Review

Regulatory T Cells and Cardiovascular Diseases

Harish Jevallee, MD; Ting-Ting Tang, MD, PhD; Xiang Cheng, MD, PhD*

Laboratory of Cardiovascular Immunology, Institute of Cardiology, Union Hospital, Tongji Medical College of Huazhong University of Science and Technology; Key Laboratory of Biological Targeted Therapy of the Ministry of Education, Wuhan, Hebei, China

Recent researches have substantiated the active participation of chronic low-grade inflammation in cardiovascular disease where immune responses contribute to disease initiation and progression. Regulatory T cells (Tregs) are a unique lineage of T cells and have been proved to play a key role in controlling both the innate and adaptive immune responses under physiological and pathological conditions. Through suppression of immune system activation, Tregs are involved in tolerance to self antigens, thus maintaining immune homeostasis. Existence and function of Tregs were a matter of considerable debate over the last few decades, but owing to innovative molecular categorization of this specialized subpopulation of T cells, they have now been established as fundamental elements in the vertebrate immune system. In view of the prospective therapeutic avenues that Tregs may offer, we hereby review the current knowledge on the role of Tregs immunity in cardiovascular disease.
[N A J Med Sci. 2011;4(4):178-182.]

Key Words: *regulatory T cells, inflammation, cardiovascular diseases*

INTRODUCTION

There is emerging evidence that both innate and adaptive immune responses play a role in cardiovascular disease including coronary artery disease (CAD),[1-3] hypertension,[4-5] myocarditis,[6-7] heart failure[8-10] and aneurysm.[11-12] Different subsets of lymphocytes and the cytokines, produced by the immune system, participate in the pathogenesis of cardiovascular disease. However, regulatory T cells (Tregs) play an essential role in the modulation of immune responses and the control of potentially harmful immune activations due to their immunoregulatory and immunosuppressive characteristics.[13-14] Recent years saw a heightened interest in Tregs following experimental studies which suggest that the immunosuppressive potential of these cells can be further exploited to treat autoimmune diseases and help in cancer immunotherapy.[15-19] Among the several types of T cell subsets with suppressive functions reported till now, naturally occurring CD4+CD25+ Tregs are the most important, because accumulating evidence points towards their crucial role in the maintenance of immunological self tolerance and negative control of pathological as well as physiological immune responses.[15,20] Thymic development of this lineage of CD4+ T cells necessitates unique interactions of their T cell receptors with self-peptide/MHC complexes[21] and presence of soluble molecules (such as CD28, B7, and CD40).[22-23] In addition, expression of forkhead/winged helix transcription factor 3 (FOXP3) is considered to be an essential factor for the proper development, maintenance and function of CD4+CD25+ Tregs.[24-25]

Received 10/1/2011; Revised 10/5/2011; Accepted 10/19/2011
***Corresponding Author:** Laboratory of Cardiovascular Immunology, Institute of Cardiology, Union Hospital, Tongji Medical College of Huazhong University of Science and Technology, Key Laboratory of Biological Targeted Therapy of the Ministry of Education. Wuhan, Hubei, China 430000. (Email: nathancx@mail.hust.edu.cn)

Tregs can be categorized into two groups according to their site of development: thymus-derived natural Tregs and periphery-induced adaptive Tregs.[26] Both groups express FOXP3 and control immune responses through contact-dependent mechanisms and release of cytokines.[27-28] Thymus-derived CD4+CD25+ Tregs can be differentiated from the adaptive Treg cells because their FOXP3 locus is demethylated[29] and they express the transcription factor Helios.[30] Besides, other T cell subsets with suppressive functions consist of Type 1 regulatory T (Tr1) cells and T helper 3 (TH3) cells, which are both extrathymically generated under a whole host of conditions.[26] Tr1 and TH3 suppress T cell proliferation through secretion of transforming growth factor‑β (TGF-β) while the former also mediates suppression through the production of interleukin-10 (IL-10).[31-32] In 2008, Vignali et al [28] reviewed the different mechanisms responsible for the function of CD4+CD25+ Tregs in controlling immunity. The latter achieve suppression of T effector cells through inhibitory cytokines (IL-10, IL-35 and TGF-β) and through direct cytotoxic effect mediated by granzyme A and perforin. Moreover, Tregs cause metabolic disruption of effector T cells by competing directly for essential growth factors such as IL-2 and hence depleting IL-2 for proper survival of T effector cells. Finally, dendritic cells, vital for effector T cells activation, may undergo altered maturation/ function as result of Tregs regulation.

