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The Role and Mechanism of Dendritic Cells in Cardiac Injury Repair

Jilong Liu, Dong Jing*

Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
**Correspondence Author*

Abstract: ***Acute inflammation around the myocardial infarct area promote the progression of heart failure post- myocardial infarction. Subsequently, adaptive immunity and anti-cardiac autoimmunity are also involved in. Monocytes recruited from bone marrow and spleen play an important role in myocardial injury and repair of myocardial infarction. Although, monocyte-derived macrophages have been extensively studied in myocardial injury, repair, and myocardial remodeling. Recently, more and more studies focus on the role of dendritic cells (DCs) in cardiac injury and repair after acute myocardial infarction, but the mechanismneeds further exploration. This review focus on discussing the role and prospects of dendritic cells in cardiac injury repair.***

Keywords: Dendritic cells, Myocardial injury repair, Adaptive immunity, Innate immunity.

1. Introduction

The "China Cardiovascular Health and Disease Report 2022" indicates that the prevalence of cardiovascular diseases in China is on a continuous rise, with 330 million people suffering from cardiovascular diseases, including 11.39 million patients with ischemic heart disease (IHD), which is one of the leading causes of cardiovascular mortality in China [1,2]. Immune cells play a crucial role in cardiac homeostasis, and an increasing number of studies show that immune cells resident or infiltrating in the myocardium play a key role in the repair process of cardiac injury [3,4]. Immune cells resident or infiltrating in the heart include macrophages, monocytes, neutrophils, dendritic cells (DCs), T and B cells, eosinophils, and mast cells, which are involved in maintaining cardiac function. DCs are the most potent professional antigen-presenting cells (APCs), activating naive T cells through antigen presentation, acting as a "bridge" between innate and adaptive immunity [5,6]. DCs are mainly divided into two major subsets based on their functions: conventional dendritic cells (cDC) and plasmacytoid dendritic cells (pDC), with other DC subsets such as regulatory dendritic cells (DCreg) and monocyte-derived cells (mo-DC), each playing different roles in cardiac injury repair, especially in regulating adaptive immunity during cardiac injury repair. This review discusses the roles and prospects of various types of DCs in cardiac injury repair.

2. Classification and Origin of DCs

Dendritic cells (DCs) are a heterogeneous group of professional antigen-presenting cells that are primarily found in the spleen and other lymphoid tissues. DCs can be classified based on their cellular lineage into myeloid DCs and lymphoid DCs, based on their cellular functions into conventional DCs (cDCs) and plasmacytoid DCs (pDCs), and based on their maturation status into mature DCs (mDCs) and immature DCs (imDCs). Other subsets of DCs include follicular DCs, regulatory DCs (DCregs), and monocyte-derived DCs (mo-DCs). In humans, DCs are widely distributed throughout the body, excluding the brain, and constitute less than 1% of peripheral blood mononuclear cells, mainly consisting of cDCs and pDCs [7].

In humans, DCs originate from the granulocyte-macrophage dendritic cell progenitor (GMDP), which is derived from hematopoietic stem cells (HSCs) in the bone marrow. GMDP can give rise to the monocyte-dendritic cell progenitor (MDP). The common DC progenitor (CDP) originates from MDPs and gives rise to conventional DC precursors (Pre-cDCs) or pDCs. Both cDC1 and cDC2 are derived from Pre-cDCs.

3. Dendritic Cells in the Heart

Dendritic cells (DCs) in the heart are primarily composed of conventional DCs (cDCs), which are further classified into cDC1 and cDC2 based on their markers and expression of different transcription factors. Cardiac cDC1 specifically express CD103, CADM1, XCR-1, DNGR-1 (Clec9a), and the transcription factor IRF8. Deletion of the transcription factor IRF8 in CD11c+ cells of mice can ablate systemic cDC1 cells [8, 9]. Cardiac cDC2s express specific markers CD172 and CD11b, as well as the specific transcription factor IRF4. Plasmacytoid DCs (pDCs), on the other hand, are mainly distributed in the bone marrow, peripheral blood, subcutaneous tissue, and lymphoid tissues rich in T cells, and are rarely found in the heart [10].

