2 macrophages, as compared with M1 macrophages, have less potential to become foam cells.[33] In a study, Isa et al. showed that ox-LDL activates M1 macrophages while having a lethal effect on M2 macrophages.[34,35] M2 macrophages are categorized into four subclasses, including M2a, M2b, M2c, and M2d (Figures 1–3).

2.1.3 | M2a macrophages

M2a phenotype, in which "a" stands for alternative, is produced in response to IL-4 and IL-13. IL-4 (a Th2-produced cytokine) and IL-13 bind to receptor IL-4Rα, improving M2 polarization through several pathways, typically Janus kinase 3 (JAK3) and Janus kinase 1(JAK1) signaling, further causing activation and translocation of signal transducer and activator of transcription 6 (STAT6). Other transcription factors involved include interferon regulatory factor 4 (IRF4) and peroxisome proliferator-activated receptor γ (PPARγ). STAT6, IRF4, and PPARγ regulate many of the genes associated with mouse M2 macrophages, such as arginase 1 (Arg1), CD206 (or macrophage mannose receptor 1, Mrc1), resistin-like-α (Retnla or Fizz1), and Ym1 (chitins 3-like 3; Chi3l3).[36] M2a macrophages strongly express mannose receptor (MR/CD206), decoy receptor IL-1RII, and IL-1 receptor antagonist. M2a macrophages exhibit an anti-inflammatory phenotype and inhibit production of TNF-α, IL-1β, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-10, IL-6, and IFN-γ. M2a macrophages are less involved in phagocytosis and contribute to deposition of extracellular matrix by producing polyamines, collagen, and transforming growth factor beta (TGF-β). Therefore, M2a macrophages may also be defined as "tissue-repairing" macrophages.[37]

2.1.4 | M2b macrophages

M2b macrophages, although sharing the same characteristics as normal M2 macrophages by exposing to immune complexes, TLR antagonists, and IL-1 receptor ligands, express pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6.[38]

2.1.5 | M2c macrophages

The inhibitory cytokine IL-10 and glucocorticoids induce production of M2c macrophages. Expression of pentraxin-3 (PTX3) and production of anti-inflammatory cytokines, including TGF-β and IL-10, increase in M2c macrophages. Actually, PTX3 is an innate immune receptor which regulates inflammation. Besides, PTX3 is considered as a marker of vascular pathology (such as myocardial infarction and heart failure).[39,40] M2c macrophages are the main source of PTX3 production.[41] There is accumulating evidence suggesting that PTX3 produced by M2c macrophages has a protective role in mice with atherosclerosis.[40] M2c macrophages express high levels of Mer receptor kinase (MerTK) that increases effective activity of these macrophages.[38,42] M2b and M2c, known as "regulator macrophages", can improve atherosclerosis by modulating tissue damage caused by long-term activation of M1 macrophages.[43] In spite of this, Fleming et al., showed that M2b and M2c macrophages lack the ability to participate in tissue repair because they, unlike M2a macrophages, are unable to synthesize extracellular matrix.[44]

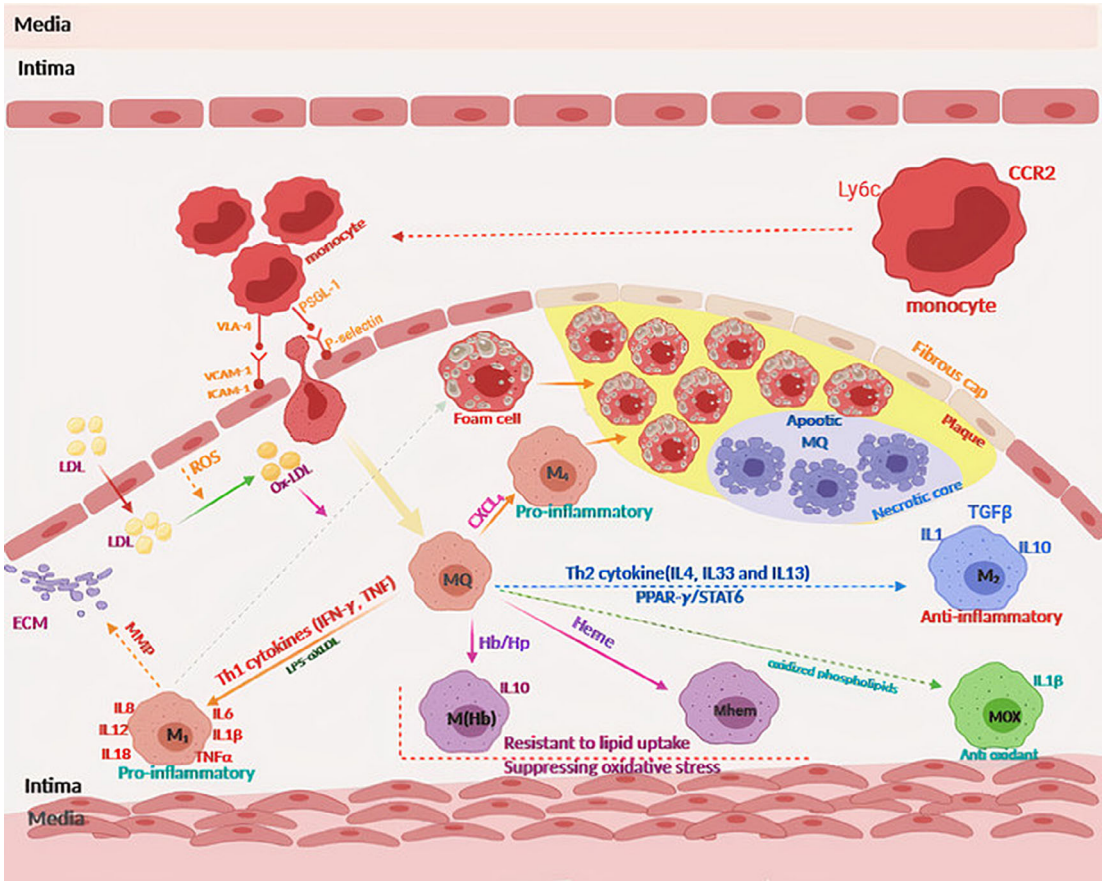

FIGURE 1 The role of macrophages in atherosclerosis. Atherosclerosis begins with the deposition of lipids. Endothelial activation increases the expression of leukocyte adhesion molecules such as E and P-selectins, VCAM-1 and ICAM-1 glycoproteins, and MCP-1 chemokine, which stimulates inflammatory monocytes by migration and infiltration. Circulating monocytes are activated, by adhering to endothelial cells (ECs), and are attracted to the atherosclerotic lesion site, by entering the sub-endothelial cell space. Inside the atherosclerosis plaque, macrophages absorb lipid particles and convert into foam cells, and finally form the early lesions of atherosclerosis. The reactive oxygen species (ROS) produced by macrophages lead to the oxidation of low-density lipoprotein (LDL) in the vascular wall and the formation of oxidized low-density lipoprotein (ox-LDL), which consequently lead to monocyte differentiation into macrophages and the formation of foam cells. Ox-LDL induces necrosis of foam cells, which forms a necrotic nucleus, leading to instability and rupture of atherosclerotic plaques. Pre-inflammatory macrophages M1 and anti-inflammatory M2 are polarized by the cytokines Th1 and Th2, respectively. Haem-induced phenotypes, such as M (Hb) and Mhem like M2, display anti-inflammatory effects such as resistance to lipid uptake and suppression of oxidative stress. Mox and M4 phenotypes have little potential for phagocytosis and, potentially have preinflammatory properties, by expressing proatherogenic markers

2.1.6 | M2d macrophages

M2d macrophages are induced through TLR antagonists and induce the production of the adenosine A2A receptor. Adenosine inhibits production of TNF-α, IL-1, and IFN-γ through binding to its receptor. Adenosine signaling also induces pro-angiogenic features in macrophages through expressing vascular endothelial growth factor (VEGF) and IL-10.[45,46]

2.1.7 | Other macrophages

It has been reported that macrophages have a high degree of flexibility, and other types of macrophages in atherosclerosis plaque include M4, Mox, M(Hb), and Mhem.[47–49] Oxidized phospholipids can result in a type of macrophages known as Mox. Nuclear erythroid-2 related factor (Nrf2), a transcription factor, can polarize Mox macrophages. These macrophages exhibit different morphological structure and a combination of biological functions of M2 and M1 macrophages. In fact, Mox macrophages have weak activity in chemotaxis and phagocytosis, and have been shown to constitute approximately 30% of the all macrophages in atherosclerotic lesions established in mice. Nevertheless, the presence of Mox macrophages in human atherosclerotic lesions has not been described until.[50] M(Hb) or hemoglobin-stimulated macrophages are another subset of macrophages present in atherosclerosis.[51] Expression of CD163 increases in