Congenital absence of Tregs, consequently, cause serious impairment of self tolerance and immunoregulation, leading to severe autoimmune diseases, immunopathology, and allergy in human.[33] Experiments in various animal models have provided supporting evidence to the autoimmune-inhibitory activity of Tregs.[34-35] Thymectomy in neonatal mice resulted in development of several autoimmune diseases

including gastritis, thyroiditis, and oophoritis in selected species of mice.[34-36] In addition, studies also showed that adult thymectomy can lead to thyroiditis and type 1 diabetes in selected strains of rats.[37-38] On the other hand, transfer of CD4+ T cells from histocompatible normal animals to NOD mice or Bio-Breeding (BB) rats, which are prone to autoimmune diseases, effectively prevented type 1 diabetes.[39-40] Therefore, these studies clearly show the crucial role of Tregs and any defect in this population can lead to disease. Genetics are considered to have the greatest impact on the mechanisms involved in Tregs defect. Factors contributing to failure of T cell regulation could be linked to either defects in the number and function of Tregs, or a resistance of effector T cells to Tregs-mediated immunosuppression.[41]

Since cardiovascular disease is the leading cause of death globally as per WHO, we hereby review the recent advances on the role of Tregs in cardiovascular diseases.

TREGS AND ATHEROSCLEROSIS

T lymphocytes play a significant role in atherosclerosis and in acute manifestation of plaque destabilization.[1-3] As atherosclerosis is the principal cause of CAD, it is worth reviewing the mechanism involved in its genesis. It is now well known that atherosclerosis occurs as a result of chronic inflammatory process within the arterial wall where endogenously modified structures, particularly oxidized lipoproteins, are the stimuli in activating both innate and adaptive immune responses.[1,3] The latter response is represented by T cells, in which Th1 response exhibits a potent pro-atherogenic effect balanced by the atheroprotective role of regulatory T cells and some Th2-related cytokines.[42]

Several animal studies have demonstrated that Tregs play a protective role in atherogenesis.[43-47] In one experiment, the functional role of CD4+CD25+ Tregs in atherosclerosis was investigated and the results showed that transfer of these T cells considerably reduced plaque progression in the ApoE knockout mouse model.[44] Tregs also have the ability to modulate the transition of macrophages into foam cells in mice, thus exerting a suppressive effect on macrophage foam-cell formation and preventing atherogenesis.[43] In addition, as supporting evidence to Tregs atheroprotective role, mice treated with oral anti-CD3 antibody, responsible for induction of Tregs, showed significant reduction in atherosclerotic lesion formation.[46] On the other hand, the few human studies on circulating Tregs numbers in patients with CAD, reported contrasting results.[48-52] Four studies showed that the Tregs number decreased in CAD patients,[48-51] while one study reported that Tregs decreased in non-ST-elevation acute coronary syndrome patients and increased in ST-elevation acute myocardial infarction.[52] This discrepancy may be partly due to the experimental method and the quality of flow cytometry-based identification of Tregs.

