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REVIEW

# Follicular regulatory T cell in atherosclerosis

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## Abstract

Atherosclerosis is a chronic inflammatory disease involving the infiltration of immune cells, such as monocytes/macrophages, neutrophils, T cells, and B cells, into the inner layer of vessel walls. T and B cell functions in the process of atherogenesis, as well as their mutual regulation, have been investigated but several aspects remain to be clarified. In the present review, we give a brief overview of the functions of follicular regulatory T cell (Tfr) on follicular T (Tfh) and B cell regulation related to atherosclerosis pathogenesis, including their influence on lymphangiogenesis and lipoprotein metabolism. We will also discuss their potential therapeutics properties in the resolution of established atherosclerotic lesions.

KEYWORDS

Atherosclerosis, Regulatory B cells, B cell, Follicular T cell

## 1 | INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of mortality worldwide.[1] Atherosclerosis is the most studied CVD. Atherosclerosis is a chronic inflammatory disease characterized by the accumulation of lipids in the artery walls and involving both the innate and adaptive immune systems.[2] The infiltration of proinflammatory monocytes in the artery walls in presence of elevated concentrations of circulating lipids triggers atherogenesis.[3–5] During this complex process, circulating monocytes infiltrate the inner layer of vessel walls and differentiate into macrophages. This phenotypical switch allows the integration of lipids in excess in the artery walls leading to inflammation, foam cell formation, and establishment of plaques composed by the infiltrated elements, connective-tissue components, but also other particles.[6,7] Over time, plaques enlarge and can break, causing thrombus formation, leading to ischemia, and myocardial infarction.[8] Although the specific roles of T and B cell subtypes are not yet totally understood, their importance in the establishment and development of atherosclerosis has been clearly established.[9–13] In this review, we will try to give an overview of the functions of immune cells in the regulation of atherosclerosis with particular emphasis on regulatory B cells (Breg), follicular T cell (Tfh), and follicular regulatory T cell (Tfr).

## 2 | T CELLS IN ATHEROSCLEROSIS

During the development of atherosclerotic lesions, T cells are recruited at a very early stage.[14] In the presence of low-density lipoprotein (LDL), adhesion molecules and chemoattractants located and expressed in the intima lead to the infiltration of T cells into the plaques.[15,16] Once in the artery wall, antigens such as LDL and/or oxidized LDL activate the lymphocytes.[17,18] T cells' activation increases inflammation through proinflammatory cytokines release and creates an amplification loop between T cells and innate-immunity cells, such as macrophages.[19]

To study atherosclerosis, transgenic mice depleted of *Apoe* or *ldlr* genes are the most currently used models.[20] In this context, Kyaw et al. determined that the majority of T cells present in atherosclerotic plaques are $CD4^+$ T cells, although $CD8^+$ T cells are present mainly in human and mouse advanced plaques[21] with functions of atherosclerotic plaque destabilization.[22] $CD8^+$ T cells indeed trigger the apoptosis of macrophages, smooth muscle cells, and endothelial cells by its cytotoxic and inflammatory ability, leading to necrotic cores creation.[22] $CD8^+$ are also able to regulate Tfh[23,24] known to be proatherogenic.[25–27] $CD4^+$ T cells have also been shown to have a proatherogenic function.[28,29] Immunosuppressed $Apoe^{-/-}$ mice are atheroprotected, but adoptive transfer of $CD4^+$ cells abolishes this



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**TABLE 1** Breg, Tfh, and Tfr cell subsets proprieties in murine atherosclerosis: discriminative biological markers; principal cytokines secreted; localization during atherosclerosis; and influence on the plaques development. GCs: germinal centers. TGF-$\beta$: Transforming growth factor beta. IFN-$\gamma$: Interferon gamma. For more information on B subsets cells[70] and T cells[92]

| Cells types | Breg | Tfh | Tfr | Refs |
|---|---|---|---|---|
| Markers | $B220^+$ $IgM^+$ | $CD4^+$ $PD\text{-}1^+$ | $CD4^+$ $PD\text{-}1^+$ | 33,35,61,69,84–87 |
| | $CD43^-$ $CD1d^+$ | $ICOS^+$ $CXCR5^+$ | $ICOS^+$ $CXCR5^+$ | |
| | | $CD25^-$ $FoxP3^-$ | $CD25^+$ $FoxP3^+$ | |
| Cytokines | IL-10; IL-35; TGF-$\beta$ | IL-4; IL-21 | IL-10; TGF-$\beta$ | 61,86,88–91 |
| Localization | | | | 34,35,69 |
| Artery wall | + | ++ | ++ | |
| Spleen | +++ | +++ | +++ | |
| Lymph nodes | +++ | *Co-localized in the GCs* | | |
| Effect on atherosclerosis | Atheroprotector | Atherogenic | Atheroprotector | 25–27,80 |

atheroprotective effect.[12] Although T cells are crucial in the generation and sustainment of atherosclerosis, a strong heterogeneity is present in T cell subtypes (Table 1).

