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Immune crossroads in atherosclerosis: role of CD8+ T Cells, CD4+ T cells and toll-like receptors in lower extremity arterial disease

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Abstract

This review delves into the intricate roles of CD8+ T cells, Th17 cells, regulatory T cells (Tregs), and Toll-like receptors (TLRs) in the pathogenesis of atherosclerosis, with a particular focus on Lower Extremity Arterial Disease (LEAD). CD8+ T cells are highlighted for their dual role in atherosclerosis, acting as both exacerbators and potential protectors within the atherosclerotic environment. Their cytotoxic activity towards cells within plaques can promote necrotic core formation and plaque instability, while certain subsets, particularly regulatory CD8+ T cells, may exert atheroprotective effects through immunosuppressive functions. Th17 cells, known for their production of pro-inflammatory cytokines, are implicated in promoting inflammation and disease progression, suggesting that targeting Th17 cells could be a viable therapeutic strategy. Conversely, Tregs are identified for their potential to maintain immune balance and prevent excessive inflammatory responses, thereby stabilizing atherosclerotic lesions. The article also explores the role of TLRs in recognizing pathogen-associated and damage-associated molecular patterns, triggering inflammatory responses that contribute to atherosclerosis development and progression. By understanding the complex interplay between these immune components, the article suggests that modulating the activity of CD8+ T cells, balancing Th17 and Treg responses, and targeting TLR-mediated signalling pathways could offer new avenues for therapeutic intervention in atherosclerosis and LEAD. This comprehensive review underscores the need for targeted therapies that can modulate immune responses, highlighting the potential of immune system targeting in managing atherosclerosis and preventing LEAD complications.

Keywords: lower extremity arterial disease, atherosclerosis, T-cells, toll-like receptors

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Introduction

Lower extremity arterial disease (LEAD) stands as a significant manifestation of peripheral artery disease (PAD), presenting a considerable global health challenge. In 2015, it was estimated that around 236.62 million adults over the age of 25 were living with PAD worldwide, a figure that has risen due to population growth [1]. LEAD is characterized by the progressive narrowing and blockage of peripheral arteries, primarily caused by the buildup of atherosclerotic plaques. This leads to decreased blood flow, ischemia, and in severe cases, limb amputation. The Canadian Cardiovascular Society's guidelines from 2022 highlight the necessity

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of a comprehensive approach to managing PAD. This approach includes lifestyle changes, pharmacotherapy, and surgical interventions when needed, aiming to enhance patient outcomes [2]. Furthermore, LEAD significantly contributes to functional disability and reduced quality of life, while also indicating a higher risk of cardiovascular events and mortality [3, 4].

The pathophysiology of LEAD is intricate and involves multiple factors, including lipid imbalances, oxidative stress, endothelial dysfunction, and a persistent inflammatory response. These elements collectively drive the onset, progression, and complications associated with atherosclerotic lesions [5]. The disease process initiates damage to the endothelium, leading to increased vascular permeability and the adhesion and migration of leukocytes. Monocytes and macrophages are among the first to infiltrate the endothelium, where they consume oxidized LDL particles and become foam cells, marking the early stages of atheroma formation. T lymphocytes, including CD4+ helper, CD8+ cytotoxic, and regulatory T cells, further influence the inflammatory environment within plaques, affecting cytokine production, immune cell recruitment, and the integrity of the fibrous cap [6–7].

This systematic review aims to thoroughly evaluate the current landscape of medical therapy and revascularization strategies for managing lower limb LEAD. It places a special focus on the effects of these strategies on the underlying immunopathogenesis and chronic subclinical inflammation. By integrating evidence from clinical trials, observational studies, and mechanistic research, the authors seek to clarify how modern therapeutic approaches can influence the inflammatory processes at the heart of LEAD's pathophysiology.

Moreover, the review delves into the specific roles of T cell subsets, including CD8+ T cells, regulatory T cells (Tregs), and Th17 cells, in the progression of atherosclerosis. CD8+ T cells, known for their cytotoxic capabilities, exacerbate the inflammatory state within plaques by releasing pro-inflammatory cytokines and cytotoxic molecules, further damaging the vascular system and destabilizing plaques [8]. Toll-like receptors (TLRs), as part of the innate immune system, play a crucial role in recognizing pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) within atherosclerotic plaques [9].

This article not only explores the immunopathogenesis of atherosclerosis in LEAD but also examines the potential of emerging therapies targeting inflammatory pathways. It evaluates their effectiveness in altering immune cell behaviour, cytokine profiles, and plaque characteristics in the context of LEAD. The incorporation of anti-inflammatory agents, immunomodulators, and targeted biologics into the treatment paradigm for LEAD represents a promising direction for improving clinical outcomes. Through an in-depth review of the literature, this article highlights advancements in understanding the role of inflammation in LEAD, the challenges in translating this knowledge into effective clinical interventions, and future research and therapy directions.