Even though animal model studies constantly show that an increase in Tregs level and function is coupled with reduced atherosclerosis, data from human studies are less clear. The underlying reason may be the cell surface phenotype and functional potential [53] of human Tregs population exhibits more heterogeneity than that of animal models. Therefore, the contrasting result observed in one study,[52] concerning association between circulating Tregs level and extent of atherosclerosis, may be partially due to difficulty in defining Tregs precisely in the human. In addition, the surface markers used to define Tregs, including expression markers (IL-10 and FOXP3), may not be enough to accurately differentiate all the subsets of Tregs and as a matter of fact, adaptive Tregs or Tr1 still lack specific surface marker molecules [54] to be detected. However, we cannot ignore the studies showing the positive results in human [48-51] and animal models. Besides determination of peripheral blood Tregs, another human study also showed decreased FOXP3+ Tregs in all developmental stages of human atherosclerotic lesions and thus suggested that Tregs has a vital role in atherosclerosis reduction. However, the exact mechanism remains to be proved and this field requires further studies with productive results to enlighten the path of potential therapeutic avenues.

TREGS AND HYPERTENSION

Over the past decade, it has been increasingly documented that vascular inflammation, following infiltration of immune cells, plays a vital role in the development of cardiovascular diseases and hypertension.[55] Besides vascular growth and proliferation of vascular smooth muscle cells, inflammation leads to vascular remodeling that contributes in the mechanisms leading to blood pressure elevation.[56-57] Thus, subsets of T lymphocytes also share important part in the pathogenesis of angiotensin II, deoxycorticosterone salt-sensitive and Dahl salt-sensitive hypertension, and in vascular remodeling.[58]

Recently, Barhoumi et al showed that adoptive transfer of Tregs to Angiotensin II-infused mice lowered systolic blood pressure, reduced inflammatory mediators and immune cells in kidney, decreased generation of superoxide and immune cell infiltration in vascular and perivascular tissue as well as reduced small artery stiffness.[59] Furthermore, two studies demonstrated that adoptive transfer of Tregs to angiotension II-infused or aortic constriction mice ameliorated cardiac damage, prevented cardiac fibrosis and improved electric remodeling though no decrease in blood pressure was noted.[60-61] These data offer promise for the discovery of new therapeutic targets to ameliorate vascular remodeling, which could lead to improved outcome of cardiovascular disease in human.

TREGS AND CHRONIC HEART FAILURE (CHF)

Heart Failure is marked by an ongoing inflammatory process directly affecting the severity and prognosis of the disease as demonstrated by the elevated level of cytokines in blood and T-cell activation.[62-63] However, the exact mechanism of immune activation remains to be elucidated. In 1990, Levine et al [64] first brought to light, the association between CHF and inflammatory cytokine, tumor necrosis factor (TNF) and since then there has been a lot of progress in this field.

Mounting evidence is now pointing towards a key role played by Tregs in chronic heart failure (CHF). Previous experiments have conclusively revealed the defects of CD4+CD25+ FOXP3+CD127low Tregs in this disease, suggesting that defective Tregs may be an underlying mechanism of immune activation in CHF patients.[65-66] Defective Tregs may be involved in the disturbed immune homeostasis and thus responsible for the uncontrolled T cells activation in CHF, which further leads to myocardial injury and deleterious effect on cardiac function. Moreover, suppressive function of Tregs was found to be affected irrespective of the etiology of CHF. Correlation analysis suggested that Tregs frequency and function positively correlated with LVEF, whereas negatively correlated with LVEDD and NT-proBNP in patients with CHF.[65]

In an attempt to explore the mechanism of Tregs defects in CHF, one study suggested that reduced Tregs number and function might be explained by impaired Tregs thymic output and increased apoptosis of these cell populations.[66] Another noteworthy research showed that an imbalance between Th17 and Tregs existed in CHF patients.[67] Though they share reciprocal developmental pathways, Th17 and Tregs exhibit opposite effects, and it was suggested that the balance between them controls inflammation.