$CD4^+$ effector T helper (Th) cells are divided in various subsets: Th1, Th2, $Foxp3^+$ regulatory T (Treg) cells, Th17 cells, and Tfh cells.[30–32] A new Treg cell subtype named Tfr has recently been described and provides a better understanding of Treg functions, particularly in autoimmunity.[30,31,33] Similar to the Tfh population, this subset expresses the receptor CXCR5, which is important for the migration and the homing of Tfh.[34,35] CXCR5 thus drives the localization of Tfr in the germinal-center (GC) in response to CXCL13. The characteristics of Tfr are also close to the Treg population. Tfr indeed expresses FoxP3 and CD25.[35,36] By their regulatory function and their localization, Tfr cells negatively regulate Tfh population.[27] To determine the exact function of T cells in atherogenesis, each subset needs to be thoroughly investigated.

Th1 cell population is widely present in plaques. Their ability to secrete proatherogenic cytokines certainly inhibits the atheroprotective action of other subsets.[37] Th2 and Th17 cell populations are also found but their functions are still unclear.[38,39] The functions of Treg cells in atherosclerosis have been largely investigated and show an overall atheroprotective role.[40,41] It is also important to consider the possible atherogenic effect of T cell populations led by their potential ability to regulate cholesterol levels through the lymphatic system.[42–44] It has been thus shown that areas with higher density of lymphatic vessels show less atherosclerotic plaques[44,45] probably by their ability to stimulate a process called reverse cholesterol transport (RCT).[43] In the context of cholesterol homeostasis, Treg cells seem to have opposite functions to other T cell subsets.[46] In $Apoe^{-/-}$ mice and in humans with coronary artery disease, Treg cells are impaired, although they are known to initially increase in numbers in early lesions.[47] Over the longer term, atherosclerosis is associated with a reduction of Treg cells.[48–51] Furthermore, depletion or reduction of this subset leads to an aggravation of atherosclerosis: bigger lesion size, diminution of plaque stability, and change in lipid profile.[40,52–56] The atheroprotective effects of Treg cells are, however, not only due the modulation of cholesterol. Treg cells have proven to have a direct effect on endothelial cell activation, lymphocyte infiltration, foam cell formation, and on macrophage differentiation.[47,57] During atherosclerosis, Treg cells can lose FoxP3 and mutate into memory, IFN-$\gamma^+$ or Tfh cells.[26,58] During this process, cells lose their ability to produce TGF-$\beta$1, a cytokine known to be atheroprotective and for its ability to modulate Tfh cell population.[59,60] Lymphangiogenesis is also inhibited through Tfh-dependent IL-4 secretion.[61,62] Diminishing Tfh cells and, in turn, IL-4 expression in mice increases the lymphangiogenesis.[25,27] Due to their close phenotypical characteristics, there is no study in our knowledge in which Tfh cell population is investigated independently of Tfr cells. Gaddis et al. as well as our laboratory studied the effect induced by the inhibition of Bcl6, a transcription factor essential for Tfr and Tfh cells with disparate results.[26,27] The different approaches used could, however, explain the discrepancy. Gaddis et al. have generated Bcl6-specific $CD4^+$ knockout $Apoe^{-/-}$ mice. In this model, they observed a slight reduction of atherosclerotic plaques in mice under western diet whereas our study, based on a Bcl6 specific inhibitor, show an increase of atherosclerotic plaques.[26,27] As Bcl6 is essential for the formation of GCs, the absence of GCs in Bcl6-depleted mice leads to a depletion of GC B cells, a cell type known to influence atherosclerosis.[63] By suppressing Bcl6 with an inhibitor, our data are not influenced by the absence of GCs in $Apoe^{-/-}$ mice and results in an up-regulation of cholesterol levels and, thus, of atherosclerotic lesions.[27] These findings are consistent with published data showing an increase of cholesterol level when Bcl6 is inhibited in mice[64] and could be explained by the disruption of the lymphatic system during atherosclerosis.[25,27] Bcl6-inhibitor used in our experiments is not strictly specific to Tfh cells and influence directly Tfr cells and other cells types such as macrophages.[65] In this context, Bcl6 influences directly macrophages by inhibiting their proliferation,[66,67] thus plaque enlargement could be due to an increased number of this cell subset. Our data show, however, no increase of $CD68^+$ cells in atherosclerotic lesions. When Tfr cells are transferred into $Apoe^{-/-}$ mice, inversely, the number of macrophages present in the plaques and their size diminish. These results indicate that the atheroprotective effect of Tfr is certainly not only explained by its control of Tfh expansion. In fact, our data demonstrate that Tfr population stimulates directly lymphangiogenesis and Breg cells proliferation.[27,68] They suggest also that Tfr cell population seems to have more significant functions in

