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TOPIC HIGHLIGHT

**Cuihua Zhang, MD, PhD, FAHA, Associate Professor,** *Series Editor*

# Role of dendritic cells in cardiovascular diseases

Yi Zhang, Cuihua Zhang

Yi Zhang, Cuihua Zhang, Department of Internal Medicine, Medical Pharmacology and Physiology and Nutritional Sciences, Dalton Cardiovascular Research Center, University of Missouri, Columbia, MO 65211, United States
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Correspondence to: Cuihua Zhang, MD, PhD, Department of Internal Medicine, Medical Pharmacology and Physiology and Nutritional Science, Dalton Cardiovascular Research Center, University of Missouri, Columbia, MO 65211, United States. zhangcu@missouri.edu
Telephone: +1-573-8822427 Fax: +1-573-8844232
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## Abstract

Dendritic cells (DCs) are potent antigen-presenting cells that bridge innate and adaptive immune responses. Recent work has elucidated the DC life cycle, including several important stages such as maturation, migration and homeostasis, as well as DC classification and subsets/locations, which provided etiological insights on the role of DCs in disease processes. DCs have a close relationship to endothelial cells and they interact with each other to maintain immunity. DCs are deposited in the atherosclerotic plaque and contribute to the pathogenesis of atherosclerosis. In addition, the necrotic cardiac cells induced by ischemia activate DCs by Toll-like receptors, which initiate innate and adaptive immune responses to renal, hepatic and cardiac ischemia reperfusion injury (IRI). Furthermore, DCs are involved in the acute/chronic rejection of solid organ transplantation and mediate transplant tolerance as well. Advancing our knowledge of the biology of DCs will aid development of new approaches to treat many cardiovascular diseases, including atherosclerosis, cardiac IRI and transplantation.



**Key words:** Dendritic cells; Atherosclerosis; Ischemia reperfusion; Transplantation

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## INTRODUCTION

Dendritic cells (DCs) were initially identified as potent antigen-presenting cells that play a key role in induction of the innate immune response[1]. Further investigation revealed DCs were also a link between the innate and adaptive immune systems[2,3]. DCs that were activated *via* endogenous or exogenous antigens progressed from immature DCs to mature DCs, which initiated the release of cytokines that activated the T cell/B cell immune responses[2,4-6]. DCs have now been confirmed to be involved in many different disease conditions, such as rheumatoid arthritis, pulmonary allergic disease, rhinitis and other autoimmune diseases[7-9]. DCs have also been implicated in various cardiac pathologies, such as atherosclerosis[10], endothelial dysfunction[11], ischemia reperfusion injury (IRI)[12] and heart transplantation[11]. The purpose of this review is to summarize the biology and function of DCs and draw attention to their role in cardiovascular diseases.

## BIOLOGY OF DCs

Steinman and Cohen originally described the role of DCs in the initiation of immune responses in 1973[13] and many workers since then have further elucidated the classification, origin, life cycle and functions of DCs.

DCs have been classified into two categories: plasmacytoid DCs (pDCs) and conventional DCs (cDCs)[2,14-16]. cDCs are sub-divided into two major populations, including non-lymphoid tissue migratory and lymphoid tissue-resident DCs[4]. pDCs and cDCs differ in origin, phenotype, localization and immunological function. pDCs, which are named for morphological similarity to plasma cells, have expression markers, including CD123 (IL-3R) and BDCA-2[17]. They recognize oligodeoxynucleotides *via* Toll-like receptors (TLR) 7 and TLR 9, whose functions are to produce cytokines of interferon (IFN)-α[18]. In contrast, cDCs have expression markers of CD1c, CD11c, CD33 and CD209 *via* TLR2, TLR4 and TLR7. cDCs usually produce different cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-12 and IL-23[19,20]. Locational differences also exist. pDCs circulate in the blood and produce IFN-α when they are activated by an exogenous virus. Lymphoid tissue-resident cDCs homeostatically reside in all lymphoid organs, while non-lymphoid tissue migratory cDCs are located in different tissues, such as skin, lung, heart, kidney, liver or intestine[4]. Those non-lymphoid tissue migratory cDCs are mobile sentinels that reside in the blood. They become "inflammatory" DCs during inflammation or infection and migrate to lymphoid organs where they accumulate to stimulate T cells[21].