Pathological cardiac remodeling due to cardiovascular insults such as myocardial infarction and hypertension is associated with inflammation.[68] Vakan H et al[60] demonstrated that Tregs transfer improves Ang II-induced cardiac damage by reducing cardiac hypertrophy and fibrosis. It thereby provides evidence of Tregs having a fundamental role in improving electric remodeling in hypertension/Ang II–induced cardiac damage.

TREGS AND ABDOMINAL AORTIC ANEURYSM

Accumulating evidence shows that immune response also contributes importantly to aneurysmal disease, and thus Tregs are also involved in abdominal aortic aneurysms (AAAs), which are a major cause of morbidity and mortality in the Western countries, even though the exact mechanism of this disease remains unclear.[69-72]

Wang et al investigated the role of Tregs in AAA formation by using C57BL/6 mice model based on the facts that infusion of Ang II promotes AAA in hypercholesterolemic mice [73] and that CD28 deficiency leads to a profound reduction in Tregs.[74] Ang II was infused into C57BL/6 CD28+/+ and CD28–/– mice and 4 weeks later it was observed that Ang II induced AAA in only 11.8% of CD28+/+ mice while 81.8% of CD28–/–mice showed AAA. These results indirectly suggest that natural Tregs are efficient inhibitors of AAA formation.[75]
To support this fact, a clinical study demonstrated that there was a decline in FOXP3 expression in peripheral CD4+CD25+ Tregs as well as a decreased number of CD4+CD25+FOXP3+ T cells in a group of AAA patients, which resulted in a lack of functional capacity of CD4+CD25+ Tregs as a whole. Accordingly it was suggested that an impaired immunoregulation by Tregs may contribute to AAA pathogenesis.[76]

TREGS AND MYOCARDITIS

Myocarditis is characterized by inflammatory infiltrates in heart tissue,[77] for which Th1 and Th2 cell mediated immunity has been held responsible, though cases independent of Th1 and Th2 have been documented.[78] On the other hand, Tregs contribute to the negative modulation of host immune responses and determine threshold for autoimmune activation.[13-14] Shi Y et al [79] reported how adoptive transfer of Tregs regulates and maintains the adequate antiviral immune response to Coxsackievirus B3 (CVB3) in heart tissue, and thereby demonstrated the protective effects of Tregs in CVB3-induced myocarditis. Tregs-transferred mice were shown to have decrease virus titers and inflammatory cells in the heart. This was due to upregulation of TGF-β and phosphorylated AKT, which resulted in decrease expression of coxsackie-adenovirus receptors in heart compared to control groups.[79-80]

Moreover, Masahiro et al showed in their study that most FOXP3-expressing CD4+ T cells constitutively express high level of glucocorticoid-induced TNFR family-related gene/protein (GITR), which contribute in prevention of autoimmune/inflammatory diseases.[81] A deficit in these cells in mice yielded in severe multiorgan inflammation, including fatal autoimmune myocarditis showing similarity to giant cell myocarditis in human. Furthermore, researchers demonstrated that more functionally active Tregs are present in γδ+ T-cell depleted mice and mice receiving CD4+ CD25+ cells from γδ+ T-cell-depleted donors had a lower incidence of coxsackievirus B3-induced myocarditis.[82]

CONCLUSION

The last decade has witnessed a very important progress in understanding the role of Tregs in cardiovascular disease. Insight from these studies, mirrors the possibility of developing novel therapeutic strategies targeting Tregs, which may alter the outcome of cardiovascular diseases and prevent complication. Nevertheless, the main subtypes of Tregs responsible for these protective effects and the exact molecular mechanisms involved in the immune reactions remain still unclear. A great deal of effort should be directed towards these issues in future so as to translate the protective role of Tregs in clinical practice.

CONFLICT OF INTEREST
No conflict of interest.

