Proceedings of ICMMGH 2027 Symposium: Clinical OMICS for Drug Discovery and Personalized Medicine
DOI: 10.54254/2753-8818/2027.MB38314

Research Progress on DC Cells in Myocardial Infarction

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Abstract. The occurrence and development of myocardial infarction (MI) are closely related to the immune inflammatory response. Dendritic cells (DCs), as professional antigen-presenting cells, take part in the pathological processes of atherosclerosis, ischemia-reperfusion and ventricular remodeling, but their role and regulatory mechanism at different stages of MI are not yet fully clear. By searching and summarizing the literature related to preclinical, clinical, comorbidity, mechanism and treatment studies, this paper reviews the role and research progress of DC in MI, and focuses on analyzing the characteristics of its subsets, its immune regulatory mechanism and its treatment strategies. Existing studies show that DC presents an obvious dependence on subsets, time phase and microenvironment, and has a bidirectional role of promoting inflammation and repairing tissue; and strategies such as tolerogenic DC, engineered DC and DC-derived exosomes provide new research directions for the immunotherapy of MI, but their clinical translation still needs further verification.

Keywords: dendritic cells, myocardial infarction, immune inflammation, myocardial remodeling, immunotherapy

1. Introduction

Myocardial infarction (MI) is one of the cardiovascular diseases that cause long-term dysfunction and death worldwide; the 2019 Global Burden of Disease study shows that the burden of cardiovascular disease is still continuously increasing, and monitoring data from China also show that in 2019 the crude incidence of acute myocardial infarction had reached 82.76/100,000 [1, 2]. From the perspective of pathophysiological mechanism, MI usually occurs on the basis of coronary atherosclerosis, when plaque rupture or erosion is followed by thrombosis, leading to acute stenosis or occlusion of the coronary lumen, and the myocardium in the corresponding blood-supply area undergoes irreversible necrosis because of persistent ischemia and hypoxia [3]. After MI occurs, the damage-associated molecular patterns released by the necrotic myocardium activate the immune inflammatory response, and take part in multiple stages of the occurrence and development of the disease. Dendritic cells (DCs), as important professional antigen-presenting cells in the body, play an important and complex immune regulatory role at different stages such as the formation of atherosclerosis, myocardial ischemia-reperfusion injury, and ventricular remodeling and fibrosis [3-5].

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DOI: 10.54254/2753-8818/2027.MB38314

Dendritic cells, as the professional antigen-presenting cells with the strongest function in the body, play a core role in starting the bridge between innate immunity and adaptive immunity by taking up, processing and presenting antigen to T lymphocytes. On the one hand they maintain peripheral immune tolerance, and on the other hand, under pathological conditions such as tumors and autoimmune diseases, they take part in the regulation and the imbalance of the immune response [6, 7]. At present, the specific effects and the regulatory mechanism that DC cells exert at different stages of MI are still not fully clear, and the functional differences of its subsets and the DC-based treatment strategies still need further research [8]. On this basis, this paper systematically summarizes the mechanism of action of DC cells in the occurrence and development of MI, in the regulation of inflammation and in ventricular remodeling, and sums up the research evidence related to their comorbidities with MI, providing a reference for exploring immunotherapy strategies after MI.

2. Dendritic cells and myocardial infarction

Because of the dynamic nature of the immune response after myocardial infarction, clinical specimens are hard to observe continuously, and research mainly relies on animal models, that is, rat/mouse coronary artery ligation, including permanent ligation and ischemia-reperfusion models, as well as in vitro culture systems. Naito et al. found in a mouse MI model that DCs infiltrate in the early stage of infarction and are precisely regulated by factors such as GM-CSF and G-CSF [9]. Subsequent studies confirmed that the infiltration of immune cells has a strict time-phase nature, and its dynamic changes are related to the process of inflammatory repair, and there are differences between the permanent ligation and the I/R model [10].

