Review Article

Interventional Cardiology

Significance of the adaptive immune response in the progression of atherosclerosis

Abstract

Atherosclerosis is a chronic inflammatory disease of the arterial wall and a major cause of cardiovascular disease. Approaches including *in vivo* imaging, cell line tracing and knockout studies in mice, as well as clinical intervention studies and advanced mRNA sequencing techniques have drawn attention to the role of T-cells and B-cells as critical factors and modifiers in the pathogenesis of atherosclerosis. $CD4^+$ T-cells are commonly found in atherosclerotic plaques. A large body of evidence indicates that T-helper cells 1 (Th-1) play a pro-atherogenic role and regulatory T-cells (T-reg) play an anti-atherogenic role. However, T-reg cells in some conditions can become proatherogenic. The role in atherosclerosis of other Th subsets of cells, such as Th-2, Th-17, follicular helper T-cells, as well as $CD8^+$ T-cells and γδ T-cells, is less understood. B-cells perform both atheroprotective and proatherogenic functions. While B1 cells and marginal zone B-cells are considered protective against atherosclerosis, follicular B-cells and innate response activator B-cells have been shown to promote atherosclerosis.

Keywords: Atherosclerosis; T-cells; B-cells; Immune response

Introduction

Atherosclerosis is a chronic vascular disease characterized by endothelial dysfunction due to the deposition and accumulation of lipoproteins (e.g., Low-Density Lipoprotein (LDL) in the intima of the arteries. Plaque rupture and subsequent arterial occlusion can lead to myocardial infarction and stroke, which are the leading causes of death worldwide. Inflammatory pathways with the recruitment and activation of several types of immune cells and the release of soluble mediators are involved in the initiation and progression of atherosclerosis [1]. Cells of the innate immune system, primarily macrophages, can take up modified oxidized LDL and transform into foam cells with the formation of fatty streaks ("early plaques") [2]. Further accumulation of lipids and infiltration of leukocytes into the formed atherosclerotic plaques create a central area with a collagen-rich fibrous cap formed by vascular smooth muscle cells [2]. Plaques can be divided into two broad categories: Stable and unstable. Stable plaques are characterized by a small lipid core, few inflammatory immune cells, and a thick fibrous membrane. Unstable plaques often have a very large lipid core, a thin fibrous membrane, and hemorrhage within the plaque [2].

Cells of the innate and adaptive immune systems are present in different layers (intima, environment, and adventitia) of arterial walls throughout the development of atherosclerotic plaques in mice and humans [3]. Studies using gene knockout mice have allowed a detailed analysis of immune cells involved in atherogenesis, while studies in humans are more limited [4]. However, it is important to emphasize that various genetic and environmental factors affect atherogenesis in mice and humans. It is well known that various subpopulations of monocytes and macrophages play a crucial role

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in the formation of atherosclerotic plaques and disease progression [5]. In this review, we will summarize the role of adaptive immune cells in human atherosclerotic plaques, which will expand our understanding of the pathogenesis of atherosclerosis.

Literature Review

CD4⁺ T-lymphocytes in atherosclerosis

Important adaptive immune response controllers, CD4⁺ T lymphocytes can develop into many T helper cell or T regulatory cell subtypes (T-reg). Th and T-reg cells can direct pro-inflammatory or anti-inflammatory effects on cells in tissues, trigger or repress the response of other immune cells, assist B-cells in the production of high-affinity IgG antibodies, or engage in cytolytic activity [6]. Hence, CD4⁺ T-lymphocytes have a variety of roles in atherosclerosis. Each CD4⁺ T-cell subpopulation has unique transcriptional patterns and cytokine release patterns that can either hasten or slow down atherosclerosis. According to this study, patients with recent strokes have plaques that are more abundant in CD4⁺ effector T-cells than patients with asymptomatic atherosclerosis. Depletion of CD4⁺ T-lymphocytes in mice either by genetics or antibodies prevents the development of atherosclerotic plaques [7]. Th1, Th2, and Th17 cells are three functionally separate subgroups of affected CD4⁺ T-cells. Individual cell analysis of human atherosclerotic plaques and peripheral blood mononuclear cells revealed that Th1 and Th2 cells make up the majority of CD4⁺ T-cells in plaques [6].