REFERENCES

1. Weber C, Zernecke A, Libby P. The multifaceted contributions of leukocyte subsets to atherosclerosis: lessons from mouse models. Nat Rev Immunol. 2008;8(10):802-815.
2. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med. 2005;352:1685–1695.
3. Tedgui A, Mallat Z. Cytokines in atherosclerosis: pathogenic and regulatory pathways. Physiol Rev. 2006;86(2):515-581.
4. Leibowitz A, Schiffrin EL. Immune Mechanisms in Hypertension. Curr Hypertens Rep. 2011 Aug 13. [Epub ahead of print]
5. Harrison DG, Guzik TJ, Goronzy J, Weyand C. Is hypertension an immunologic disease? Curr Cardiol Rep. 2008;10(6):464-469.

6. Rose NR. Myocarditis: infection versus autoimmunity. J Clin Immunol. 2009;29(6):730-737.
7. Esfandiarei M, McManus BM. Molecular biology and pathogenesis of viral myocarditis. Annu Rev Pathol. 2008;3:127-155.
8. Liao YH, Cheng X. Autoimmunity in myocardial infarction. Int J Cardiol. 2006;112(1):21-26.
9. Satoh M, Minami Y, Takahashi Y, Nakamura M. Immune modulation: role of the inflammatory cytokine cascade in the failing human heart. Curr Heart Fail Rep. 2008;5(2):69-74.
10. Torre-Amione G. Immune activation in chronic heart failure. Am J Cardiol. 2005;95(11A):3C-8C
11. Shimizu K, Mitchell RN, Libby P. Inflammation and cellular immune responses in abdominal aortic aneurysms. Arterioscler Thromb Vasc Biol. 2006;26(5):987-994.
12. Lindholt JS, Shi GP. Chronic inflammation, immune response, and infection in abdominal aortic aneurysms. Eur J Vasc Endovasc Surg. 2006;31(5):453-463.
13. Sakaguchi S, Ono M, Setoguchi R, et al. Foxp3+ CD25+ CD4+ natural regulatory T cells in dominant self-tolerance and autoimmune disease. Immunol Rev. 2006;212:8-27.
14. Sakaguchi S, Yamaguchi T, Nomura T, Ono M. Regulatory T cells and immune tolerance. Cell. 2008;133(5):775-87.
15. Fehérvari Z, Sakaguchi S. CD4+ Tregs and immune control. J Clin Invest. 2004;114(9):1209-1217.
16. Shimizu J, Yamazaki S, Sakaguchi S. Induction of tumor immunity by removing CD25+CD4+ T cells: a common basis between tumor immunity and autoimmunity. J Immunol. 1999;163(10):5211-5218.
17. Baecher-Allan C, Hafler DA. Suppressor T cells in human diseases. J Exp Med. 2004;200(3):273-276.
18. Viglietta V, Baecher-Allan C, Weiner HL, Hafler DA. Loss of functional suppression by CD4+CD25+ regulatory T cells in patients with multiple sclerosis. J Exp Med. 2004;199(7):971-979.
19. Ehrenstein MR, Evans JG, Singh A, et al. Compromised function of regulatory T cells in rheumatoid arthritis and reversal by anti-TNFalpha therapy. J Exp Med. 2004;200(3):277-285.
20. Sakaguchi S. Naturally arising CD4+ regulatory t cells for immunologic self-tolerance and negative control of immune responses. Annu Rev Immunol. 2004;22:531-562.
21. Jordan MS, Boesteanu A, Reed AJ, et al. Thymic selection of CD4+CD25+ regulatory T cells induced by an agonist self-peptide. Nat Immunol. 2001;2(4):301-306.
