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Review

Regulatory T lymphocytes in myocardial infarction: A promising new therapeutic target

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ABSTRACT

Myocardial infarction (MI) is one of the leading causes of death especially in developed countries. Although the advent of early myocardial reperfusion therapy contributes to decreasing the mortality of patients with MI, cardiac ischemia-reperfusion injury and adverse remodeling during the repair process still remain the major factors impairing cardiac function and resulting in unsatisfactory prognosis. Excessive inflammation and immune responses play a crucial role during the whole process of MI. Regulatory T lymphocytes, characterized by immunosuppressive capacity, are associated with many immune-related diseases. Recent studies have proven a protective role of regulatory T cells in MI, which is mainly achieved by modulating inflammation and immune responses. In this review, we will summarize current knowledge of regulatory T lymphocytes, and highlight their roles in the onset of MI, ischemia-reperfusion injury, as well as post-infarct cardiac healing and remodeling.

1. Introduction

Myocardial infarction (MI) refers to cardiac ischemic necrosis arising from a sudden reduction of oxygen supply from coronary arteries with severe stenosis or obstruction. Due to the high morbidity and mortality, MI has become one of the most concerning health issues in the modern society [1]. Fortunately, with the advent of early myocardial reperfusion such as percutaneous coronary intervention and thrombolytic therapy, the mortality has been decreasing over the past decades [2]. Nevertheless, reperfusion therapy per se unwantedly causes another kind of injury called ischemia-reperfusion injury (IRI), which undermines the full benefits of reperfusion therapy and there is still no effective treatment [3]. In addition, the number of the patients with heart failure after MI has increased, which mostly results from adverse ventricular remodeling [4], making the patients exposed to a higher risk of further cardiovascular events than others. Thus, it still remains a great challenge to work out an effective management for MI.

Previous studies indicated that inflammatory responses are critically involved in MI. Necrotic cardiomyocytes release large quantities of intracellular contents, triggering an immense inflammatory cascade [5]. The inflammatory process helps to clear dead cells and promote scar formation, preventing the heart from rupture; however, excessive inflammation leads to degradation of extracellular matrix and apoptosis of cardiomyocytes, resulting in ventricular remodeling and heart failure [6]. Hence timely control of the post-infarct inflammation may be an effective approach for treating MI.

In the past decades, regulatory T lymphocytes (Tregs), characterized by negatively regulating inflammation and immune responses, have drawn great attention in many disorders including autoimmune diseases [7], cancer [8], infective diseases [9], allograft rejection [10] and ischemic diseases [11]. Recently, increasing evidence has demonstrated the involvement of Tregs in MI (see Table 1). Patients with acute coronary syndrome (ACS) exhibit a significant down-regulation in the frequency and function of peripheral Tregs compared with patients with stable angina and normal artery subjects [12]. And infusion of Tregs into murine MI models can reduce the infarct size and attenuate MI-induced cardiac dysfunction [13].

This review will respectively discuss the roles of Tregs in the onset of MI, myocardial IRI, as well as cardiac repair and remodeling process after MI.

2. General knowledge of Tregs

Regulatory T cells, once named as suppressor T cells [14], are a specific subset of T lymphocytes with immunosuppressive capacity. It is estimated that, under physiological conditions, the population of Tregs occupies 5–10% of $CD4^+$ T cells in human peripheral blood [15].

Tregs comprise two subsets: naturally-occurring Tregs (nTregs) and induced Tregs (iTregs) [16]. The former subpopulation develops in the

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Table 1
Major findings on Tregs in clinical and experimental studies.

	Findings on Tregs	References
Humans	The frequency and suppressive ability of peripheral $CD4^+CD25^+$ Tregs were down-regulated in patients with ACS compared with patients with stable angina and normal coronary artery subjects.	Adi et al. [12]
	The percentages of both $CD27^+$ Tregs and $CD27^-$ Tregs were lower in patients with STEMI compared with normal controls, and the ratio of the two subsets was skewed towards the less suppressive $CD27^-$ Tregs.	Gennaro et al. [28]
	Decreased number of Tregs was shown in vulnerable atherosclerotic lesions than in stable lesions.	Dietel et al. [39] de Boer et al. [40]
	Low levels of baseline circulating $CD4^+Foxp3^+$ T cells were related with higher risk for development of MI.	Wigren et al. [29]
	The production of Tregs by thymus was attenuated in patients with NSTEACS compared with patients with stable angina and patients with chest pain syndrome, as indicated by lower frequency of peripheral recent thymic emigrant Treg cells ($CD4^+CD25^+CD127^{low}$ $CD45RO^-CD45RA^+CD31^+$ Tregs).	Zhang et al. [30]
	The circulating apoptotic Tregs ($CD4^+CD25^+CD127^{low}$ annexin-V^+ 7-AAD^- Tregs) was significantly higher in patients with NSTEACS than in patients with stable angina and patients with chest pain syndrome.	Zhang et al. [30]
	Recruitment of Tregs was found in post-infarct hearts of mice.	Saxena et al. [32]
Mice	Expansion of Tregs by using IL-2/anti-IL-2 complex increased the stability of atherosclerotic plaques.	Foks et al. [41]
	Partial depletion of Tregs by before ischemia-reperfusion by using anti-CD25 monoclonal antibodies exacerbated IRI, while adoptive transfer of Tregs alleviated IRI.	Fleming et al. [44] Linfert et al. [45]
	The protection of rosuvastatin against myocardial IRI was partially mediated by immunosuppression of Tregs.	Ke et al. [50]
	Expansion of Tregs in vivo by both adoptive transfer and administration of CD28 superagonistic antibody improved ventricular contractility and attenuated remodeling, while Treg depletion by anti-CD25 antibodies contributes to early post-infarct dilation and increased left ventricular end-diastolic volume.	Matsumoto et al. [13] Saxena et al. [32] Tang et al. [54]

