Regulatory T cells and cardiovascular diseases

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Abstract

Inflammation is a major underlying mechanism in the progression of numerous cardiovascular diseases (CVDs). Regulatory T cells (Tregs) are typical immune regulatory cells with recognized immunosuppressive properties. Despite the immunosuppressive properties, researchers have acknowledged the significance of Tregs in maintaining tissue homeostasis and facilitating repair/regeneration. Previous studies unveiled the heterogeneity of Tregs in the heart and aorta, which expanded in CVDs with unique transcriptional phenotypes and reparative/regenerative function. This review briefly summarizes the functional principles of Tregs, also including the synergistic effect of Tregs and other immune cells in CVDs. We discriminate the roles and therapeutic potential of Tregs in CVDs such as atherosclerosis, hypertension, abdominal arterial aneurysm, pulmonary arterial hypertension, Kawasaki disease, myocarditis, myocardial infarction, and heart failure. Tregs not only exert anti-inflammatory effects but also actively promote myocardial regeneration and vascular repair, maintaining the stability of the local microenvironment. Given that the specific mechanism of Tregs functioning in CVDs remains unclear, we reviewed previous clinical and basic studies and the latest findings on the function and mechanism of Tregs in CVDs.

Keywords: Adoptive transfer; Aortic aneurysm, abdominal; Atherosclerosis; Cardiovascular diseases Hypertension T-lymphocytes, regulatory

Introduction

Regulatory T cells (Tregs) are components of the adaptive immune system, which differentiate from naïve T cells upon antigen or cytokine stimulation and principal inflammatory responses that are currently recognized.[1] Tregs express high-affinity interleukin-2 receptor alpha chain and forkhead box protein P3 (Foxp3). The latter is a transcription factor responsible for both the differentiation and functioning of Tregs.[2] The primary population of Tregs originates from the thymus, known as thymus-derived Tregs, while peripheral conventional T cells (Tconvs) compromise an undetermined proportion of Tregs, known as peripheral Tregs.[3] Tconvs can differentiate into inducible Tregs *in vitro*.[4]

Tregs can exert their immunosuppressive activity in different microenvironments, and their complex function is not fully understood. Extensive research has unveiled the mechanisms underlying the suppressive function of Tregs. Inhibitory cytokines such as transforming growth factor-beta (TGF-β), interleukin (IL)-10, IL-35, and extracellular surface enzymes CD39 and CD73 are involved in these mechanisms.[5-8] In addition to self-immune suppression, Tregs can participate in tissue homeostasis and repair/regeneration.[9,10]

Previous fundamental and clinical studies have substantiated the beneficial role of Tregs in cardiovascular disease (CVD). Tregs can rapidly respond to inflammatory signals, suppress inflammation, and accelerate the repair of injured cardiovascular tissues. This review briefly outlines the functional principles of Tregs and dissects the mechanisms by which Tregs modulate various CVDs.

General Biological Functions of Tregs in CVDs

Tregs are mainly involved in immune suppression [Figure 1] and tissue regeneration and repair [Figure 2]. Based on their role in immune regulation and tissue homeostasis, Tregs have significant implications for CVDs. In addition, Tregs can act synergistically with various immune cells in CVDs.

Immunosuppressive function of Tregs

Autoimmunity and inflammatory reactions exist in various CVDs. For instance, oxidation of low-density

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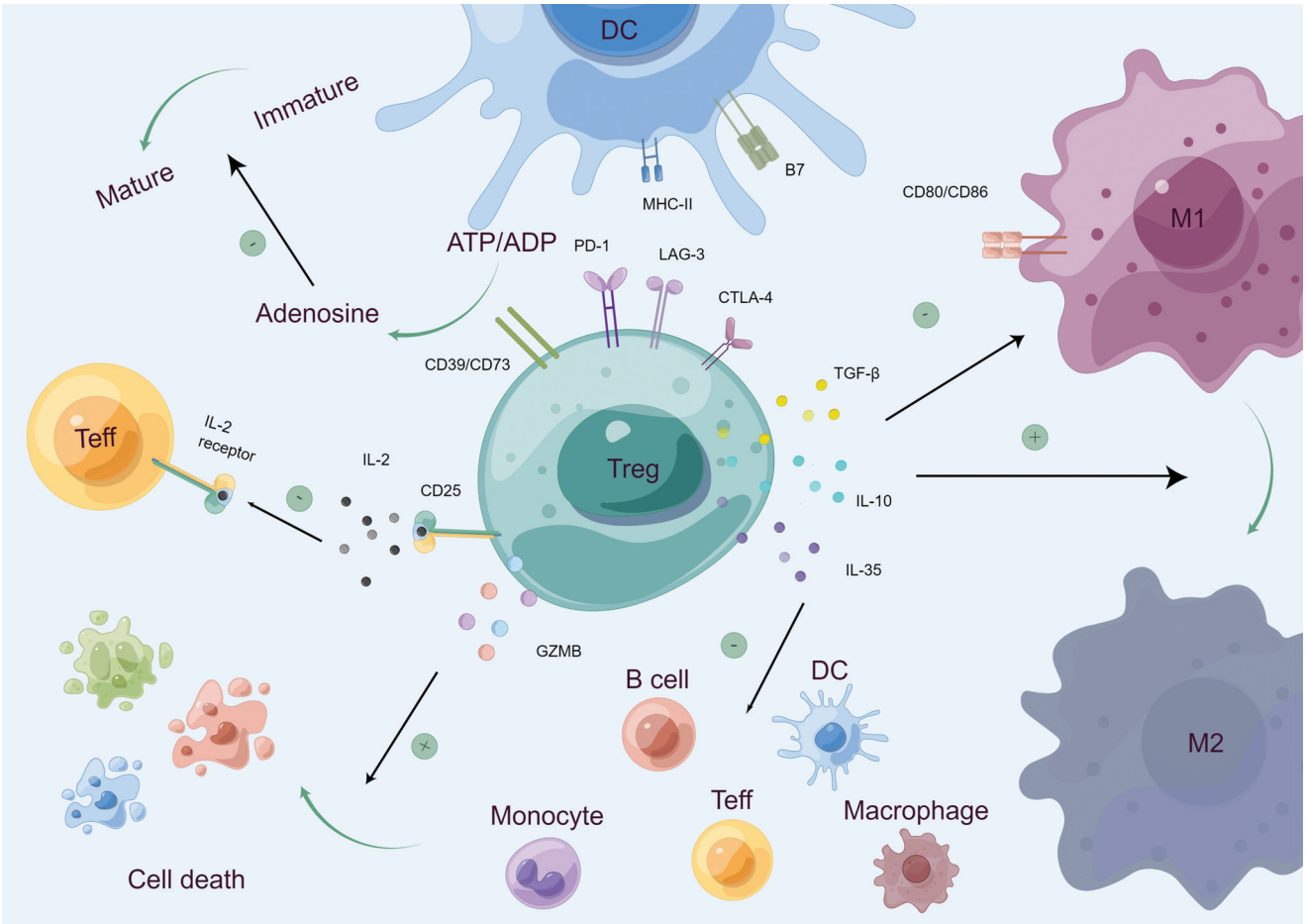