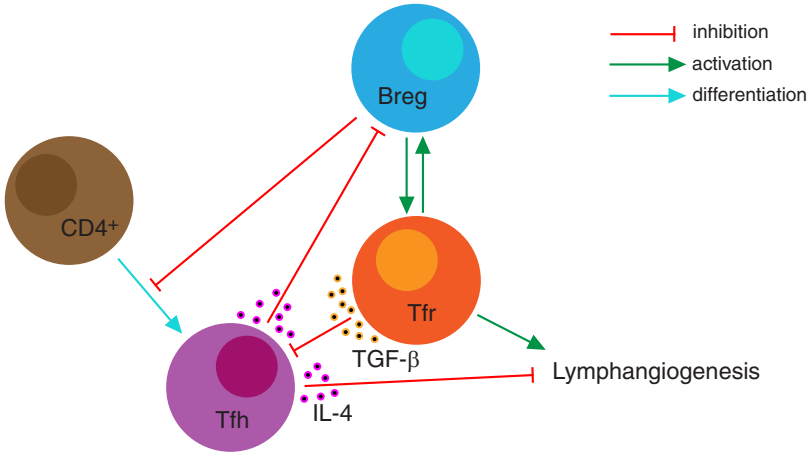


**FIGURE 1** **Mutual regulation between Tfr, Tfh, and Breg cells and their influence on lymphangiogenesis.** Tfr cell population is a key player in the repression of atherosclerosis. Its atheroprotective function is derived by its capacity to inhibit Tfh cells via TGF-$\beta$ secretion,[93] its direct up-regulation of lymphangiogenesis,[68] and also by the creation of a positive loop between Tfr and Breg cells, itself a Tfr cell activator.[27] In presence of Breg cells, the differentiation of $CD4^+$ cells in Tfh cells during atherosclerosis is diminished[83] and, in turn, Tfh cell population blocks Breg cells by secreting IL-4.[81] IL-4 cytokine is also important on the down-regulation of lymphangiogenesis[61,62]

atherosclerosis than Tfh cell population. Finally, adoptive transfer of Tfr cells in mice with established atherosclerotic plaques is unable to decrease atherosclerosis despite the reduction of Tfh cell population. Thus, Tfr and Tfh cell populations are involved in atherogenesis but not in the sustainment or resolution of established atherosclerotic lesions.[27]

## 3 | B CELLS IN ATHEROSCLEROSIS

In regard of previous data on the functions of Tfh and Tfr cell populations, their particular role in B cell regulation have to be investigated. It is now well established that B cell dysfunction contributes to the development of autoimmune diseases through diverse mechanisms, such as autoantibody production or immune modulations. Although the exact function of B cell subsets in atherogenesis is still controversial and remains to be fully defined, B cell subsets are now more finely characterized. B cells are separated in three subtypes: B1, B2, and Breg. The B1 subset is composed of two populations: B1a ($B220^{low}IgM^{high}CD43^+CD5^+$) and B1b ($B220^{low}IgM^{high}CD43^+CD5^-$). Meanwhile, the B2 subset is composed by Marginal zone B2 (MZB) cells ($B220^+IgM^{high}CD21^{high}CD43^-CD23^-$) and Follicular B2 (FOB) cells ($B220^+IgM^{low}CD21^+CD43^-CD23^+$). The third subset is Breg ($B220^+CD43^-IgM^{high}CD1d^{high}$).[69,70] In mouse models, B cell populations have been identified at different stages of atherosclerotic lesions whereas, in humans, their presence is restricted to advanced plaques.[11,71,72] Furthermore, splenectomy in mice has shown to enhance the development of atherosclerotic lesions, a process that is reversed by B cells adoptive transfer, suggesting an atheroprotective function of B cells.[73,74] Similar to T cells, B cell populations seem, however, having both atheroprotective and atherogenic properties.[73] Thus, the exact functions of independent B cell subsets required to be further investigated in atherosclerosis. In this context, B1a and B1b cell populations have been shown to possess atheroprotective properties through IgM secretion.[75,76] The effects of B2 cell population on atherosclerosis are unclear. It has been indeed demonstrated that B2 depletion in mice decreases atherosclerotic plaques whereas adoptive transfer aggravates the lesions.[77] Inversely, MZB cells have been recently proven to protect against atherosclerosis plaque formation.[24] Thus, within B2 cell populations, a distinction should be made between atherogenic FOB cells and atheroprotective MZB cells.[78] Concerning Breg cells, their role in atherosclerosis is still debated. The controversy is mainly based on the function of IL-10 derived from Breg cell population in atherosclerosis.[79,80] Although one of the phenotypical characteristics of Breg cells is their ability to produce IL-10, spontaneous *ex vivo* IL-10 production by B cells is difficult to observe. Identification of Breg population based on IL-10 production in vitro thus may potentially lead to misinterpretation.