The role of DCs in MI differs according to subset and stage. Anzai et al., through the depletion of CD11c+ cells, found that the absence of DCs can lead to a continuous rise of inflammatory factors and abnormal activation of monocytes/macrophages, aggravating left ventricular remodeling and the deterioration of cardiac function, which suggests that they have a protective regulatory function [11]. In contrast, Lee et al. found that depleting conventional DCs (cDCs) can improve cardiac function and reduce fibrosis and inflammatory infiltration, while depleting plasmacytoid DCs (pDCs) has no such effect, suggesting that the functional heterogeneity of DC subsets is significant [12]. Besides regulating endogenous DCs, inducing tolerogenic DCs (tDCs) is also a potential immune strategy. Sun Haitao et al. gave Galectin-9 before surgery to induce the generation of tDCs, and observed a reduction of infarct size, a decrease of inflammatory infiltration, inhibition of myocardial apoptosis and improvement of ejection fraction [13]. In addition, the microenvironment has a key regulatory effect on DC function; the DAMPs, cfDNA and HMGB1 released by the necrotic myocardium can stimulate pDCs to produce IFN-I, amplifying inflammation and aggravating injury [14].

At present, the clinical research on the involvement of DCs in MI mainly focuses on the number and subset changes of peripheral blood DCs, the infiltration of DCs in myocardial tissue, and their association with myocardial injury and prognosis. A number of studies show that the peripheral blood DCs of AMI patients present transient dynamic changes. Studies have found that the myeloid (mDCPs) and plasmacytoid (pDCPs) DC precursor cells in the peripheral blood of AMI patients are both significantly reduced, more markedly in STEMI patients than in NSTEMI patients, while the number of DCs in the infarcted myocardium increases, suggesting that the reduction of peripheral blood DCs may be related to their recruitment to the infarct area [15, 16]. Further studies confirmed that at admission for AMI the circulating mDC and pDC are lower than in healthy controls and patients with stable angina pectoris, and that the mDC activation markers CD40 and CD83 are elevated, and that the number of DCs recovers about 7 d after onset, presenting a transient feature

DOI: 10.54254/2753-8818/2027.MB38314

[17]. The changes of peripheral blood DCs are related to the degree of myocardial injury and the state of inflammation. The reduction of DC precursor cells in the acute phase of AMI is accompanied by an increase of inflammatory indicators, suggesting that DCs take part in the regulation of immune inflammation in the acute phase [17, 18]. The mDC of STEMI patients gradually recovers 5-7 d after PCI, further supporting their participation in the acute inflammatory and immune recruitment process [17]. At the tissue level, the degree of DC infiltration also affects prognosis. Circulating DC precursor cells can be recruited to the infarcted myocardium and take part in local repair [18]. In addition, in patients with cardiac rupture the numbers of $CD209^+$ and $CD11c^+$ DCs in the infarct area are markedly fewer than in those without rupture, and the degree of reparative fibrosis is reduced; the number of DC infiltration is positively correlated with the degree of fibrosis, suggesting that DCs may maintain the structural stability of the myocardium by promoting tissue repair [19].

Hypertension, hyperlipidemia and diabetes, as important risk factors for myocardial infarction, all take part in the process of vascular immune inflammation and myocardial injury by affecting the recruitment, activation and antigen-presenting function of DCs. Under the state of hypertension, angiotensin II induces oxidative stress and produces lipid oxidation products such as γ-ketoaldehydes; after DCs take them up, they present them as autoantigens, up-regulate CD80/CD86 and secrete pro-inflammatory factors such as IL-6, IL-1β and IL-23, activating T cells and breaking the immune tolerance of the vessel wall [20-23]. Animal experiments confirmed that blocking the B7/CD28 pathway can inhibit T cell activation and prevent hypertension [24]. Clinical studies show that patients with hypertension, coronary heart disease and diabetes all have changes in the number and subset composition of peripheral blood DCs, and these are related to target organ damage and the degree of inflammation [25-35]. In hyperlipidemia, LDL and ox-LDL are taken up by DCs through scavenger receptors such as CD36, CD205 and LOX-1, inducing their maturation and enhancing their antigen-presenting ability, and continuous immune activation can promote plaque progression and destabilization [28, 29]. Diabetes, through high glucose and AGEs signaling, enhances the generation of reactive oxygen species inside DCs and their maturation and activation, aggravating vascular endothelial dysfunction and the progression of atherosclerosis [33]. Animal experiments also confirmed that the enhanced activation of DCs under the above disease states can affect the myocardial injury and repair effect after MI [36]. The above evidence suggests that DC may be the key immune link connecting metabolic abnormality, vascular inflammation and MI, and that the abnormal activation of the DC-T cell axis may be one of the important common mechanisms by which the three promote the occurrence of MI. However, the specific role and mechanism of different DC subsets under each disease background still lack systematic understanding, and their value of clinical translation awaits in-depth exploration [36].