Figure 1: The immunosuppressive function of Tregs. The immunosuppressive function of Tregs comprises the production of inhibitory cytokines (such as IL-10/TGF-β/IL-35), the deprivation of IL-2, the degradation of ATP/ADP through CD39/CD73, the induction of cytolysis, and the modulation of APCs. This figure was drawn using Figdraw 1.0 (https://www.figdraw.com/static/index.html#/). ADP: Adenosine diphosphate; APCs: Antigen-presenting cells; ATP: Adenosine triphosphate; B7: B7 superfamily; CTLA-4: Cytotoxic T lymphocyte-associated antigen 4; DC: Dendritic cell; GZMB: Granzyme B; IL-10: Interleukin-10; IL-2: Interleukin-2; IL-35: Interleukin-35; LAG-3: Lymphocyte activation gene-3; M1: M1-type macrophage; M2: M2-type macrophage; MHC: Major histocompatibility complex; PD-1: Programed cell death protein-1; Teff: Effector T cell; Tregs: Regulatory T cells; TGF-β: Transforming growth factor-beta.

lipoprotein (LDL) in the lesion can trigger inflammatory and immune responses, lead to endothelial dysfunction, and promote the synthesis and production of pro-inflammatory cytokines. This process actively accelerates the development of atherosclerotic plaques. Tregs inhibit the immune response through several mechanisms [Figure 1], such as secreting inhibitory cytokines and regulating the function of antigen-presenting cells (APCs).[1] Tregs possess a unique T cell receptor (TCR) repertoire that differentiates them from $CD4^+$ Tconvs. This unique repertoire enables Tregs to modulate target T cells and APCs, suppressing T cell expansion and cytokine production.[11] CD25 on Tregs binds to interleukin (IL)-2 with high affinity, thereby controlling $CD8^+$ T killer cells and other target cells. On the other hand, cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) in Tregs prevents T cell activation by dendritic cells (DCs). Furthermore, the coordinated expression of ectoenzyme CD39/CD73 on Tregs enables the degradation of adenosine triphosphate (ATP) or adenosine diphosphate, leading to adenosine monophosphate formation. This triggers Treg suppression by hampering ATP-driven DC maturation. Apart from inducing apoptosis through perforin and granzyme to suppress B cell response, Tregs act through programed death ligand-1 to engage self-reactive B cells and inhibit T-cell-dependent antibody production.[12,13]

Reparative/regenerative function of Tregs

Tregs primarily contribute to the repair of CVDs by stimulating angiogenesis and enhancing the regeneration of cardiomyocytes [Figure 2].[14] Vascular growth factors and IL-10 are involved in the pro-angiogenic properties of Tregs.[15] Tregs or IL-10 can directly enhance endothelial cell (EC) proliferation. In addition, amphiregulin released by Tregs can act through different mechanisms to induce EC proliferation and promote angiogenesis.[14]

Tregs promote cardiac repair and neonatal cardiac regeneration after myocardial injury.[16] Tregs facilitate macrophage polarization toward the M2 phenotype, thereby contributing to myocardial repair.[17] M2 macrophages possess anti-inflammatory properties and promote tissue repair. However, excessive activation of pro-fibrotic factors or promoting scar formation may be harmful.[18]