CD8+ cells

This participation of naïve CD8+ T cells takes place in response to an encountered specific antigen presented by major histocompatibility complex class I (MHC I or human leukocyte antigen (HLA)) on an antigen-presenting cell (APC) through the T cell receptor (TCR). Such interaction provokes the activation and differentiation of CD8+ T cells into effector T cells, accompanied by clonal expansion. Activation and proliferation of T-cells are thus carefully controlled so that in the background of a highly potent response to infection, the outcome shows only limited and temporary immune pathology. However, CD8+ T cells can also result in exaggerated immune responses and thus immunopathology damage [10].

Because of their cytotoxic functionality within the adaptive immune response, CD8+ T cells play an opposite role in the pathogenesis of atherosclerosis. Again, this duality of CD8+ T cells' action in atherosclerosis represents another level of complexity that exists among immune responses in atherosclerotic lesions. These cells are mainly recognized to be cytotoxic and can both exacerbate and convert to protective mediators of the atherosclerotic process, depending on the biological context of their activation and the prevalent microenvironment of the plaque [11]. They act in various ways like the cytotoxic activities of these CD8+ T cells toward the cells in atherosclerotic plaques including vascular smooth muscle cells (VSMC), endothelial cells, and macrophages through induction of cell death. There is a promotion of necrotic core formation, and plaque instability [12]. This is further amplified by the presence of the pro-inflammatory cytokines, for instance, the tumour necrosis factor--alpha (TNF-α), which further, through its secretion of cytotoxic molecules such as granzyme B and perforin, amplifies local inflammation while concomitantly destabilizing plaques [13–14].

Additionally, CD8+ T cells can affect monocyte recruitment and differentiation into macrophages, which enhances the inflammatory environment and lipid buildup in plaques [15]. The antigen-specific activation of CD8+ T cells targeting atherosclerosis-relevant antigens brings out involvement in mediating adaptive immunity, suggesting that oxLDL epitopes within the

plaque can drive CD8+ T cell-mediated cytotoxicity and inflammation [16]. A more recent study confirms that antigen-specifically reactions against vascular cells promote arterial inflammation and lesion formation. Researchers bred Apoe−/− mice expressing β-Galactosidase in vascular smooth muscle cells in the aorta. However, they found CD8+ against dendritic cells with larger atherosclerotic lesions than control in Apoe −/− mice [17]. In the context of LEAD, such evidence of plaque stability and inflammation being crucial determinants for both disease progression and clinical outcomes suggests systemic and local effects by CD8+ T cells specific for atherosclerosis.

All of these functions of CD8+ T cells may have a strong impact on the stability of plaques in arteries of the legs, among which arterial disease seems to have much more advanced and more complex lesions. The induction of cell death and promotion of necrotic core formation by CD8+ T cells can lead to plaque rupture, a critical event that precipitates acute cardiovascular complications such as myocardial infarction and stroke [18]. Cochain et al. showed that CD8+T cells contribute to inflammation and further destabilize plaques in a Ldlr-/- mouse model, emphasizing the importance of very specific therapeutic strategies for the modulation of these cells in PAD [19]. In another study, Depuydt et al. analyzed atherosclerotic plaques taken during carotid endarterectomy in 61 patients. Their research revealed a statistically significant accumulation of T cells, especially CD8+, in the examined material. The comparison with blood T cells provides insights into the systemic immune response and its relationship with localized inflammation in the plaques [20]. Conversely, certain subsets of CD8+ T cells exhibit atheroprotective roles, highlighting the complexity of their involvement in atherosclerosis. Regulatory CD8+ T cells, characterized by the expression of CD25 and other markers, can exert immunosuppressive functions, inhibiting the activation and proliferation of effector T cells and reducing inflammation within the plaque. Zhou et al. observe the expression of CD8+CD25+ T cells in atherosclerotic apoE (-/-) mice. These cells exhibited a suppressive phenotype and function, capable of reducing the proliferation of splenic CD4+ T cells and significantly reducing atherosclerosis in recipient mice through adoptive transfer experiments [21]. They can modulate the immune response by secreting anti-inflammatory cytokines to promote the regression of inflammation to a more homeostatic condition resulting in stabilization of the inflamed lesion. A proper understanding of the complex role of CD8+ T cells in atherosclerosis brings new opportunities to therapeutic targeting. Inhibition of the cytotoxic function of the CD8+ T cells modulation of their states of activation or the enhancement of the regulatory subset of CD8+ T cells would bring new ways in which atherosclerosis can be managed.