Compared to cDCs in other tissues, cardiac cDCs are recruited to the heart through the chemokine receptor CCR2 [10], migrate to the draining mediastinal lymph nodes, and present cardiac self-antigens to specific αβ T cells, leading to the expansion of regulatory T cells (Treg cells) [11], and inducing a cardiac immune tolerance environment. Although the heart does not directly contact the external environment, the number of DCs in a healthy heart is comparable to that in barrier tissues such as the skin [12]. Given the key role of DCs in inducing immune tolerance and their significant presence in the heart, it has been proposed to use cardiac DCs as a potential target for inducing self-tolerance [13].

4. The Role of cDCs in Ischemic Heart Disease (IHD)

cDCs based on their expressed marker molecules and functions, can be further divided into two subsets: Type I

conventional dendritic cells (cDC1) and Type II conventional dendritic cells (cDC2). The most important function of cDC1 is cross-presentation of antigens, capturing exogenous antigens and presenting them to CD8+ T cells; whereas cDC2 mainly performs classical antigen presentation, presenting exogenous antigens to CD4+ T cells [7, 9]. During the healing process of myocardial infarction (MI), cDCs of bone marrow origin, which are CD11c+ and CD11b+, accumulate early in the boundary area of the infarction and reach a peak on the 7th day [15]. After MI, cDCs are recruited to lymphoid organs where they aggregate and stimulate T cell differentiation [16]. Studies have shown that cDCs prevent destructive autoimmunity after cardiac injury by activating conventional FOXP3+ CD4+ T helper cells and FOXP3+ CD4+ Treg cells [17]. It has been demonstrated that a reduction in the number of cDCs is associated with cardiac rupture after MI, and the absence of cDCs increases the recruitment of pro-inflammatory monocytes and the production of pro-inflammatory cytokines [17]. Research by Anzai Atsushi et al. indicates that in a DC-depleted mouse MI model, although there is no significant increase in the infarct area, the pathological remodeling of the left ventricle is significantly worse compared to the control group, with thinner heart walls in the infarct area and impaired neovascularization. Further studies found that in DC-depleted mice, there is a significant increase in the infiltration of monocytes and M1 macrophages highly expressing Ly6C (Ly6Chigh) in the infarct area and surrounding region, while there is a significant decrease in monocytes and M2 macrophages with low expression of Ly6C (Ly6Clow). Additionally, in DC-depleted MI model mice, the expression of inflammatory factors and Matrix Metalloproteinase 9 (MMP-9) is significantly increased, while the expression of the anti-inflammatory factor IL-10 is significantly decreased. These results suggest that DC depletion activates pro-inflammatory monocytes and M1 macrophages, suppresses anti-inflammatory monocytes and M2 macrophages, enhances inflammatory responses and degradation of extracellular matrix, thereby delaying myocardial repair after MI and leading to worsening heart function [18, 19]. Liu Haibo et al.'s research indicates that dendritic cell-derived exosomes (DEXs) administered through the tail vein can promote myocardial repair in MI by activating CD4+ T cells, improving cardiac function in mice after MI [20]. Zhang Youming et al.'s research shows that the injection of hydrogel-loaded DC-derived exosomes in the infarct area of MI mice can regulate inflammation by inducing the generation of Treg cells and promoting the differentiation of macrophages from M1 to M2, thereby improving cardiac function after MI [21]. These research results suggest that cDCs in the myocardium after MI inhibit pathological remodeling of the heart after MI by regulating the immune homeostasis of T cells and macrophages. Conversely, some literature reports that cDCs exacerbate MI myocardial damage and cardiac function. Forte E, Perkins B, and Sintou A, et al.'s research indicates that cDC1 after MI can present antigens to CD8+ T cells [20], and this "cross-presentation" may induce autoimmunity-mediated myocardial damage; conversely, blocking the cross-presentation function of cDC1 can prevent pathological remodeling and cardiac function decline in mice after ischemic injury [20]. However, Forte E, Perkins B, Sintou A, et al. used a single large dose of the β-adrenergic agonist isoproterenol to construct the MI model, which is different from the traditional coronary ligation MI model, and modeling may induce autoantibodies other than MI. Therefore, the role of cDC1 in traditional MI still needs further research. In addition, Inui H, Nishida M, Ichii M, et al.'s research shows that XCR1+ cDC1, which is positive for the chemokine receptor 1, induces the activation of CD4+ Type 1 helper T cells (Th1), exacerbating cardiac remodeling after ischemic myocardial injury; the depletion of XCR1+ cDC1 cells after MI inhibits the activation of CXCR3+ Th1 cells and prevents cardiac dysfunction [21]. However, XCR1 is not the main chemokine receptor for DCs in the heart; DCs in the heart are mainly recruited to the heart through the chemokine receptor CCR2 [10]. The mechanism by which XCR1+ cDC1 activation exacerbates myocardial injury after MI requires further research.