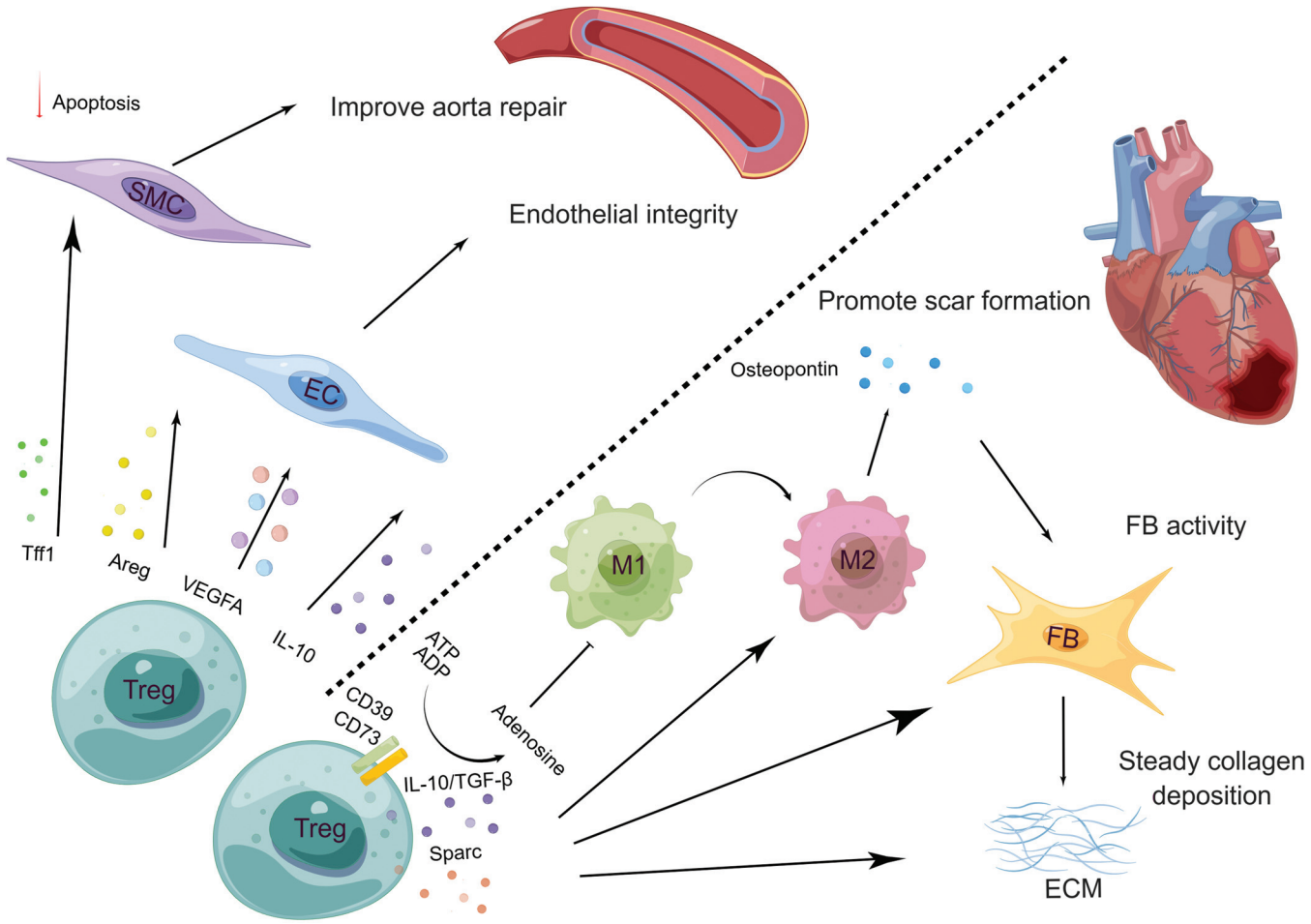

Figure 2: The reparative/regenerative function of Tregs. Tregs preserve endothelial integrity and improve aorta repair by the secretion of Areg/VEGFA/IL-10/Tff1. Tregs promote cardiac repair by the expression of CD39/CD73 and the production of IL-10/TGF-β/Sparc. This figure was drawn using Figdraw 1.0 (https://www.figdraw.com/static/index.html#/). ADP: Adenosine diphosphate; Areg: Amphiregulin; ATP: Adenosine triphosphate; EC: Endothelial cell; ECM: Extracellular matrix; FB: Fibroblast; IL-10: Interleukin-10; M1: M1-type macrophage; M2: M2-type macrophage; SMC: Smooth muscle cell; Sparc: Secreted proteins acidic and rich in cysteine; Tff1: Trefoil factor 1; TGF-β: Transforming growth factor-beta; Tregs: Regulatory T cells; VEGFA: Vascular endothelial growth factor A.

In addition, the paracrine effect of Tregs may be associated with cardiomyocyte regeneration.[18] CD39/CD73 can catalyze the production of adenosine, which protects cardiomyocytes against apoptosis through the reperfusion injury salvage kinase pathway.[19]

Synergistic effect of Tregs and other immune cells in CVDs

Except for Tregs, there are other types of immune cells that are beneficial in CVDs. The crosstalk between Tregs and those immune cells leads to anti-inflammatory effects and promotes tissue repair in myocardial infarction (MI), atherosclerosis (AS), and abdominal aortic aneurysm (AAA).[17,20,21] In addition to their ability to secrete IL-10 to promote the polarization of macrophages to the anti-inflammatory phenotype M2, Tregs can inhibit CD80/CD86 by expressing CTLA-4, thereby downregulating the expression of proinflammatory factors and matrix metalloproteinases (MMPs).[22] The role of type 2 immune responses is ambiguous in CVDs, but type 2 innate lymphoid cells (ILC2s), which have a similar secretion profile to Th2, play a protective role in AS, MI, and AAA via IL-5/IL-13.[23-25] In addition, Tregs directly interact with ILC2s, secrete IL-10 and TGF-β to expand ILC2 population and promote IL-13 secretion.[26] Indoleamine 2,3-dioxygenase controls the kynurenine pathway, regulates T-cell-mediated inflammatory response, and induces tolerance.[27] DCs overexpressing indoleamine 2,3-dioxygenase can promote Tregs expansion and protect against AS by increasing kynurenine levels in the aorta.[27] The effect of B cells on AS is heterogeneous in different subgroups of B cells. Glucocorticoid-induced tumor necrosis factor (TNF) receptor-associated protein ligands on B cells can bind to glucocorticoid-induced TNF receptor-associated protein receptors on Tregs and promote the proliferation and survival of Tregs.[28]

Heterogeneity of Tregs in CVDs

In the MI model, heart Tregs had predominantly thymic origin characterized by high expression of Helios and neuropilin-1, while only a small proportion of Tregs transformed from Tconvs.[29] After MI, the myosin-heavy alpha chain protein-reactive $CD4^+$ T cells can express Foxp3 and convert to a Tregs phenotype *in vivo*.[30] High-throughput sequencing revealed a unique transcriptional profile of Tregs in the heart after MI, with high expression of CTLA-4 and killer cell lectin-like receptor G1 and

strong anti-inflammatory activity. Secreted protein acidic and rich in cysteine (SPARC) was identified as the functional coordinators of this unique group of Tregs, contributing to cardiac scar repair.[29] Two populations of Tregs with high expression of programed cell death protein-1 (PD-1) were identified in the thoracic aorta constriction model.[31] One population expressed Foxp3 and had the characteristics of Tconvs, while the other expressed retinoic acid receptor-related orphan receptor A and GATA-binding protein 3, mimicking the characteristics of Th17 cells.[31] Similarly, a population of dysfunctional Tregs expressing TNF-alpha receptor 1, with proinflammatory features, was identified one week after MI.[32]

