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Review

BDCA3$^+$CLEC9A$^+$ human dendritic cell function and development

Q1 Evelyn van der Aa, Nadine van Montfoort, Andrea M. Woltman*

Department of Gastroenterology and Hepatology, Erasmus MC-University Medical Center, Rotterdam, The Netherlands

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ABSTRACT

Dendritic cells (DC) are the most potent antigen presenting cells (APC). They comprise a family of different subsets and play an essential role in the induction and regulation of immune responses. Recently, gene expression profiling identified BDCA3$^+$CLEC9A$^+$ DC as a separate human DC subset. This subset was identified in blood, where they represent the smallest population of human DC, as well as in lymphoid and peripheral tissues. This review summarizes the phenotypic, functional and developmental characteristics of BDCA3$^+$CLEC9A$^+$ DC in relation to their mouse equivalents CD8α$^+$ DC and CD103$^+$ DC and other human DC subsets. Apart from being potent antigen presenting cells, their specialized functional capacities compared to other human DC subsets, indicate that these BDCA3$^+$CLEC9A$^+$ DC cells are of major importance in the induction of anti-viral and anti-tumor immunity. Further characterization of their functional properties, developmental pathways and underlying molecular mechanisms may identify target molecules to fully exploit the immune modulatory function of BDCA3$^+$CLEC9A$^+$ DC and potential use of these cells in immunotherapy.

Contents

Abbreviations: APC, antigen presenting cell; Ag, antigen; CLEC9A, C-type lectin 9A; CCR7, C-C chemokine receptor 7; CADM1, cell adhesion molecule 1; XCL1, chemokine (C motif) ligand 1; CLA, cutaneous lymphocyte antigen; CTL, cytotoxic T lymphocytes; DAMP, damage-associated molecular pattern; DC, dendritic cell; F-actin, filamentous actin; HPC, hematopoietic progenitor cells; IRF, interferon regulatory factor; IFN, interferon; LPS, lipopolysaccharide; MHC class I, major histocompatibility complex class I; moDC, monocyte-derived DC; mDC, myeloid dendritic cell; Necl2, nectin-like molecule 2; PRR, pattern recognition receptor; PBMC, peripheral blood mononuclear cells; pDC, plasmacytoid dendritic cell; polyI:C, polyinosine-polycytidylic acid; TM, thrombomodulin; TLR3, Toll-like receptor 3; XCR1, XC chemokine receptor 1.

* Corresponding author at: Erasmus MC-University Medical Center Rotterdam, Department of Gastroenterology and Hepatology, Na-1006, Wytemaweg 80, 3015 CN Rotterdam, The Netherlands. Tel.: +31 107032759; fax: +31 107032793.
E-mail address: a.woltman@erasmusmc.nl (A.M. Woltman).

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1. BDCA3$^+$CLEC9A$^+$ DC as a unique human DC subset

Dendritic cells (DC) represent a heterogeneous population of professional APC that are found in almost all tissues. Due to their unique ability to stimulate naive T cells, DC serve as a major link between innate and adaptive immunity [1,2]. Additionally, they interact with other cells of the innate and adaptive immune system. DC comprise a family of different subsets that all share the capacity to activate naive T cell responses, but vary in ontogeny, localization, phenotype and specialized immune functions [3,4].

Most of the present knowledge on DC has been obtained from studies of DC in mice. In mice, DC are divided into plasmacytoid DC (pDC), conventional lymphoid-resident DC and migratory DC. The lymphoid-resident DC can be further divided into CD8α^+ and CD8α^- DC, whereas migratory DC include CD103$^+$ DC, CD11b$^+$ DC and Langerhans cells [5–7]. CD8α^+ lymphoid-resident DC are more efficient than CD8α^- DC at cross-presentation of exogenous antigen (Ag) and priming of CD8$^+$ T cells, due to different intrinsic molecular properties [7]. CD103$^+$ migratory DC were identified as the equivalent of CD8α^+ DC in peripheral tissues since they share a common gene signature, developmental pathway, functional capacities, and several phenotypic characteristics [7–11].

Direct correlation of human and mouse DC subsets has been hampered by a lack of common surface markers. Human DC, which are characterized by expression of HLA-DR and lack of lineage markers, can be divided into two main categories: pDC and myeloid DC (mDC). mDC, which in contrast to pDC express CD11c$^+$, can be further divided into BDCA1$^+$ DC and BDCA3$^+$ DC [12]. Comparative genomic analysis indicated that the gene expression profile of human blood BDCA3$^+$ DC is comparable to that of mouse CD8α^+ and CD103$^+$ DC, suggesting that BDCA3$^+$ DC might also be functionally related to this lineage [13].

2. Phenotypic characteristics

The finding of the equivalence between CD8α^+ and BDCA3$^+$ DC was confirmed by the identification of markers that were expressed on both DC subsets, including CLEC9A (c-type lectin domain family 9A), also known as DNGR-1, XCR1 (XC chemokine receptor 1), Necl2 (Nectin-like molecule 2), also known as CADM1 (cell adhesion molecule 1), and TLR3 (Toll-like receptor 3) [14–21]. These markers will be discussed in more detail below.