## 4 | T AND B CELLS AND THEIR MUTUAL REGULATION IN ATHEROSCLEROSIS

The recent studies from our group indicate that Tfr cells exert part of their atheroprotective functions through the regulation of Breg cells differentiation.[27] Our findings indicate also that Tfr cells control Breg cell population through cell-cell interaction. It thereby seems that Breg and Tfr cell populations are mutually self-regulated, leading to an amplification loop of regulation dampening Tfh cells frequency and, in turn, atherogenesis (Fig. 1). Consistently, whereas Tfh cell are the main producers of IL-4 in GCs, IL-4 is able to indirectly inhibit Breg cells expansion.[81] The lack of Tfh cells regulation leads to nonantigen-specific B cells expansion, leading to autoimmune pathologies.[35,82] The association of atherosclerosis and autoimmune diseases is correlated with the increase of the Tfh cell population during atherosclerotic plaque development.[23,27] The number of Tfh cells present in secondary lymphoid organs of $Apoe^{-/-}$ mice is, however, reduced after the establishment of the lesions via a B cell-dependent process.[24] In this context, we have demonstrated that MZB, Breg and Tfr cell populations increase during lesions development.[27] FOB and Breg expansions are Tfr-dependent but not MZB, as demonstrated by adoptive transfer of Tfr cells.[27] Consistently, Achour et al. have further demonstrated that human Breg cells control Tfh cells maturation, expand Tfr cells, and inhibit Tfh cell–mediated antibody secretion.[83] These observations highlight the pleiotropic functions of both Tfr and Tfh cells in the modulation of anti- and proatherosclerotic immune processes in an $Apoe^{-/-}$ mouse model.

## 5 | CONCLUSION

The role of immune cells in atherosclerosis has already been well studies, particularly T and B cells. Recent discoveries of new lymphocyte subsets, however, require constant updating of our knowledge to have a better understanding of the disease. The ability of Tfh and Tfr cells to modulate atherosclerosis permitted to highlight the mutual regulation between B and T cells. Although further investigations are required in the field of immunomodulation of atherosclerosis, the atheroprotective properties of Tfr population through the control of Tfh cells, Breg cells, lymphangiogenesis, and lipid metabolism make Tfr cell population a key player of atherogenesis (Fig. 1). Moreover, the appearance of new T cell subsets spotlights the importance to further consider T and B cells subsets interactions, their localization and their functions, not only in the artery wall but also on the lymphatic system, all promising lines of research. More largely, the study of immune system and its potential outcomes will certainly participate to unravel the complicated multifactorial physiopathology of atherosclerosis.