Compared with the heart Tregs, aorta Tregs have received less attention. In AS, Th1-like Tregs with high expression of interferon-gamma (IFN-γ) and C-C chemokine receptor-5 in the aorta exhibited reduced expression of immunosuppressive genes compared to Tconvs.[33] Recently, Li *et al*[21] identified and functionally characterized a special group of Tregs that potentially inhibited AAA progression in mice AAA models. These Tregs with a tissue-specific phenotype and function potentially regulate smooth muscle cell (SMC) survival in AAA by secreting trefoil factor 1.

Tregs and Progression of Specific CVDs

The progression of various CVDs is related to the accumulation of immune cells and inflammatory molecules. Although the intricate role of the immune microenvironment in CVDs is not fully understood, inhibiting the immune response and inflammation remains a crucial method for preventing and treating CVDs.[34] Given the regulatory function of Tregs in immune response and tissue repair, Tregs are pivotal for maintaining cardiovascular homeostasis [Figure 3]. Therefore, Tregs are a potential therapeutic target for many CVDs and received increasing attention for their roles in CVDs.

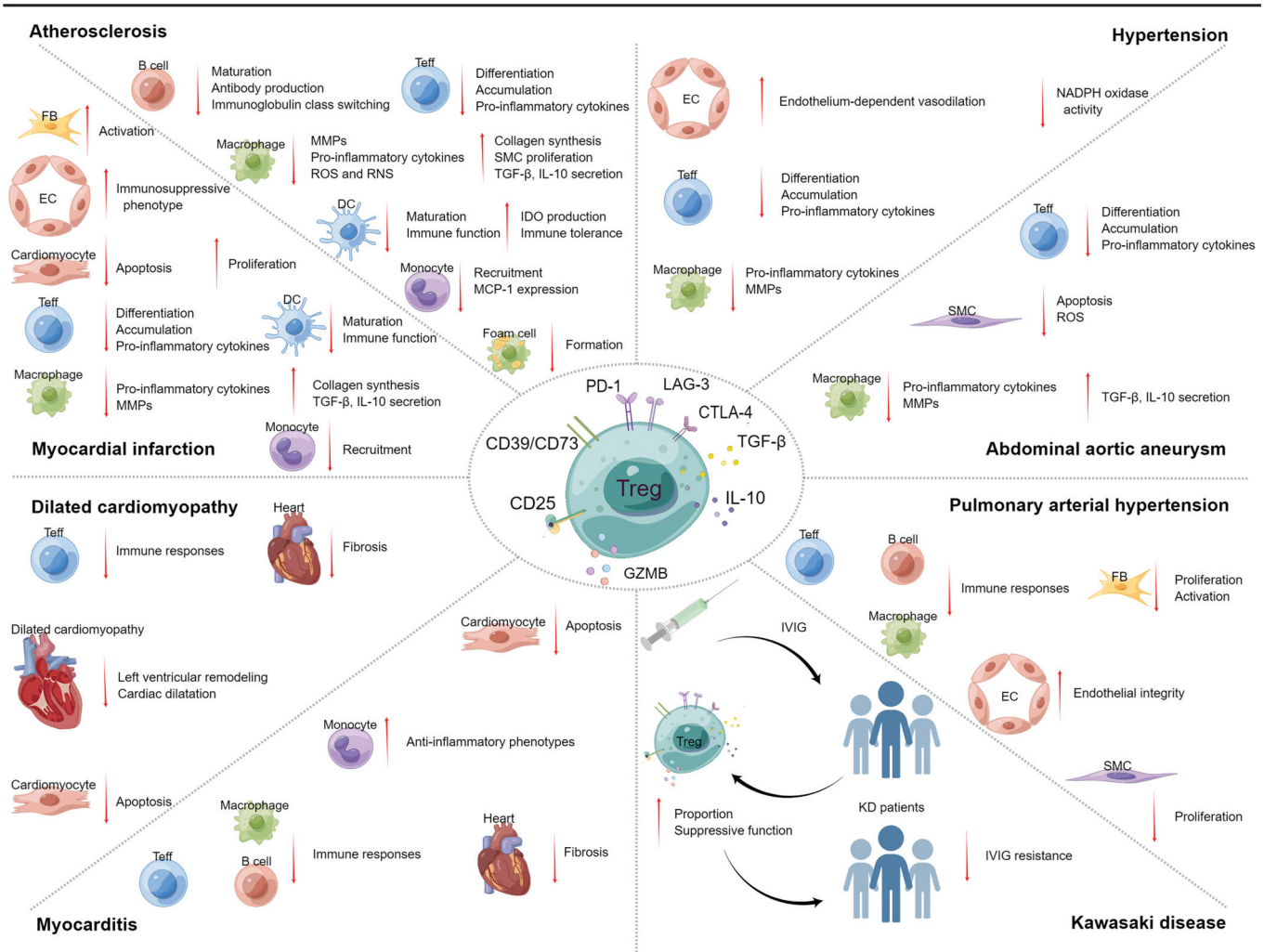

Figure 3: Tregs and CVDs. Tregs maintain cardiovascular homeostasis through their function in immune responses and tissue repair. This figure was drawn using Figdraw 1.0 (https://www.figdraw.com/static/index.html#/). CTLA-4: Cytotoxic T lymphocyte-associated antigen 4; CVDs: Cardiovascular disease; DC: Dendritic cell; EC: Endothelial cell; FB: Fibroblast; GZMB: Granzyme B; IDO: Indoleamine 2,3-dioxygenase; IL-10: Interleukin-10; IVIG: Intravenous immunoglobulin; KD: Kawasaki disease; LAG-3: Lymphocyte activation gene-3; M1: M1-type macrophage; M2: M2-type macrophage; MCP-1: Monocyte chemoattractant protein-1; MHC: Major histocompatibility complex; MMPs: Matrix metalloproteinases; NADPH: Nicotinamide adenine dinucleotide phosphate; PD-1: Programed cell death protein-1; RNS: Reactive nitrogen species; ROS: Reactive oxygen species; SMC: Smooth muscle cell; Teff: Effector T cell; TGF-β: Transforming growth factor-beta; Tregs: Regulatory T cells.