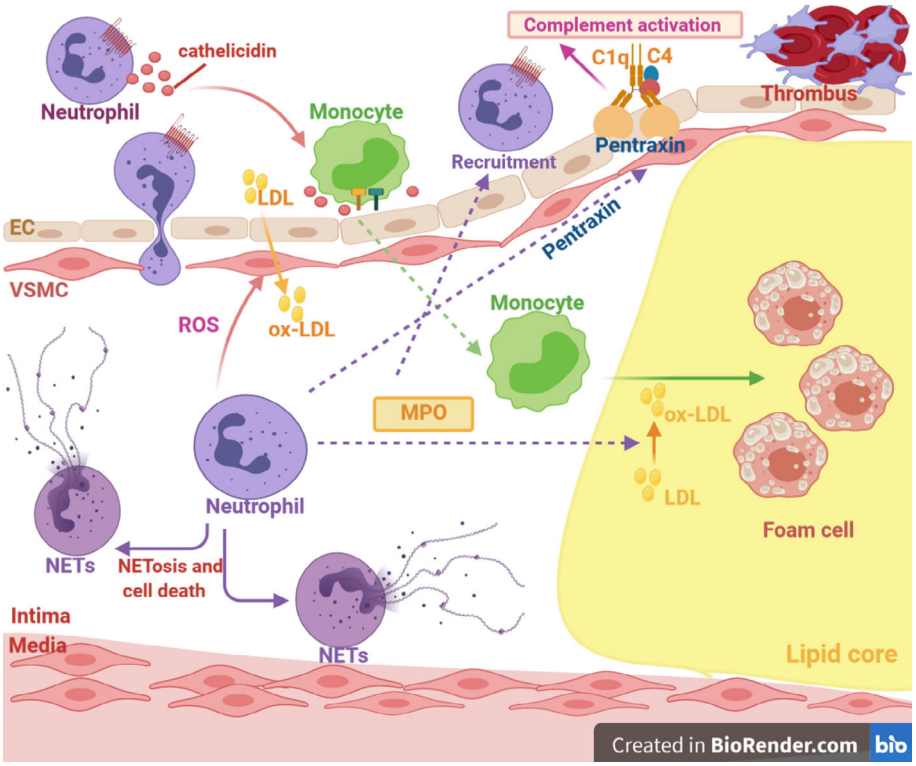

FIGURE 2 Role of neutrophils in atherosclerosis. Neutrophils are of the most important components of innate immune responses and contain numerous inflammatory mediators that are freely activated. Activated oxygen species, myeloperoxidase (MPO), and matrix metalloproteinases (MMPs) are involved in extracellular matrix degradation and atherosclerotic plaque erosion. By binding to C1q, pentraxin induces complement activation and allows leukocytes to be recruited. On the luminal side, activated neutrophils secrete granular proteins, for example, cathelicidin and cathepsin G, which directly or indirectly attract myeloid cells. Neutrophils activate and dysregulate endothelial layer cells (ECs) and extracellular matrix (ECM) by secretion of reactive oxygen species (ROS) and proteases on the luminal and intimal sides of atherosclerotic plaques. MPO attracts neutrophils and Ox-LDL. Ox-LDL is swallowed by macrophages and differentiates them into foam cells. Neutrophils can additionally be exposed to NETosis, in which neutrophils release extracellular traps that can play a role in thrombus formation, antigen-presenting cell activation, or endothelial cell cytotoxicity

these macrophages. The Hb/Hp complex stimulates human monocytes to increase CD163 expression and induces the M (Hb) phenotype in atherosclerotic plaques.[52] The Hb/Hp complex secretes anti-inflammatory cytokines such as IL-10.[53] Besides, M(Hb) macrophages increase cholesterol efflux by increasing LXRa activity, and prevent formation of foam cells. Raised activity of LXRa additionally stimulates expression of ferroportin, an iron exporter (which is an iron exporter) and decreases the amount of intracellular iron. Decreased levels of intracellular iron lead to the decreased ROS production by M(Hb) macrophages. Finn et al. approved the effect of the decreased ROS production by M(Hb) macrophages in atherosclerotic plaque in humans.[51] Platelet-derived chemokine CXCL4 induces the production of M4 cells.[54] CXCL4 chemokine (or platelet factor 4 [PF4]) is expressed in numerous cells implicated in atherosclerosis, including monocytes, endothelial cells, and macrophages.[55,56] CXCL4 expression in human atherosclerotic plaques is directly related to severity of the disease.[57] M4 and Mhem macrophages have pro-atherogenic and atheroprotective roles through decreased and increased expression of CD163, respectively.[58]

2.2 | The role of monocytes in atherosclerosis

Monocytes may differentiate into macrophages and myeloid DCs.[59] Monocytes originate from the myeloid lineage in the bone marrow and enter the blood stream, showing a relatively brief half-life in the blood.[60] Monocytes have various phenotypes in humans and mice. Mouse monocytes can be identified by expression of CD115, CD11b, CCR2, and CX3CR1.[61,62] Based on this, two subgroups of mouse monocytes have been identified, the first and second phenotypes are $Gr1^{+}Ly6C^{high}CCR2^{+}CX3CR^{low}$ and $Gr1^{-}Ly6C^{low}CCR2^{-}CX3CR1^{high}$, respectively. $Ly6C^{hi}$ (inflammatory) monocytes are discharged from the blood

