Regulatory T Cells and Cardiovascular Diseases

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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.


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 failure8-10 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 complexes21 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

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 demethylated29 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 al33 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.34 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. In addition, studies also showed that adult thymectomy can lead to thyroiditis and type I diabetes in selected strains of rats. 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 I diabetes. 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.

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. 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. 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.

Several animal studies have demonstrated that Tregs play a protective role in atherogenesis. 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. 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. In addition, as supporting evidence to Treg role, mice treated with oral anti-CD3 antibody, responsible for induction of Tregs, showed significant reduction in atherosclerotic lesion formation. On the other hand, the few human studies on circulating Tregs numbers in patients with CAD, reported contrasting results. Four studies showed that the Tregs number decreased in CAD patients, while one study reported that Tregs decreased in non-ST-elevation acute coronary syndrome patients and increased in ST-elevation acute myocardial infarction. 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 of human Tregs population exhibits more heterogeneity than that of animal models. Therefore, the contrasting result observed in one study, 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 to be detected. However, we cannot ignore the studies showing the positive results in human 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. 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. 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.

Recently, Barhoumi et al showed that adaptive 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. Furthermore, two studies demonstrated that adaptive transfer of Tregs to angiotensin II-infused or aortic constriction mice ameliorated cardiac damage, prevented cardiac fibrosis and improved electric remodeling though no decrease in blood pressure was noted. 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. However, the exact mechanism of immune activation remains to be elucidated. In 1990, Levine et al 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.63-66 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 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.1-14 Shi Y et al 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.

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