AS

AS is a well-recognized inflammatory disease, and numerous studies have investigated the potential protective role of Tregs in AS.[35] Animal models of AS and human studies on AS have shown decreased Treg abundance in atherosclerotic lesions, possibly due to increased Treg apoptosis and impaired generation of Tregs in the thymus.[36] Patients with chronic coronary artery disease also exhibit reduced Treg levels, with oxidative stress as a potential contributing factor.[37] Diet-induced hyperlipidemia altered Treg metabolism and migration, thereby increasing the proportion of Tregs in the spleen.[36] Hypercholesterolemia enhanced Foxp3 expression and increased the abundance of peripheral Tregs, possibly through TCR stimulation, Treg development, and T cell proliferation.[38] However, the combination of lipid accumulation with the local environment of AS lesions is unfavorable for Tregs, leading to disrupted immune function of Tregs. Therefore, a reduction in Tregs was observed in AS plaques. [36]

Anti-CD25 antibodies, which deplete Tregs, increased lesion area and plaque vulnerability in apolipoprotein-E-deficient ($ApoE^{-/-}$) mice.[39] Diphtheria toxin-mediated Treg depletion led to more severe AS lesions in Low density lipoprotein receptor deficient ($LDLR^{-/-}$) mice.[40] Conversely, transferring Tregs to $ApoE^{-/-}$ mice led to AS regression and enhanced plaque stability.[41,42] Tregs induced by LDL can inhibit effector T cells and improve AS. However, reduction in cholesterol levels during AS regression can enhance both the abundance and function of Tregs in the AS plaque.[43] Furthermore, Foxp3 exists in different isoforms, and variable splicing of Foxp3Δ2 controls the transcriptional program that protects against human AS plaques.[44]

The pathogenesis of AS involves various factors, such as endothelial dysfunction, immune cell infiltration, and foam cell formation. The mechanisms by which Tregs protect against AS are complex and widely studied. Tregs may prevent AS through their beneficial effects on ECs. Tregs can induce an immunosuppressive phenotype of ECs by downregulating CD86 and inhibiting adhesion molecules.[45] The chemokine ligand-receptor axis, involving the C-X3-C motif chemokine ligand 1 (CX3CL1) and its receptor C-X3-C chemokine receptor 1 (CX3CR1), plays a crucial role in the development of AS by regulating the recruitment of monocytes and the proliferation of SMCs. CX3CR1 is critical for the selective homing of Tregs to AS plaques. Transferring $CX3CR1^{+}$ Tregs can prevent plaque advancement and lipid deposition, improve plaque stability through elevated levels of collagen and SMC, and inhibit the pro-inflammatory pathways.[42] Tregs can suppress lipid accumulation in macrophages by downregulating class A scavenger receptors and CD36, thereby preventing macrophage transformation into foam cells.[46] Researchers have discovered that Tregs can improve plaque stability by suppressing the secretion of pro-inflammatory cytokines, MMP-2, and MMP-9.[47] In the late stage of AS, defective macrophage phagocytosis promotes disease progression. In contrast, Treg expansion can enhance efferocytosis of macrophages via IL-13/IL-10 and activate cross-cell signaling pathways, thus improving the internalization of apoptotic cells.[20]

Several animal and clinical studies have reported a negative relationship between Th1 cells and Tregs.[48] Treg ablation can enhance the immune response of $CD4^{+}$ Tconvs and worsen AS.[48] Despite the controversial role of Th17 in AS, an imbalance between Th17 and Treg response has been observed in patients with acute coronary syndrome and $ApoE^{-/-}$ mice with AS. These findings suggest that Treg function in AS partly depends on Th17.[49]

Suppressive cytokines produced by Tregs play a significant role in the inhibitory effect of Tregs on AS. TGF-β can decelerate the progression of AS by attenuating the function of inflammatory cells in atherosclerotic lesions. Conversely, TGF-β deficiency can enhance inflammatory cell infiltration and collagen degradation, thereby accelerating the progression of atherosclerotic lesions.[50] IL-10 derived from type 1 Tregs suppresses the immune response and reduces plaque size and inflammation.[7] IL-35 can maintain the inhibitory function of Tregs in hyperlipidemia by potentiating C-C chemokine receptor 5 signaling, thereby inducing Treg migration, enhancing protein kinase B/mammalian target of rapamycin signaling pathway in Tregs, and promoting the signaling pathways of "T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motifs (ITIM) domains" and PD-1.[51] Based on DCs' role in T cell activation, DCs contribute to the development of AS,[27] and Tregs can inhibit DCs to protect against AS through immune inhibitory cytokines (IL-10 and TGF-β), cell surface molecules (CTLA-4 and PD-1), and lymphocyte activation gene-3.[52] By forming a positive feedback loop with Tregs, soluble fibrinogen-like protein 2 demonstrates robust immune inhibitory functions and confers protection against AS.[53]