22. Salomon B, Lenschow DJ, Rhee L, Ashourian N, Singh B, Sharpe A, Bluestone JA. B7/CD28 costimulation is essential for the homeostasis of the CD4+CD25+ immunoregulatory T cells that control autoimmune diabetes. Immunity. 2000;12(4):431-440.
23. Kumanogoh A, Wang X, Lee I, et al. Increased T cell autoreactivity in the absence of CD40-CD40 ligand interactions: a role of CD40 in regulatory T cell development. J Immunol. 2001;166(1):353-360.
24. Hori S, Nomura T, Sakaguchi S. Control of regulatory T cell development by the transcription factor Foxp3. Science. 2003;299(5609):1057-1061.
25. Fontenot JD, Gavin MA, Rudensky AY. Foxp3 programs the development and function of CD4+CD25+ regulatory T cells. Nat Immunol. 2003;4(4):330-336.
26. Buckner JH. Mechanisms of impaired regulation by CD4(+)CD25(+)FOXP3(+) regulatory T cells in human autoimmune diseases. Nat Rev Immunol. 2010;10(12):849-859.
27. Sakaguchi S, Miyara M, Costantino CM, Hafler DA. FOXP3+ regulatory T cells in the human immune system. Nat Rev Immunol. 2010;10(7):490-500.
28. Vignali DA, Collison LW, Workman CJ. How regulatory T cells work. Nat Rev Immunol. 2008;8(7):523-532.
29. Janson PC, Winerdal ME, Marits P, Thörn M, Ohlsson R, Winqvist O. FOXP3 promoter demethylation reveals the committed Treg population in humans. PLoS One. 2008;3(2):e1612.
30. Thornton AM, Korty PE, Tran DQ, et al. Expression of Helios, an Ikaros transcription factor family member, differentiates thymic-derived from peripherally induced Foxp3+ T regulatory cells. J Immunol. 2010;184(7):3433-3441.
31. Groux H, Bigler M, de Vries JE, Roncarolo MG. Interleukin-10 induces a long-term antigen-specific anergic state in human CD4+ T cells. J Exp Med. 1996;184(1):19-29.
32. Weiner HL. Induction and mechanism of action of transforming growth factor-beta-secreting Th3 regulatory cells. Immunol Rev. 2001;182:207-214.
33. Gambineri E, Torgerson TR, Ochs HD. Immune dysregulation, polyendocrinopathy, enteropathy, and X-linked inheritance (IPEX), a syndrome of systemic autoimmunity caused by mutations of FOXP3, a critical regulator of T-cell homeostasis. Curr Opin Rheumatol. 2003;15(4):430-435.
34. Sakaguchi S, Takahashi T, Nishizuka Y. Study on cellular events in post-thymectomy autoimmune oophoritis in mice. II. Requirement of Lyt-1 cells in normal female mice for the prevention of oophoritis. J Exp Med. 1982;156(6):1577-1586.
35. Sakaguchi S, Fukuma K, Kuribayashi K, Masuda T. Organ-specific autoimmune diseases induced in mice by elimination of T cell subset. I. Evidence for the active participation of T cells in natural self-tolerance; deficit of a T cell subset as a possible cause of autoimmune disease. J Exp Med. 1985;161(1):72-87.
36. Asano M, Toda M, Sakaguchi N, Sakaguchi S. Autoimmune disease as a consequence of developmental abnormality of a T cell subpopulation. J Exp Med. 1996;184(2):387-396.