## REFERENCES


1. Benjamin EJ, Virani SS, Callaway CW, et al. Heart Disease and Stroke Statistics-2018 Update: a Report from the American Heart Association. *Circulation*. 2018.
2. Libby P. Inflammation in atherosclerosis. *Nature*. 2002;420:868–874.
3. Ross R, Harker L. Hyperlipidemia and atherosclerosis. *Science*. 1976;193:1094–1100.
4. Tacke F, Alvarez D, Kaplan TJ, et al. Monocyte subsets differentially employ CCR2, CCR5, and CX3CR1 to accumulate within atherosclerotic plaques. *J Clin Invest*. 2007;117:185–194.
5. Swirski FK, Nahrendorf M. Leukocyte behavior in atherosclerosis, myocardial infarction, and heart failure. *Science*. 2013;339:161–166.
6. Stary HC, Chandler AB, Dinsmore RE, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Arterioscler Thromb Vasc Biol*. 1995;15:1512–1531.
7. Ley K, Miller YI, Hedrick CC. Monocyte and macrophage dynamics during atherogenesis. *Arterioscler Thromb Vasc Biol*. 2011;31:1506–1516.
8. Hansson GK, Robertson AK, Soderberg-Naucler C. Inflammation and atherosclerosis. *Annu Rev Pathol*. 2006;1:297–329.
9. Hansson GK, Holm J, Jonasson L. Detection of activated T lymphocytes in the human atherosclerotic plaque. *Am J Pathol*. 1989;135:169–175.
10. Zhou X, Stemme S, Hansson GK. Evidence for a local immune response in atherosclerosis. CD4+ T cells infiltrate lesions of apolipoprotein-E-deficient mice. *Am J Pathol*. 1996;149:359–366.
11. Zhou X, Hansson GK. Detection of B cells and proinflammatory cytokines in atherosclerotic plaques of hypercholesterolaemic apolipoprotein E knockout mice. *Scand J Immunol*. 1999;50:25–30.
12. Zhou X, Nicoletti A, Elhage R, Hansson GK. Transfer of CD4(+) T cells aggravates atherosclerosis in immunodeficient apolipoprotein E knockout mice. *Circulation*. 2000;102:2919–2922.
13. Caligiuri G, Paulsson G, Nicoletti A, Maseri A, Hansson GK. Evidence for antigen-driven T-cell response in unstable angina. *Circulation*. 2000;102:1114–1119.
14. Shimokama T, Haraoka S, Watanabe T. Immuno-histochemical and ultrastructural demonstration of the lymphocyte-macrophage interaction in human aortic intima. *Mod Pathol*. 1991;4(1):101–107.
15. Paulsson G, Zhou X, Tornquist E, Hansson GK. Oligoclonal T cell expansions in atherosclerotic lesions of apolipoprotein E-deficient mice. *Arterioscler Thromb Vasc Biol*. 2000;20:10–17.
16. Hermansson A, Ketelhuth DF, Strodthoff D, et al. Inhibition of T cell response to native low-density lipoprotein reduces atherosclerosis. *J Exp Med*. 2010;207:1081–1093.
17. Stemme S, Faber B, Holm J, Wiklund O, Witztum JL, Hansson GK. T lymphocytes from human atherosclerotic plaques recognize oxidized low density lipoprotein. *Proc Nat Acad Sci U S A*. 1995;92:3893–3897.
18. Afek A, George J, Gilburd B, et al. Immunization of low-density lipoprotein receptor deficient (LDL-RD) mice with heat shock protein 65 (HSP-65) promotes early atherosclerosis. *J Autoimmun*. 2000;14:115–121.
19. Ait-Oufella H, Taleb S, Mallat Z, Tedgui A. Recent advances on the role of cytokines in atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2011;31:969–979.
20. Getz GS, Reardon CA. Animal models of atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2012;32:1104–1115.
21. Gewaltig J, Kummer M, Koella C, Cathomas G, Biedermann BC. Requirements for CD8 T-cell migration into the human arterial wall. *Hum Pathol*. 2008;39:1756–1762.
22. 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;127:1028–1039.
23. Clement M, Guedj K, Andreata F, et al. Control of the T follicular helper-germinal center B-cell axis by CD8(+) regulatory T cells limits atherosclerosis and tertiary lymphoid organ development. *Circulation*. 2015;131:560–570.
24. Nus M, Sage AP, Lu Y, et al. Marginal zone B cells control the response of follicular helper T cells to a high-cholesterol diet. *Nat Med*. 2017;23:601–610.
25. Davenport P, Tipping PG. The role of interleukin-4 and interleukin-12 in the progression of atherosclerosis in apolipoprotein E-deficient mice. *Am J Pathol*. 2003;163:1117–1125.
26. Gaddis DE, Padgett LE, Wu R, et al. Apolipoprotein AI prevents regulatory to follicular helper T cell switching during atherosclerosis. *Nat Commun*. 2018;9:1095.
27. Burger F, Baptista D, Roth A, Fraga-Silva RA, Martel C, Stergiopulos N, Mach F, Brandt KJ. Follicular regulatory helper T cells control the response of regulatory B cells to a high-cholesterol diet and the lymphangiogenesis. 2018; to be published.
28. Emeson EE, Shen ML, Bell CG, Qureshi A. Inhibition of atherosclerosis in CD4 T-cell-ablated and nude (nu/nu) C57BL/6 hyperlipidemic mice. *Am J Pathol*. 1996;149:675–685.
29. Buono C, Binder CJ, Stavrakis G, Witztum JL, Glimcher LH, Lichtman AH. T-bet deficiency reduces atherosclerosis and alters plaque antigen-specific immune responses. *Proc Nat Acad Sci U S A*. 2005;102:1596–1601.
30. Breitfeld D, Ohl L, Kremmer E, et al. Follicular B helper T cells express CXC chemokine receptor 5, localize to B cell follicles, and support immunoglobulin production. *J Exp Med*. 2000;192:1545–1552.
31. Kim CH, Rott LS, Clark-Lewis I, Campbell DJ, Wu L, Butcher EC. Subspecialization of CXCR5+ T cells: b helper activity is focused in a germinal center-localized subset of CXCR5+ T cells. *J Exp Med*. 2001;193:1373–1381.
32. Zhu J, Yamane H, Paul WE. Differentiation of effector CD4 T cell populations (*). *Annu Rev Immunol*. 2010;28:445–489.
33. Zhu Y, Zou L, Liu YC. T follicular helper cells, T follicular regulatory cells and autoimmunity. *Int Immunol*. 2016;28:173–179.