Inducing or transferring antigen-specific self-reactive Tregs *in vivo* may be a new direction for Treg therapy in AS. Administering an apolipoprotein B-100 (ApoB) fusion protein through intranasal immunization can effectively stimulate antigen-specific Tregs and prevent AS development. However, the adoptive transfer of ApoB-reactive Tregs did not improve AS, possibly because $ApoB^{+}$ Tregs transformed into a pathogenic phenotype *in vivo*.[54] Similarly, a subset of dysfunctional plastic Tregs with Th1-like features and IFN-γ expression has been identified in AS.[33] A recent study demonstrated that lysophosphatidic acid accumulates in the lymphatic vessels, which inhibits TGF-β production in lymphatic ECs, thus influencing the stability and trafficking of Tregs in AS.[55]

Hypertension (HP)

Blood pressure is mainly controlled by blood vessels, and inflammation has been implicated in various pathological processes leading to HP.[56] In animal models of HP, increased blood pressure is linked to low Foxp3 expression, reduced numbers of Tregs, and impaired function of Tregs.[57] Angiotensin II (Ang II) upregulates the expression of monocyte chemoattractant protein-1 in the vascular system, which is well-known for its role in promoting the infiltration of various immune cells associated with HP.[58] Treg ablation

aggravates Ang II-induced microvascular damage by regulating innate and adaptive immune responses.[59] Distribution of Treg subpopulations in children with primary HP is correlated with the severity of HP and the extent of organ damage.[60] Patients with primary aldosteronism and refractory HP exhibit an imbalance between Th17 and Tregs.[61]

Endothelial dysfunction triggers many CVDs, including HP. Hypertensive patients and animal models have impaired endothelium-dependent vasodilation.[62] In addition, reduced Treg numbers were linked to enhanced endothelial dysfunction and HP.[57] Injecting purified Tregs into Ang II-treated mice improved endothelium-dependent vasodilation and reduced systolic blood pressure.[63] Treg-derived cytokines may be involved in this process.[63] Studies have reported that Tregs improve microvascular endothelial damage by secreting IL-10, thereby attenuating nicotinamide adenine dinucleotide phosphate oxidase activity and protecting against HP.[64] Furthermore, CD4-targeted nicotinamide adenine dinucleotide phosphate oxidase 2 (Nox2) deficiency in mice inhibited HP caused by increased Treg abundance and reduced Th17 abundance.[65] Administration of wild-type Tregs into IL-10 knockout mice improved endothelial function and reduced blood pressure.[64] Developmental endothelial locus-1 can interact with αvβ3 integrin and inhibit the activated precursor of MMP2, thereby maintaining Tregs activity and IL-10 secretion in HP.[57] The protective effects of CD4-targeted Nox2 deficiency in these transgenic mice were attenuated by anti-CD25 antibody, whereas Nox2-deficient Treg transfer significantly suppressed myocardial remodeling.[65] $CD4^+$ T cells can express cystathionine-γ-lyase to promote the production of endogenous hydrogen sulfide, which protects against HP.[66] Recent studies have found that hydrogen sulfide promotes the differentiation and proliferation of Tregs by activating protein kinases, thereby reducing inflammation and preventing HP.[66] Complement component 3a and complement component 5a can inhibit the function of Tregs by downregulating Treg surface receptors. Blocking the complement receptors of Tregs can prevent HP-related end-organ damage.[67]

After administering Ang II type 1 receptor antagonist for three months, the abundance of Tregs and Treg-related cytokines increased and blood pressure decreased in patients with HP.[68] However, Tregs can improve myocardial hypertrophy and vascular damage, but they do not significantly affect blood pressure.[69]

AAA

AAA is characterized by persistent vascular degeneration and vascular remodeling.[70] The progression of AAA can increase the likelihood of rupture.[70] As the mechanisms underlying AAA are unclear, effective clinical treatments are currently lacking. Recent studies connected Tregs to the pathogenesis of AAA.[70] Patients with AAA have a lower number of Tregs with impaired function.[70] It has been reported that sirtuin 1-induced Foxp3 deacetylation can regulate the expression of Foxp3 in Tregs.[70] *In vitro*-expanded Tregs from patients with AAA inhibited the growth of aneurysm in a humanized mouse model.[71] Transferring Tregs inhibited inflammation, downregulated the expression of MMPs, promoted the production of anti-inflammatory cytokines, preserved aortic SMCs, inhibited cell apoptosis and oxidative stress, and dose-dependently prevented the development of AAA.[22] Treatment with IL-2 increased the abundance of Tregs and protected against aneurysm formation by inhibiting local inflammation in the abdominal aorta.[71] Propionate alleviated aneurysm by regulating the expansion and recirculation of Tregs in the colon.[72] Tissue-resident Tregs in colonic lamina propria have unique functions and phenotypes and produce local sustaining factors. Propionate can promote the migration of colonic Tregs to lymph nodes and inflamed AAA lesion.[72] Similarly, statin prevented the development of AAA by inducing Treg accumulation in $ApoE^{-/-}$ mice.[73] Simvastatin increased Treg abundance and upregulated Treg-related cytokines (TGF-β and IL-10) while reducing IL-17 abundance in the aorta and plasma. In addition, simvastatin promoted Treg production by regulating intestinal microecology.[73]

Recently, a cluster of Tregs with unique transcriptional characteristics and TCR spectra were found in blood vessels, with high proliferation via the IL-33/IL-33 receptor axis.[21] On the other hand, aorta Tregs can also secrete trefoil factor 1 to inhibit the apoptosis of arterial SMC and improve arterial damage.[21,74]

Pulmonary arterial hypertension (PAH)

The pathogenesis of PAH is multifactorial and complex, and Treg dysfunction is closely related to the susceptibility of animals and patients to PAH.[75] By analyzing data from 62 patients with PAH, researchers found that Treg dysfunction occurs in all forms of PAH.[76] The progression of PAH can be partly attributed to the reduced number and impaired function of Tregs.[77] In a Treg-deficient PAH model, females experienced more severe PAH than males, indicating that females rely more on Treg function to ameliorate pulmonary vascular damage in PAH.[78]