Overall, cDCs play a positive role in the pathological remodeling of the ventricles after myocardial infarction (MI), but the roles of different subsets of DCs in myocardial injury and repair warrant further investigation.

5. The Role of DCreg in Ischemic Heart Disease (IHD)

DCs recognize a plethora of Pathogen-associated molecular patterns (PAMPs) and Damage-associated molecular patterns (DAMPs) through Pattern recognition receptors (PRRs), processing and presenting antigens to T cells to stimulate their differentiation [5,6]. Immature dendritic cells (iDCs) in tissues interact with PAMPs or DAMPs through their PRRs, becoming activated and differentiating into mature dendritic cells (mDCs) [21]; this is accompanied by the expression of MHC-II molecules, co-stimulatory molecules such as CD80 and CD86, cytokines, and the chemokine receptor CCR7 [22]. Subsequently, mDCs enter the lymph nodes, where they present processed antigens to naïve T lymphocytes, inducing T cell proliferation and activation [23]. Under physiological or pathological conditions in humans, mDCs or iDCs can transform into DCregs, which possess negative immune regulatory functions [18]. DCregs can timely terminate immune responses to maintain local immune homeostasis and prevent immune damage caused by excessive T cell activation. Given the significant role of DCregs in inducing immune tolerance, scientists have generated DCregs from monocytes ex vivo and widely applied them in the treatment of autoimmune diseases and organ transplantation [23]. The characteristics of DCregs include reduced or absent expression of co-stimulatory signals (CD40/80/86), accompanied by the expression of immune co-inhibitory molecules and anti-inflammatory cytokines [18]. In humans and mice, DCregs can target different immune cells and induce immune tolerance through various pathways. The specific mechanisms are as follows:

5.1 T cells recognize antigens presented by DCregs, the interaction between the T cell receptor (TCR) and the MHC on DCreg cells, under conditions of low co-stimulatory signals (the binding of T cell CD28 to CD80/CD86 on DCs), prevents T cells from producing IL-2 and proliferating [19].

5.2 Co-inhibitory molecules in DCregs, such as programmed death-ligand 1 (PD-L1), induce T cell contact-dependent inhibitory signals, suppressing T cell proliferation and promoting T cell anergy, which is specifically manifested as

inducing a state of unresponsiveness in T cells [20, 21]. PD-L is an inhibitory surface receptor that binds to programmed cell death protein 1 (PD-1) expressed on T cells [22], triggering the recruitment of phosphatases SHP-1 and SHP-2, which target the TCR and CD28 signaling pathways, promoting immune tolerance by inducing anergy and Treg differentiation [21].

5.3 DCregs express low levels of CD80 and CD86 molecules that can bind to cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), mediating its internalization and degradation [20], inhibiting the activation of naïve T cells [23]. DCregs can induce high expression of CTLA-4 on T cells, suppressing the activation of CD4+ and CD8+ T cells [24].