Depuydt et al. found a statistically significant accumulation of the T cells, predominantly CD8+, in the examined atherosclerotic plaques. The comparison with blood T cells provides insights into the systemic immune response and its relationship with localized inflammation in the plaques [20]. The study by Maga et al. underscores the significance of activated effector CD8+ cells in the progression of atherosclerosis and restenosis due to their adhesion and homing to the injured vascular wall in patients with LEAD [22].

Th17 cells

Th17 cells, a subset of CD4+ T helper cells, are distinguished by their production of IL-17 and other pro-inflammatory cytokines such as Il-21, Il-22, Il-26 or granulocyte-macrophage colony-stimulating factor (GM-CSF), and serve fundamental roles in host defence against extracellular pathogens, apart from playing roles in pathogenesis in various systemic autoimmune diseases [23–24]. The involvement of these cells in atherosclerosis is thus another example of this dual nature of immunological responses, where protective mechanisms against pathogens can inadvertently promote disease under certain conditions. Therefore, Th17 cells, through their secretion of IL-17 and other pro-inflammatory cytokines, play a multifaceted role in the development of atherosclerosis. Wang et al. found that Th17 cells play a significant role in promoting inflammation and advancing disease progression in hyperlipidaemic patients and atherosclerotic mice. Authors emphasize the potential of targeting Th17 cells as a therapeutic strategy for managing atherosclerosis and related arterial diseases [25]. IL-17 may stimulate macrophages to secrete other proinflammatory cytokines, such as IL-1β, IL-6, and TNF-α so that they reinforce the local inflammatory response [26]. Th17--derived cytokines can also attract neutrophils to the plaque, which exacerbates inflammation and renders the plaque unstable. Chronic inflammation imposed by Th17 cells is not only involved in the progression of atherosclerotic plaques but also affects their instability. Indeed, it has been reported that the presence of Th17 cells and their derivative cytokine, IL-17, is associated with features related to ruptured lesions, such as thin fibrous caps, large lipid cores, and increased infiltration of inflammatory cells that predominate, predispose, and rupture plaques, thus contributing to acute cardiovascular events [27]. Th17 may also activate the vascular smooth muscle cells (VSMCs) to produce some inflammatory mediators and matrix metalloproteinases

(MMPs) which can degrade the extracellular matrix and weaken the structural integrity of the plaque. Furthermore, Th17 cells can promote endothelial cell activation, enhancing the expression of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), which facilitate the adhesion and infiltration of more leukocytes into the intima [28].

In the context of LEAD, the role of Th17 cells gains additional significance due to the critical impact of inflammation on disease progression. Moaaz et al. revealed a significant increase of Il-17 activated by Il-9 in a group of 84 patients with LEAD. The presence of Th17 cells and their signature cytokine, IL-17, in atherosclerotic plaques and their association with disease markers in hyperlipidaemic patients, underscore the potential of these cells as targets for therapeutic intervention [29]. In another study, authors identify Th17 cells as a new angiogenic T cell subset and provide new insight into the mechanism by which T cells promote neovascularization after ischemia of lower limbs [30].

Tregs

Tregs are a subset of CD4+ T cells that help maintain immune system balance by regulating the activity of effector T cells and antigen-presenting cells (APCs). They achieve this through several mechanisms, notably the secretion of inhibitory cytokines such as transforming growth factor-beta (TGF-β) and IL-10 [31]. These cytokines are instrumental in suppressing pro-inflammatory responses and promoting the differentiation of naïve T cells into additional regulatory phenotypes, thereby curtailing the proliferation and activity of various immune cells [32]. Experimental models have demonstrated that enhancing the function or number of FOXP3+ Tregs can significantly inhibit the development of atherosclerotic lesions. This protective effect is attributed to Tregs' ability to modulate lipoprotein metabolism, reduce inflammatory cell infiltration into lesions, and facilitate the clearance of lipoproteins such as very-low-density lipoprotein (VLDL) and chylomicron remnants [33]. The promotion of plaque stability by regulatory T cells (Tregs) is a critical aspect of their protective role in atherosclerosis and contributes to plaque stability through several mechanisms [34]. Tregs can suppress the local inflammatory environment within atherosclerotic plaques, which is a key determinant of plaque stability. By secreting anti-inflammatory cytokines such as IL-10 and TGF-β, Tregs inhibit the activity of pro-inflammatory cells, including macrophages, Th1 cells, and Th17 cells [35]. This suppression reduces the production of matrix metalloproteinases (MMPs), enzymes that degrade the extracellular matrix and weaken the fibrous cap, making the plaque more prone to rupture [36]. Ait-Oufell et al. found that Treg cell depletion in mice leads to the development of atherosclerosis in peripheral arteries. Moreover, transferring these Treg cells to mice reduced the size of the lesions and shifted the immune response towards an anti-atherogenic profile. This protective effect was associated with T-cell signalling through TGF-β [37]. The potential of Tregs as therapeutic targets in atherosclerosis and LEAD is significant. Strategies to enhance Treg populations or their function within atherosclerotic lesions could offer a novel approach to disease management.