The origin of DCs still remains controversial. The initial concept was that all DCs were derived from a hemopoietic stem cell ($CD34^+$ common myeloid precursor, CMP) in bone marrow[1]. Later studies demonstrated some DCs may originate from common lymphoid precursors (CLP)[22]. Recent evidence supports the idea that the FLT3 expressing hemopoietic precursors, as a growth factor for hemopoietic progenitors, are the precursors of both CLP and CMP pathways to produce cDCs and pDCs in the steady state[23-25], while granulocyte-macrophage colony-stimulating factor, a primary growth factor for DCs, will increase the number of monocyte-derived DCs during inflammation and infection[26]. León *et al*[27] suggested that monocyte-derived DCs, which form at an infection site, control the induction of protective T helper 1 response. In contrast to the traditional concept that DCs are end-stage and nondividing cells, Liu *et al*[28] reported that there are two processes that account for DC homeostasis in lymphoid organs: (1) most DCs arise *via* a constant replenishment by DC precursors that replace dying nondividing DCs; and (2) about 5% of resident DCs replicate *in situ* for a limited number of divisions before dying.

Accumulated evidence indicates that DCs have several important checkpoints in their life cycles, including antigen-capture, maturation, migration, antigen-presentation and homeostasis[1,4,6]. In most tissues, other than secondary lymphoid tissues (lymph node and spleen), immature DCs monitor exogenous and endogenous antigens to fulfill their sentinel/surveillance functions. In the steady-state, without an overt presence of stimuli, those immature DCs induce and maintain peripheral self-tolerance[29]. In the inflammatory state, where there is infection from bacteria/virus or intrinsic damage induced by hypoxia or ischemia, the immature DCs will capture antigens by various mechanisms, including phagocytosis, macropinocytosis, or receptor-mediated antigen uptake (C-type lectin receptors, scavenger receptors and complementary receptors), which in turn initiates DC maturation and migration[2]. Several factors have been proposed to induce and regulate DC maturation, including pathogen-related molecules (LPS, bacterial DNA or double-strand RNA), pro-inflammatory signals (TNF-α, IL-1, IL-6, IL-10, transforming growth factor-β and prostaglandins) and T cell-derived signals (CD40L)[2]. These factors induce activation of pattern recognition receptors (PRRs), such as TLRs and CD1 receptors, both of which are bacteria and virus antigen presenting receptors[6]. TLRs also combine with endogenous ligands to induce an immune response after ischemia, hypoxia or tissue damage[30,31]. DC maturation is accompanied by the loss of endocytic phagocytic receptors, morphological changes of DCs, up-regulation of co-stimulatory molecules like CD40, CD58, CD80 and CD86, and MHC-Ⅱ molecules/production of pro-inflammatory cytokines (TNF-α and IL-12)[2,4]. Commensurate with the activation of TLRs and CD1-mediated maturation, immature DCs will down-regulate DC's endocytic capacity and migrate from local tissues to secondary lymphoid organs. The anatomical routes for DC trafficking were reported to include afferent lymphatics or high endothelial venules[19]. Migratory mature DCs and lymphoid tissue-resident cDCs reach the T-cell zone in the lymph nodes and spleen, which in turn presents antigens to naïve T cells to initiate an adaptive immune response[20]. T cell activation consists of several effectors, such as helper T cell, regulatory T cells and cytotoxic T cells, which in turn secrete cytokines to activate other cells (macrophages, NK cells and eosinophils), or to lyse the infected cells[2]. DCs are eliminated by apoptosis after their interaction with T cells[2,6].