Th1 lymphocytes: Th1 lymphocytes express the transcription determining factor T-bet, chemokine receptors such as CXCR3 and CCR5, and secrete interferon-γ. Several experimental studies have shown that Th1 lymphocytes contribute to athero-sclerosis and are the most prominent subpopulation of T lymphocytes in plaques. In atherosclerotic Apoe -/- mice, Th1 lymphocytes express the chemokine 5 receptor of the atherosclerotic plaque receptor CC motif (CCR5) in the lymph nodes [8]. CyTOF and CITE-seq data for human atherosclerotic plaques show that CCR5 expression is upregulated in plaque-derived T-cells. In addition, Th1 cells are more abundant in the plaques of patients with recent stroke compared with patients with asymptomatic atherosclerosis [6]. Th1 cells from mouse atherosclerotic lesions secrete IFNγ and express the T-box transcription factor TBX21 (also known as T-bet) (nine). Inflammatory cytokines in addition to IFNγ, such as IL-2, IL-3, Tumor Necrosis Factor (TNF), and lymphotoxin, which can activate macrophages, T-cells, and other plaque cells, accelerate the inflammatory response. Deficiency of IFNγ, its receptor, or T-bet protects mice from atherosclerosis [9]. Therefore, the introduction of IFNγ in Apoe mice -/- increased atherosclerosis compared to untreated mice. IFNγ can directly reduce plaque stability by inhibiting proliferation of Vascular Smooth Muscle Cells (VSMCs), influencing macrophage polarization and modulating cardiovascular risk factors [10]. Some studies have shown that IFNγ induces the proliferation of GMCS, which can stabilize the plaque. In one study, IFNγ-deficient bone marrow cells were transplanted into Ldlr -/- mice and this resulted in greater atherosclerotic lesions compared to control mice [6].

Th2 lymphocytes: Th2 cells have a role in the immune system's defence against allergies, asthma, and other parasitic disorders. IL-4 is the major cytokine produced by Th2 cells. The transcription factor GATA3, a key regulator of Th2 differentiation, is expressed as a result of IL-4 binding to the T-cell receptor and activating signal transducer and transcription activator 6. A sizable number of T-cells in mouse atherosclerotic plaques exhibit transcripts for Th2-associated cytokines such IL-4, IL-5, IL-10, and IL-13 [11]. It is not yet apparent whether Th2 cells promote atherosclerosis or guard against it. According to the common carotid intima thickness test, those with high Th2 cell counts have lower preclinical atherosclerosis loads than people with low Th2 cell counts. Moreover, there is a negative correlation between the release of IL-4 from active mononuclear leukocytes and clinical atherosclerosis [12].

Uncertainty surrounds IL-4's contribution to atherosclerosis progression. In Apoe mice, IL-4 has been demonstrated to counteract Th1 responses and lessen the development of atherosclerotic plaques. IL-4 depletion had an atheroprotective impact in mice Ldlr -/- fed a high-fat diet, according to earlier findings [6]. Exogenous IL-4 was ad-ministered, but it had no effect on atherosclerosis in Apoe/animals with angiotensin II-induced atherosclerosis. Apoe/mice given a high-fat diet were immunised with ApoB peptide, which enhanced IL-4 expression in T-cells, but had little effect on the mice's atherosclerotic lesions [13].

