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Review

Myeloid dendritic cells: Development, functions, and role in atherosclerotic inflammation

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ABSTRACT

Myeloid dendritic cells (mDCs) comprise a heterogeneous population of professional antigen-presenting cells, which are responsible for capture, processing, and presentation of antigens on their surface to T cells. mDCs serve as a bridge linking adaptive and innate immune responses. To date, the development of DC lineage in bone marrow is better characterized in mice than in humans. DCs and macrophages share the common myeloid progenitor called macrophage–dendritic cell progenitor (MDP) that gives rise to monocytoid lineage and common DC progenitors (CDPs). CDP in turn gives rise to plasmacytoid DCs and predendritic cells (pre-mDCs) that are common precursor of myeloid CD11b+ and CD8α+ DCs. The development and commitment of mDCs is regulated by several transcription and hematopoietic growth factors of which CCr7, Zbtb46, and Flt3 represent 'core' genes responsible for development and functional and phenotypic maintenance of mDCs. mDCs were shown to be involved in the pathogenesis of many autoimmune and inflammatory diseases including atherosclerosis. In atherogenesis, different subsets of mDCs could possess both proatherogenic (*e.g.* proinflammatory) and atheroprotective (*e.g.* anti-inflammatory and tolerogenic) activities. The proinflammatory role of mDCs is consisted in production of inflammatory molecules and priming proinflammatory subsets of effector T cells. In contrast, tolerogenic mDCs fight against inflammation through arrest of activity of proinflammatory T cells and macrophages and induction of immunosuppressive regulatory T cells. Microenvironmental conditions trigger differentiation of mDCs to acquire proinflammatory or regulatory properties.

Contents

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Introduction

Dendritic cells (DCs) comprise a heterogeneous population of blood-borne professional antigen-presenting cells characterized by ability to catch, process, and present antigens to T cells, which in turn recognize the antigen and induce the antigen-specific immune response (Banchereau and Steinman 1998). Therefore, DCs are key players in induction of immune response and link together innate and humoral immunity. Depending on the origin, location, and function, DCs could be divided to several subpopulations. After leaving the bone marrow and entering the bloodstream, DC progenitors give rise to resident and migratory DCs that complete their differentiation. DCs could reside in lymphoid and non-lymphoid tissues where they engulf antigens and present them to local T cells. In peripheral tissues, migratory non-lymphoid tissue DCs patrol the circulatory system where they uptake antigens and migrate to lymph nodes to present antigens to T lymphocytes (Broggi et al. 2013).

In the periphery, migratory DCs are presented as three main subpopulations. Plasmacytoid DCs (pDCs) are characterized with a relatively low expression of human leukocyte antigen (HLA) class I and class II molecules, high surface expression of Toll-like receptor (TLR)-7 and -9, and production of high amounts of Type I interferons (IFNs) (Haniffa et al. 2013). pDCs play a pivotal role in induction of antiviral and antibacterial responses (Chistiakov et al. 2014a). Human pDCs express the surface markers CD123, blood dendritic cell antigen (BDCA)-2 (CD303), and BDCA-4 (CD304), but do not express high levels of CD11c or CD141 that separates them from conventional DCs (cDCs) (Dzionek et al. 2000). In humans, myeloid (or conventional) DCs (mDCs) are presented by two main subpopulations including CD1c/BDCA-1$^+$ cells and CD141/BDCA-3+ cells that account for ~50% and 5–10% of a total peripheral DC population respectively (MacDonald et al. 2002). Murine counterparts of human DCs are shown in Table 1 (Robbins et al. 2008). Mouse and human DCs (and pDCs especially) were shown to share many evolutionarily conserved molecular pathways (Robbins et al. 2008) suggesting for significant functional preservation of DCs among mammals.

DCs were shown to play a crucial role in various pathologic conditions involving inflammatory and autoimmune background such as atherosclerotic disease (Chistiakov et al. 2014b). In atherosclerosis, human DCs could present self-antigens to CD4$^+$, CD8$^+$, and natural killer (NK) T cells in HLA class II-, HLA class I-, and CD1d-dependent manner respectively. This indeed leads to the activation of naïve T cells, mainly toward the proinflammatory phenotype (Koltsova et al. 2012). However, the anti-inflammatory and immunosuppressive response also occurs in atherosclerosis. Regulatory DC subsets contribute to the anti-inflammation, which is atheroprotective (Schmidt et al. 2012). Previously, we considered developmental and functional aspects of pDCs, with emphasis on their contribution in atherosclerosis (Chistiakov et al. 2014a). In this review, we characterize development and function of mDCs and consider their role in atherogenesis.