DCs play a critical role by bridging the innate and adaptive immune responses[5,32]. The innate immune response is the first line of defense against foreign pathogens and tissue injuries or malignancies. DCs, as an important component of the innate immune response, scan and detect the environmental signs of foreign infection or tissue damage. DCs then become activated, which is followed by their migration to lymph nodes and maturation *via* TLR activation. TLRs are type I transmembrane protein receptors and are expressed on the surface of DCs[33]. There were 11 human and 13 mouse TLRs cloned after the first TLR was reported in 1997[34]. In the innate immune response, TLR activation initiates acute inflammatory responses by releasing inflammatory cytokines/chemokines to recruit neutrophils and the activation of macrophages, leading to the killing of pathogens directly[35]. On the other hand, TLR activation was found to ini-

tiate, maintain, modulate and terminate the innate host defenses by either producing pro-inflammatory cytokines or stimulating DC maturation to initiate T-cell expansion and activate antigen-specific adaptive immune responses[36]. In addition, TLRs promote the expression of co-stimulatory molecules (CD80 and CD86) to maintain the activation of adaptive immunity. DC activation *via* TLRs serves as a major link between innate and adaptive immunity[37]. Accumulated evidence has demonstrated that the engagement of DCs and TLRs defends against skin/pulmonary infection and autoimmune diseases[7-9] and also plays a key role in cardiovascular diseases, such atherosclerosis, myocardial IRI and cardiac transplantation[10-12].

## DCs AND ATHEROSCLEROSIS

The mechanisms of atherosclerosis have evolved to include inflammation as one of its important causes. Atherosclerosis can be characterized as a disease arising from the immune response[38,39]. Vascular inflammation has been linked to innate and adaptive immunity that includes DCs playing an important role in the pathogenesis of atherosclerosis[10], as well as arising through traditional pathways, such as those involving macrophages and monocytes.

DCs reside in healthy arteries in small amounts, as well as in other organs such as kidney, lung or intestines. DCs have been reported to occur in the adventitia and intima of large arteries, including aorta, coronary and carotid arteries[40]. In contrast, DCs were not present in normal veins and they only occurred in diseased veins after vessel injury[41]. The vascular resident DCs are "immature DCs", which are continuously and efficiently monitoring exogenous and internal antigens in the steady physiological state. DCs are reported to be key elements of vascular-associated lymphoid tissues, which function as sentinels to screen for potential harmful antigens that arise in vascular tissues[42,43].

Direct evidence for a relationship between DCs and atherosclerosis came in 1995 when Bobryshev and his group reported that DCs accumulated in atherosclerotic lesions[44]. They went on to demonstrate a greater amount of DCs clustered in the intima of atherosclerosis-prone areas than in the atherosclerosis-resistant areas of the non-diseased aorta[45]. Thus, DCs occurred in healthy arteries and pre-atherosclerosis stage arteries, and in atherosclerotic lesions[46]. Subsequent work further implicated DCs in atherosclerosis[47,48]. Both local vascular DCs and blood DCs *via* inflamed neo-vessels were shown to contribute to the formation of atherosclerotic lesions[46,47]. Kawahara *et al*[49] confirmed that the expression of vascular DCs was observed in human atherosclerotic carotid plaques, which may be strongly associated with the occurrence of ischemic stroke; they found a close relationship between the mean signal intensity of DCs in plaques and the symptoms of patients with significant carotid plaques as well. Mechanisms that govern how vascular DCs contribute to the pathogenesis of atherosclerosis have been proposed. Vascular DCs activated by different antigens (viral, bacterial or auto-antigens) are followed by activation of T cells and natural killer cells and initiate an inflammatory response in the arterial wall[10]. Bacci *et al*[50] demonstrated that smooth muscle cells, DCs and mast cells are sources of TNF-α and nitric oxide in human carotid artery atherosclerosis.