5.4 In addition to cell-cell contact-dependent mechanisms, DCregs can also induce T cell immune tolerance by producing cytokines and metabolites. DCregs produce interleukin-10 (IL-10), transforming growth factor-β (TGF-β), and retinoic acid [24], which inhibit the activity of effector T cells (Teff) and induce the differentiation of Tregs and regulatory B cells (Bregs) [24]. Furthermore, DCregs highly express indoleamine 2,3-dioxygenase 1 (IDO1), a key enzyme in tryptophan catabolism [27], and induce the differentiation of mouse Treg cells by breaking down tryptophan to produce kynurenine (Kyn) [28]. At the same time, DCregs regulate T cell metabolism by generating lactic acid, inducing T cell immune tolerance [29].

5.5 DCregs can directly induce T cell apoptosis through clonal deletion. For example, the interaction between TRAIL (TNF-related apoptosis-inducing ligand) on human dendritic cells and death receptors on T cells can promote apoptosis by activating the caspase pathway. In addition, DCregs highly express FasL, which can bind to Fas on the surface of activated T cells, directly inducing apoptosis of activated T cells [30].

In summary, DCregs induce T cell immune tolerance through various mechanisms, including cell-cell contact, production of metabolites, and cytokines. Choo, Eun Ho et al. used DCregs carrying cardiac antigens to induce Treg proliferation, promote M2 macrophage polarization, improve the cardiac immune microenvironment in MI mice, ameliorate ventricular remodeling, and protect cardiac function [31]. Wang, Wenfeng et al.'s research indicates that a reduction in DCregs leads to the destruction of the cardiac immune tolerance microenvironment, increased infiltration of CD8+ T cells, promotion of myocardial cell damage after infarction, and deterioration of cardiac function [32].

6. The Role of pDCs in Ischemic Heart Disease (IHD)

Plasmacytoid dendritic cells (pDCs) are a unique subset of dendritic cells (DCs) that play a role in immune regulation by secreting high levels of Type I interferons. pDCs are crucial in antiviral immunity and are associated with the onset and progression of many autoimmune and inflammatory diseases [33]. Research by Lee, Jun Seong, et al., indicates that depleting pDCs in mice with myocardial infarction (MI) does not affect heart function, suggesting their role may lie in producing Type I interferons and protecting tissues from viral infections. The role of pDCs in myocardial injury and repair requires further investigation [34].

7. The Role of DCs in Stem Cell Transplantation Therapy for Ischemic Heart Disease (IHD)

Nowdays, end-stage heart failure caused by ischemic heart disease (IHD) poses a severe threat to human health. Stem cells, such as embryonic stem cells (ESCs) and induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs), are potential therapeutic approaches for repairing the damaged myocardium in IHD. In acute myocardial infarction (MI) mouse models, iPSC-CMs have been shown to improve left ventricular function and reduce pathological remodeling of the heart [34]; mesenchymal stem cell (MSC) transplantation can improve cardiac function in patients with heart failure with reduced ejection fraction (HFrEF) and elevated levels of high-sensitivity C-reactive protein greater than 2mg/L [35]. Therefore, iPSC-CMs hold significant advantages and potential value in the treatment of IHD. However, following cardiac transplantation of iPSC-CMs, long-term administration of immunosuppressants is required, and hearts with heart failure cannot tolerate the toxic side effects of high doses and long-term use of immunosuppressants, which can more easily lead to further deterioration of cardiac function. Thus, it is particularly urgent to innovate therapy for iPSC-CM treatment of IHD to address issues such as arrhythmias and side effects of immunosuppressants that arise from stem cell heart transplantation [34,35]