Comparative analysis of two main subsets of human and mouse mDCs

For human and murine DCs, a list of surface markers and receptors essential to distinguish mDCs from pDCs is presented in Table 2. Both human and mouse mDCs express myeloid markers CD13 and CD33 and CD32, an immune inhibitory Fc receptor (Guilliams et al. 2014).

Human migratory CD141$^+$ mDCs express TLR3 and release large amounts of interleukin (IL)-12 and IFN-β in response to activation with poly(I:C), a mimic of double stranded RNA and ligand for TLR3 (Kaisho 2012). CD141+ mDCs express C-type lectin domain 9A (CLEC9A), a receptor sensing necrotic cell antigens (Sancho et al. 2009) and hence are capable to engulf dead cells and cross-present cell-associated and soluble antigens upon activation of TLR3 ligands (Iborra et al. 2012; Zelenay et al. 2012). Both human CD141$^+$ mDCs and mouse CD8α$^+$ mDCs coexpress TLR3, CLEC9A, and chemokine (C motif) ligand receptor 1 (XCR1) (Poulin et al. 2010). Compared to other DC subpopulations, XCR1 was shown to represent the most selective marker for both CD141$^+$ and CD8α$^+$ mDCs (Crozat et al. 2010). In addition, both mDC subsets were found to share expression of transcription factors (interferon regulatory factor (IRF) 8 and basic leucine zipper transcription factor, ATF-like 3 (BATF3)) and surface markers such as nectin-like molecule 2 (Necl2) and langerin (CD207). Like mouse CD8α$^+$ mDCs, human CD141$^+$ DCs lack expression of IRF4, CD11b, and TLR7 (Iborra et al. 2012). Human hematopoietic progenitors differentiate to CD141$^+$ DCs in the presence of FMS-like tyrosine kinase 3 ligand (Flt3L), a key master regulator of DC development. Down-regulation of BATF3 in hematopoietic progenitors was observed to prevent differentiation of CD141$^+$ DCs but not CD1c$^+$ DCs (Poulin et al. 2012) thereby indicating the relationship in the ontogeny of human CD141$^+$ DCs and mouse CD8α$^+$ mDCs. Furthermore, both DC subpopulations are functionally related due to superior capacity to antigen cross-presentation, *e.g.* ability to present an extracellular antigen not in a classical major compatibility complex (MHC) class II-dependent manner, but through a MHC-I-mediated presentation mechanism (Bachem et al. 2010).

However, despite many phenotypical and functional similarities between these mDC subsets, there are some differences. For

Table 1
Major subsets of circulating human and mouse DCs.

Dendritic cell subset	Surface markers	
	Human	Mouse
Plasmacytoid	CD11c$^+$CD123$^+$BDCA-2^{+++} BDCA-4^{+++}TLR7^{+++} TLR9^{+++}CD1c^{low}CD141c^{low}	CD11c$^+$B220$^+$mPDCA-1^{+++}CD11b$^-$Clec12a^{+++}SiglecH^{+++}Tlr7^{+++}Tlr9^{+++}
Myeloid (subset 1)	CD1c/BDCA-1^{+++} CD11c^{++} TLR2^{+++}TLR4^{+++}	CD11b^{+++}CD209a$^+$Tlr7$^+$Tlr9$^+$Tlr12^{+++}Tlr13^{+++}
Myeloid (subset 2)	CD141/BDCA-3^{+++} CD11b$^-$CD11c^{++} CLEC9A$^+$ XCR1$^+$ TLR3^{+++} TLR10^{+++}	CD8α^{+++}Clec9a^{+++} Xcr1$^+$Ly75^{+++}Tlr3^{++} Tlr11^{+++}

BDCA, blood dendritic cell antigen; CLEC9A, C-type lectin domain 9A; Ly75, Lymphocyte antigen 75; mPDCA-1, mouse plasmacytoid dendritic cell antigen-1; TLR, Toll-like receptor; XCR1, chemokine (C motif) ligand receptor 1; SiglecH, sialic acid-binding immunoglobulin H-type lectin.