Treg — regulatory T lymphocyte; ACS — acute coronary syndrome; STEMI — ST-segment elevation myocardial infarction; MI — myocardial infarction; NSTEACS — non-ST-segment elevation acute coronary syndrome; IRI — ischemia-reperfusion injury.

thymus, and is identified by co-expression of CD4, CD25 and fork head box P3 (Foxp3) [17]. Induced Tregs include type 1 regulatory T (Tr1) cells [18], T helper-3 (Th3) regulatory cells [19] and $CD8^+Foxp3^+$ Tregs [20], and are differentiated from naive $CD4^+$ T cells in periphery lymphoid organs when exposed to particular stimulations, such as interleukin (IL)-10, interferon (IFN)-α and oral administration of antigen [14,21] (see Fig. 1a, b).

Both of these two subsets of Tregs have immunosuppressive capacity. They play roles in inhibiting the proliferation of $CD4^+$ and $CD8^+$ T cells and their production of IFN-γ [18], suppressing the maturation and function of dendritic cells (DC) [22], enhancing differentiation of anti-inflammatory M2 macrophage [23] and reducing the secretion of pro-inflammatory cytokines by monocytes [23]. Even an 'inverted pyramid' model was proposed by Vicente Bodi to describe the interactions between Tregs and other cell types. This model demonstrated that a few Tregs, at the bottom of the inverted pyramid, control the upper parts containing neutrophils, monocytes, effector T lymphocytes etc. [24]. Through inhibiting both innate and adaptive immune responses, Tregs play a crucial role in the maintenance of immunologic homeostasis, and their deficiency or dysfunction leads to certain kinds of immune-related diseases, such as systemic lupus erythematosus and rheumatoid arthritis [16,25].

On the whole, the mechanisms underlying Treg-mediated immune suppression include secretion of anti-inflammatory cytokines and cell-contact-dependent interaction with other cell types [20](see Fig. 1d). Some studies demonstrated that nTregs exerted immune suppression via cell–cell contact, whereas Tr1 cells inhibited immune responses through secreting IL-10 and transforming growth factor (TGF)-β [26], and the function of Th3 cells was TGF-β dependent [27].

3. Potential peripheral Tregs defect in MI

Numerical and functional alterations of Tregs have been reported in patients with MI. Adi Mor and colleagues first demonstrated a significant reduction in the frequency of peripheral $CD4^+CD25^+$ Tregs in patients with ACS, compared with patients who suffered from stable angina and normal coronary artery subjects. In addition, Tregs derived from patients with ACS were severely compromised in their ability to suppress responder $CD4^+CD25^-$ T cell proliferation [12]. Similarly, another study demonstrated that the percentages of circulating $CD27^+$ Tregs and $CD27^-$ Tregs were both decreased in patients with ST-segment elevation myocardial infarction (STEMI) compared with normal controls. In addition, the ratio of these two subsets was skewed towards the less suppressive $CD27^-$ Tregs [28].

The association between Tregs and MI was further supported by a prospective study by Maria Wigren et al. [29]. They addressed that low levels of baseline circulating $CD4^+Foxp3^+$ T cells were linked to higher risk for development of MI, suggesting that Tregs might play a protective role in MI and represent an attractive therapeutic target. However, the relation between levels of Tregs and the severity and prognosis of patients with MI is to be elucidated.

4. Possible mechanisms underlying peripheral Tregs defect in MI

The possible causes of the reduction in circulating Tregs number during MI include impaired output from thymus, increased apoptosis and trafficking of peripheral Tregs to inflammatory sites.

The frequency of recent thymic emigrant Treg cells (indicated as $CD4^+CD25^+CD127^{low}CD45RO^-CD45RA^+CD31^+$ Tregs) in peripheral blood was lower in patients with non-ST-segment elevation acute coronary syndrome (NSTEACS) than in patients with chronic stable angina (CSA) and patients with chest pain syndrome (CPS), suggesting that the production of Tregs by thymus was attenuated in NSTEACS patients [30]. This was further supported by the observation that intracellular T cell receptor excision circle (TREC) level, a marker of newly generated T cells, was markedly lower in Tregs from NSETACS patients [30].

Increased apoptosis of Tregs also partially accounts for peripheral Tregs defect in NSTEACS patients [30]. The number of circulating $CD4^+CD25^+CD127^{low}$ annexin-V^+ 7-AAD^- Tregs, which represented apoptotic Tregs, was significantly higher in NSTEACS patients than in CSA and CPS patients. Besides, higher expression of proapoptotic gene *Bak* and lower expression of antiapoptotic gene *Bcl-2* were shown in purified Tregs from patients with NSTEACS. The apoptosis might be spontaneous or induced by increased plasma level of oxidized low density lipoprotein (LDL) in patients.

It has been well documented that certain subsets of Tregs can migrate into inflamed tissues to limit the inflammatory responses [31]. Emerging evidence has shown the recruitment of Tregs in post-infarct hearts of mice [32]. This gave rise to the notion that Tregs probably trafficked from peripheral blood circulation to inflammatory hearts, leading to the reduction in circulating Tregs (see Fig. 1c). This is probably mediated by specific chemokine receptors (CCRs) expressed on the surface of Tregs. These CCRs interact with inflammatory cytokines secreted by antigen-presenting cells, including neutrophils, macrophages, activated T cells etc., guiding Tregs into inflammatory sites [33]. It has