34. Gunn MD, Ngo VN, Ansel KM, Ekland EH, Cyster JG, Williams LT. A B-cell-homing chemokine made in lymphoid follicles activates Burkitt's lymphoma receptor-1. *Nature*. 1998;391:799–803.

35. Linterman MA, Pierson W, Lee SK, et al. Foxp3+ follicular regulatory T cells control the germinal center response. *Nat Med*. 2011;17:975–982.

36. Chung Y, Tanaka S, Chu F, et al. Follicular regulatory T cells expressing Foxp3 and Bcl-6 suppress germinal center reactions. *Nat Med*. 2011;17:983–988.

37. Frostegard J, Ulfgren AK, Nyberg P, et al. Cytokine expression in advanced human atherosclerotic plaques: dominance of pro-inflammatory (Th1) and macrophage-stimulating cytokines. *Atherosclerosis*. 1999;145:33–43.

38. Hedrick CC. Lymphocytes in atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2015;35:253–257.

39. Gong F, Liu Z, Liu J, Zhou P, Liu Y, Lu X. The paradoxical role of IL-17 in atherosclerosis. *Cell Immunol*. 2015;297:33–39.

40. Ait-Oufella H, Salomon BL, Potteaux S, et al. Natural regulatory T cells control the development of atherosclerosis in mice. *Nat Med*. 2006;12:178–180.

41. Zhou J, Dimayuga PC, Zhao X, et al. CD8(+)CD25(+) T cells reduce atherosclerosis in apoE(-/-) mice. *Biochem Biophys Res Commun*. 2014;443:864–870.

42. Kataru RP, Kim H, Jang C, et al. T lymphocytes negatively regulate lymph node lymphatic vessel formation. *Immunity*. 2011;34:96–107.

43. Martel C, Li W, Fulp B, et al. Lymphatic vasculature mediates macrophage reverse cholesterol transport in mice. *J Clin Invest*. 2013;123:1571–1579.

44. Savetsky IL, Ghanta S, Gardenier JC, et al. Th2 cytokines inhibit lymphangiogenesis. *PLoS One*. 2015;10:e0126908.

45. Kutkut I, Meens MJ, McKee TA, Bochaton-Piallat ML, Kwak BR. Lymphatic vessels: an emerging actor in atherosclerotic plaque development. *Eur J Clin Invest*. 2015;45:100–108.

46. Foks AC, Frodermann V, ter Borg M, et al. Differential effects of regulatory T cells on the initiation and regression of atherosclerosis. *Atherosclerosis*. 2011;218:53–60.

47. Maganto-Garcia E, Tarrio ML, Grabie N, Bu DX, Lichtman AH. Dynamic changes in regulatory T cells are linked to levels of diet-induced hypercholesterolemia. *Circulation*. 2011;124:185–195.

48. Mor A, Luboshits G, Planer D, Keren G, George J. Altered status of CD4+CD25+ regulatory T cells in patients with acute coronary syndromes. *Eur Heart J*. 2006;27:2530–2537.

49. Mor A, Planer D, Luboshits G, et al. Role of naturally occurring CD4+ CD25+ regulatory T cells in experimental atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2007;27:893–900.

50. Ji QW, Guo M, Zheng JS, et al. Downregulation of T helper cell type 3 in patients with acute coronary syndrome. *Arch Med Res*. 2009;40:285–293.