Th17/Treg balance

The Th17/Treg balance is a critical determinant of the immune environment within atherosclerotic plaques, influencing the progression of atherosclerosis [38]. This balance between pro-inflammatory Th17 cells and anti-inflammatory Tregs not only modulates local inflammation within the arterial wall but also impacts systemic immune responses, which can have profound effects on plaque stability [39]. Chai et. al. studied a population of mice fed a high-fat diet for 8 weeks. They observed a statistically significant increase in Th17 lymphocytes without an increased percentage of Treg lymphocytes compared to the control group. The authors confirm that the imbalance between Th17/Treg plays a crucial role in the formation of atherosclerotic lesions [40]. In another study, the authors confirmed that in patients with coronary artery disease (CAD), there is a notable increase in Th17 cells and the levels of IL-17, IL-6, and IL-23 in their peripheral blood compared to healthy individuals. Conversely, there is a significant decrease in the number of Treg cells, IL-10, TGF-β, and Foxp3 levels, as well as in the Treg to Th17 ratio. These findings indicate a pronounced imbalance between Th17 and Treg cells in CAD patients, highlighting the potential contribution to plaque instability and the occurrence of CAD episodes [41]. Modulating the Th17/Treg balance towards a more anti-inflammatory state could therefore represent a promising therapeutic strategy for managing LEAD. This could involve interventions aimed at reducing Th17 cell differentiation or enhancing Treg proliferation and function. Angong Niuhuang Pill, from traditional Chinese medicine, has been shown to protect atherosclerotic ApoE–/– mice. Authors found that this substance can reduce the expression level of Th17 cells and increase the expression level of Treg cells. This results in decreasing chronic inflammation, reducing plaque collagen fibres, and decreasing inflammatory cell infiltration by modulating ROR-γt and Foxp3 expression [41]. It confirms that targeting the Th17/Treg balance represents a promising strategy for managing

atherosclerosis and improving outcomes for patients with LEAD.

TLRs

Toll-like receptors (TLRs) represent an important subclass of pattern recognition receptors playing an essential role in the development of innate immune responses and being activated by pathogen-associated molecular patterns (PAMPs) as well as danger-associated molecular patterns (DAMPs) [42]. This recognition triggers a cascade of inflammatory responses that contribute significantly to the development and progression of atherosclerosis. Both the TLR2-TLR1 and TLR2-TLR6 heterodimers have been implicated in promoting atherosclerosis in ApoE−/− mice and LDLR−/− mice [43–44]. One of the primary actions of TLRs in atherosclerosis is the induction of endothelial dysfunction, a precursor to atherosclerotic plaque development. Activation of TLRs on endothelial cells by DAMPs, such as ox-LDL or PAMPs leads to the upregulation of adhesion molecules (e.g., VCAM-1, ICAM-1) and the secretion of chemokines. This facilitates the recruitment and adhesion of circulating monocytes and T cells to the endothelium, promoting their transmigration into the intima where they contribute to plaque formation [45–47]. Ishibashi et al. found that TLR3 can regulate the activity of MMP-2 and MMP-9 in macrophages, thus affecting the instability of atherosclerotic plaques [48]. TLRs also amplify local and systemic inflammation by activating NF-κB and other transcription factors in immune cells, leading to the production of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6). This inflammatory milieu further enhances the recruitment of immune cells to the lesion as well as amplifies endothelial dysfunction and activates smooth muscle cell migration and proliferation, all processes associated with the complexity and vulnerability of plaques [49]. The chronic inflammation induced by TLR activation exacerbates the progression of occlusive plaques, which can lead to critical limb ischemia, a severe complication of LEAD. TLR-mediated inflammation not only accelerates plaque growth but also contributes to plaque instability [50]. Furthermore, inflammation activated by TLR3 can impair angiogenesis and the development of collateral circulation, critical compensatory mechanisms in response to arterial occlusion [51]. However, the fact that TLRs are implicated in LEAD might provide an opportunity to target the receptors and their related inflammatory pathways for a new therapeutic strategy to provide proper control over the disease. Cen et al. examined atherosclerotic plaques taken from human popliteal arteries; the other group consisted of apoE-deficient mice. Both study groups showed increased expression of TLR-3. Thus, the authors confirmed the involvement of TLR-3 in the immunopathogenesis of lower limb atherosclerosis. In addition, a TLR-3-specific inhibitor (SMU-CX24) was isolated, which has great potential in the pharmacological treatment of atherosclerosis [52]. By modulating TLR signalling, it may be possible to reduce inflammation, stabilize plaques, and improve outcomes for patients with cardiovascular diseases. The article by Li et al. investigates the therapeutic potential of corilagin, a natural compound, in treating Peripheral Artery Disease (PAD) by targeting the Toll-like receptor 4 (TLR4) signalling pathway. Corilagin effectively inhibits TLR4 activation, leading to a reduction in inflammatory responses and endothelial dysfunction [53]. The complexity of TLR signalling pathways and their crucial roles in host defence against pathogens necessitates careful consideration to avoid unintended immunosuppressive effects. Furthermore, the heterogeneity of atherosclerotic disease and the specific contributions of different TLRs to its pathogenesis require targeted approaches to modulate TLR activity effectively.