Vascular DCs not only contribute to the formation of atherosclerosis, but also play a crucial role in plaque destabilization. Plaque destabilization is an important risk factor for acute myocardial infarction and acute stroke after coronary or carotid artery plaque rupture. Clinical cardiology has confirmed that more than 50% of coronary artery plaques rupture in the plaque shoulder and the markedly increased number of DCs (more than 90%) were located in the plaque shoulder - the plaque-prone area[51]. Yilmaz *et al*[52] analyzed the frequency of different immune cells in atherosclerotic carotid plaque and demonstrated that immune cells were strongly associated with neovascularization. They concluded that enhanced recruitment of immune cells through neovessels into the upstream shoulder might contribute to plaque destabilization. In addition, Niessner *et al*[53] recently reported that human coronary and carotid plaques contain myeloid DCs (mDCs) in close cell-cell contact with T cells and mDCs are highly activated to produce the T-cell-attracting chemokines CCL19 and CCL21, which results in plaque destabilization. The evidence of co-accumulation of DCs and natural killer T cells within rupture-prone regions in human atherosclerotic plaques from Bobryshev's group supports the view that DCs shape the functional activity of natural killer cells to destabilize plaque[54]. Furthermore, Erbel *et al*[55] demonstrated that activated and fully mature DCs are represented in the inflammatory infiltrate that characterizes unstable carotid and coronary atheroma. More recently, Yilmaz *et al*[56] investigated the different levels of DC precursors and demonstrated a significantly lower level of circulating DC precursors in stable coronary artery disease (CAD) patients compared to healthy individuals, which is an independent predictor of the presence of stable CAD.

Inflammation as a mechanism of atherosclerosis and the involvement of DCs in the process of atherosclerosis have inspired possible therapeutic interventions for atherosclerosis by changing the DC profile. Statin was found to inhibit the maturation and antigen-presenting function of DCs, which may show a beneficial effect in atherosclerosis[57]. Vaccine therapy may also prevent atherosclerosis[58].

## INTERACTION BETWEEN DCs AND ENDOTHELIAL CELLS

DCs have a close anatomical and functional relationship with endothelial cells (ECs). Immature DCs patrol in the blood in the steady state. Under inflammatory conditions, DCs will capture antigens and migrate from peripheral tissue to nearby lymph nodes to present antigens. When DCs are exiting from the bloodstream, they (either from blood or from tissue) will need to tether to the ECs, during which some proteins, such as E-selectins or P-selectins, may be involved. Robert *et al*[59] have demonstrated that

blood DCs constitutively interact with normal murine skin endothelium *in vivo via* selectins. In contrast, ECs play a crucial role in the inflammatory response. Their activation significantly promotes vascular permeability, edema and leukocyte recruitment, including DC activation. EC and DC cell lineages are closely related and they exert a reciprocal effect on their differentiation. Fernandez Pujol *et al*[60] provided evidence of a phenotypic overlap between monocyte-derived DCs and microvascular endothelium and confirmed that DCs derived from peripheral monocytes express endothelial markers.

Increasing evidence has supported the idea that the adhesion and migration of DCs are affected by EC activation. Weis *et al*[61] found the endothelial determinants of DC adhesion and migration and concluded that adhesion and migration of DCs are increased by endothelial activation and prevented by the augmentation of endothelial NO synthase activity. Inflamed lymphatic endothelium was also found to be able to suppress DC maturation and function *via* the MAC-1/ICAM-1-dependent mechanism[62]. Angelot *et al*[63] reported that EC-derived microparticles induce pDC maturation and the production of inflammatory cytokines. More recently, Zhu *et al*[64] suggested that homocysteine increased vascular oxidative stress and decreased NO release, which enhanced DC adhesion to and transmigration across the endothelium, indicating the importance of DC-EC interaction.

DC-EC cross-talk plays a pivotal role in angiogenesis[65]. There are several mechanisms responsible for this cross-talk. DCs were found to have the ability to transdifferentiate into endothelial-like cells to contribute to vasculogenesis[65]. DCs can produce and release pro- and anti-angiogenic mediators, including the potent angiogenic growth factor vascular endothelial growth factor-A, which directly acts on the endothelium by combining its signaling receptors on the EC surface. Furthermore, DCs, upon activation, can release cytokines and chemokines, which increase or decrease the responsiveness of ECs. IFN-α-producing pDCs can inhibit EC motility and promote the production of anti-angiogenic chemokines[66]. Therefore, a better understanding of DC-EC cross-talk in the pathophysiological process of angiogenesis will aid in the discovery of important mechanisms for inflammatory diseases.