51. Wang Z, Mao S, Zhan Z, Yu K, He C, Wang C. Effect of hyperlipidemia on Foxp3 expression in apolipoprotein E-knockout mice. *J Cardiovasc Med (Hagerstown)*. 2014;15:273–279.

52. Gotsman I, Grabie N, Gupta R, et al. Impaired regulatory T-cell response and enhanced atherosclerosis in the absence of inducible costimulatory molecule. *Circulation*. 2006;114:2047–2055.

53. Feng J, Zhang Z, Kong W, Liu B, Xu Q, Wang X. Regulatory T cells ameliorate hyperhomocysteinaemia-accelerated atherosclerosis in apoE-/- mice. *Cardiovasc Res*. 2009;84:155–163.

54. van Es T, van Puijvelde GH, Foks AC, et al. Vaccination against Foxp3(+) regulatory T cells aggravates atherosclerosis. *Atherosclerosis*. 2010;209:74–80.

55. Weber C, Meiler S, Doring Y, et al. CCL17-expressing dendritic cells drive atherosclerosis by restraining regulatory T cell homeostasis in mice. *J Clin Invest*. 2011;121:2898–2910.

56. Klingenberg R, Gerdes N, Badeau RM, et al. Depletion of FOXP3+ regulatory T cells promotes hypercholesterolemia and atherosclerosis. *J Clin Invest*. 2013;123:1323–1334.

57. Lin J, Li M, Wang Z, He S, Ma X, Li D. The role of CD4+CD25+ regulatory T cells in macrophage-derived foam-cell formation. *J Lipid Res*. 2010;51:1208–1217.

58. Zhou X, Bailey-Bucktrout SL, Jeker LT, et al. Instability of the transcription factor Foxp3 leads to the generation of pathogenic memory T cells in vivo. *Nat Immunol*. 2009;10:1000–1007.

59. Robertson AK, Rudling M, Zhou X, Gorelik L, Flavell RA, Hansson GK. Disruption of TGF-beta signaling in T cells accelerates atherosclerosis. *J Clin Invest*. 2003;112:1342–1350.

60. Gojova A, Brun V, Esposito B, et al. Specific abrogation of transforming growth factor-beta signaling in T cells alters atherosclerotic lesion size and composition in mice. *Blood*. 2003;102:4052–4058.

61. Yusuf I, Kageyama R, Monticelli L, et al. Germinal center T follicular helper cell IL-4 production is dependent on signaling lymphocytic activation molecule receptor (CD150). *J Immunol*. 2010;185:190–202.

62. Crotty S. Follicular helper CD4 T cells (TFH). *Annu Rev Immunol*. 2011;29:621–663.

63. Nurieva RI, Chung Y, Martinez GJ, et al. Bcl6 mediates the development of T follicular helper cells. *Science*. 2009;325:1001–1005.

64. LaPensee CR, Lin G, Dent AL, Schwartz J. Deficiency of the transcriptional repressor B cell lymphoma 6 (Bcl6) is accompanied by dysregulated lipid metabolism. *PLoS One*. 2014;9:e97090.

65. Allman D, Jain A, Dent A, et al. BCL-6 expression during B-cell activation. *Blood*. 1996;87:5257–5268.

66. Yu RY, Wang X, Pixley FJ, et al. BCL-6 negatively regulates macrophage proliferation by suppressing autocrine IL-6 production. *Blood*. 2005;105:1777–1784.

67. Wei Y, Zhu M, Corbalan-Campos J, Heyll K, Weber C, Schober A. Regulation of Csf1r and Bcl6 in macrophages mediates the stage-specific effects of microRNA-155 on atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2015;35:796–803.

68. Vuorio T, Nurmi H, Moulton K, et al. Lymphatic vessel insufficiency in hypercholesterolemic mice alters lipoprotein levels and promotes atherogenesis. *Arterioscler Thromb Vasc Biol*. 2014;34:1162–1170.

69. Tsiantoulas D, Diehl CJ, Witztum JL, Binder CJ. B cells and humoral immunity in atherosclerosis. *Circ Res*. 2014;114:1743–1756.

70. Tsiantoulas D, Sage AP, Mallat Z, Binder CJ. Targeting B cells in atherosclerosis: closing the gap from bench to bedside. *Arterioscler Thromb Vasc Biol*. 2015;35:296–302.

71. Michael Munro J, Van der Walt JD, Munro CS, Chalmers JAC, Cox EL. An immunohistochemical analysis of human aortic fatty streaks. *Human Pathol*. 1987;18:375–380.