Most research indicates that other Th2 associated cytokines, like IL-5 and IL-13, are athero-protective in contrast to IL-4. Although plasma IL-5 levels in people are negatively correlated with carotid intima thickness, increased plasma IL-5 levels are linked to myocardial infarction and unstable angina [14]. The vaccination of mice when compared to non-immunized mice, Ldlr -/- modified LDL induces an immune response that is characterised by antigen-specific production of IL-5 and IL-13 with negligible quantities of IL-4 and IFN. This immune response has an atheroprotective impact. In comparison to mice treated with phosphate buffered saline, the administration of IL-13 to Ldlr -/- mice fed a high-fat diet modulates established atherosclerotic lesions by increasing collagen content in the lesions and decreasing the expression of vascular cell adhesion molecule 1. This results in a reduction in macrophage infiltration into Plaques (PBS) [15]. In Apoe/mice fed a high-fat diet, IL-33 therapy prevented the development of atherosclerosis while increasing IL-4, IL-5, and IL-13 levels and

decreasing IFN levels in the serum and lymph nodes in comparison to mice treated with PBS. IL-33 preferentially stimulates Th2 cytokine production. In contrast, mice lacking the IL-33 or ST2 receptor did not differ from control mice in the progression of atherosclerosis [16]. It should be emphasised that congenital lymphoid cells of subtype 2 also produce IL-4, IL-5, and IL-13 (ILC2) [17]. In Ldlr -/- mice given a high-fat diet, genetically eliminating ILC2 sped up the development of atherosclerosis, which was then reversed by reintroducing wild-type ILC2 but not IL-5 or IL-13 deficient ILC2. The function of IL-5 and IL-13 produced by T-cells is still being investigated. To discriminate between the impact of cytokines produced by Th2 and ILC2 cells on atherosclerosis, particular T-cell deficient mice are required [18].

Th17 lymphocytes: Th17 lymphocytes are characterized by the expression of the nuclear receptor RORγt (RORC), which determines the transcription factor Th17. Th17 cells have excellent plasticity in various inflammatory processes [19]. In immune, endothelial, and stromal cells, IL-17 induces the secretion of pro-inflammatory cytokines IL-6 (granulo-cyte-colony-stimulating factor) and granulocyte-macrophage colony-stimulating factor, as well as chemokines [20]. In contrast, IL-6 and TGFβ induce a subtype of Th17 cells that produce IL-10 concurrently with IL-17 and are atheroprotective. Moreover, IL-17 is also produced by γδ T-cells and ILC3 cells. Because of this complexity, experimental studies on the role of IL-17 in Apoe -/- mice have yielded conflicting results; Some studies suggest that IL-17A is proatrogenic, others atheroprotective, but there are also studies that suggest that IL-17 does not affect atherosclerosis [21]. IL-17a -/- Apoe -/- mice and I L-17ra -/- Apoe -/- mice fed a diet rich in fats had less atherosclerotic plaques in the aortic arch and aortic roots, but a similar number of plaques in the thoracoabdominal aorta compared to Apoe -/- mice [22]. In contrast, *in vivo* administration of IL-17A reduces the amount of plaque in aortic roots in Ldlr -/- mice compared to control mice. Moreover, some studies in mouse models of atherosclerosis suggest that IL-17 may contribute to plaque stability by increasing the production of type I collagen [23].

Some clinical studies have shown that plasma levels of IL-17 and peripheral Th17 cells are elevated in patients with unstable angina or acute myocardial infarction compared to healthy patients. However, in larger clinical trials, plasma levels of IL-17 were similar in individuals with and without coronary artery disease, and low serum levels of IL-17 were associated with a higher risk of cardiovascular events in patients with acute myocardial infarction [24]. In human atherosclerosis, IL-17 is produced simultaneously with IFNγ T-cells that infiltrate coronary artery plaques, and IL-17 and IFNγ synergistically enhance pro-inflammatory responses of SMCs. In contrast, according to some experimental studies, IL-17 expression in human carotid atherosclerotic plaques has been associated with a stable plaque phenotype, with lower macrophage content and higher GMCS content [6]. The main cytokines produced by CD 4⁺ T-lymphocytes are indicated in Figure 1.