## DCs AND IRI

CAD is a major problem in the USA and worldwide; early reperfusion of occluded coronary artery by thrombolytic therapy or percutaneous coronary interventions is the standard treatment. IRI, however, has become an important problem since it limits the full potential benefit of reperfusion therapy[67]. IRI was reported to involve several mechanisms, including oxygen paradox, calcium paradox, pH paradox, immune response and inflammation. Based on classic models, acute ischemia leads to endothelial activation and production of oxygen free radicals, which promotes the secretion of inflammatory cytokines/chemokines and activity of adherent molecules[68]. Such changes recruit effector cells into the post-ischemic tissues. Reperfusion then further increases endothelial permeability and cell activation, which exacerbates the inflammatory reaction.

Recently, increasing evidence has demonstrated that both the innate immune response and the adaptive immune response mediated by T cell activation contribute to IRI[69,70]. DCs, which bridge innate and adaptive immune responses, are an important component in the pathogenesis of IRI[69]. Ischemia leads to tissue damage, which releases endogenous ligands, such as heat shock proteins, matrix components and products of necrotic cells. These ligands will combine with a family of PRRs, such as TLRs, which activate the first line of defense in the innate immune system[30]. TLRs were reported to be expressed in many cells, including antigen presenting cells, such as DCs. As discussed above in the biology of DCs, immature DCs will migrate to secondary lymphoid tissues (spleen and lymph nodes) to stimulate naïve T lymphocytes and trigger naïve T cell response.

The role of DCs in the hepatic and renal IRI have been extensively studied. DCs were found to be present in healthy liver and kidney. The number of DCs in the liver and kidney was significantly increased during ischemia and reperfusion[71,72]. Wu *et al*[73] demonstrated that renal IRI resulted in DC infiltration of the outer medulla of the kidney after 2 d of reperfusion. Resident liver DCs migrated from the sinusoidal lumen to the hepatic lymph *via* the space of Disse to become mature DCs[74]. Loi *et al*[75] showed that liver IRI itself induces DC maturation, migration and preferential production of inhibitory cytokines in a mouse IRI model. Resident DCs were reported to be the predominant secretory source of TNF-α in early renal ischemia-reperfusion injury and *in vivo* depletion of DCs from the kidney substantially attenuated TNF-α secretion following IRI[76]. Furthermore, TLR signaling activation in the pathogenesis of liver and renal IRI were found in several recent studies[77,78].

DCs exist in the heart and cardiac DCs are closely associated with the endocardial blood vessels and connective tissue. Cardiac DCs were reported to be aligned parallel to cardiac myocytes with their processes interdigitating between the myocytes[79]. Cardiac DCs are fewer in number but higher in density than in other organs, including liver, pancreas and kidney[80]. Zhang *et al*[81] reported the accumulation of DCs in the "border zones" of infarct sites at 7 d post-infarct in a rat myocardial infarction model. Compared to the numerous published studies for liver and renal IRI, there is a lack of experiments or studies regarding the role of DCs in the pathogenesis of cardiac IRI. However, the role of TLR on IRI has been extensively studied. TLR2 and TLR4 activations were confirmed to be related to IRI by different groups of researchers, showing the reduction of infarct size and inflammation in TLR4 deficient mice after 1 h of ischemia and 24 h of reperfusion[82]. Sakata *et al*[83] recently demonstrated that

TLR deficient murine hearts showed better cardiac function after myocardial infarction than the wild-type. More studies are warranted to explore the role of DCs on cardiac ischemia-reperfusion injury.

## DCs AND CARDIAC TRANSPLANTATION

Cardiac transplantation has proven to be an effective treatment for advanced heart failure patients, although the shortage of heart donors limits clinical application. An evolving understanding of the multiple pathways involved in immune activation has resulted in many advances in immunology for transplantation medicine[84]. The adaptive immune responses medicated with T cell/B cell activation have been emphasized for the regulation of transplant rejection and the advance of immunosuppressive agents has improved long-term survival after transplantation. The traditional infectious-non-self model indicates that the activation of PRRs identifies pathogen-associated molecular patterns to produce significant cytokine release by the engagement of TLR, which in turn activates the adaptive immune response. Recently, the innate immune response after transplantation has attracted much attention. Based on the new "Danger Model", the damaged or necrotic self-tissue, rather than foreign tissue, is what will activate innate immune responses *via* increased TLR reactivity, leading to increased cytokine release[31]. DCs, as an important bridge between innate and adaptive immune responses, therefore play a significant role in the field of transplantation medicine.