2.1. BDCA3/CD141/Thrombomodulin

BDCA3 is a cell surface-expressed transmembrane glycoprotein, also known as Thrombomodulin (TM) or CD141. Together with BDCA1, BDCA2 and BDCA4, BDCA3 is generally used to classify human DC. However, BDCA3 expression is not restricted to the typical BDCA3$^+$ DC subset as discussed here, since intermediate expression of BDCA3 has also been found on monocytes and other DC, such as blood pDC, pulmonary Langerhans-type and interstitial DC, and skin interstitial DC [11,22–26]. In addition, *in vitro* maturation of blood DC is associated with upregulation of BDCA3 on pDC and BDCA1$^+$ mDC [12]. In many studies which analyze the function of BDCA3$^+$ DC, these DC were isolated by magnetic separation using MACS beads directed against BDCA3. The typical BDCA3$^+$ DC subset expresses higher levels of BDCA3 than other DC, so optimal use of antibodies will result in enrichment of these BDCA3^{hi} DC. However, since BDCA3 expression is not selectively expressed by the BDCA3^{hi} DC subset, this type of isolation should be performed with caution, since it may also result in isolation of a heterogeneous BDCA3$^+$ cell population that includes other DC subtypes and/or monocytes, as mentioned above. Therefore, it is important to use BDCA3 in combination with discriminating markers that are unique to the BDCA3^{hi} DC subset to assure selection of BDCA3$^+$ DC that belong to the CD8α^+-like lineage.

The function of BDCA3 expression on DC is thus far unknown. Besides its expression on DC, BDCA3 is predominantly expressed on vascular endothelial cells, where it is generally denominated as TM and well known for its anticoagulant activity. By binding thrombin, which is a pro-coagulant playing an important role in the coagulation cascade, TM/BDCA3 reduces thrombin's pro-coagulant activity. However, the expression of TM/BDCA3 on other cells than endothelial cells suggests an additional function of TM/BDCA3. Indeed, more recently TM/BDCA3 was described to have also a potent anti-inflammatory function through several direct and indirect mechanisms, which are reviewed by Li et al. [8]. In brief, these mechanisms include blocking of the pro-inflammatory factors thrombin, lipopolysaccharide (LPS) and necrotic or inflammatory cell-derived high mobility group box 1 (HMGB1) protein, activation of the anti-inflammatory proteins activated protein C (aPC) and activated thrombin-activatable fibrinolysis inhibitor (TAFI) and activation of inhibitors of the complement system [8].

Although high expression of this marker on BDCA3$^+$ DC might suggests an anti-inflammatory function of this DC subset, the exact function of BDCA3 expression on these cells remains to be elucidated.

2.2. CLEC9A

Although low levels of CLEC9A are expressed on mouse pDC and a subset of human monocytes, high CLEC9A expression is restricted to mouse CD8α^+ and CD103$^+$ DC and human BDCA3^{hi} DC, which share a common transcriptomic profile and set of phenotypic characteristics [15,16,27]. This indicates that CLEC9A, in combination with BDCA3, can be used as a distinctive marker to identify DC of this lineage and therefore, the human BDCA3^{hi} DC subset will be further referred to as BDCA3$^+$CLEC9A$^+$ DC in the present review. CLEC9A is a damage-associated molecular pattern (DAMP) receptor that senses necrotic cells [27]. Ligation of CLEC9A does not activate DC, but regulates cross-presentation of necrotic cell-associated Ag *via* recruitment and activation of the tyrosine kinase Syk [27,28]. However, until recently the ligand for CLEC9A was not known. Two different research groups reported filamentous actin (F-actin), which is exposed on cells upon cellular damage or necrosis, as a CLEC9A ligand [29,30].

2.3. XCR1

XCR1 is a chemokine receptor which binds to its unique ligand chemokine (C motif) ligand 1 (XCL1), selectively expressed by CD8$^+$ T cells, Th1 cells and NK cells [17]. In both human and mice, XCR1 was shown to play an important role in the interaction between XCL1-producing CD8$^+$ T cells and XCR1$^+$ DC and subsequent activation of CD8$^+$ T cells [31–33]. Upon interaction with XCR1$^+$ DC, CD8$^+$ T cells secreted high levels of XCL1, which enhanced the survival and effector functions of CD8$^+$ T cells [33].

XCR1 is selectively expressed on human BDCA3$^+$ DC, mouse CD8α^+ DC, mouse CD103$^+$ DC, and sheep CD26$^+$ DC. This selective expression was confirmed by the observation that BDCA3$^+$CLEC9A$^+$ DC were the only human DC subset that migrates to XCL1 [18]. Since low CLEC9A expression can also be found on other cells, whereas XCR1 expression is highly restricted to BDCA3$^+$CLEC9A$^+$ DC in human, XCR1 seems to be the ideal marker to identify DC belonging to the BDCA3$^+$ CD8α^+-like DC subset [17]. However, the specificity of currently available antibodies against human XCR1 is debatable, and therefore, thorough research on this marker has been hampered.

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