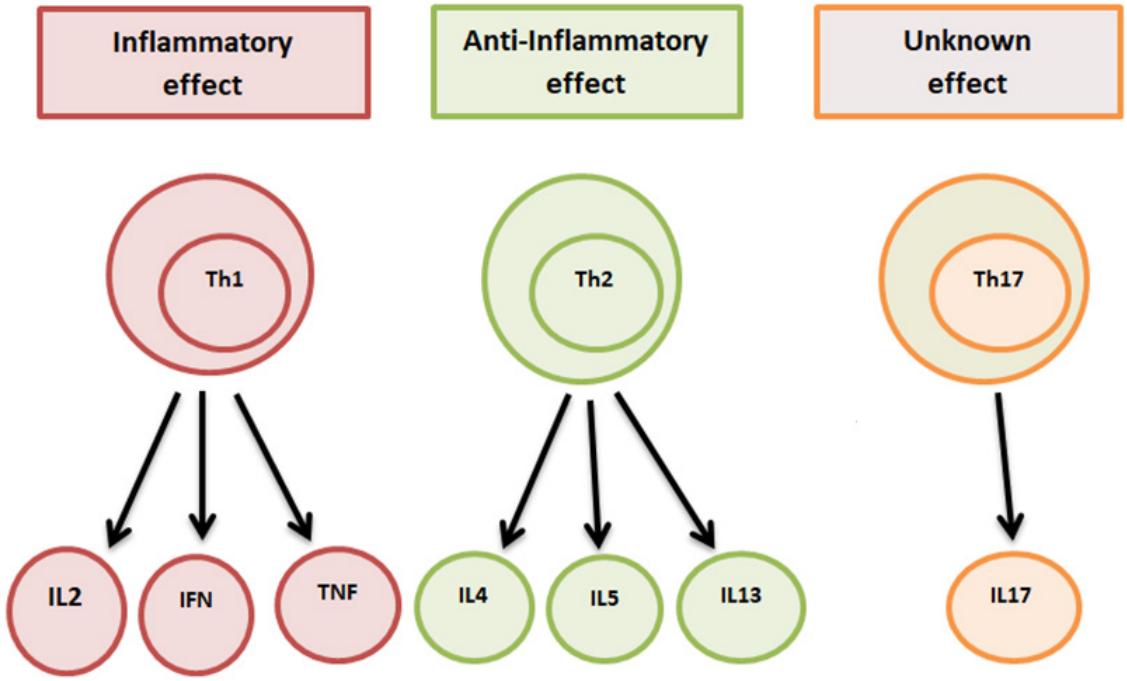

Figure 1: Main cytokines produced by CD 4⁺ T-lymphocytes.

CD8⁺ T-lymphocytes in atherosclerosis

Class I major histocompatibility complex antigenic peptides are recognised by CD8⁺ T-cells (MHC-I). They can develop into cytotoxic T-cells, which have the ability to use a variety of cytotoxic pathways to destroy cancerous cells as well as virus-infected and other aberran T-cells. Contrary to healthy individuals, coronary artery disease patients have higher blood levels of cytotoxin producing CD8⁺ T-cells, and CD8⁺ T-cells are prevalent in both human and mouse atherosclerotic plaques [25]. A higher percentage of CD8⁺ T-cells than CD4⁺ T-cells are seen in areas with fibrous caps in human atherosclerotic lesions that are progressing [26]. A subgroup of CD8⁺ T-cells with frequencies that associated with TCR clonality were found in human atherosclerotic plaques after T-Cell Receptor (TCR) sequencing, indicating clonal proliferation in the plaques. However, similar to CD4⁺ T-cells, the antigenic specificity of plaque CD8⁺ T-cells is unknown in the majority of atherosclerosis research [6].