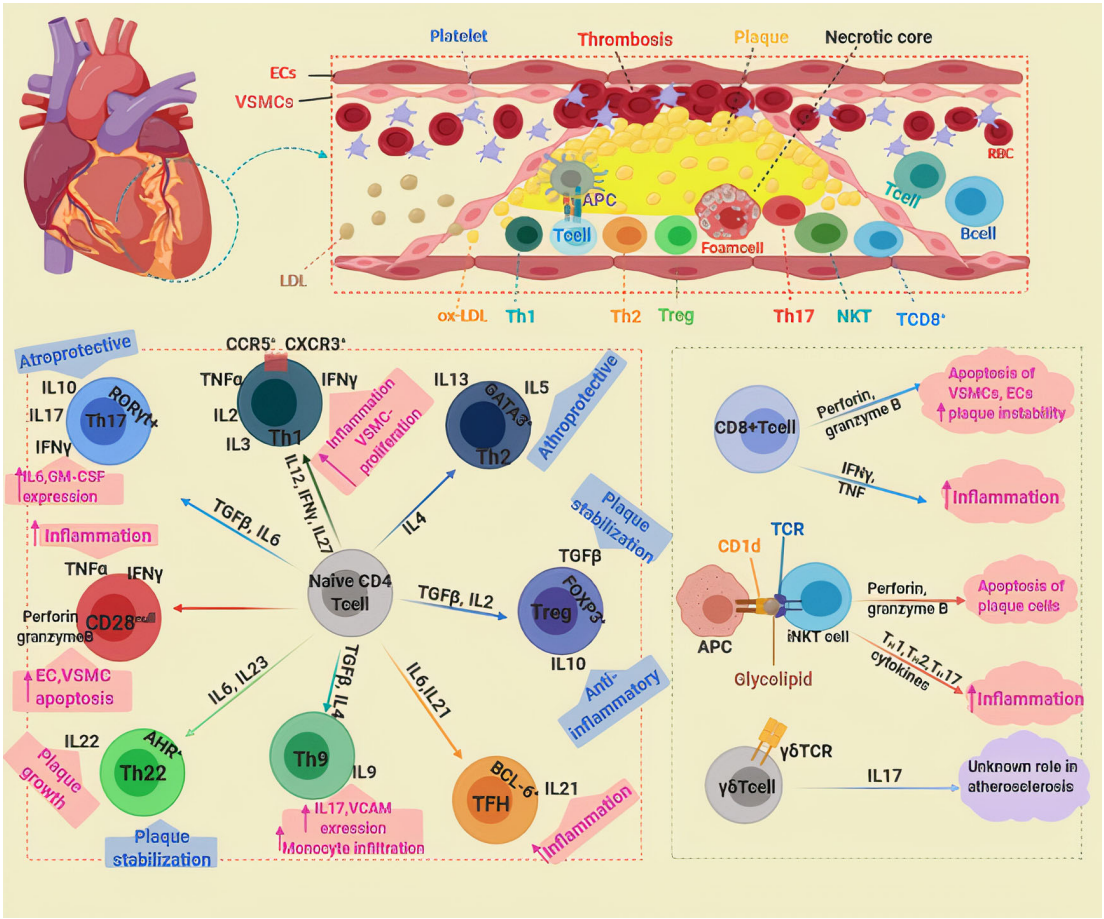

FIGURE 3 Role of T cells in atherosclerosis. Naive $CD4^+$ T helper (Th) cells have several subsets, and in fact, stimulatory molecules stimulate T cells to express transcription factors that lead to differentiation into Th phenotypes. $CD4^+$ T cells can have both pro-atherogenic and atheroprotective characteristics. Atherosclerotic lesions contain Th1, Th2, Th9, Th17, Th22, Treg, and follicular helper T (TFH) cells. Actually, these cells exert their atheroprotective effects by cytotoxicity activity against antigen-presenting cells (APCs) and the inhibition of production of inflammatory subsets of CD4 + T cells. Invariant natural killer T (iNKT) cells are activated by interplay of T cell receptor (TCR) receptors with CD1d molecules, comprising antigenic glycolipids presented in APCs. Activation of iNKT cells gives rise to the rapid discharge of cytokines associated with T helper 1 (Th1), Th2 and, Th17 cells and activate other immune system cells in atherosclerotic lesions. iNKT cells can additionally develop atherosclerosis through apoptosis induction of atherosclerosis plaque cells by releasing cytotoxic proteins such as perforin and granzyme B. γδ T cells are a subset of T cells detected in atherosclerotic lesions of mice. γδ T cells are a rich source of IL-17, thus, these cells can regulate atherosclerosis through the production of IL-17. Nevertheless, the definite role of γδ T cells in atherosclerosis is unclear

in a CCR2-CCL2-dependent manner, and are vital in the case of inflammation. $Ly6^{Clow}$ (patrolling) monocytes migrate into the bloodstream via CX3CR1-CX3CL1 signaling. Elevated blood cholesterol during atherosclerosis plays a very important role in expansion of Ly-$6C^{high}$ monocytes. In this regard, investigations performed on mice have indicated that the frequency of Ly-$6C^{high}$ monocytes is raised in the first days following acute myocardial infarction. However, the frequency of Ly-$6C^{low}$ monocytes is raised following acute myocardial infarction and can boost wound healing and regeneration of blood vessels.[63–66] Entry of monocytes into atherosclerotic plaques depends on various molecules, of which chemokines and their receptors play a crucial role. CCR2 deficiency in mice has been indicated to dramatically decrease growth of atherosclerotic plaque.[63] Deficiency in common ligand of E-selectin and P-selectin on leukocytes has been found to reduce the transfer of $Ly6C^{high}$ monocytes toward atherosclerotic plaque in mice.[67] Deficiency or blockage of VCAM-1, PECAM-1, ICAM-1, or p-selectin has been shown to decrease adhesion and monocyte rolling and also progression of atherosclerotic plaque in mice.[68–70] Filtration of monocyte subtypes to atherosclerotic plaques indicates that these cells can differentiate into diverse subtypes of macrophages. $Ly6C^{low}$ and $Ly6C^{high}$ monocytes become macrophages M2 and M1, respectively. Therefore, both monocyte subtypes may play a vital role in inhibition and progression of

atherosclerosis.[71,72] In the humans, $CD14^{high}$ monocytes are the major subtype of circulating monocytes, and $CD14^{low}$ monocytes are the rare subtype of circulating monocytes. $CD14^{+}$ monocytes are determined by expression of CD14 and CD16 (or FcγRIII receptor, which has a pivotal role in identification of immune complexes).[73,74] According to expression of FcγRIII (CD16) receptor, monocytes in the humans are classified into three subgroups, including non-classical ($CD14^{+}$ $CD16^{++}$), intermediate ($CD14^{++}$ $CD16^{+}$), and classical ($CD14^{++}$ $CD16^{-}$).[75–78] $CD14^{high}CD16^{-}$ monocytes account for about 80%-90% of circulating monocytes, and these cells express high and low levels of chemokine receptor CCR2 and CX3CR1, respectively. Nevertheless, $CD14^{+}CD16^{high}$ monocytes are $CX3CR1^{high}$ and $CCR2^{low}$ in terms of expression.[73,79] $CD14^{high}CD16$ monocytes produce low levels of TNF-α and high levels of IL-10, whereas $CD14^{+}CD16^{high}$ monocytes produce low levels of anti-inflammatory cytokines (e.g., IL-10), and high levels of pro-inflammatory cytokines (e.g., TNF-α).[80] $CD14^{+}CD16^{high}$ monocytes promote atherosclerosis by increased production of TNF-α.[74] The number of classical monocytes is raised in the first days following acute myocardial infarction and decreases after 7 days. Additionally, the number of non-classical monocytes is raised through a decrease in the number of classical monocytes.[81] Non-classical monocytes are expanded in the patients with CAD, and the number of this subset is directly associated with CAD severity,[82] revealing phenotypic complexity of monocytes in the patients with CVD.[82,83]

2.3 | The role of neutrophils in atherosclerosis

Neutrophils, also known as neutrocytes or heterophils, are the most abundant type of granulocytes and makeup 40%-70% of all white blood cells in the human body.[84] Neutrophils, as the most frequent population of circulating white blood cells,[85] are among the first cells to eliminate microbial pathogens by phagocytosis, production of ROS, myeloperoxidase, and various proteolytic enzymes.[86] Most neutrophil functions occur in response to signals transmitted through receptors, such as RIG-I-like receptors, NOD-like receptors, C-type lectin receptors, and TLRs.[87,88] Bone marrow-derived neutrophils express high and low levels of CXCR4 and CXCR2, respectively. The CXCL12 chemokine binds to CXCR4 ligand to transmit signals in order to maintain neutrophils in the bone marrow and induces return of old neutrophils to the bone marrow.

Figure 2 shows the role of neutrophils in the atherosclerotic lesion site. Elevated cholesterol levels increase the expression of CXCR2 and its ligand CXCL1 and release of neutrophils from the bone marrow. Impaired expression of CXCL12-CXCR4 stimulates neutrophils and increases the size of atherosclerotic plaque.[89] Studies on mouse models of atherosclerosis have shown a direct relationship between the number of peripheral neutrophils and size of the atherosclerotic lesion. Importantly, it is predicted that regulating factors of neutrophil homeostasis are involved in progression of atherosclerotic disease by influencing the number of peripheral neutrophils.[89] During inflammatory processes, the number of neutrophils increases in the bloodstream, and the IL-8 cytokine attracts these cells to necrotic nucleus and exerts its effective function.[90] An increase in neutrophils influx and inflammatory activity of these cells in atherosclerotic plaques may play a vital role in progression of atherosclerosis through secretion of various mediators, including PTX3, ROS, neutrophil elastases, MPO, leukotriene B4, neutrophil extracellular traps (NET), connexin, IFN-γ, and MMPs.[91] For example, leukotriene B4 and its receptor BLT1 activate neutrophils and recruit them to atherosclerotic plaques.[92] Neutrophils in human atherosclerotic lesions produce PTX3 in response to inflammatory signals (e.g., bacterial products, TNF-α, and IL-1).[41] The PTX3 protein also increases inflammation, chemotaxis, phagocytosis, tissue damage, and, finally, progression of atherosclerosis by activating classical complement pathway.[93,94] Primary granules in neutrophils contain a good source of MPO enzyme,[95] which increase the production of ox-LDL.[96] Circulating neutrophils have lower MPO, while elevated MPO levels of plasma in the patients with hyperlipidemia reveal depletion of neutrophil granules.[97] MPO can also result in the accumulation of cholesteryl ester in macrophages, and the formation of foam cells can develop atherosclerosis. Moreover, MPO may attract neutrophils to necrotic nucleus in atherosclerosis.[98] Several studies have shown an increase in the circulating levels of PTX3 and MPO in the patients with atherosclerosis, and an increase in these two markers has been mentioned as prognostic markers for acute and chronic heart failure, which may be a major risk factor for CVD in the humans.[99,100] Secondary and tertiary granules of neutrophil containing large amounts of MMP-2 and MMP-9 destroy endothelial cells by influencing collagen type IV, which is a pivotal agent in the endothelial cell membrane.[101] NETs are among novel mechanisms of neutrophils against microorganisms. NETs include core components, DNA, primary granules (elastase and MPO), secondary granules (PTX3 and lactoferrin), and third granules (MMM9).[90] Inflammation in atherosclerosis can cause the release of NETs from neutrophils.[102] NETs lead to thrombosis due to deposition of fibrin protein.[103] Furthermore, NETs cause apoptosis of

endothelial cells and destabilization of atherosclerotic plaque.[104]