Taken together, preclinical studies show that the role of DCs in MI presents a bidirectionality dependent on subsets, time phase and microenvironment, and that immune intervention strategies targeting DC function provide a new direction for the treatment of MI and lay an experimental foundation for subsequent clinical translation. In terms of clinical research, the number of peripheral blood DCs in patients in the acute phase of MI is reduced, accompanied by DC activation and recruitment to the infarct area, and its dynamic changes are associated with the inflammatory process, tissue repair and patient prognosis. On this basis, the level of peripheral blood DCs may become a potential biomarker reflecting the immune inflammatory state of MI and the assessment of prognostic risk. But current research still faces such limitations as insufficient sample size, and inconsistent definition of DC subsets and detection methods, and its clinical predictive value still needs further verification by large-sample prospective studies.

DOI: 10.54254/2753-8818/2027.MB38314

3. The immune regulatory mechanism of dendritic cells in the pathogenesis of myocardial infarction

3.1. Dendritic cells and atherosclerosis

The pathological understanding of atherosclerosis (AS) has shifted from the theory of simple lipid deposition to the paradigm of a chronic inflammatory disease, and the interactive activation of innate immunity and adaptive immunity runs through the whole course of its occurrence and development. DC, as an important professional antigen-presenting cell in the body, can be detected in the aorta of both healthy people and AS patients, and is generally recognized as the key bridge connecting innate immunity and adaptive immunity; at each stage of AS development it has multiple functions such as lipid uptake, antigen presentation and cytokine secretion [37, 38]. In plaque formation, DC can take up modified antigens such as ox-LDL and present them to naive T cells, and through related co-stimulatory signals and inflammatory factors promote T cell activation, thereby enhancing the local adaptive immune response [39-41]. This process is accompanied by the up-regulation of heat shock protein 60/90 expression, the phosphorylation of the Akt/ERK signaling pathway and the regulation of microRNAs such as let-7c; activated DCs can drive T cells to secrete pro-inflammatory factors such as interferon-γ and interleukin-17, aggravating the local inflammatory injury of the plaque [40, 41]. Studies show that the DCs infiltrating AS plaques are mainly the conventional dendritic cell type 1 (cDC1) and type 2 (cDC2) subsets, and different subsets have differentiated effects on immune regulation. Among them, cDC1 has an outstanding cross-presentation ability, can promote the activation of CD8+ T cells, and drives CD4+ Th1 polarization; it is an important driver of local cytotoxicity and inflammatory injury in the plaque [42-44]. This functional differentiation of subsets suggests that the antigen presentation and T cell activation mediated by DC may be an important link connecting the chronic inflammation of AS with the immune response after myocardial ischemia, and may aggravate immune pathological injury through the continuous presentation of damaged myocardial antigen; this provides a clue for further exploring the immune pathological mechanism mediated by DC in MI [45].