CD8⁺ T lymphocytes have been found to play both a proatherogenic and an atheroprotective role in experimental trials. Inflammatory cytokines produced by CD8⁺ T-cells and the cytotoxic activity of CD8⁺ T-cells against lesion stabilizing cells like GMCS might increase inflammatory responses in atherosclerotic plaques and lead to the growth and instability of lesions. On the other hand, atherosclerosis might be prevented by CD8⁺ T-cells cytotoxic action against Antigen Presenting Cells (APCs). It has been hypothesised that MHC class I-dependent cytotoxic CD8⁺ T lymphocytes encourage plaque inflammation and necrotic core buildup. In one investigation, Apoe -/- mice with CD8⁺ T-cells reactive to ApoB were found [27]. In mice, atherosclerosis was reduced when CD8⁺ T-cells were removed with antibodies, indicating that CD8⁺ T-cells may be proatherogenic. Compared to CD8 T-cells from animals without atherosclerosis, these pathogenic CD8⁺ T-cells produce more IFN [28]. A study in Ldlr -/- mice fed a high-fat diet revealed that CD8⁺ T-cells influence peripheral monocyte numbers and monopolists through the generation of IFN, which in turn promotes atherosclerosis [29]. Another study, however, found that athero-sclerosis did not develop in Apoe -/- mice fed a high-fat diet as a result of IFN produced by CD8⁺ T-cells. In this mouse model, a study of the adoptive transfer of CD8⁺ T-cells deficient in perforin, granzyme B, TNF, or IFNγ into lymphopenic Apoe -/- mice showed that CD8⁺ T-cells contribute to the development of atherosclerotic plaques through perforin-mediated and granzyme-B-mediated apoptosis of macrophages, GMCS and endothelial cells, followed by increased inflammation caused by the secretion of TNF. It should be noted that most CD8⁺ T-cells in these investigations on adoptive transfer are probably not specific for atherosclerotic antigens [30].

It has been suggested by other experimental research that CD8⁺ T-lymphocytes may also have an atheroprotective effect. In vaccination investigations, CD8⁺ T-lymphocytes with regulatory roles in atherosclerosis have been assessed. The athero-protective effects of vaccination with ApoB-related peptide (p210) in Apoe/ mice are mediated by CD8⁺ T-lymphocytes. Comparatively to the transfer of CD8⁺ T-cells from control mice, adaptive transfer of CD8⁺ T-cells from mice vaccinated with p210 reduced atherosclerosis in Apoe/animals. When compared to animals injected with PBS, p210 vaccination decreased the amount of dendritic cells at the immunisation site, in atherosclerotic plaques, and in plaque macrophages as well as their immunoreactivity [31].

Regulatory T-cells in atherosclerosis

It has been suggested by other experimental research that CD8⁺ T-lymphocytes may also have an atheroprotective effect. CD8⁺ T-cells that have regulatory roles in the expression of the transcription factor fork-head box protein P3, the IL-2 receptor subunit (also known as CD25), and CTLA4 in humans, as well as the absence of CD127 expression, define the traditional subgroup of T-reg cells. While FOXP3 is momentarily produced by CD4⁺ T-cells during activation, it should be highlighted that FOXP3 is a reliable marker of T-reg cells in mice but is not a reliable marker of human T-reg cells. T-reg cells defend against atherosclerosis in mice [32]. Clinical evidence also points to a strong adverse association between T-reg and atherosclerosis, with myocardial infarction patients having lower levels of T-reg cells and IL-10, a cytokine generated by T-reg, than patients with stable angina or healthy people [33].

As in other T-cells, the activity of T-reg cells is increased when their TCR binds their cognate antigenic peptides represented by class II MHC molecules. However, as with other subsets of T-cells, in atherosclerosis studies, the anti-genic specificity of T-cells is generally unknown. When stimulated, T-reg cells can produce high levels of IL-10 and TGFβ. IL-10 is an anti-inflammatory cytokine whose deficiency exacerbates atherosclerosis in mice; it should be noted that the source of IL-10 was not identified in this early study. TGFβ has a plaque stabilizing effect in Apoe -/- mice [6]. Treg cells exert their atheroprotective properties by secreting IL-10 and TGFβ and by suppressing the proliferation of proinflammatory effector T-cells [34]. The atheroprotective effects of IL-2 complex treatment and anti-CD3 treatment in atheroprone mice were associated with an increase in the number of T-reg cells.