Neutrophils are also involved in development of atherosclerosis by secreting azurocidin, proteinase 3, and defensin. Azurocidins can lead to activation of protein kinase c and a raise in the expression of VCAM-1 and ICAM-1, followed by recruitment and attracting the monocytes.[105] Besides, proteinase 3 is able to increase expression of cell adhesion molecules and adhesion of neutrophils and monocytes to endothelial cells.[106] Defensins not only intensify expression of chemokines and cell adhesion molecules, but also impair endothelial function through increased production of oxygen free radicals.[107,108]

2.4 | The role of mast cells in atherosclerosis

Mast cells, also known as a mastocyte, are a migrant cell in connective tissue containing many granules rich in heparin and histamine. Notably, mast cells are a type of granulocyte derived from the myeloid stem cell that is a part of neuroimmune and immune systems.[109] Mast cells, as a type of innate immune cell agents, play a fundamental role in allergic patients. Mast cells are detected not only in all the vascular tissues, nerves, near blood vessels, mucus-producing glands, smooth muscle cells, and hair follicles,[110] but also in carotid arteries of healthy individuals as well as in advanced and early atherosclerotic plaques.[111] The presence of mast cells in atherosclerotic plaques indicates their potential role in the disease.[111] in vivo studies revealed that mast cell deficiency significantly decreases atherosclerosis in mice.[112] Activation of mast cells by allergens or microorganisms releases inflammatory mediators from the granules. Classic mast cells are activated by binding FcεRI receptors to immunoglobulin E (IgE) with high affinity.[113] Reduced expression of FcεR1a has been found to lead to a dramatic decrease in the lipid deposition in aortic arch of mice, which might be due to inactivation of mast cells by FcεR1a and severe decline in release of inflammatory mediators, which can decrease the number of inflammatory cells such as macrophages and T cells in atherosclerotic plaque.[114,115] Mast cells are also activated by different mechanisms, such as IgG or immune complexes.[116] In animal models of atherosclerosis, the immune complex of oxLDL-IgG has been observed in plaques, and the presence of these complexes may be implicated in activation of mast cells.[117]

In vitro studies demonstrated that the oxLDL-IgG immune complex secrets inflammatory cytokines (such as IL-8 and TNF-α) and some other mediators (e.g., histamine and tryptase) from human mast cells.[118] TLRs are among other pathways related to activation of mast cells. Previous studies have demonstrated that TLR4 antagonist decrease activity of mast cells, presumably indicating that mast cells are activated by TLR4. Additionally, activation of mast cells by TLR4 induces apoptosis in vascular smooth muscle cells of atherosclerotic plaques.[119,120] Furthermore, the receptor of complement system components C3a and C5a can be activated mast cells in the plaque.[121] Mast cells can be involved in onset of atherosclerosis through diverse mediators, such as histamine (which raises vascular permeability).[122] Likewise, mast cells can play a considerable role in the progress of atherosclerotic plaques by secreting different cytokines. Based on studies conducted on a mouse model of atherosclerosis, deficiency in IFN-γ or IL-6 produced by mast cells is associated with a decrease in plaque size.[112] Secretion of inflammatory mediators by mast cells induces expression of adhesive molecules, VCAM-1, E-selectin, P-selectin, and ICAM-1 in endothelial cells and enhances recruitment and adhesion of leukocytes to vascular endothelium. This occurrence may indicate that function of mast cells in atherosclerosis is dramatically related to secretion of cytokines.[123] Histamine is another compound found in the granules of mast cells. Histamine levels are considerably raised in the patients with atherosclerosis compared to healthy individuals, which may indicate the role of histamine in progression of atherosclerosis.[124] in vitro investigations have implicated that secretion of histamine and protease mediators by mast cells could induce apoptosis of macrophages. Furthermore, protease secretion can lead to apoptosis of endothelial cells and smooth muscle cells of the vascular wall.[125] in vivo experiments in mice have shown that a noticeable increase in the secretion of protease tryptase raises formation of carotid plaque and makes the carotid artery to become narrow, whereas a decrease in the secretion of tryptase decreases the size of carotid plaques.[126] Studies on mouse models of atherosclerosis have indicated that tryptase increases the expression of IL-8 chemokines, which have an ability to attract monocytes and neutrophils to endothelial cells, and monocyte chemoattractant protein-1(MCP-1) and may have a striking role in the development of atherosclerosis.[127] In the human beings, tryptase promotes the formation of foam cells by repressing activation of nuclear receptor liver × receptor (LXR) -a, and reverse transport of cholesterol.[128,129] Moreover, tryptase could boost angiogenesis through degradation of collagen type IV, vitronectin, and fibronectin.[130] Inhibition of protease chymase in mice has been shown to diminish plaque development and size of necrotic nucleus.[131] Chymase destabilizes the plaques by stimulating apoptosis of smooth muscle cells (SMC)

and degradation of vitronectin and fibronectin.[132] Heparin is another compound present in mast cell granules that may increase the formation of foam cells.[133] Therefore, mast cells cause plaque instability and exposing of necrotic nucleus through secretion of various mediators, such as histamine, heparin, proteases (tryptase and chymase), and multiple cytokines (such as IL-6, IL-8, MCP1, TNF-α, and IFN-γ).[134]

2.5 | The role of natural killer cells (NKs) in atherosclerosis

Natural killer cells (NK cells) or large granular lymphocytes (LGL) are a type of cytotoxic lymphocytes which are vital to the innate immune system.[109] NKs recognize pathological changes in the tissues through inhibitory and activating receptors. Decreased and increased expression of MHC-I molecules leads to utilization of activating receptors and inhibitory receptors, respectively.[135,136] The interplay of NK cells with the infected cells can trigger activating receptors, secreting perforin, granzyme, and anti-inflammatory cytokines (e.g., IL-1β, TNF-α, and IFN-γ), and exciting inflammation and direct destruction of target cells.[135–137] In the humans, NK cells have been demonstrated to exist in atherosclerosis lesions.[138] NK cells are leading sources for production of IFN-γ. Moreover, various studies have shown that a decrease in the IFN-γ levels significantly reduces atherosclerotic plaques in mice, which may indicate the role of NK cells in atherosclerosis.[139,140] In atherosclerotic plaques, there are different chemokines for attracting innate immune cells. For example, CX3CL1 and MCP-1 chemokines play a vital role in attracting NK cells to necrotic nucleus.[141,142] Overall, the function of NK cells in atherosclerosis has not been identified.

2.6 | The role of DCs in atherosclerosis

DCs are antigen-presenting cells (APCs) in the mammalian immune system. Their chief function is antigen processing and its presentation on the cell surface to T cells of the immune system. They act as messengers among innate and adaptive immune systems.[143] DCs are derived from common precursor $CD34^+$ in the bone marrow and placed in various tissues of the body.[144] DCs have a pivotal role in both innate and adaptive immune systems.[145] Various receptors (integrins, TLRs, scavenger receptors, Fc receptors, and C-type lectins) are expressed to uptake antigens at the surface of DCs. For example, TLR4 plays a vital role in the onset and development of atherosclerosis.[146] Lipopolysaccharide (LPS) from Gram-negative bacteria, ox-LDL, and heat-shock proteins (HSPs) are detected by TLR4, leading to activation of signaling transduction.[147,148] However, there are studies representing that ox-LDL may inhibit TLR4 signaling.[149] Activation of TLR4 at DC levels via *Chlamydia pneumonia* may be involved in the development of atherosclerosis.[150] Identification of nucleic acids in infectious pathogens by TLR7, TLR8, and TLR9 may be involved in the destabilization of atherosclerotic plaques.[151,152] Antigens processed by DCs, accompanied by MHC molecules, are presented to T cells.[153] Expression of chemokine receptors, MHC molecules, cytokines (TNF-α and IL-12), and costimulatory molecules increases during DC maturation, resulting in the expansion of different $CD4^+$ T cell subtypes, such as T helper (Th) cells (Th17, Th1, and Th1).[145,154] Secretion of CCL12 and CCL5 chemokines and expression of adhesive molecules, E-selectin, P-selectin, and integrins induce DC recruitment to atherosclerotic plaques.[155,156] The CX3CL1 chemokine seems to be an important agent for infiltrating DCs into atherosclerotic plaques, because deficiency of fractalkine (FKN) receptor leads to a decrease in the number of DCs and atherosclerosis.[157] Studies performed on mouse models manifested that the decreased number of DCs reduces lipid accumulation and the number of foam cells, and ultimately reduces the size of atherosclerotic plaques.[158] in vitro investigations revealed that ox-LDL increases expression of CD83, HLA-DR, CD36, and CD86 molecules through activation and maturation of human DCs.[159,160] Ox-LDL also diminishes the expression of chemokine receptors CCR7 and CCL21 in DCs, which can decrease the migration of these cells.[161] Interactions of DCs with NK cells enhance production of IL-12 and IFN-γ and may have a role in the formation and progression of atherosclerosis plaques.[139] The presence of classical myeloid DCs (mDCs) and plasmacytoid DCs (pDCs) has been approved in atherosclerosis plaques. pDCs are activated by the help of the TLR9 ligand, and increase the expression of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) at the level of $CD4^+$ T cells, apoptosis of vascular smooth muscle cells (VSMCs), and, finally, instability of atherosclerotic plaque, by secreting type I interferon (IFN).[162] Clinical studies demonstrated a decrease in the population of pDCs and mDCs in the peripheral blood from the patients with atherosclerosis compared with the control group.[163]