72. Aubry MC, Riehle DL, Edwards WD, et al. B-Lymphocytes in plaque and adventitia of coronary arteries in two patients with rheumatoid arthritis and coronary atherosclerosis: preliminary observations. *Cardiovasc Pathol*. 2004;13:233–236.

73. Caligiuri G, Nicoletti A, Poirier B, Hansson GK. Protective immunity against atherosclerosis carried by B cells of hypercholesterolemic mice. *J Clin Invest*. 2002;109:745–753.

74. Doran AC, Lipinski MJ, Oldham SN, et al. B-cell aortic homing and atheroprotection depend on Id3. *Circ Res*. 2012;110:e1–e12.

75. Kyaw T, Tay C, Krishnamurthi S, et al. B1a B lymphocytes are atheroprotective by secreting natural IgM that increases IgM deposits

and reduces necrotic cores in atherosclerotic lesions. *Circ Res*. 2011;109:830–840.

76. Rosenfeld SM, Perry HM, Gonen A, et al. B-1b cells secrete atheroprotective IgM and attenuate atherosclerosis. *Circ Res*. 2015;117:e28–39.
77. Kyaw T, Tay C, Khan A, et al. Conventional B2 B cell depletion ameliorates whereas its adoptive transfer aggravates atherosclerosis. *J Immunol*. 2010;185:4410–4419.
78. Nus M, Tsiantoulas D, Mallat Z. Plan B (-cell) in atherosclerosis. *Eur J Pharmacol*. 2017;816:76–81.
79. Sage AP, Nus M, Baker LL, Finigan AJ, Masters LM, Mallat Z. Regulatory B cell-specific interleukin-10 is dispensable for atherosclerosis development in mice. *Arterioscler Thromb Vasc Biol*. 2015;35:1770–1773.
80. Strom AC, Cross AJ, Cole JE, et al. B regulatory cells are increased in hypercholesterolaemic mice and protect from lesion development via IL-10. *Thromb Haemost*. 2015;114:835–847.
81. Taitano SH, Lundy SK. Regulation of regulatory B cells by Th2 cytokines. *J Immunol*. 2016;196:204.24.
82. Dhaeze T, Stinissen P, Liston A, Hellings N. Humoral autoimmunity: a failure of regulatory T cells?. *Autoimmun Rev*. 2015;14:735–741.
83. Achour A, Simon Q, Mohr A, et al. Human regulatory B cells control the TFH cell response. *J Allergy Clin Immunol*. 2017;140:215–222.
84. Schaerli P, Willimann K, Lang AB, Lipp M, Loetscher P, Moser B. CXC chemokine receptor 5 expression defines follicular homing T cells with B cell helper function. *J Exp Med*. 2000;192:1553–1562.
85. Haynes NM, Allen CDC, Lesley R, Ansel KM, Killeen N, Cyster JG. Role of CXCR5 and CCR7 in follicular Th cell positioning and appearance of a programmed cell death gene-1(High) germinal center-associated subpopulation. *J Immunol*. 2007;179:5099–5108.
86. Reinhardt RL, Liang HE, Locksley RM. Cytokine-secreting follicular T cells shape the antibody repertoire. *Nat Immunol*. 2009;10:385–393.
87. Maceiras AR, Graca L. Identification of Foxp3+ T follicular regulatory (Tfr) cells by flow cytometry. In: Espéli M and Linterman M, eds. *T follicular Helper Cells: Methods and Protocols*. New York, NY: Springer New York; 2015:143–150.
88. Nurieva RI, Chung Y, Hwang D, et al. Generation of T follicular helper cells is mediated by interleukin-21 but independent of T helper 1, 2, or 17 cell lineages. *Immunity*. 2008;29:138–149.
89. Yang M, Rui K, Wang S, Lu L. Regulatory B cells in autoimmune diseases. *Cell Mol Immunol*. 2013;10:122–132.
90. Rosser EC, Mauri C. Regulatory B cells: origin, phenotype, and function. *Immunity*. 2015;42:607–612.
91. Sage PT, Sharpe AH. T follicular regulatory cells in the regulation of B cell responses. *Trends Immunol*. 2015;36:410–418.
92. Ketelhuth DF, Hansson GK. Cellular immunity, low-density lipoprotein and atherosclerosis: break of tolerance in the artery wall. *Thromb Haemost*. 2011;106:779–786.
93. Mallat Z, Gojova A, Marchiol-Fournigault C, et al. Inhibition of transforming growth factor-beta signaling accelerates atherosclerosis and induces an unstable plaque phenotype in mice. *Circ Res*. 2001;89:930–934.

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