The FOXP3 splice variant controls some effector functions of T-reg cells and is associated with the stability of human atherosclerotic plaques [35]. A study in Apoe -/- mice deficient in MHC class II showed that the lack of antigen presentation on MHC class II molecules exacerbates atherosclerosis by reducing the number of T-reg cells. In patients with subclinical atherosclerosis, the number of T-reg cells in the blood is positively correlated with

plasma LDL levels [36]. Similarly, in mice, hypercholesterolemia initially promotes T-reg cell differentiation, followed by increased TCR signaling events, an effect that may be a response to increased inflammation, intracellular lipid accumulation in cells, or an antigen-specific response [37]. These data suggest that a subpopulation of T-reg cells is responsive to antigens associated with elevated plasma LDL levels or to components of LDL particles. Such LDL-reactive or ApoB-reactive T-reg cells have TCRs that specifically respond to atherosclerosis antigens. One class of antigens associated with atherosclerosis is ApoB peptides. The existence of T-cells reactive with the ApoB peptide has been shown in humans and mice using human and mouse MHC class II tetramers loaded with a sequence identical to the human and mouse ApoB peptide [38].

Other types of T-lymphocytes in atherosclerosis

Natural killer T-cells: Natural Killer T-cells (NKT) are divided into two subgroups: Invariant NKT-cells (iNKT) (or type I), which have few TCR variants, and type II NKT-cells, which have more variable TCRs. So far, only iNKT-cells have been studied in atherosclerosis. iNKT-cells can be activated by interaction of the TCR with antigen-presenting CD1d molecules containing antigenic glycolipids present on APCs [39]. Some glycolipids are of microbial origin, and some are intrinsic glycolipids [40]. Activation of iNKT-cells leads to a rapid release of cytokines Th-1, Th-2 and Th-17, depending on the expression of the same transcription factors that determine the corresponding subtypes of T h cells: T-bet, GATA3 and RORγt, respectively [41]. Like $CD8^+$ T-cells, iNKT-cells can also express the cytotoxic proteins perforin and granzyme B. Most studies using Apoe -/- mice and Ldlr -/- mice suggest that iNKT-cells are proatherogenic. iNKT-cells are thought to contribute to atherosclerosis by secreting cytokines that can activate other immune cells present in an atherosclerotic lesion [41].

γδ T-cells: Unlike αβ T-cells γδ T-cells do not recognize specific antigens [42]. Only a few studies of γδ T-cells in atherosclerosis in mice have been published since the presence of γδ was reported in 1993 T-cells in human atherosclerotic lesions. γδ T-cells are among the T-cell subpopulations described in atherosclerotic lesions in mice [43]. Interestingly, the content of intracellular cholesterol in γδ T-cells regulates their activation, proliferation, and effector functions [44]. In addition, γδ T-cells are an abundant source of IL-17 in mice and may modulate atherosclerosis through IL-17 production. However, Apoe -/- mice genetically deficient in γδ T-cells showed similar early development of atherosclerosis as Apoe -/- mice with γδ T-cells [45]. To date, the exact role of this subgroup of T-cells in atherosclerosis is unclear.

B-lymphocytes in atherosclerosis

B-cells are a heterogeneous group of cells that either originate in the bone marrow or arise during embryonic development. B1-B-cells, which can be phenotypically and functionally divided into B1a and B1B-cells, are predominantly derived from precursors found in the fetal liver, while B2-B-cells are derived from bone marrow precursors [46]. These B2 cells further differentiate into Follicular B-cells (FO) and Marginal Zone B-cells (MZ). Other less studied subsets of B-cells include Innate Response Activator (IRA) B-cells and regulatory B-cells (Breg). In the context of atherosclerosis, it is well known that the role of B-cells is subset specific: IRA and FO B-cells promote atherogenesis, while B1 and MZ B-cells protect against atherogenesis [47].