This decrease in the number of DCs derived from blood circulation may be in light of the increased presence of DCs in atherosclerotic plaques, showing the possible role of these cells in the development of atherosclerotic plaques.[163,164] Activation of DCs destabilizes atherosclerotic plaques in two following ways; in the first way, DCs can differentiate naive T cells into

different subsets of effector T cells. Activation of cytotoxic T cells causes rupture and exposing of necrotic nucleus of plaques. In the second way, DCs destroy extracellular matrix connections and rupture plaques by producing some proteases, such as metalloproteinases. The interaction between mDC, pDC, and other immune cells activates other immune cells, rupture of plaques, eventually leading to atherosclerosis. DCs under certain physiological or pathological conditions may express anti-inflammatory cytokines and inhibitory receptors and cause tolerogenic immune responses. Different environmental stimuli help DCs suppress immune responses by producing regulatory and anergic T cells. Regulatory DCs can present antigens but show a different expression profile, containing lower levels of stimulatory molecules and inflammatory cytokines and higher levels of anti-inflammatory cytokines. In addition, regulatory DCs are resistant to maturation signals.[165] Regulatory DCs enhance immune tolerance by decreasing expression of stimulatory molecules, enhancing expression of inhibitory molecules (e.g., indoleamine 2,3-dioxygenase [IDO]), promoting induction of anti-inflammatory cytokines (e.g., TGF-β and IL-10), and inhibiting production of inflammatory cytokines (e.g., TNFα and IL-12).[166] Regulatory DCs interfere with anergy and depletion of inflammatory T cells as well as production and proliferation of atheroprotective Tregs.[167,168] Accumulation of apolipoprotein B100 (ApoB100), LDLs, and ox-LDLs in the blood vessel wall attracts immune cells and gives rise to chronic inflammation. Loading DCs with ApoB100 and ox-LDL reduces production of non-inflammatory cytokines.[169] DCs may be useful in inducing tolerance against autoantigens in the walls of arteries and in creating new treatment methods for atherosclerosis by forming a cell population of $CD4^+$ $Foxp3^+$ Tregs. Tregs can inhibit atherosclerosis by secreting inhibitory cytokines, TGF-β and IL-10.[170] Overall, DCs may play a dual role in the disease.

3 | THE ROLE OF SPECIFIC IMMUNITY IN ATHEROSCLEROSIS

As mentioned above, atherosclerosis, characterized by inflammation, lipid accumulation, cell death, and fibrosis, is a chronic inflammatory disease, which causes arterial plaque. Identification of T cells in human atherosclerotic plaques has indicated the possible role of the specific immune system in the disease. Recently, a wide variety of researches have confirmed the role of specific immunity in atherosclerosis. In the following, we represented a summary regarding the role of specific immunity in atherosclerosis (Table 2).

3.1 | The role of T lymphocytes in atherosclerosis

T cells are a lymphocyte, derived from the thymus gland which play a pivotal role in the immune response. T cells can be discriminated from other lymphocytes by the presence of a T-cell receptor on cell surface.[171] APCs such as macrophages, DCs, and B cells trigger T lymphocyte responses. T cell activation begins with binding of TCR to the MHC molecule and binding of costimulatory molecules such as CD28 and CD40L.[172] T cells act as a source of inflammatory cytokines such as IL-6, IL-12, and TNF-α.

Ox-LDL is produced in the arterial wall by increased oxidative stress, and may activate T cells in atherosclerotic plaques. Specific T cells, induced against ox-LDL autoantigens, are formed over the process of atherosclerosis,[173] and the presence of these cells is essential for production of specific IgG autoantibodies against ox-LDL.[174,175] Moreover, transfer of these specific T cells can exacerbate atherosclerosis.[176] Therefore, immune responses by B and T cells play a major role in inflammation and formation of atherosclerotic plaques. The β2-glycoprotein I is another autoantigen involved in atherosclerosis. Indeed, β2-glycoprotein I is a phospholipid-binding protein found in the human atherosclerotic plaques.[177] Immunization of mice with defective low-density lipoprotein receptor (LDLR) has been found to accelerate the formation of atherosclerotic plaque.[178] Figure 3 shows the role of different resident T lymphocyte subsets in the atherosclerotic lesion site.

3.1.1 | $CD4^+$ T cell subsets in atherosclerosis

$CD4^+$ T cells have different subtypes, including Th1, Th2, Treg, Th9, Th22, Th17, and $CD28^{null}$ T cell. T helper cells, with high flexibility, are converted into different subsets of $CD4^+$ T cells depending on the environmental conditions.

The role of Th1 cells in atherosclerosis

Th cells have a vital role in adaptive immunity. Conversion of T lymphocytes into Th1 depends on neighboring inflammatory cytokines, those existing around T lymphocytes. IL-12 activates the signal transducer and activator of T-box transcription factor (TBX21) (or T-bet) and transcription-4 (STAT-4) transcription factors, which are necessary for the formation of Th1 cells. Th1 cells activate other cells of the immune system by secretion of different cytokines especially IFN-γ. Th1 cells are the most abundant population of T cells present in atherosclerotic plaques.[173,179] The absence of IFN-γ or IFN-γ receptors in mouse models suggests the decreased susceptibility of atherosclerosis.[180–182] Furthermore, injection of recombinant IFN-γ causes an

TABLE 2 The role of specific immune cells in atherosclerosis

Specific immune cells	Function during atherosclerosis	Atheroprotective or pro-atherogenic	Ref
T lymphocytes	• $CD4^+$ T cell	Pro-atherogenic	173,179,186–190
	• Th1 cells	Atheroprotective	201,203
	• The most abundant population of T cells present in atherosclerotic plaques	Has not been identified	211,212
	• Activate other cells of the immune system by secretion IFN-γ	Has not been identified	216,217
	• IFN-γ: prompts the formation of atherosclerotic plaques, formation of foam cells, and rupture of atherosclerotic plaques	Has not been identified	218,221
	• IFN-γ: decreasing concentrations of serum cholesterol, scavenger receptor A, suppression of LDLR-related protein, MMP9, CD36, and inhibition of lipoprotein lipases	Pro-atherogenic	217
	• Th2 cells	Pro-atherogenic	230,231
	• Produce IL-25, IL-4, IL-5, IL-9, and IL-13	Atheroprotective	249,250
	• Protective role against atherosclerosis because they suppress Th1 cells	Atheroprotective and pro-atherogenic	251,252,254
	• IL-4: activation of mast cells, apoptosis of SMCs, plaque rupture, increased protease production, and decreased collagen production		
	• IL-5: protective role in atherosclerosis		
	• Th17 cells		
	• Failure in signaling of IL-17 receptor (IL-17R: decrease in the size of atherosclerosis plaque and serum concentration of anti-oxLDL IgG antibodies		
	• IL-17 cytokine is related to lipid-rich, complicated, and unstable plaques		
	• Th9 cells		
	• Main source of IL-9		
	• Plasma level of IL-9 is higher in patients with atherosclerosis than healthy individuals		
	• Th22 cells		
	• The level of Th22 cells in the blood from patients with acute coronary syndrome was reported to increase compared with the healthy control group		
	• Plasma level of IL-22 is higher in patients with symptomatic atherosclerosis than those with asymptomatic atherosclerosis		
	• T^{FH} cells		
	• The pathway ICOS and its ligand (ICOSL) is vital for differentiation and sustaining of TFH cells		
	• It has been reported that blocking the ICOS-ICOSL signaling pathway: decreases the progression of atherosclerosis and leads to a reduction in the number of TFH cells		
	• $CD28^{null}$ T cells		
	• Patients with acute coronary syndrome have more TCD28null cells in their blood compared with healthy people, and their CD28null T cells are resistant against apoptosis		
	• Tregs		
	• TGF-β and IL-10 are two main cytokines of Treg cells which are responsible for many		