3.2. Dendritic cells and ischemia-reperfusion

Mouse and rat myocardial ischemia-reperfusion models show that local myocardial DCs undergo recruitment and activation as early as the early stage of reperfusion [46, 47]. Studies have observed that after myocardial injury the number of DC infiltration can increase nearly 10-fold, suggesting that DCs deeply participate in the immune inflammatory response related to ischemic injury. The tissue injury caused by ischemia-reperfusion releases endogenous danger signals such as HMGB1, which bind to Toll-like receptor 4 (TLR4) on the DC surface, and through the TLR4/MyD88/NF-κB pathway induce DC migration, adhesion and maturation, and up-regulate the expression of co-stimulatory molecules such as CD80 and CD86 [46, 48]. The above co-stimulatory molecules provide the necessary second signal for T cell activation, enabling DC to start the acquired immune response [47, 48]. On this basis, after ischemia-reperfusion some DCs can, through the cross-presentation pathway, present injury-associated antigens to CD8+ T cells, promoting the excessive proliferation of cytotoxic T cells and the release of effector molecules, aggravating local myocardial inflammatory injury and inducing adverse ventricular remodeling. Further studies show that knocking out the Clec9a gene that mediates cross-presentation can reduce the above immune pathological injury and improve cardiac function, suggesting that the cross-presentation mediated by

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DC may be an important link connecting ischemic tissue injury with the activation of adaptive immunity, and a potential intervention target [49, 50].

3.3. Dendritic cells and ventricular remodeling and fibrosis

DCs take part in the inflammatory response after myocardial infarction, and play an important regulatory role in the process of ventricular remodeling and fibrosis. In patients with heart failure after infarction, there is significant infiltration of cytotoxic T lymphocytes in the local heart, and among them the CLEC9A$^+$ dendritic cells (that is, the cDC1 subset), which have the ability of cross-presentation, play a key regulatory role in this process. cDC1 can cross-present the autoantigens released by necrotic cardiomyocytes to CD8$^+$ T cells, inducing their activation and proliferation. Knocking out the Clec9a gene in mice can specifically block this cross-presentation function, inhibit CD8$^+$ T cell activation, and thereby significantly reduce myocardial fibrosis and immune pathological injury and improve cardiac function, suggesting that the cDC1-CD8$^+$ T cell axis is an important immune mechanism driving adverse ventricular remodeling [50]. In addition, DCs can also secrete inflammatory mediators such as IL-6 and interact with macrophages, fibroblasts and others, taking part in the construction of the local inflammatory and fibrotic microenvironment after infarction [51, 52]. However, DCs present an obvious functional duality in the process of ventricular remodeling. Human myocardial infarction autopsy studies show that the number of infiltrating DCs is positively correlated with the degree of reparative fibrosis, suggesting that they have a certain tissue repair potential [52, 53]. And the elevated expression of CD163 and TWEAK in peripheral blood mDC of AMI patients is associated with long-term deterioration of cardiac function, suggesting that abnormal persistent DC immune activation may take part in adverse remodeling [54]. In contrast, DCs that have acquired a tolerant phenotype through induction can up-regulate regulatory T cells and promote the transformation of macrophages toward a reparative phenotype, reducing fibrosis and improving cardiac function [55]. In summary, DCs have a dual role of pro-inflammatory injury and tissue repair after myocardial infarction, and their functional state may be one of the key factors deciding the outcome of remodeling (Table 1).

Table 1. Core roles and mechanisms of dendritic cells at each stage of myocardial infarction

Pathological stage	DC subset/molecule	Core role	Main mechanism/pathway	Key evidence
Atherosclerosis	cDC1, cDC2	Take up ox-LDL and present antigen, activate T cells, drive plaque inflammation	Cross-presentation, Th1 polarization, Akt/ERK pathway	cDC1 promotes CD8$^+$ T activation and CD4$^+$ Th1 polarization
Ischemia-reperfusion	CD11c$^+$ DC	Recruited and activated in the early stage of reperfusion, infiltration increases nearly 10-fold; cross-presentation activates CD8$^+$ T and aggravates injury	HMGB1-TLR4/MyD88/NF-κB, cross-presentation	Knocking out Clec9a reduces injury and improves cardiac function
Ventricular remodeling and fibrosis	cDC1 (CLEC9A$^+$)	Cross-presentation of autoantigens activates CD8$^+$ T and drives adverse remodeling; at the same time has tissue repair potential	cDC1-CD8$^+$ T axis, IL-6, Treg/macrophage polarization	Knocking out Clec9a reduces fibrosis; DC infiltration is positively correlated with reparative fibrosis