In stem cell transplantation therapy, recipient-derived CD4+ helper T cells and CD8+ T lymphocytes attack donor-derived target cells, leading to immune rejection [35]. As professional antigen-presenting cells, dendritic cells (DCs) facilitate immune rejection by inducing and increasing CD4+ T cells and CD8+ T lymphocytes through their antigen-presenting function [37]. In the early stages of stem cell transplantation (within 20 hours), CD4+ T cells and CD8+ T lymphocytes rapidly increase in the lymph nodes [38]. Studies using a C57BL/6J mouse model of stem cell transplantation have shown that the absence of antigen-presenting cells (APCs) does not induce immune rejection reactions to stem cell transplants [37]. Conversely, modulating DCs can reduce the proliferation and activation of reactive T cells, prevent the migration of DCs to lymphoid organs, and decrease the number of activated T cells by inhibiting DC maturation or downregulating co-stimulatory molecules on DCs, thereby reducing immune rejection after stem cell transplantation. Current research indicates that regulatory dendritic cells (DCregs), plasmacytoid DCs (pDCs), and semi-mature dendritic cells (smDCs) induce immune tolerance after stem cell transplantation [39]. DCregs express low levels of co-stimulatory molecules and secrete high levels of immunosuppressive factors, which can induce the development of regulatory T cells (Tregs) and promote immune tolerance following stem cell transplantation [20]. Studies on the transplantation of hepatocytes derived from mouse embryonic stem cells (ESCs) have shown that smDCs from the donor mouse can significantly reduce the infiltration of CD4+ T lymphocytes in the recipient's transplanted tissue, extending the survival time of the transplanted cells and

confirming that smDCs can induce immune tolerance and mitigate immune rejection reactions [39]. Additionally, preventing DCs from migrating to lymphoid organs and reducing the number of DCs can induce immune tolerance after stem cell transplantation. CCR7 is the receptor required for DC migration to lymph nodes, and CD3 monoclonal antibodies can inhibit CCR7 expression in DCs, significantly suppressing immune rejection reactions in mouse stem cell grafts [40,41]. The rejection response after stem cell transplantation can also be alleviated by inhibiting DC maturation or downregulating co-stimulatory molecules on DCs. The serum protease inhibitor 1-antitrypsin (A1AT) can reduce serum heparan sulfate (HS) levels, inhibit DC maturation, and suppress the proliferation of alloreactive T cells, thereby significantly improving immune rejection and survival rates after stem cell transplantation [42]. Furthermore, in a mouse model of stem cell transplantation, the autophagy gene Atg16L1 has been found to reduce T cell proliferation by downregulating the expression of co-stimulatory molecules on DCs [43], decreasing the rejection response after stem cell transplantation.

Overall, dendritic cells (DCs) play a crucial role in immune modulation during the process of stem cell transplantation [44, 45]. Currently, the application of DCs in stem cell transplantation has made certain progress [46]. The combined use of DCs and stem cells for the treatment of ischemic heart disease (IHD) is a very promising therapeutic approach, but there are still many scientific questions that need to be addressed. The efficacy and safety of DCs in clinical applications require further evaluation. The combination regimens, timing, dosage, and frequency of use for DCs in conjunction with stem cell transplantation await clinical clarification. Elucidating these scientific issues will provide new solutions for optimizing stem cell therapy for IHD.

8. Outlook

Dendritic cells (DCs) are key immune regulatory factors in cardiac injury repair, serving as professional antigen-presenting cells that mediate an environment of immune tolerance by targeting various immune cells. However, the understanding of the roles of different types of DCs in cardiac injury repair is still incomplete. A significant amount of current research focuses on the roles of conventional DCs (cDCs) and regulatory DCs (DCregs) in cardiac injury repair, while the role of plasmacytoid DCs (pDCs) in cardiac injury and repair is less understood. Clinical trials regarding DCregs in organ transplantation are largely in phases 1 and 2 [47]. The molecular mechanisms underlying the induction of immune tolerance by DCregs are still unclear, and more scientific research is needed in the future. Stem cells, as a very promising therapeutic approach for the repair of myocardium in ischemic heart disease (IHD), it is worth exploring whether DCs can be engineered and co-transplanted with stem cells for the treatment of IHD in the future.

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