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Review

Cross-presentation by human dendritic cell subsets

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ABSTRACT

Dendritic cells (DCs) are a heterogeneous population of professional antigen-presenting cells. Several murine DC subsets differ in their phenotype and functional properties, in particular in their ability to cross-present antigens (*i.e.* to present exogenous antigens on their MHC class I molecules). In humans, distinct DC subpopulations have also been identified but whether some human DC subsets are also specialized at cross-presentation remains debated. Here we review the DC subsets that have been identified in humans and we discuss recent work that addresses their ability to cross-present antigens and their efficiency for $CD8^+$ T cells activation.

1. Introduction

Dendritic cells (DCs) are a heterogeneous population of antigen presenting cells that initiate and orient immune responses. DCs can be defined by their typical morphology and some key functional properties: the constitutive expression of MHC class II molecules and the capacity to stimulate naive T cells [1]. In several mammalian species, such as mouse, sheep [2], swine [3] and human, different subpopulations can be distinguished based on phenotypic markers.

In the absence of inflammation, DC subsets can be divided into plasmacytoid DCs (pDCs) and classical DCs (cDCs). During inflammation, an additional subset termed "inflammatory DC" appears [4]. cDCs are composed of two main lineages defined by their ontogeny as well as molecular signatures [5]. Comparative transcriptomic analysis has shown that these lineages are conserved across mammalian species [2,6]. By analogy to murine DC subsets, the two lineages of cDCs are usually referred to as "CD8-like" and "CD11b-like" DCs. These subsets include resident and migratory DCs. Resident DCs are present in lymphoid organs during their entire life cycle, whereas migratory DCs are present in peripheral tissues and non-lymphoid organs (such as skin, liver, lung, kidney, intestine and other organs) and subsequently migrate to draining lymph nodes through the lymph. Finally, Langerhans cells are also part of the DC family, but these migratory DCs that are present in the epidermis form a distinct cell lineage [7] (Fig. 1).

DC subsets have been extensively studied in mice. "CD8-like" DCs require IRF8 and Batf3 transcription factors for their development and comprise resident $CD8^+$ and migratory $CD103^+$ DCs, which both selectively express TLR3, Clec9A and XCR1 [8–11]. By contrast, "CD11b-like" DCs are independent of Batf3 and IRF8, and comprise resident $CD8^-CD11b^+$ and migratory $CD11b^+$ DCs. Numerous studies have shown that these two DC types have different functions [5], such as the ability to cross-present antigens, which is largely restricted to the CD8-like DCs in the absence of inflammation [12]. Cross-presenting DCs activate cytotoxic $CD8^+$ T cell responses, and are therefore of particular importance for vaccination. Whether this functional specialization is also conserved in human DC lineages has recently been the focus of much attention. In this review, we describe the different human DC subsets that have been identified so far and discuss the current understanding of the cross-presentation properties of human DC subsets.

2. Human DC subsets

Similar to murine DCs, human DCs can be divided into pDCs and cDCs [13], the latter also comprising resident and migratory DCs [14] (Fig. 2). In the spleen, tonsil and lymph nodes, two main subsets of resident cDCs have been described: BDCA1/$CD1c^+$ DCs and $Clec9A^+$ BDCA3/$CD141^+$ DCs [14–16]. These two DC populations are also found in the blood [17,18]. Although $HLA\text{-}DR^+CD16^+$ cells that are found in the blood were described in some early studies as $CD16^+$ DCs, it is now clear that these cells are a subset of monocytes [19]. Conservation of gene signatures and of phenotypic markers suggests that $Clec9A^+CD141^+$ DCs are homologue to murine CD8-like DCs, while $CD1c^+$ DCs are homologous to murine CD11b-like

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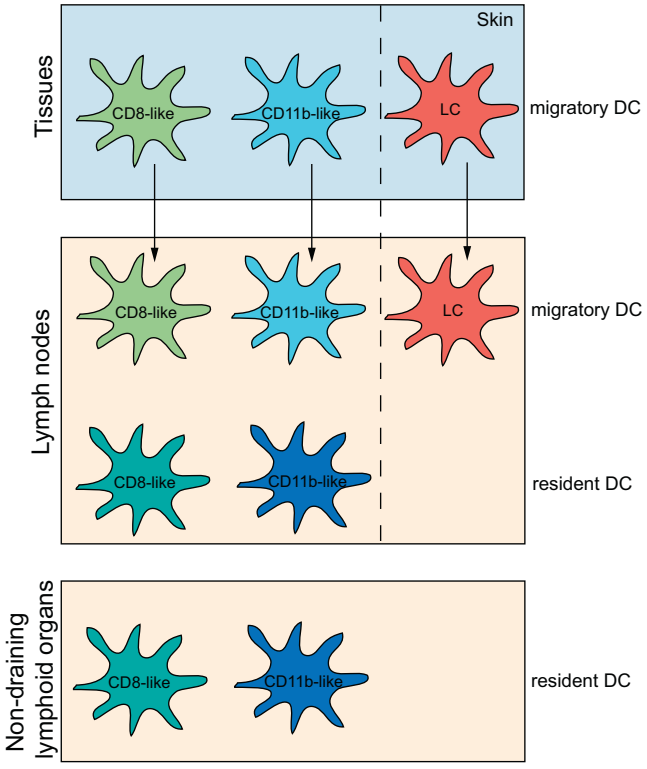

Fig. 1. Classical dendritic cell subsets. Migratory DCs are present in peripheral tissues then migrate to draining lymph nodes. Resident DCs remain in lymphoid organs during their entire life span. Both types of DCs comprise two main subsets: CD8-like and CD11b-like DCs. The migratory DCs that are present in the epidermis, the Langerhans cells (LC), represent a distinct lineage.