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4. Research progress on dendritic-cell-based therapy for myocardial infarction

4.1. Dendritic-cell-based immunotherapy

Based on the ability of DCs to regulate immune tolerance and the inflammatory response, researchers can induce tolerogenic DCs through in vitro antigen loading and treatment with immune regulatory factors, and, with the help of signals such as IL-10, TGF-β and vitamin D3, induce them to acquire a tolerant phenotype and then reinfuse them, using their antigen-presenting and immune regulatory functions to induce a protective immune response while inhibiting pathological inflammation. This strategy has already been explored in early clinical studies in fields such as autoimmune diseases, but DC immunotherapy targeting MI is at present still mainly at the stage of preclinical research [56, 57]. In MI animal models, tDCs induced by infarcted myocardial lysate can promote the generation of myocardial-specific Tregs, and push macrophages to transform from an inflammatory phenotype to a reparative phenotype, improving ventricular remodeling and cardiac function after infarction.

Recently, engineered DC therapy has further developed in the direction of lesion targeting and local immune regulation. The team of Hu Xinyang/Xu Yang at Zhejiang University has developed an engineered DC intervention strategy (iCDC) that has both immunosuppressive and lesion-targeting abilities. The modified iCDC can localize to the area of cardiac injury, and by inhibiting the activity of locally over-activated immune cells and pro-fibrotic stromal cells, and inducing the clonal expansion of regulatory T cells (Treg), it establishes a stable immune tolerance microenvironment in the local heart and reduces inflammatory cardiac fibrosis. In multiple mouse models of ischemia-reperfusion injury, myocardial infarction and pressure overload, as well as in non-human primate myocardial infarction models, iCDC has shown the effect of improving cardiac fibrosis, perfusion and systolic function, and no obvious systemic toxicity has been seen, providing important preclinical evidence for injury-targeted immune regulatory therapy [58]. The team at Soochow University, starting from the angle of blocking the DC-T cell co-stimulatory signal, has developed mannose-modified CTLA-4 small extracellular vesicles (CM@sEVs). These vesicles can precisely target the mannose receptor on the DC surface, and by displaying CTLA-4 to competitively bind CD80/CD86, block its interaction with CD28 on T cells, specifically inhibiting the excessive activation and proliferation of $CD8^+$ T cells driven by DCs; while reducing the immune pathological injury after myocardial infarction, they support myocardial repair, providing a new idea for cell-free therapy targeting the DC-T cell axis [59]. The above studies show that targeting DC and the immune regulatory network it mediates is expected to become a new direction for the intervention of inflammation and adverse remodeling after MI.

4.2. Therapy based on dendritic-cell-derived exosomes

Dendritic cell-derived exosomes (DEX) are membrane-bound extracellular vesicles released by DCs; they can carry MHC molecules and various bioactive components such as proteins, lipids and nucleic acids, and have the potential to transmit immune regulatory information. As a cell-free substitute product of DC, DEX has both the features of being cell-free and of being easy to modify by engineering. The surface of DEX carries MHC class I/II molecules and co-stimulatory molecules such as CD80 and CD86, and can partly simulate the antigen-presenting and T cell activating functions of DC, but problems such as the standardization of its preparation, its stability in vivo and its targeted delivery still remain to be solved [60, 61]. After myocardial infarction, local DC-derived exosomes can take part in distal immune regulation. Studies have found that the expression of CCR7

DOI: 10.54254/2753-8818/2027.MB38314

on the surface of MI-DEX is elevated, and under the action of the CCL19/CCL21 chemotactic signal it can enhance migration to the spleen, and by activating splenic $CD4^+$ T cells and promoting the expression of anti-inflammatory factors such as IL-4 and IL-10, it improves cardiac function after MI; enhancing the CCR7 expression of DEX can further increase its migration and cardioprotective effect [62]. Other studies show that DEX delivered by hydrogel can also exert a cardioprotective effect by promoting the expansion of regulatory T cells and the polarization of macrophages toward the M2 type, suggesting that the immune regulatory pathway of DEX is not limited to the single $CD4^+$ T cell pathway [63]. The above studies show that DEX can take part in myocardial repair by regulating various immune cells such as T cells and macrophages. In the future, drawing on the idea of engineering modification, through surface modification with targeting ligands such as mannose or the loading of specific immune regulatory molecules, it is expected to further enhance the therapeutic effect of DEX, and to provide a more controllable and more accessible direction of translation for the cell-free immunotherapy of myocardial infarction [59].