TABLE 2 (Continued)

Specific immune cells	Function during atherosclerosis	Atheroprotective or pro-atherogenic	Ref
	effects of Treg cells and have strong anti-atherogenic activities • Inhibit the activation of T cells and, subsequently, decrease the progression of atherosclerosis, can lead to differentiation of macrophages into the anti-inflammatory M2 phenotype, inhibit the formation of foam cells and differentiation of inflammatory M1 phenotype • $CD8^+$ T cells • In patients with CAD, the blood level of cytotoxin-producing $CD8^+$ T cells increases compared with healthy individuals • The cytotoxic activity of $CD8^+$ T cells, relative to lesion-stabilizing cells (e.g., VSMCs), and production of inflammatory cytokines by $CD8^+$ T cells may amplify inflammatory responses in atherosclerotic plaques • In contrast, the cytotoxic activity of $CD8^+$ T cells, relative to APCs, may limit the progression of atherosclerosis		
B lymphocytes	• B cells can be divided into two distinct categories, including **B1** and **B2** • B2 cells incorporate marginal zone B cells and follicular B cells, and B1 cells include B-1b and B1a cells • B cells, which help in formation of lymphoid follicles, can play a role in atherosclerosis • *Regulatory B cells* are a subset of B lymphocytes, producing IL-10 • IL-10: decreases the risk of atherosclerosis by exerting apoptosis, modulating lipid metabolism, and inhibiting production of pro-inflammatory mediators	Has not been identified	262,263,270
Other T lymphocytes	• NKT cells • Classified into two subgroups including • Invariant NKT (type I or iNKT) cells whose TCRs are not very variable • Type II NKT cells, which have highly variable TCRs • iNKT cells the only NKTs studied in atherosclerosis • The iNKT cells can activate immune cells in plaque, by secreting cytokines and promoting atherosclerosis development • γδ T cells • Moreover, a study accomplished on mice revealed that γδ T cells are a rich source of IL-17 and can regulate atherosclerosis by producing IL-17	Pro-atherogenic Has not been identified	272 281

increase in the size of atherosclerotic plaques.[183] Studies in mice with defective LDLR have shown that the formation of atherosclerotic plaques in the mice receiving bone marrow transplantation from donor mice with a failure in IFN-γ is more severe compared with those receiving from healthy donor mice.[184] In addition to

Th1 cells, IFN-γ is released by NKT cells, NK cells, macrophages, and muscle cells.[185] IFN-γ prompts the formation of atherosclerotic plaques through lipid uptake by macrophages and the formation of foam cells, attraction of macrophages and T cells, the increased expression of MHC-II, as well as increased activation of APC and release of Th1 cytokine.[186,187] Moreover, IFN-γ may cause rupture of atherosclerotic plaques by decreasing proliferation of SMCs, decreasing synthesis of collagen, and increasing production of extracellular matrix-degrading proteins.[188–190] IFN-γ may have an anti-atherosclerotic effect by decreasing concentrations of serum cholesterol, scavenger receptor A, suppression of LDLR-related protein, MMP9, CD36, and inhibition of lipoprotein lipases.[190] A disorder in transcription factor T-bet in mouse models has been shown to decrease the atherosclerosis severity.[191] Insufficiency of MHC class II-associated invariant chain (CD74) has been reported to cause a decrease in the activation of T cells and atherosclerosis in mice.[192] Interplay between the CD40L on activated T cells and the CD40 receptor on APCs results in initiation of inflammation.[193] Inhibition of the activation pathway of CD40-CD40L in mouse models has been suggested to have the potential to decrease the size of atherosclerotic plaques.[194–196] There are some studies demonstrating the role of IL-18 in atherosclerosis. IL-18 deficiency in mice can lead to a decrease in the activity of Th1 cells and size of atherosclerotic plaque.[197] IL-18, IFN-γ, and IL-12 are Th1 cell response-related cytokines, which can accelerate atherosclerosis, showing their important potential as appropriate targets for the treatment of atherosclerosis.

The role of Th2 cells in atherosclerosis

Th2 cells are implicated in allergic diseases (e.g., asthma and atopy), and their role in atherosclerosis depends on the stage and place of disease and release of cytokines. In addition, the role of Th2 cells in atherosclerosis has not been exactly determined, and its differentiation is initiated with IL-4. This cytokine can activate STAT6 and, subsequently, induce the GATA3 transcription factor. GATA3 can inhibit production of IFN-γ and increase production of IL-5 and IL-4. Th2 cells also produce IL-25, IL-5, IL-9, and IL-13, leading to the production of antibodies by B cells. In atherosclerosis-prone mice, the response of TH2 cells has been shown to have a protective role against development of early atherosclerotic plaques.[198] It seems that Th2 cells have a protective role against atherosclerosis because they suppress Th1 cells (having a pro-atherogenic role), while atherosclerosis severity has been found to decrease in IL-4$^{-/-}$ ApoE$^{-/-}$ mice.[199,200] IL-4 has pro-atherogenic effects, including activation of mast cells, apoptosis of SMCs, plaque rupture, increased protease production, and decreased collagen production.[201] Furthermore, it can stimulate elastase (MMP-12), that can damage arterial walls and increase the formation of the aneurysm.[202] The role of IL-13 in atherosclerosis has not been well understood, while IL-5 has an opposite effect in comparison with IL-4 and has a protective role in atherosclerosis. Receiving bone marrow transplantation from mice with a disorder in producing IL-5 has been reported to lead to plaque formation.[203] Anti-atherogenic characteristics of IL-5 may be due to the production of protective antibodies.[204] IL-33 is a member of IL1-family cytokine that also incorporates IL-18 and IL-1β. IL-33 was first identified to have a relationship with Th2 cell differentiation in 2005.[205] It has been declared that the injection of IL-33 to mice can elevate the concentration of Th2 cytokines in lymph nodes and serum as well as the production of atheroprotective IgM-type anti-oxLDL antibodies, leading to a decrease in the expansion of atherosclerotic plaque.[206] Accordingly, the increase in the Th2 cell response cannot be assumed as an appropriate method for the limitation of vascular inflammation and a decrease in the severity of atherosclerosis.

The role of Th17 cells in atherosclerosis

Th17 helper cells are a subtype of T helper cells which are different from Th2 and Th1 subtypes in terms of growth and development. Th17 cells have a special role in fighting against extracellular pathogens and fungal infections. Th17 cells are effective in defending against bacterial and fungal pathogens and produce IL-17.[207,208] TGF-β along with IL-4 causes the formation of Th9 but TGF-β along with IL-6 causes the formation of Th17. IL-6 activates the signal transducer and activator of transcription 3 (STAT3), which is necessary for the expression and function of retinoic acid-related orphan receptor gamma t (RORγt).[209] While unable to directly induce differentiation of Th17, TGF-β suppresses transcription factors needed for differentiation of Th1 and Th2. Production of both Th17 and Th9 subtypes is suppressed through induction of CD4^{+} Foxp3^{+} T cells, which have a protective role against atherosclerosis. Results from a study indicated that IL-17 is generated by T cells in human vessels and IL-17 along with IFN-γ results in an inflammatory response in VSMCs.[207] Th17 cells play a role in autoimmune diseases, but their role in atherosclerosis is not completely understood.[210] There are some studies performed on the role of IL-17 in atherosclerosis, showing that a failure in signaling of IL-17 receptor (IL-17R) in mice causes a decrease in the size of atherosclerosis plaque and serum concentration of anti-oxLDL IgG antibodies.[211] Erbel et al. in a study showed that mRNA expression of the IL-17 cytokine increases in symptomatic carotid plaques, unlike

asymptomatic plaques; they concluded that mRNA expression of the IL-17 cytokine is related to lipid-rich, complicated, and unstable plaques.[212] The nuclear receptor of ROR-γt is necessary for differentiation of Th0 to Th17.[213] Other crucial transcription factors for Th17 differentiation include Aryl hydrocarbon receptor, runt-related transcription factor 1 (RUNX1), STAT3, and ROR-α.[214,215] IL-23 and IL-21 are required for the maintenance and proliferation of Th17, respectively. IL-17A, IL-21, IL-22, and IL-17F are produced by Th17 cells. Both IL-4 and IFN-γ have been shown to suppress differentiation of Th17 in different mice models.[207]

The role of Th9 cells in atherosclerosis

Th9 cells are a subset of T cells, which are commonly along with the Th2 phenotype. These cells are the main source of IL-9. The IL-9 production in Th9 cells is induced by TGF-β and IL-4 and repressed by IFN-γ.[216] According to the study, the plasma level of IL-9 is higher in patients with atherosclerosis than healthy individuals. Other studies have shown that the IL-9 level is higher in human atherosclerotic plaques than vascular samples from healthy individuals.[217] Besides, other studies suggested that the plasma levels of IL-9 are raised in the patients with acute coronary syndrome compared with healthy individuals, although there are presently no reports about change in the amount of Th9 cells in the blood.[218] It is not yet known whether Th9 cells contribute to progression or inhibition of atherosclerosis.