37. Penhale WJ, Farmer A, McKenna RP, Irvine WJ. Spontaneous thyroiditis in thymectomized and irradiated Wistar rats. Clin Exp Immunol. 1973;15(2):225-236.
38. Fowell D, Mason D. Evidence that the T cell repertoire of normal rats contains cells with the potential to cause diabetes. Characterization of the CD4+ T cell subset that inhibits this autoimmune potential. J Exp Med. 1993;177(3):627-636.
39. Boitard C, Yasunami R, Dardenne M, Bach JF. T cell-mediated inhibition of the transfer of autoimmune diabetes in NOD mice. J Exp Med. 1989;169(5):1669-1680.
40. Greiner DL, Mordes JP, Handler ES, Angelillo M, Nakamura N, Rossini AA. epletion of RT6.1+ T lymphocytes induces diabetes in resistant iobreeding/Worcester (BB/W) rats. J Exp Med. 1987;166(2):461-475.
41. Buckner JH. Mechanisms of impaired regulation by CD4(+)CD25(+)FOXP3(+) egulatory T cells in human autoimmune diseases. Nat Rev Immunol. 2010;10(12):849-859.
42. Taleb S, Tedgui A, Mallat Z. Adaptive T cell immune responses and atherogenesis. Curr Opin Pharmacol. 2010;10(2):197-202.
43. 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(5):1208-1217.
44. 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(4):893-900.
45. Taleb S, Herbin O, Ait-Oufella H, et al. Defective leptin/leptin receptor signaling improves regulatory T cell immune response and protects mice from atherosclerosis. Arterioscler Thromb Vasc Biol. 2007;27(12):2691-2698.
46. Sasaki N, Yamashita T, Takeda M, et al. Oral anti-CD3 antibody treatment induces regulatory T cells and inhibits the development of atherosclerosis in mice. Circulation. 2009;120(20):1996-2005.
47. 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(1):155-163.
48. Han SF, Liu P, Zhang W, et al. The opposite-direction modulation of CD4+CD25+Tregs and T helper 1 cells in acute coronary syndromes. Clin Immunol. 2007;124:90-97.
49. 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.
50. Sardella G, De Luca L, Francavilla V, et al. Frequency of naturally-occurring regulatory T cells is reduced in patients with ST-segment elevation myocardial infarction. Thromb Res. 2007;120:631-634.
51. Cheng X, Yu X, Ding YJ, et al. The Th17/Treg imbalance in patients with acute coronary syndrome. Clin Immunol. 2008;127:89-97.
52. Ammirati E, Cianflone D, Banfi M, et al. Circulating CD4+CD25hiCD127lo regulatory T-Cell levels do not reflect the extent or severity of carotid and coronary atherosclerosis. Arterioscler Thromb Vasc Biol. 2010;30(9):1832-1841.
53. Costantino CM, Baecher-Allan CM, Hafler DA. Human regulatory T cells and autoimmunity. Eur J Immunol. 2008;38:921–924.
54. Bacchetta R, Gambineri E, Roncarolo MG. Role of regulatory T cells and FOXP3 in human diseases. J Allergy Clin Immunol. 2007;120:227–235.
55. Virdis A, Schiffrin EL. Vascular inflammation: a role in vascular disease in hypertension? Curr Opin Nephrol Hypertens. 2003;12(2):181-187.