4.3. Therapy of induced tolerogenic dendritic cells

Tolerogenic dendritic cells are a DC subset whose function leans toward immunosuppression; they are usually obtained through induction by signals such as IL-10, TGF-β and vitamin D3. Compared with mature DC, tDC presents a lower level of co-stimulatory molecule expression and a weaker ability to activate T cells; its immune regulatory function is realized mainly by inducing the activation and expansion of regulatory T cells (Treg) and by inhibiting the proliferation and activation of effector T cells [64]. In a mouse model of myocardial infarction, the reinfusion of tDC can induce the expansion of Treg in the local heart, and improve ventricular remodeling and cardiac function after infarction [65]. This effect may be related to the release of factors such as IL-10 and TGF-β and to the immune suppression mediated by Treg; the above factors help to drive macrophages to transform from the pro-inflammatory phenotype (M1) to the reparative phenotype (M2), synergistically improving ventricular remodeling and cardiac function [64, 65]. The patent of the team of the Catholic University of Korea (US9833473B2) has disclosed a preparation method that uses myocardial infarction cardiac protein extract and serum to induce tDC in vitro, and has confirmed that this tDC can inhibit excessive remodeling of the left ventricle after infarction and reduce the incidence of heart failure [65]. Other studies show that tDC induced by atorvastatin preconditioning can, by inhibiting the activation of the TLR-4/NF-κB signaling pathway, reduce the secretion of pro-inflammatory cytokines and the level of oxidative stress, lessen the apoptosis of cardiomyocytes and the degree of fibrosis after infarction, and improve left ventricular systolic function and remodeling indicators [66].

What deserves attention is that the iCDC therapy developed by the Zhejiang University team represents the advancement of the tDC strategy from natural induction to engineered modification; through gene editing and lesion-targeting modification, it endows DC with an immunosuppressive ability and a lesion-specific homing ability far stronger than those obtained by natural induction, and it shows a stable cardioprotective effect in various rodent and non-human primate myocardial infarction models [58]. On the whole, enhancing the lesion targeting and the in vivo stability of tDC on the premise of retaining its immune tolerance function is the key topic for pushing forward the clinical translation of this strategy.

DOI: 10.54254/2753-8818/2027.MB38314

5. Conclusion and prospects

In summary, DC presents dependence on subsets, on time phase and on microenvironment at different stages of myocardial infarction. After myocardial ischemia and reperfusion, DC can promote the adaptive immune response through such pathways as activation, antigen presentation and cross-presentation; among them, the cross-presentation mediated by cDC1 and the activation of $CD8^+$ T cells may take part in persistent immune injury and adverse ventricular remodeling. On the other hand, tolerogenic DC can, through such pathways as promoting the Treg response and regulating macrophage function, exert a tissue protective effect. Therefore, DC is not a purely pro-inflammatory cell; its functional state may jointly affect the outcome of repair and remodeling after myocardial infarction. At present, related research still has such problems as insufficient connection between animal experiments and clinical evidence, the definition of DC subsets and the detection methods not yet being unified, and the limited size of clinical samples. In the future, techniques such as single-cell sequencing can be used to finely distinguish the dynamic changes of DC subsets and functional states, and multi-center large-sample prospective studies can be used to verify the value of peripheral blood DC as a prognostic marker of MI. In terms of treatment, cell-free strategies such as engineered DC and exosomes provide a new direction for lesion-targeted immune regulation, but their treatment timing, targeting, safety and standardized preparation still need systematic verification, so as to push the related results toward clinical translation.

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