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Plasmacytoid dendritic cells: Biomarkers or potential therapeutic targets in atherosclerosis?

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ABSTRACT

Plasmacytoid dendritic cells (pDCs) represent a unique subset of dendritic cells that play distinct and critical roles in the immune response. Importantly, pDCs play a pivotal role in several chronic autoimmune diseases strongly characterized by an increased risk of vascular pathology. Clinical studies have shown that pDCs are detectable in atherosclerotic plaques and others have suggested an association between reduced numbers of circulating pDCs and cardiovascular events. Although the causal relationship between pDCs and atherosclerosis is still uncertain, recent results from mouse models are starting to define the specific role(s) of pDCs in the disease process. In this review, we will discuss the role of pDCs in innate and adaptive immunity, the emerging evidence demonstrating the contribution of pDCs to vascular pathology and we will consider the possible impact of pDCs on the acceleration of atherosclerosis in chronic inflammatory autoimmune diseases. Finally, we will discuss how pDCs could be targeted for therapeutic utility.

Contents

Abbreviations: AMI, Acute myocardial infarction; ACPA, anti-citrullinated protein antibodies; APC, antigen presenting cells; apoE, apolipoprotein-E; BDCA, blood dendritic cell antigen; BST-2, bone marrow stromal antigen; CVD, cardiovascular diseases; CACs, circulating angiogenic cells; cDCs, conventional dendritic cells; CAD, coronary artery disease; DT, diphtheria toxin; ECs, endothelial cells; EPCs, endothelial precursor cells; G-CSF, granulocyte colony-stimulating factor; HEVs, high endothelial venules; HFD, high fat diet; IDO, indoleamine 2,3-dioxygenase; IFN, Interferon; IRF, Interferon Regulatory Factor; LDLr, low density lipoprotein receptor; LNs, lymph nodes; LAG-3, lymphocyte activation marker-3; MDPs, macrophage/dendritic cell precursors; MHC-II, major histocompatibility complex class II; NETs, neutrophil extracellular traps; NOD, non-obese diabetic; ODN, Oligonucleotides; ox-LDL, oxidized low density lipoprotein; pDCs, plasmacytoid dendritic cells; RA, rheumatoid arthritis; RF, rheumatoid factor; SLE, systemic lupus erythematosus; tDCs, total dendritic cells; TNF, tumor necrosis factor; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; T1D, type 1 diabetes; VEGF, vascular endothelial growth factor; VSMCs, vascular smooth muscle cells; WT, wild type.

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1. Introduction

The immune system is a key contributor to atherosclerosis-related cardiovascular diseases (CVD), therefore understanding the cellular and molecular mechanisms underlying immune responses is of central importance in current cardiovascular research (Hansson, 2005; Galkina & Ley, 2009; Libby et al., 2011). Multiple leukocyte subsets have been shown to play a significant role in cardiovascular diseases and among them, dendritic cells are receiving growing interest. Dendritic cells can be classified into two distinct lineages; conventional dendritic cells (cDCs) and plasmacytoid dendritic cells (pDCs). While the majority of studies have tended to focus on the role of cDCs (for review see Cybulsky & Jongstra-Bilen, 2010; Niessner & Weyand, 2010; Puddu et al., 2010; Koltsova & Ley, 2011; Manthey & Zernecke, 2011; Moore & Tabas, 2011; Butcher & Galkina, 2012; Cheong & Choi, 2012), pDCs are now emerging as important contributors to CVD (Sorrentino et al., 2010; Butcher & Galkina, 2012; Cheong & Choi, 2012; Döring & Zernecke, 2012).

pDCs are innate immune cells whose name derives from their plasma cell-like morphology (Colonna et al., 2004). They are often referred to as 'type 1 interferon (IFN) producing cells' owing to their ability to rapidly secrete vast amounts of IFN-α/β following stimulation (Asselin-Paturel et al., 2005). Type 1 interferons possess intrinsic anti-viral activity (Gilliet et al., 2008) as well as driving antiviral responses such as the expansion of CD8+ cytotoxic T cells (Schlecht et al., 2004) and the induction of a Th1 polarized CD4+ T cell-mediated responses (Cella et al., 2000). Following stimulation, pDCs undergo phenotypic and morphological changes including a shift to a dendritic-like morphology coupled with upregulation of major histocompatibility complex class II (MHC-II) and T cell costimulatory molecules. Despite early controversies regarding the true professional antigen presenting cell (APC) functions of pDCs, there is now convincing evidence that pDCs can act as bona fide APCs in vivo (Villadangos & Young, 2008) with both immunogenic (Salio et al., 2004; Schlecht et al., 2004; Sapoznikov et al., 2007) and tolerogenic (De Heer et al., 2004; Ochando et al., 2006; Irla et al., 2010; Hadeiba et al., 2012) functions being described.

Evidence is emerging that circulating pDCs are reduced in coronary artery disease (Van Vré et al., 2006; Yilmaz et al., 2006, 2009; Van Brussel et al., 2010) and patients with decompensated heart failure also have reduced blood pDC counts although these cells display an enhanced activation state (Sugi et al., 2011). The reduced number of circulating pDCs could reflect the mobilisation of pDCs to the site of inflammation as occurs in other autoimmune diseases such as systemic lupus erythematosus (Migita et al., 2005). Vascular pDCs have been identified in human and mouse Kawasaki disease, giant arteritis (Schulte et al., 2009; Yilmaz & Arditi, 2009) and in human atherosclerotic lesions (Niessner et al., 2006; Daissormont et al., 2011; Döring et al., 2012). Results from animal models are controversial but interesting. Recently, pDCs have been shown to protect against atherosclerosis by tuning T-cell proliferation/activity in an atherosclerotic lesion-induced model in low density lipoprotein receptor $(LDLr)^{-/-}$ mice (Daissormont et al., 2011). On the contrary, in apolipoprotein-E $(apoE)^{-/-}$ mice, pDC depletion inhibited plaque formation (Macritchie et al., 2012) and auto-antigenic protein–DNA complexes stimulated pDCs to promote atherosclerosis (Döring et al., 2012).