The role of Th22 cells in atherosclerosis

Th22 cells have a unique property as they express IL-22 and the major transcription factor of the aryl hydrocarbon receptor, but not IL-17 and IFN-γ.[219] The cytokines responsible for stimulation and differentiation of Th22 cells are unknown.[220] In addition, it is not known whether Th22 cells have an anti-atherogenic or pro-atherogenic role. The level of Th22 cells in the blood from patients with acute coronary syndrome was reported to increase compared with the healthy control group.[218,221] Other studies revealed that the plasma level of IL-22 is higher in patients with symptomatic atherosclerosis than those with asymptomatic atherosclerosis.[218,221,222] Results from a study on the mice susceptible to atherosclerosis with IL-22 deficiency indicated that IL-22 decreases atherosclerosis by suppressing pro-atherogenic intestinal microbes.[223]

The role of TFH cells in atherosclerosis

T follicular helper (TFH) cells are a subset of CD4 T cells migrating to B-cell follicles after activating and promoting formation of germinal center and switching of B-cell isotype, which requires B cell lymphoma 6 (Bcl6) transcription factor.[224] Moreover, TFH cells are possible to have a pro-atherogenic profile. According to the evidence, atherogenic media increases autoimmune responses of CXCR3 $^{+}$ TFH cells in the mice susceptible to atherosclerosis.[225] Nevertheless, in mice fed a high-cholesterol diet, B cells of marginal zone repressed the TFH cell response, and thereby, limited progression of atherosclerosis.[226] Furthermore, in some mice, TFH cells having pro-atherogenic activity in germinal centers could be regulated by a subset of $CD8^{+}$ T cells that have a regulatory function.[227] The pathway related to inducible T cell co-stimulator (ICOS) and its ligand (ICOSL) is vital for differentiation and sustaining of TFH cells. It has been reported that blocking the ICOS-ICOSL signaling pathway in $Apoe^{-/-}$ mice decreases the progression of atherosclerosis and leads to a reduction in the number of TFH cells in secondary lymphoid organs.[228] Interestingly, TFH cells can be derived from Tregs. These cells have an pro-atherogenic profile and can increase the severity of atherosclerosis in mice. In the patients with CAD, the plasma level of IL-21 (the major cytokine in TFH) is negatively correlated with expression of forkhead box P3 (FOXP3) in Treg cells.[228]

The role of $CD28^{null}$ T cells in atherosclerosis

$CD4^{+}CD28^{null}$ T cells are characterized by the absence of CD28 expression that is the major costimulatory receptor for $CD4^{+}$ T cells. $CD28^{null}$ T cells have cytotoxic and inflammatory properties. Attractively, $CD28^{null}$ T cells are detected exclusively in the humans and non-human primates, but not in mice.[229] Patients with acute coronary syndrome have more $TCD28^{null}$ cells in their blood compared with healthy people, and their $CD28^{null}$ T cells are resistant against apoptosis.[230,231] Additionally, unstable plaques may develop by the effects of T cells, such as $CD28^{null}$ T cells. Besides, some of the $CD28^{null}$ T cell subsets react to HSP60 and HSP70, two proteins that are likely to be among atherosclerosis antigens.[232,233] Among the patients with end-stage renal disease, individuals with atherosclerosis have more $CD28^{null}$ cells than those without atherosclerosis.[234]

The role of Tregs in atherosclerosis

$CD4^{+}FoxP3^{+}$ regulatory T cells are a subtype of T cells which can repress immune system responses.[235] Indeed, Tregs are a subtype of T cells playing a role in inhibiting immune reactions, maintaining hemostasis, and inducing self-tolerance. Tregs are divided into two main subsets, including natural Tregs (nTregs) and induced Tregs (iTregs). The nTregs detect self-antigens, after being developed in the thymus. These cells are also recognized by expression of CD4, CD25 surficial receptors (a subunit of IL-2 receptor), and FOXP3 transcription factor.[236] The iTregs are derived from nTregs, in the presence of IL-10. Those iTregs formed by IL-10 are known as TR1.[237] It has

been indicated that transmission of $CD4^+CD25^+$ T or TR1 cells can lead to a decrease in the expansion of atherosclerotic plaque in mouse models.[238–240] those iTregs, stimulated by TGF-β are known as Th3 cells.[241] The mechanism related to suppression of immune system is developed through the activity by Treg cells.[235] TGF-β and IL-10 are two main cytokines of Treg cells which are responsible for many effects of Treg cells and have strong anti-atherogenic activities. Inactivation of TGF-β or using neutralizing antibodies has been shown to accelerate the development of plaque and vascular inflammation in mouse models of atherosclerosis.[242–244] The presence of Tregs in atherosclerosis was shown first by the immunohistochemistry method and following in the aorta of mice using polymerase chain reaction (PCR) technique.[245,246] There is no evidence demonstrating that the presence of Treg cells has a direct role in the development of the disease. Chemokines play a role in recruitment of $CD4^+FoxP3^+$ regulatory T cells. There are documents showing that the size of atherosclerotic plaque is smaller in $CXCL10^{-/-}ApoE^{-/-}$ and $CXC3^{-/-}ApoE^{-/-}$ mice, where there is a less number of T cells and infiltrated macrophages, and an increased number of $CD4^+FoxP3^+$ regulatory T cells.[246,247] Furthermore, some studies conducted on mouse models revealed that the elimination of Tregs by anti-CD25 antibodies elevates the size of atherosclerotic plaque.[239] Tolerance against potential antigens in atherosclerotic plaque has an indispensable role and, according to our knowledge, Tregs play a critical role in creating tolerance. There is evidence showing that mice with a low number of Tregs in spleen suffer from systemic tolerance defect compared with non-atherosclerotic mice.[238,248] Although they can inhibit the activation of T cells and, subsequently, decrease the progression of atherosclerosis, Tregs are likely to form remarkable protection against atherosclerosis by targeting APCs. Tregs can lead to differentiation of macrophages into the anti-inflammatory M2 phenotype as well as inhibit the formation of foam cells in vitro and differentiation of inflammatory M1 phenotype.[249,250]

3.1.2 | The role of $CD8^+$ T cells in atherosclerosis

$CD8^+$ T cells identify antigen peptides presented by MHC class I. These cells can create cytotoxic T cells that have the ability to kill virus-infected cells and other abnormal cells (e.g., cancerous cells) using various cytotoxic pathways. In patients with CAD, the blood level of cytotoxin-producing $CD8^+$ T cells increases compared with healthy individuals, and $CD8^+$ T cells in atherosclerotic plaques are plentiful in the humans and mice.[251,252] In advanced stages of human atherosclerosis, the number of $CD8^+$ T cells is higher than $CD4^+$ T cells, which are principally found in the fibrous cap regions.[252,253] In the majority of studies related to atherosclerosis, similar to $CD4^+$ T cells, the specific antigen of $CD8^+$ T cells associated with atherosclerosis plaque is unknown. Experimental researches highlighted both atheroprotective and pro-atherogenic roles of $CD8^+$ T cells.[254] The cytotoxic activity of $CD8^+$ T cells, relative to lesion-stabilizing cells (e.g., VSMCs), and production of inflammatory cytokines by $CD8^+$ T cells may amplify inflammatory responses in atherosclerotic plaques and intensify the progression and instability of lesion. In contrast, the cytotoxic activity of $CD8^+$ T cells, relative to APCs, may limit the progression of atherosclerosis. MHC class I-dependent cytotoxic $CD8^+$ T cells contribute to creating inflammation in atherosclerotic plaques and necrotic nuclei.[254] Furthermore, a decrease in the number of $CD8^+$ T cells by antibodies was found to decrease the severity of atherosclerosis in mice, showing the pro-atherogenic role of $CD8^+$ T cells.[255,256] In these cells, the production of granzyme B and IFN-γ is higher than $CD8^+$ T cells in non-atherosclerotic mice.[256] Results from a study on $Ldlr^{-/-}$ mice fed with high-fat diets revealed that $CD8^+$ T cells develop atherosclerosis by regulating the level of peripheral monocytes, through production of IFN-γ.[255] However, findings from another study revealed that IFN-γ produced by $CD8^+$ T cells has no role in atherosclerosis in $Apoe^{-/-}$ mice fed with high-fat diet.[257] A number of experimental researches manifested that $CD8^+$ T cells can play an atheroprotective role. Some studies demonstrated regulatory functions of $CD8^+$ T cells in atherosclerosis. In the $Apoe^{-/-}$ mice, $CD8^+$ T cells were found to exert their atheroprotective effects by ApoB-related peptide (p210).[258] In the Apoe-deficient mice, a subset of $CD8^+$ T cells, called $CD8^+$ Treg, was reported to decrease the severity of atherosclerosis and potentially atherogenic IgGs by blocking the ICOS-ICOSL signaling among B cells and TFH cells of germinal centers.[227]