Impaired Treg response can exacerbate inflammation-mediated endothelial injury, leading to PAH. Therefore, Tregs might prevent PAH by inhibiting vascular inflammation and mitigating vascular damage.[79] Tregs have a critical function in repairing pulmonary arterial ECs and preserving endothelial integrity through IL-10 secretion and bone morphogenetic protein receptor 2.[80] Additionally, SMCs in pulmonary arteries may undergo aberrant proliferation, which contributes to the progression of PAH.[81] Tregs can suppress SMC proliferation in pulmonary arteries by downregulating cell cycle-associated proteins, like cyclin D1 and cyclin-dependent kinases. This mechanism effectively protects against hypoxia-induced PAH.[81] Additionally, Tregs suppress excessive proliferation and activation of fibroblasts (FBs) through several mechanisms, including downregulating TGF-β and FB growth factor 9, suppressing the C-X-C motif chemokine ligand 12 (CXCL12)/C-X-C chemokine receptor type 4 (CXCR4) axis, inhibiting leukotriene B4 production, and releasing IL-10 and IFN-γ.[82-84]

Kawasaki disease (KD)

KD is a vasculitis that mainly affects medium-sized arteries and affects the coronary arteries in children.[85] Treatment

methods that modulate abnormal host immune responses may improve patients' outcomes.[85] Many studies have demonstrated decreased expression of Foxp3, TGF-β, and IL-10 in patients with KD.[85] KD is associated with a significant reduction in the number and function of Tregs.[86]

Intravenous immunoglobulin (IVIG) injection serves as the primary treatment for KD.[86] Treg deficiency in KD may disrupt the immune environment and lead to IVIG resistance.[86] Consistently, IVIG was reported to increase the proportion and function of Tregs.[87] IVIG promotes the internalization of IgG by tolerogenic bone marrow DCs to enhance IL-10 secretion and increase the expansion of Tregs, recognizing the heavy constant region of IgG.[87] In addition to IVIG-sensitive patients, IVIG-resistant patients exhibited lower proportions and absolute numbers of Tregs before treatment, implying that a pre-existing Treg deficiency may serve as an indicator for IVIG resistance in patients with KD.[88]

Myocarditis

Myocarditis is a prevalent inflammatory myocardial disease triggered by several pathogens. The pathogenesis of myocarditis is not yet fully understood, and autoimmune mechanisms play a significant role in its development.[89] Studies have shown that the proportion of Tregs is negatively correlated with disease severity in experimental autoimmune myocarditis.[90] In addition, coxsackievirus B3 promoted Treg apoptosis in an experimental myocarditis model.[91] However, patients with myocarditis exhibited an increased abundance of activated Tregs, characterized by elevated expression of Foxp3.[92]

Tregs exert protective effects on myocarditis by releasing suppressive cytokines and modulating the behavior of various immune cells. IL-10 reduced cardiomyocyte apoptosis and improved survival rate in experimental models of myocarditis.[91] Stromal/progenitor cells preserved cardiac function in inflammation by producing extracellular vesicles, which was correlated with an increased number of splenic IL-10$^+$ Tregs.[93] In addition, Tregs can alleviate myocarditis and mitigate myocardial damage by facilitating the differentiation of monocytes into an anti-inflammatory phenotype.[89] Transferring virus-induced Tregs during the early stage of myocarditis can prevent myocardial fibrosis.[94] Th17/Treg imbalance can exacerbate autoimmune myocarditis.[95]

Dilated cardiomyopathy (DCM)

Immunopathogenic pathways may play a role in the development of DCM, which is characterized by ventricular enlargement and compromised myocardial contractility.[96] In individuals with DCM, the number and function of Tregs are compromised, and Tregs produce a high amount of IFN-γ.[97] Decreased abundance of latent-associated peptide$^+$ Tregs, impaired TGF-β secretion, and defective contact-dependent mechanisms were observed in DCM. Increased Treg abundance prevented left ventricular remodeling and averted cardiac dilatation.[98] Tregs ameliorate human DCM by inhibiting Th1 response.[99] Additionally, a 6-month immunoadsorption therapy in patients with DCM notably enhanced left ventricular ejection fraction and increased the abundance of Tregs in peripheral blood.[100]

MI and heart failure (HF)

Tregs are linked to cardiac remodeling in MI. However, the function of Tregs is compromised in MI.[32] Adoptive transfer and injection of CD28 super-agonist antibody induced Treg amplification and improved cardiac function. Tregs exert a protective effect on the heart through IL-10 and cell–cell contact.[101] After MI, Tregs infiltrate into the damaged area and improve the phenotype and capacity of FBs.[102] Tregs can limit post-MI inflammation, excessive matrix degradation, and cardiac remodeling.[103] However, Treg ablation by anti-CD25 antibody did not alter the size of the infarction zone or the structure of the heart in experimental MI, indicating that Treg-based therapy may improve post-MI remodeling but is less effective on the infarct size.[104]

There is an increased susceptibility to HF following MI, which is linked to cardiac remodeling. Activated T cells are the key instigators of HF. Th2 and Th17 are dominant in the failing heart relative to Th1 and Tregs.[105] Tregs have been implicated in left ventricular dysfunction in HF.[106] Researchers claimed that increased apoptosis and compromised thymic output led to Treg defects in patients with chronic HF.[107]