DCs are potent antigen presenting cells involved in direct, indirect and semi-direct pathways of alloantigen recognition by the host immune system[84-86]. First, for the direct pathway, donor-derived DC and monocytes/macrophages that originally exist in the donor heart will leave the graft after transplantation and migrate to the recipient's secondary lymph system (including lymph node and spleen). They present donor antigen to recipient T cells directly to induce an adaptive immune response. This direct pathway is responsible for the acute rejection. Larsen *et al*[87] demonstrated that donor resident DCs migrate from cardiac allografts into the host spleen during the first days after transplantation. In contrast, for the indirect pathway, the recipient's DCs migrate into the graft after heart transplantation, where they pick up and process the donor antigen, to activate the recipient's adaptive immune response after their presentation to the recipient's T cells. The indirect pathway may actually be the cause of chronic rejection. Kofler *et al*[11] reported that DCs frequently infiltrate the cardiac allograft with a peak during the first postoperative year and confirmed the graft-infiltrating DCs and coronary endothelial dysfunction after human heart transplantation. Finally, for the semi-direct pathway, recipient T cells recognize donor MHC molecules, which are transferred from donor cells to the surface of recipient cells intact[88]. Loverre *et al*[89] also reported that myloid and pDCs were significantly increased, with few mature DCs during delayed graft function. In addition, DC binding and transmigration on allogenic ECs exposed to calcineurin inhibitors were concentration-dependently increased, indicating that long-term immunosuppression mediates enhanced invasion of DCs to the donor organ and aggravates chronic rejection[90]. Furthermore, DCs have been used as tools for controlling allograft rejection in organ transplantation[91,92]. Shlomchik *et al*[93] provided evidence of prevention of graft versus host disease by inactivation of host antigen-presenting cells.

DCs not only induce an immune response and participate in organ rejection, but also mediate transplant tolerance[84,94]. Hawiger *et al*[95] first reported that, in the absence of additional stimuli, DCs induce transient antigen-specific T cell activation followed by T cell deletion and unresponsiveness. Subsequently, Bonifaz *et al*[96] demonstrated that small amounts of injected antigen, targeted to DCs by the DEC-205 adsorptive pathway, are able to induce solid peripheral $CD8^+$ T cell tolerance, indicating a constitutive tolerance role for DCs in peripheral lymphoid organs in the steady state. It is commonly accepted that, in the steady state, $CD8^-$ and $CD8\alpha^+$ DCs remain quiescent after capturing and processing exogenous antigen, which in turn express low levels of co-stimulatory molecules and then induces deficient activation of naïve T cells, T cell apoptosis or anergy and the generation of regulatory T cells. Huang *et al*[97] found that a distinct DC subset constitutively endocytoses and transports apoptotic cells to T cell areas, suggesting a role for those DCs in inducing and maintaining peripheral self-tolerance. In addition, Lambolez *et al*[98] showed that self-antigen presentation exclusively by peripheral DCs resulted in very efficient deletion of the majority of antigen-specific T cells with the remaining cells left in an anergic state. Finally, evidence has accumulated that deliberately generated tolerogenic DCs might be a useful tool for the induction of donor-specific tolerance to prevent rejection after solid organ transplantation. Jiga *et al*[99] found that mitomycin treatment converts rat DCs into tolerogenic cells, whose mechanism is mediated by decreased ICAM-1, CD80 and CD86.

In summary, DCs are a bridge connecting the innate immune response and the adaptive immune response. DCs play an essential role in the pathogenesis of many cardiovascular diseases, including atherosclerosis, cardiac IRI and cardiac transplantation. DCs also interact with other cells, such as endothelial, natural killer and T cells, to affect immunogenic responses in the body. DCs have great potential for use in the treatment/prevention of cardiovascular disease.

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