Conclusions

This article has elucidated the intricate roles of various immune cells and the complex interplay of pro-inflammatory and anti-inflammatory mechanisms in the pathogenesis of atherosclerosis, with a specific focus on LEAD. the pro-inflammatory roles of CD8+ T cells and Th17 cells in promoting plaque instability and progression underscore the need for targeted therapies that can modulate these responses. Strategies aimed at reducing the cytotoxic effects of CD8+ T cells, inhibiting Th17 cell differentiation, or shifting the Th17/Treg balance towards a more anti-inflammatory state could provide significant benefits in managing atherosclerosis and preventing the complications associated with LEAD. Moreover, TLRs are upregulated in the case of inflammatory processes occurring in atherosclerosis Targeting TLR-mediated signalling pathways could help in attenuating the chronic inflammatory state that exacerbates plaque progression and instability. This review highlights the complexity of immune cell involvement and offers insight into potential therapeutic strategies targeting the immune system. Future research should focus on unravelling the detailed mechanisms of immune cell action in atherosclerosis and developing targeted interventions that can modulate these responses to prevent the progression of LEAD and improve clinical outcomes for patients. The integration of anti-inflammatory agents, immunomodulators, and targeted biologics into the treatment paradigm for LEAD represents a promising

avenue for enhancing patient care and addressing the challenges posed by this pervasive disease.