B-1 lymphocytes: B1-lymphocytes are self-renewing B-cells, which are mainly localized in the abdominal and pleural cavities, where they make a significant contribution to the natural level of IgM in plasma [46]. There are two subgroups of B1 B-cells based on the expression of CD5 expression: $CD5^+$ B1a cells and CD5-B1B-cells. B1a B-cells spontaneously produce IgM in T-Independent (TI) responses, while B1B-cells can participate in both TI and T-cell dependent responses, and T-cell-dependent responses provide a long-term memory of IgM to various pathogens. Interestingly, B1B-cells can also exhibit IgA isotype switching and have a relatively high somatic mutation rate in IgA-associated heavy chain variable regions [47]. B1a and B1b B-cells have an atheroprotective effect mainly through the production of IgM-Abs, which can bind to an Oxidation-Specific Epitope (OSE) in LDL, apoptotic cells, or cell wall polysaccharides of pathogens such as Streptococcus pneumonia. Studies have shown that a decrease in the number of B1a cells exacerbates atherosclerosis, while adoptive transfer of B1a or B1B-cells reduces atherogenesis [48]. Mechanically, B-cells expressing B1 IgM reduce the uptake of oxidized LDL by macrophages and stabilize atherosclerotic plaques by increasing the number of macrophages expressing TGFβ1, which clear apoptotic cells and shift the balance towards lower levels of TNFα, IL-1β and IL-18 [47].

IRA B-cells are derived from B1a cells and develop in the spleen in response to lipopolysaccharide stimulation. They are characterized by the secretion of Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), which is responsible for their proatherogenic effects in atherosclerosis [49]. In this study, mixed chimeric mice lacking B-cell-derived GM-CSF (B-cell deficient IRA) were found to develop smaller atherosclerotic lesions containing fewer macrophages and effector T-cells. In addition, GM-CSF derived from IRA B-cells increases Dendritic Cell (DC) activation and exacerbates atherosclerosis by shifting adaptive immune responses towards a more pro-inflammatory atherogenic phenotype [49].

B-2 lymphocytes: Initial studies on the role of B2 B-cells (FO and MZ B-cells) in atherosclerosis have shown a protective role for B-cells. Splenectomy drastically aggravated atherosclerosis in Apoe -/- mice, and adoptive spleen B-cell transfer reduced the number of plaques in splenectomy Apoe -/- recipients. B-cell deficiency has been associated with increased plaque in Ldlr -/- mice. In contrast, depletion of B2 cells has been associated with a reduction in the progression of atherosclerosis caused by a decrease in pro atherogenic Th1 cells in the spleen and atherosclerotic plaques [50]. In accordance with these data, a recent study found that repeated administration of B2 cells to B-cell deficient mice leads to an exacerbation of atherosclerosis [51]. In addition, the production of high-affinity IgG and IgE has been shown to exacerbate atherosclerosis by stimulating the inflammatory response of macrophages and mass T-cells in atherosclerotic lesions [52].

Since B2 cells are composed of FO and MZ B-cells, further studies have demonstrated the specific role of B2 cell subpopulations in atherogenesis [53]. FO B-cells, which are predominantly found in the follicles of the spleen, make up the majority of resident B-cells in the spleen and form the major population of mature B2 cells. FO B-cells support the Th1 response and its production of pro-inflammatory cytokines [54]. In addition, activated by Tfh cells, FO cells differentiate into Germinal Center (GC) cells, which are involved in GC formation. The production of high-affinity anti-gen-specific IgG and IgE is the result of GC B-cell proliferation and affinity maturation [55]. A number of studies have demonstrated a pro-atherogenic role for FO B-cells, mainly through IgG production and activation of Th1 cells. To date, it is not entirely clear how much of the resulting FO B-cell phenotype is the result of IgG production, direct exposure of T-cells through antigen presentation to support effector responses, or its effect on other antigen presenting cells [52]. The significance of different lymphocyte populations in the development of atherosclerosis is summarized in Table 1.