56. Savoia C, Schiffrin EL. Vascular inflammation in hypertension and diabetes: molecular mechanisms and therapeutic interventions. Clin Sci (Lond). 2007;112(7):375-384.
57. Shao J, Nangaku M, Miyata T, et al. Imbalance of T-cell subsets in angiotensin II-infused hypertensive rats with kidney injury. Hypertension. 2003;42(1):31-38.
58. Schiffrin EL. T lymphocytes: a role in hypertension? Curr Opin Nephrol Hypertens. 2010;19(2):181-6.
59. Barhoumi T, Kasal DA, Li MW, et al. T regulatory lymphocytes prevent angiotensin II-induced hypertension and vascular injury. Hypertension. 2011;57(3):469-476.
60. Vakan H, Kleinewietfeld M, Qadri F, et al. Regulatory T cells ameliorate angiotensin II-induced cardiac damage. Circulation. 2009;119(22):2904-2912.
61. Kanellakis P, Dinh TN, Agrotis A, Bobik A. CD4+CD25+Foxp3+ regulatory T cells suppress cardiac fibrosis in the hypertensive heart. J Hypertens. 2011;29(9):1820-1828.
62. Yndestad A, Damås JK, Oie E, Ueland T, Gullestad L, Aukrust P. Systemic inflammation in heart failure--the whys and wherefores. Heart Fail Rev. 2006;11(1):83-92.
63. Yndestad A, Holm AM, Müller F, et al. Enhanced expression of inflammatory cytokines and activation markers in T-cells from patients with chronic heart failure. Cardiovasc Res. 2003;60(1):141-146.
64. Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. N Engl J Med. 1990;323(4):236-241.
65. Tang TT, Ding YJ, Liao YH, et al. Defective circulating CD4CD25+Foxp3+CD127(low) regulatory T-cells in patients with chronic heart failure. Cell Physiol Biochem.2010;25(4-5):451-458.
66. Tang TT, Zhu ZF, Wang J, et al. Impaired thymic export and apoptosis contribute to regulatory T-cell defects in patients with chronic heart failure. PLoS One. 2011;6(9):e24272.
67. Li N, Bian H, Zhang J, Li X, Ji X, Zhang Y. The Th17/Treg imbalance exists in patients with heart failure with normal ejection fraction and heart failure with reduced ejection fraction. Clin Chim Acta. 2010;411(23-24):1963-1968.
68. McKinsey TA. Targeting inflammation in heart failure with histone deacetylase inhibitors. Mol Med. 2011;17(5-6):434-441.
69. Sakalihasan N, Limet R, Defawe OD. Abdominal aortic aneurysm. Lancet. 2005;365(9470):1577-1589.
70. Shimizu K, Mitchell RN, Libby P. Inflammation and cellular immune responses in abdominal aortic aneurysms. Arterioscler Thromb Vasc Biol. 2006;26(5):987-994.
71. Kuivaniemi H, Platsoucas CD, Tilson MD 3rd. Aortic aneurysms: an immune disease with a strong genetic component. Circulation. 2008;117(2):242-252.
72. Jagadesham VP, Scott DJ, Carding SR. Abdominal aortic aneurysms: an autoimmune disease? Trends Mol Med. 2008;14(12):522-529.
73. Cassis LA, Gupte M, Thayer S, et al. ANG II infusion promotes abdominal aortic aneurysms independent of increased blood pressure in hypercholesterolemic mice. Am J Physiol Heart Circ Physiol. 2009;296(5):H1660-1665.
74. Boomer JS, Green JM. An enigmatic tail of CD28 signaling. Cold Spring Harb Perspect Biol. 2010;2(8):a002436.
75. Wang Y, Bonnin P, Ait-Oufella H, Tharaux PL, Tedgui A, Mallat Z. Natural CD4+CD25+ Regulatory T Cells Control The Development Of Abdominal Aortic Aneurysm. Circulation. 2007;116:II_137 (Abstract).
76. Yin M, Zhang J, Wang Y, et al. Deficient CD4+CD25+ T regulatory cell function in patients with abdominal aortic aneurysms. Arterioscler Thromb Vasc Biol. 2010;30(9):1825-1831.
77. Magnani JW, Dec GW. Myocarditis: current trends in diagnosis and treatment. Circulation. 2006;113(6):876-890.
78. Cunningham MW. T regulatory cells: sentinels against autoimmune heart disease. Circ Res. 2006;99(10):1024-1026.
79. Shi Y, Fukuoka M, Li G, et al. Regulatory T cells protect mice against coxsackievirus-induced myocarditis through the transforming growth factor beta-coxsackie-adenovirus receptor pathway. Circulation. 2010;121(24):2624-2634.
80. Marchant DJ, McManus BM. Regulating viral myocarditis: allografted regulatory T cells decrease immune infiltration and viral load. Circulation. 2010;121(24):2609-2611.
81. Ono M, Shimizu J, Miyachi Y, Sakaguchi S. Control of autoimmune myocarditis and multiorgan inflammation by glucocorticoid-induced TNF receptor family-related protein(high), Foxp3-expressing CD25+ and CD25- regulatory T cells. J Immunol. 2006;176(8):4748-4756.
82. Huber SA. Depletion of gammadelta+ T cells increases CD4+ FoxP3 (T regulatory) cell response in coxsackievirus B3-induced myocarditis. Immunology. 2009;127(4):567-576.