Both immune and parenchymal cells play crucial roles in the initial stages of cardiac injury and HF. Tregs can reduce monocyte migration and shift macrophage polarization toward the M2 phenotype. IL-35, which is primarily expressed by Tregs, can prevent cardiac rupture after MI by maintaining the viability of CX3CR1$^+$ lymphocyte antigen 6C precursor (Ly6C)^{low} macrophages.[108] Tregs can promote the generation of tolerogenic DCs by releasing extracellular vesicles and suppressing co-stimulatory molecules, thereby hampering effector T cell activation.[109] Tregs can also protect against MI by regulating the expansion and function of effective T cells.[101,110] Tregs can prevent cardiomyocyte apoptosis after cardiac injury and improve cardiac function.[111] In addition, Tregs can directly enhance cardiomyocyte proliferation through paracrine mechanisms.[18] ECs play a pivotal role in preserving vascular integrity, while hypoxia stimulates angiogenesis by activating ECs in the ischemic heart. Tregs preserve the integrity of the endothelium and reduce leukocyte transmigration.[112] Studies have found that Tregs differentiate into Th1-like cells with anti-angiogenic properties in HF, which is linked to TNF superfamily member 1 expression in Tregs.[32]

A unique subset of Tregs resides in the parenchymal tissue of the heart and maintains local homeostasis. By expressing high levels of secretory acidic and cysteine-rich proteins, these cells can rescue the infarct area and enhance collagen expression and maturation.[29] The distinctive cardiac environment fosters the differentiation of antigen-specific Tregs and modulates local immune response.[30] The impact of Tregs on MI is influenced by

Table 1: Adoptive transfer of Tregs in CVDs.

CVDs	Treatment objects	Approaches	Effects	Reference
AS	*Rag2*$^{-/-}$*ApoE*$^{-/-}$ mice	Transferring telomerase reverse transcriptase$^{-/-}$ Tregs	Resulted in atherosclerotic regression and enhanced plaque stability	[123]
	ApoE$^{-/-}$ mice	Transferring Tregs	Enhanced the stability of vulnerable plaques	[47]
	Hyperhomocysteinemia-accelerated AS in *ApoE*$^{-/-}$ mice	–	Decreased infiltration of immune cells into plaque	[43]
	LDLR$^{-/-}$ mice	Transferring CX3CR1^{+} Tregs	Reduced plaque progression and lipid deposition and improved plaque stability	[42]
	ApoE$^{-/-}$ mice	Transferring ApoB^{+} Tregs	Did not improve AS	[54]
	ApoE$^{-/-}$ mice	Transferring Mir146a^{+} Tregs	Unable to adequately reduce AS	[33]
HP	Ang II–infused hypertensive mice	Transferring Tregs	Improved microvascular endothelial damage and protected against HP	[63]
	IL-10$^{-/-}$ mice	–	Improved endothelial dysfunction and reduced blood pressure	[64]
	Ang II-induced aortic aneurysm	–	Did not affect blood pressure	[69]
AAA	*Rag1*$^{-/-}$ mice underwent $CaCl_2$ aneurysm induction	Transferring Tregs from AAA patients	Inhibited aneurysm	[71]
	ApoE$^{-/-}$ mice	Transferring Tregs	Dose-dependently prevented Ang II-induced AAA	[22]
Myocarditis	CVB3-infected mice	–	Relieved myocarditis inflammation and cardiac damage and improved myocarditis progression	[93]
MI	Adult male Lewis rats with experimental infarction	–	Improved cardiac function	[101]
	Mice with experimental infarction	–	Reduced infarct size and improved functional performance	[102]

AAA: Abdominal aortic aneurysm; Ang II: Angiotensin II; ApoB: Apolipoprotein B; ApoE: Apolipoprotein E; AS: Atherosclerosis; CVB3: Coxsackievirus B3; CVD: Cardiovascular disease; CX3CR1: C-X3-C chemokine receptor 1; HP: Hypertension; IL-10: Interleukin-10; LDLR: Low-density lipoprotein receptor; MI: Myocardial infarction; Mir146a: MicroRNA 146a; Rag: Recombination activating gene; –: None.

chemokines and their ligands. CXCR4 blockade can enhance Treg mobilization and promote tissue repair after MI.[113] C-C motif chemokine ligand 17 (CCL17) inhibition promotes Treg migration and reduces ventricular remodeling.[114]

Concluding Remarks and Future Perspectives

As described above, *in vitro* and *in vivo* experiments have shown that transferring effective Tregs can mitigate the progression of many CVDs, making them potential therapeutic targets for patients with CVDs [Table 1]. Currently, the field of adoptive Treg therapy is progressing toward a more targeted approach known as antigen-specific Treg therapy. This involves enriching or modifying Tregs to become antigen-specific cells. Tregs can promote the regeneration of damaged cardiomyocytes and blood vessels and inhibit myocardial fibrosis, thereby preserving cardiac function. However, there are currently no clinical trials on Treg therapy specifically targeting tissue repair and regeneration. In addition, vaccine inoculation and immune regulation may be future methods of antigen-specific treatment. However, induced Tregs may undergo phenotypic conversion to pathogenic phenotypes in the damaged organ.[115] Tregs usually are viable for a few weeks in animal models; therefore, another major limitation of Treg therapy is the relatively short survival time of transferred Tregs.

Besides adoptive transfer, there are various approaches to regulate the number and function of Tregs. Antigen-specific Tregs can be induced by AS-related antigens.[116,117] Many drugs, such as rapamycin, fingolimod, vitamin B17, and cholesterol-lowering medications, can promote Treg expansion.[35] Conventional tools for Treg expansion include antibodies, such as anti-CD3/CD28 antibodies, and cytokines like IL-2.[73,118-120] Low-dose IL-2 can increase the average number of circulating Tregs by at least 75%.[121] Additionally, ultraviolet radiation enhances the function of Tregs.[122] However, these approaches still have limited clinical application for Treg-based therapy of CVDs, mainly due to their non-specific regulation and imbalanced Treg homeostasis. Targeting Treg homeostasis is currently necessary and fundamental for developing biological drugs.

Extensive preclinical and clinical studies have confirmed the role of Tregs in various CVDs. Adoptive transfer of Tregs or other methods of Treg amplification exhibited a

protective effect on CVDs. Although the detailed molecular mechanisms underlying the protective effects of Tregs on these CVDs are unclear, Tregs are a promising therapeutic target in CVDs.

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Conflicts of interest

None.

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