Importantly, pDCs have been shown to play a pivotal role in several chronic autoimmune diseases, strongly characterized by an increased risk of CVD, such as systemic lupus erythematosus (SLE) (Chan et al., 2012), rheumatoid arthritis (RA) (Kavousanaki et al., 2010) and Type 1 diabetes (T1D) (Diana et al., 2011).

In this review, we will describe the role of pDCs in innate and adaptive immunity, highlight their role in atherosclerosis and will discuss the impact of pDCs in chronic inflammatory autoimmune diseases on the acceleration of atherosclerosis. Finally, we will discuss how pDCs could be targeted for therapeutic utility in CVD.

2. The phenotype and origin of plasmacytoid dendritic cells

pDCs, named because of their plasma cell-like morphology, have markedly distinct functions compared with cDCs. Although characterization of the pDC lineage has presented a considerable challenge as they express molecular markers expressed by other cell types, a definitive array of markers now clearly identifies this subset. In humans, pDCs circulate in the blood as lineage immature or pre-pDCs that express blood dendritic cell antigen-2 and 4 (BDCA-2, BDCA-4) (Dzionek et al., 2001; Colonna et al., 2004), ILT7 (Rissoan et al., 2002), MHC-II, CD4, CD45RA and CD123 (interleukin-3 receptor alpha) but lack expression of other T and B cell lineage markers and CD11c. Murine pDCs are characterized through expression of B220 (Bjorck, 2001), Ly6C, bone marrow stromal antigen (BST-2) (Blasius et al., 2006a), lymphocyte activation marker-3 (LAG-3) (Workman et al., 2009), CCR9 (Wendland et al., 2007), siglec-H, (Blasius et al., 2006b) in addition to low levels of CD11c. The immature phenotype is characterized by low expression of MHC-II and costimulatory molecules and a markedly limited T-cell stimulatory potential (Mittelbrunn et al., 2009). Pre-pDCs typically mature and produce large amounts of IFN-α/β in response to stimuli. Critically, pDCs express several unique markers and antibodies have been generated against these to deplete pDCs in mice as described below.

The origin of pDCs remained contentious for several years as it was originally thought that cDCs and pDCs arose from distinct progenitors (Fogg et al., 2006; Waskow et al., 2008). However later studies using CX3CR1 reporter mice demonstrated that like cDCs and monocytes, pDCs arise from common $CSF\text{-}1R^{+}CX3CR1^{+}Flt3^{+}$ macrophage/dendritic cell precursors (MDPs) (Auffray et al., 2009). pDCs expand following treatment with Flt3L in humans and mice in vitro (Blom et al., 2000; Gilliet et al., 2002) and in vivo (Brawand et al., 2002; Pulendran et al., 2000). Furthermore, granulocyte colony-stimulating factor (G-CSF) can drive mobilization of pDCs from the bone marrow (Arpinati et al., 2000). Following their release from the bone marrow, pDCs recirculate through the blood and can be found in the spleen, lymph node, thymus (Bjorck, 2001) and also in peripheral tissues such as the liver, lung, skin (Blasius et al., 2004) and arteries (Daissormont et al., 2011; Döring et al., 2012; MacRitchie et al., 2012). pDCs have a turnover period of approximately 2 weeks, much longer than other subsets such as $CD4^{-}CD8^{+}$ cDCs which turnover every few days (O'Keeffe et al., 2002). From murine studies we now know that pDCs recirculating in blood enter lymph nodes via high endothelial venules (HEVs) (Liu et al., 2009), rather than through afferent lymphatics from peripheral tissues such as the intestine and liver (Yrlid et al., 2006). Consistent with this entry route, pDCs localize to areas of lymph nodes adjacent to HEVs (Cella et al., 1999).

3. Function of plasmacytoid dendritic cells and their role in the inflammatory response

pDCs represent a unique subset of DCs which play distinct and critical roles in the immune response and these can differ depending on anatomical location and context. In original reports on the function of pDCs recovered from human blood, it was shown that after stimulation with influenza virus or CD40L, they are proficient producers of type I IFNs and thus are critical in the anti-viral response (Cella et al., 1999; Kadowaki et al., 2000). Consistent with this pDCs express TLR7 and TLR9 that recognizes single stranded viral RNA and CpG oligonucleotides (ODN) respectively, but lack expression of TLR2, 3, 4 or 5 (Kadowaki et al., 2001; Iwasaki & Medzhitov, 2004). TLR7 and TLR9 induce the production of type 1 IFNs and NFκB-dependent cytokines through constitutive expression of Interferon Regulatory Factor (IRF) 7 which binds to MyD88 forming a complex with IRAK1, IRAK4, TRAF3, TRAF6 and IKKα (Kawai & Akira, 2010). Phosphorylated IRF7 then translocates to the nucleus and facilitates the production of type 1 IFNs (Kawai & Akira, 2010). Expression of FcgammaRIIa (CD32), which modulates type I interferon production, by human pDCs ensures