Article information and declarations

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References

1. Lin J, Chen Y, Jiang N, et al. Burden of peripheral artery disease and its attributable risk factors in 204 countries and territories from 1990 to 2019. Front Cardiovasc Med. 2022; 9: 868370, doi: 10.3389/fcvm.2022.868370, indexed in Pubmed: 35498034.
2. Abramson BL, Al-Omran M, Anand SS, et al. Primary Panel, Secondary Panel:. Canadian Cardiovascular Society 2022 Guidelines for Peripheral Arterial Disease. Can J Cardiol. 2022; 38(5): 560–587, doi: 10.1016/j.cjca.2022.02.029, indexed in Pubmed: 35537813.
3. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA. 2001; 286(11): 1317–1324, doi: 10.1001/jama.286.11.1317, indexed in Pubmed: 11560536.
4. Annex BH, Cooke JP. New directions in therapeutic angiogenesis and arteriogenesis in peripheral arterial disease. Circ Res. 2021; 128(12): 1944–1957, doi: 10.1161/CIRCRESAHA.121.318266, indexed in Pubmed: 34110899.
5. Cecchini AL, Biscetti F, Manzato M, et al. Current medical therapy and revascularization in peripheral artery disease of the lower limbs: impacts on subclinical chronic inflammation. Int J Mol Sci. 2023; 24(22), doi: 10.3390/ijms242216099, indexed in Pubmed: 38003290.
6. Saenz-Pipaon G, Martinez-Aguilar E, Orbe J, et al. The role of circulating biomarkers in peripheral arterial disease. Int J Mol Sci. 2021; 22(7), doi: 10.3390/ijms22073601, indexed in Pubmed: 33808453.
7. Yang WX, Wang FF, Li FF, et al. Immunological analysis of peripheral artery disease. , doi: 10.21203/rs.3.rs-457946/v1.
8. Hinkley H, Counts DA, VonCanon E, et al. T cells in atherosclerosis: key players in the pathogenesis of vascular disease. Cells. 2023; 12(17), doi: 10.3390/cells12172152, indexed in Pubmed: 37681883.
9. Jin M, Fang J, Wang JJ, et al. Regulation of toll-like receptor (TLR) signaling pathways in atherosclerosis: from mechanisms to targeted therapeutics. Acta Pharmacol Sin. 2023; 44(12): 2358–2375, doi: 10.1038/s41401-023-01123-5, indexed in Pubmed: 37550526.
10. Mayer A, Zhang Y, Perelson AS, et al. Regulation of T cell expansion by antigen presentation dynamics. Proc Natl Acad Sci U S A. 2019; 116(13): 5914–5919, doi: 10.1073/pnas.1812800116, indexed in Pubmed: 30850527.
11. Zhou J, Dimayuga PC, Zhao X, et al. CD8(+)CD25(+) T cells reduce atherosclerosis in apoE(-/-) mice. Biochem Biophys Res Commun. 2014; 443(3): 864–870, doi: 10.1016/j.bbrc.2013.12.057, indexed in Pubmed: 24342615.
12. Feil S, Fehrenbacher B, Lukowski R, et al. Transdifferentiation of vascular smooth muscle cells to macrophage-like cells during atherogenesis. Circ Res. 2014; 115(7): 662–667, doi: 10.1161/CIRCRESAHA.115.304634, indexed in Pubmed: 25070003.
13. Kyaw T, Winship A, Tay C, et al. Cytotoxic and proinflammatory CD8+ T lymphocytes promote development of vulnerable atherosclerotic plaques in apoE-deficient mice. Circulation. 2013; 127(9): 1028–1039, doi: 10.1161/CIRCULATIONAHA.112.001347, indexed in Pubmed: 23395974.
14. Blanco P, Pitard V, Viallard JF, et al. Increase in activated CD8+ T lymphocytes expressing perforin and granzyme B correlates with disease activity in patients with systemic lupus erythematosus. Arthritis Rheum. 2005; 52(1): 201–211, doi: 10.1002/art.20745, indexed in Pubmed: 15641052.
15. Schürch CM, Riether C, Ochsenbein AF. Cytotoxic CD8+ T cells stimulate hematopoietic progenitors by promoting cytokine release from bone marrow mesenchymal stromal cells. Cell Stem Cell. 2014; 14(4): 460–472, doi: 10.1016/j.stem.2014.01.002, indexed in Pubmed: 24561082.
16. Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. Nature. 2011; 473(7347): 317–325, doi: 10.1038/nature10146, indexed in Pubmed: 21593864.
17. Cochain C, Zernecke A. Protective and pathogenic roles of CD8 T cells in atherosclerosis. Basic Res Cardiol. 2016; 111(6): 71, doi: 10.1007/s00395-016-0589-7, indexed in Pubmed: 27783202.
18. Laera N, Malerba P, Vacanti G, et al. Impact of immunity on coronary artery disease: an updated pathogenic interplay and potential therapeutic strategies. Life (Basel). 2023; 13(11), doi: 10.3390/life13112128, indexed in Pubmed: 38004268.
19. Cochain C, Koch M, Chaudhari SM, et al. CD8+ T cells regulate monopoiesis and circulating Ly6C-high monocyte levels in atherosclerosis in mice. Circ Res. 2015; 117(3): 244–253, doi: 10.1161/CIRCRESAHA.117.304611, indexed in Pubmed: 25991812.
20. Depuydt MAC, Schaftenaar FH, Prange KHM, et al. Single-cell T cell receptor sequencing of paired human atherosclerotic plaques and blood reveals autoimmune-like features of expanded effector T cells. Nat Cardiovasc Res. 2023; 2(2): 112–125, doi: 10.1038/s44161-022-00208-4, indexed in Pubmed: 38665903.
21. Zhou J, Dimayuga PC, Zhao X, et al. CD8(+)CD25(+) T cells reduce atherosclerosis in apoE(-/-) mice. Biochem Biophys Res Commun. 2014; 443(3): 864–870, doi: 10.1016/j.bbrc.2013.12.057, indexed in Pubmed: 24342615.
22. Maga P, Mikolajczyk TP, Partyka L, et al. Involvement of CD8+ T cell subsets in early response to vascular injury in patients with peripheral artery disease in vivo. Clin Immunol. 2018; 194: 26–33, doi: 10.1016/j.clim.2018.06.006, indexed in Pubmed: 29936303.
23. Tedgui A, Mallat Z. Cytokines in atherosclerosis: pathogenic and regulatory pathways. Physiol Rev. 2006; 86(2): 515–581, doi: 10.1152/physrev.00024.2005, indexed in Pubmed: 16601268.