3.2 | The role of B lymphocytes in atherosclerosis

B cells (B lymphocytes) are a type of white blood cells in the lymphocyte subtype, which play a vital role in the humoral immunity component of the adaptive immune system by secreting antibodies. Moreover, B cells present antigens, which are categorized as professional APCs, and secrete cytokines.[259] B cells can be divided into two distinct categories, including B1 and B2. B1 cells account for a minute percentage of B lymphocytes and are derived from the committed precursors of fetus or infant. Actually, B1 and B2 cells are predominant in fetus and adults,

respectively. B2 cells incorporate marginal zone B cells and follicular B cells, and B1 cells include B-1b and B-1a cells. B1 cells cooperate in innate immunity by producing normal IgM antibodies. B2 cells are the principal population of B cells produced in the bone marrow. After activation by specific antigens, B2 cells produce IgG antibodies and differentiate into plasma cells. Other functions of B2 cells include cytokine production, organization of lymphoid tissues, and antigen presentation.[260,261] B cells are detected in atherosclerotic plaques in humans and mice. B cells, which help in formation of lymphoid follicles, can play a role in atherosclerosis.[262,263] IgG and IgM antibodies are present in atherosclerotic plaques at all stages of disease progression.[264] Specific antibodies against ox-LDL were observed in humans and mice.[265] In the mice, the anti-oxLDL IgM antibody was demonstrated to provide protection against atherosclerosis, showing that humoral and B cell immunity has anti-atherogenic properties.[266] It has been reported that the administration of IgG1 antibodies against ox-LDL epitopes in Apoe$^{-/-}$ mice decreases the severity of atherosclerosis.[267] Moreover, bone marrow transplantation from B cell-defective mice to Ldlr$^{-/-}$ mice (compared towith bone marrow transplantation from healthy mice) was shown to increase the severity of atherosclerosis, which indicates the important role of B cells in the development of atherosclerosis.[268] Regulatory B cells are a subset of B lymphocytes, producing IL-10, and are considered as regulatory cells.[269] Breg cells seem to play an atheroprotective role. The incidence of atherosclerosis in null mice for IL-10 has been found to be significantly higher than the control group.[244] IL-10 decreases the risk of atherosclerosis by exerting apoptosis, modulating lipid metabolism, and inhibiting production of pro-inflammatory mediators.[270] Breg cells express Fas ligand, actually inducing apoptosis in target cells, presumably representing an essential mechanism for suppressing pro-inflammatory immune responses in atherosclerotic plaque.[270,271] Surface markers of Breg cells have not been fully identified, so their role in atherosclerosis is unclear yet.

TABLE 3 Clinical trials of inflammation modulation in atherosclerotic cardiovascular disease

Agent	Pathway/target	Clinical trial (ref. #)
Succinobulol	Oxidized LDL	ARISE[282]
BI-204 (MLDL1278A)	oxLDL antibody	GLACIER[283]
Inclacumab	P-selectin	SELECT-ACS[284]
Inclacumab	P-selectin	SELECT-CABG[285]
Colchicine	Neutrophil mobility	LoDoCo[286]
Colchicine	Neutrophil mobility	ColCot
Anakinra	IL-1RI	IL-HEART[287]
Canakinumab	IL-1β	CANTOS[288]
Etanercept	TNF-α	ENTRACTE
Tocilizumab	IL-6	ENTRACTE
Methotrexate	IL-6, TNF	CIRT
Verespladib	sPLA2	VISTA-16[289]
Darapladib	LpPLA2	STABILITY[290]
Darapladib	LpPLA2	SOLID-TIMI 52[291]
Atreleuton	5-LO inhibitor	1. FRANCIS[292] 2. VISTA-16[293]
Veliflapon	FLAP inhibitor	Hakonarson et al.[294]
Losmapimod	p38 MAPK inhibitor	1. Elkhawad et al.[295] 2. SOLSTICE[296] 3. LATITUDE-TIMI[297]

Abbreviations: 5-LO, 5-lipoxygenase; FLAP, 5-lipoxygenase activating protein; IL, interleukin; LDL, low-density lipoprotein; LpPLA2, lipoprotein-associated phospholipase A2; oxLD, oxidized low-density lipoprotein; p38 MAPK, p38 mitogen-activated protein kinase; sPLA2, secretory phospholipase A2; TNF, tumor necrosis factor.

4 | OTHER T LYMPHOCYTES IN ATHEROSCLEROSIS

4.1 | The role of natural killer T (NKT) cells in atherosclerosis

Natural killer T (NKT) cells are classified into two subgroups including invariant NKT (type I or iNKT) cells whose TCRs are not very variable, and type II NKT cells, which have highly variable TCRs. To date, iNKT cells the only NKTs studied in atherosclerosis. The iNKT cells can be activated by TCR interplay with antigens presented by CD1d molecules, which include antigen glycolipids presented in APCs.[272] Some glycolipids have a microbial origin.[273] The iNKT cells, similar to CD8$^+$ T cells, can express cytotoxic proteins such as granzyme and perforin.[274] Most researches performed on mice indicated that iNKT cells play a pro-atherogenic role.[275] The iNKT cells can activate immune cells in plaque, by secreting cytokines and promoting atherosclerosis development.

4.2 | The role of γδ T cells in atherosclerosis

γδ T cells, unlike αβ T cells, fail to identify specific antigens.[276] There are a few studies conducted on mice about

γδ T cells in atherosclerosis.[277–279] Results from the first study conducted in 1993 showed the presence of γδ T cells in human atherosclerotic plaque.[280] Interestingly, the amount of intracellular cholesterol in γδ T cells regulates their function activation, and proliferation.[277] Moreover, a study accomplished on mice revealed that γδ T cells are a rich source of IL-17 and can regulate atherosclerosis by producing IL-17.[281] According to the documents, progress of early atherosclerosis in $Apoe^{-/-}$ mice, whose γδ T cells are genetically defective, is similar to $Apoe^{-/-}$ mice γδ having T cells.[278] To date, the definite role of this T cell subset has not been determined in atherosclerosis.

5 | CONCLUSION

The present review was conducted to investigate how immune system cells influence atherosclerosis. Studies demonstrated that LDLs stimulate specific and innate immunity in atherosclerosis. Atherosclerosis is exacerbated by pro-inflammatory responses mediated by immune cells. However, some cells, such as M2 macrophages, tolerogenic DCs, Bregs, and Tregs reduce inflammatory activity of the immune system in atherosclerotic lesions. Therefore, these regulatory factors can be useful in the treatment and production of therapeutic agents for atherosclerosis. Interestingly, increasing the population of atheroprotective cells such as Tregs can be considered as a treatment for atherosclerosis. For example, inducing IL-2, a key cytokine for Treg differentiation and proliferation, can increase Tregs population and prevent atherosclerosis development. The function of a number of immune cells, including Th2 cells, Th17 cells, $CD8^+$ T cells, and some subtypes of DCs, is still unknown in atherosclerosis because both protective and pro-atherogenic functions have been observed. Therefore, there is a need for further studies to determine the function of such cells in human atherosclerosis and to develop therapies stimulating their protective functions. Another suggested treatment includes stimulating the production of antibodies against LDL or oxLDL-related antigens, which can help inhibit inflammation. Various clinical trials demonstrated the importance of inflammation as a goal for future treatments to decrease the severity of atherosclerosis (Table 3). Nevertheless, the potential risks of anti-inflammatory treatment, such as infection and cancer cannot be ignored.

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CONFLICT OF INTEREST

The authors declared that they have no conflicts of interest.

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