Table 1: Significance of different populations of lymphocytes in the development of atherosclerosis

Population of lymphocytes	Significance in atherosclerosis
Th1 lymphocytes	Rather atherogenic: The possibility of a dual nature of the action of IFNγ
Th2 lymphocytes	Rather atheroprotective: The influence of IL-5 and IL-13 is determined, but the action of IL-4 is not clear
Th17 lymphocytes	Role is not clear
$CD8^+$ T-lymphocytes	Atherogenic role-in atherosclerotic plaques and atheroprotective-in relation to APCs bearing lipid autoantigens
Regulatory T-cells	Atheroprotective
NKT	Atherogenic
γδ T-cells	Role not clear
B-1 lymphocytes	Atheroprotective
B-2 lymphocytes	Both atherogenic and atheroprotective (depending on phenotype)

Discussion

A number of reviews have considered the role of the adaptive immune response in the atherosclerosis progression, but many aspects of the influence of different subpopulations of lymphocytes are still not fully understood [56,57]. Emerging evidence indicates that atherosclerosis is a chronic inflammatory disease with an autoimmune component. LDL peptides and ApoB seem to be the most significant autoantigens that can both stimulate an autoimmune response in atherosclerotic plaque and have an atheroprotective effect under vaccination conditions. T- cells are well understood in the context of atherosclerosis and are believed to play an important role in atherosclerosis. The pro-atherosclerotic role of Th-1 cells and the anti-atherogenic role of T-reg cells have been clearly shown in mice. The role of other Th-2 and $CD8^+$ T-cell subtypes is less clear and controversial across studies. Advances in single cell analysis technologies are providing a much deeper understanding of T-cell subpopulations in atherosclerotic lesions, lymph nodes, and blood. Methods are available for sampling local molecules released from coronary plaques or debris from ruptured plaques [58]. However, all these approaches do not solve the problem of identifying the antigenic specificity of T-cells. The newly identified MHC class II restricted epitopes in ApoB have been used to design tetramers to detect antigen-specific T-cells in the development of atherosclerosis in humans and mice. Prophylactic tolerogenic vaccines based on ApoB and other atherosclerosis antigens are effective in animal models, but it is currently unknown whether and how these approaches can be safely applied in the clinical setting [59].

Significant progress has also been made in understanding the functions of B-cells in the development and progression of atherosclerosis. Recent studies that have focused on the role of B-cell subsets have provided new knowledge and opportunities to identify components of the B-cell response in cardiovascular disease. However, the multiple functions of B-cells (antibody production, cytokine release, and antigen presentation) and the B-cell's unique mode of adaptation to hyperlipidemic and inflammatory environments add varying levels of complexity to the overall effects of B-cells in atherogenesis and are not yet fully understood. The Sirtuin 1 protein, which plays an important role in the regulation of metabolism, apoptosis, and aging, can serve as a potential therapeutic target [60]. Sirtuin 1 gene inactivation is known to play a role in the pathogenesis of a number of diseases, including atherosclerosis [61]. In addition, it is known that Sirtuin 1 regulates the maturation and proliferation of T-lymphocytes and its inactivation leads to impaired T-cell tolerance [62]. Since, according to one of the hypotheses, atherosclerosis is considered as an autoimmune disease on its own lipoproteins, this issue requires further consideration.

Conclusion

There is strong evidence that adaptive immune cells are involved in all phases of human atherosclerosis, from plaque formation to destabilization. More extensive studies using plaque tissues are needed to characterize effector cells and map critical pathways during atherogenesis. Studies in patients with various stages of atherosclerosis currently provide valuable information, but the heterogeneity of plaque characteristics makes it difficult to directly compare the characteristics of plaques and circulating immune cells. Early detection of vulnerable lesions remains the primary goal of biomarker discovery. Future studies, including circulating cellular biomarkers, should improve the identification of vulnerable lesions so that effective intervention can be implemented before clinical manifestations become evident.

Author Contributions

Writing-original draft preparation, A.V.B.,M.A.P.; writing-review and editing, V.N.S., I.I.E, I.I.N.; supervision, A.N.O. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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