24. Takatori H, Kanno Y, Watford WT, et al. Lymphoid tissue inducer-like cells are an innate source of IL-17 and IL-22. J Exp Med. 2009; 206(1): 35–41, doi: 10.1084/jem.20072713, indexed in Pubmed: 19114665.
25. Wang Y, Li W, Zhao T, et al. Interleukin-17-producing CD4+ T cells promote inflammatory response and foster disease progression in hyperlipidemic patients and atherosclerotic mice. Front Cardiovasc Med. 2021; 8: 667768, doi: 10.3389/fcvm.2021.667768, indexed in Pubmed: 33981738.
26. Tiemessen MM, Jagger AL, Evans HG, et al. CD4+CD25+Foxp3+ regulatory T cells induce alternative activation of human monocytes/macrophages. Proc Natl Acad Sci U S A. 2007; 104(49): 19446–19451, doi: 10.1073/pnas.0706832104, indexed in Pubmed: 18042719.
27. Wang J, Gao Y, Yuan Y, et al. Th17 Cells and IL-17A in ischemic stroke. Mol Neurobiol. 2024; 61(4): 2411–2429, doi: 10.1007/s12035-023-03723-y, indexed in Pubmed: 37884768.
28. Taleb S, Tedgui A, Mallat Z. IL-17 and Th17 cells in atherosclerosis: subtle and contextual roles. Arterioscler Thromb Vasc Biol. 2015; 35(2): 258–264, doi: 10.1161/ATVBAHA.114.303567, indexed in Pubmed: 25234818.
29. Moaaz M, Lotfy H. Changes and significance of T helper-9 cells and interleukin-9 in patients with atherosclerotic chronic lower limb ischemia: Effect on IL-17 release. Vascular. 2020; 28(4): 378–389, doi: 10.1177/1708538120905430, indexed in Pubmed: 32063130.
30. Hata T, Takahashi M, Hida S, et al. Critical role of Th17 cells in inflammation and neovascularization after ischaemia. Cardiovasc Res. 2011; 90(2): 364–372, doi: 10.1093/cvr/cvq397, indexed in Pubmed: 21156823.
31. Yamaguchi T, Wing JB, Sakaguchi S. Two modes of immune suppression by Foxp3(+) regulatory T cells under inflammatory or non-inflammatory conditions. Semin Immunol. 2011; 23(6): 424–430, doi: 10.1016/j.smim.2011.10.002, indexed in Pubmed: 22055883.
32. Yamaguchi T, Kishi A, Osaki M, et al. Construction of self-recognizing regulatory T cells from conventional T cells by controlling CTLA-4 and IL-2 expression. Proc Natl Acad Sci U S A. 2013; 110(23): E2116–E2125, doi: 10.1073/pnas.1307185110, indexed in Pubmed: 23690575.
33. Joly AL, Andersson J. Alternative splicing, FOXP3 and cardiovascular disease. Aging (Albany NY). 2019; 11(7): 1905–1906, doi: 10.18632/aging.101897, indexed in Pubmed: 30981208.
34. Joly AL, Seitz C, Liu S, et al. Alternative splicing of controls regulatory T cell effector functions and is associated with human atherosclerotic plaque stability. Circ Res. 2018; 122(10): 1385–1394, doi: 10.1161/CIRCRESAHA.117.312340, indexed in Pubmed: 29618596.
35. Meng X, Yang J, Dong M, et al. Regulatory T cells in cardiovascular diseases. Nat Rev Cardiol. 2016; 13(3): 167–179, doi: 10.1038/nrcardio.2015.169, indexed in Pubmed: 26525543.
36. Hu W, Wei R, Wang L, et al. Correlations of MMP-1, MMP-3, and MMP-12 with the degree of atherosclerosis, plaque stability and cardiovascular and cerebrovascular events. Exp Ther Med. 2018; 15(2): 1994–1998, doi: 10.3892/etm.2017.5623, indexed in Pubmed: 29434795.
37. Ait-Oufella H, Salomon BL, Potteaux S, et al. Natural regulatory T cells control the development of atherosclerosis in mice. Nat Med. 2006; 12(2): 178–180, doi: 10.1038/nm1343, indexed in Pubmed: 16462800.
38. Ren J, Li B. The functional stability of FOXP3 and ROR t in Treg and Th17 and their therapeutic applications. Adv Protein Chem Struct Biol. 2017; 107: 155–189, doi: 10.1016/bs.apcsb.2016.10.002, indexed in Pubmed: 28215223.
39. Xie Jj, Wang J, Tang Tt, et al. The Th17/Treg functional imbalance during atherogenesis in ApoE(-/-) mice. Cytokine. 2010; 49(2): 185–193, doi: 10.1016/j.cyto.2009.09.007, indexed in Pubmed: 19836260.
40. Chai Y, Yin Z, Fan Q, et al. Protective effects of angong niuhuang pill on early atherosclerosis in apoe mice by reducing the inflammatory response. Evid Based Complement Alternat Med. 2019; 2019: 9747212, doi: 10.1155/2019/9747212, indexed in Pubmed: 31236126.
41. Cheng X, Yu X, Ding YJ, et al. The Th17/Treg imbalance in patients with acute coronary syndrome. Clin Immunol. 2008; 127(1): 89–97, doi: 10.1016/j.clim.2008.01.009, indexed in Pubmed: 18294918.
42. Vijay K. Toll-like receptors in immunity and inflammatory diseases: Past, present, and future. Int Immunopharmacol. 2018; 59: 391–412, doi: 10.1016/j.intimp.2018.03.002, indexed in Pubmed: 29730580.
43. Curtiss LK, Black AS, Bonnet DJ, et al. Atherosclerosis induced by endogenous and exogenous toll-like receptor (TLR)1 or TLR6 agonists. J Lipid Res. 2012; 53(10): 2126–2132, doi: 10.1194/jlr.M028431, indexed in Pubmed: 22822027.
44. Mullick AE, Tobias PS, Curtiss LK. Modulation of atherosclerosis in mice by Toll-like receptor 2. J Clin Invest. 2005; 115(11): 3149–3156, doi: 10.1172/JCI25482, indexed in Pubmed: 16211093.
45. Fukuda D, Nishimoto S, Aini K, et al. Toll-Like Receptor 9 Plays a Pivotal Role in Angiotensin II-Induced Atherosclerosis. J Am Heart Assoc. 2019; 8(7): e010860, doi: 10.1161/JAHA.118.010860, indexed in Pubmed: 30905257.
46. Sager HB, Dutta P, Dahlman JE, et al. RNAi targeting multiple cell adhesion molecules reduces immune cell recruitment and vascular inflammation after myocardial infarction. Sci Transl Med. 2016; 8(342): 342ra80, doi: 10.1126/scitranslmed.aaf1435, indexed in Pubmed: 27280687.
47. Gimbrone MA, García-Cardeña G. Endothelial cell dysfunction and the pathobiology of atherosclerosis. Circ Res. 2016; 118(4): 620–636, doi: 10.1161/CIRCRESAHA.115.306301, indexed in Pubmed: 26892962.
48. Ishibashi M, Sayers S, D'Armiento JM, et al. TLR3 deficiency protects against collagen degradation and medial destruction in murine atherosclerotic plaques. Atherosclerosis. 2013; 229(1): 52–61, doi: 10.1016/j.atherosclerosis.2013.03.035, indexed in Pubmed: 23676255.
49. Bhaskar S, Sudhakaran PR, Helen A. Quercetin attenuates atherosclerotic inflammation and adhesion molecule expression by modulating TLR-NF- B signaling pathway. Cell Immunol. 2016; 310: 131–140, doi: 10.1016/j.cellimm.2016.08.011, indexed in Pubmed: 27585526.
50. Patel H, Shaw SG, Shi-Wen Xu, et al. Toll-like receptors in ischaemia and its potential role in the pathophysiology of muscle damage in critical limb ischaemia. Cardiol Res Pract. 2012; 2012: 121237, doi: 10.1155/2012/121237, indexed in Pubmed: 22454775.

51. Grelier A, Cras A, Balitrand N, et al. Toll-like receptor 3 regulates cord blood-derived endothelial cell function in vitro and in vivo. Angiogenesis. 2013; 16(4): 821–836, doi: 10.1007/s10456-013-9358-5, indexed in Pubmed: 23748743.
52. Cen X, Wang B, Liang Y, et al. Small molecule SMU-CX24 targeting toll-like receptor 3 counteracts inflammation: A novel approach to atherosclerosis therapy. Acta Pharm Sin B. 2022; 12(9): 3667–3681, doi: 10.1016/j.apsb.2022.06.001, indexed in Pubmed: 36176917.
53. Li Y, Wang Y, Chen Y, et al. Corilagin ameliorates atherosclerosis in peripheral artery disease via the toll-like receptor-4 signaling pathway and in vivo. Front Immunol. 2020; 11: 1611, doi: 10.3389/fimmu.2020.01611, indexed in Pubmed: 32849545.