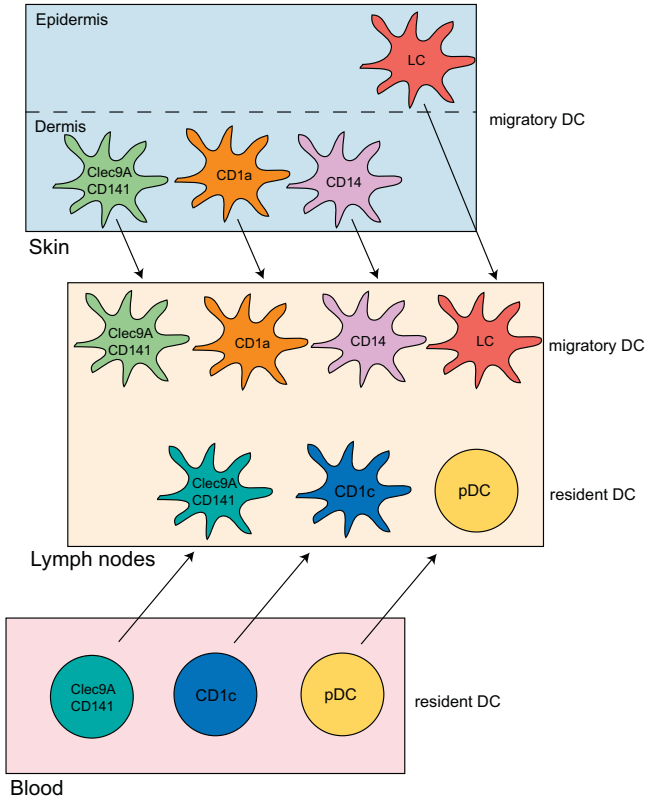

Fig. 2. Human dendritic cell subsets. Skin DCs are the best known tissue DCs. Migratory skin DCs are composed of epidermal Langerhans cells (LC), dermal $CD1a^+$, $CD14^+$ and $Clec9A^+CD141^+$ DCs. They migrate to draining lymph nodes *via* the afferent lymph. Resident DCs are present in the blood and lymphoid organs. They are composed of pDCs, $CD1c^+$ DCs and $Clec9A^+CD141^+$ DCs.

DCs [6,20–24]. However, the transcription factors involved in the differentiation of the two lineages in humans may be different from the mouse, as IRF8 mutations in patients cause the absence of all cDC subsets in contrast to mice [25].

Tissue DC subsets are less well characterized, except for the skin. In human lung and liver, populations of $Clec9A^+CD141^+$ DCs and $CD1c^+$ DCs can be found [26,27]. In vaginal mucosa, three populations have been identified: Langerhans cells, $CD1c^+CD14^-$ DCs and $CD14^+$ DCs [28]. Human skin contains four subsets of DCs: epidermal Langerhans cells, dermal $CD1a^+$ DCs, dermal $CD14^+$ DCs and a small population of dermal $Clec9A^+CD141^+$ DCs [26,29,30]. All of these DC subsets can migrate through the lymph to skin-draining lymph nodes [14,26,31]. Transcriptomic analysis suggests that tissue $Clec9A^+CD141^+$ DCs and blood $Clec9A^+CD141^+$ DCs belong to the same DC lineage and similarly that tissue $CD1c^+$ DCs and blood $CD1c^+$ DCs belong to the same lineage [26]. However, the lineage origin of skin $CD1a^+$ DCs and $CD14^+$ DCs remains unclear. Of note, CD141 and CD1c are not absolute markers for tissue migratory DCs, as CD141 is also highly expressed on dermal $CD14^+$ DCs, and CD1c on Langerhans cells, dermal $CD1a^+$ and $CD14^+$ DCs [14].

Finally, human inflammatory DCs that resemble murine inflammatory DCs in their phenotype and origin have recently been identified [32].

Due to constraints of accessibility, blood has been the dominant source of human DCs, either for the direct analysis of blood DC populations or for the *in vitro* generation of model DCs, whose *in vivo* counterparts remain elusive. This stands in sharp contrast with the mouse system, where *bonafide* cDCs cannot be found in blood. Rather, committed cDC precursors originating from the bone marrow circulate through the blood to lymphoid organs and tissues where they undergo a final stage of maturation before becoming cDCs [33,34]. Evidence suggests that human blood cDCs might actually be a precursor form of cDCs, whereas blood pDCs would be terminally differentiated [14,35,36]. The most widely used *in vitro* DC model is the generation of DCs from blood monocytes cultured in the presence of GM-CSF and IL-4 [37]. Analysis of gene signatures suggests that these DCs could be *in vitro* equivalents of inflammatory DCs [32]. DCs can also be generated *in vitro* from blood $CD34^+$ hematopoietic precursors [38], generating in the presence of GM-CSF, Flt3-ligand and TNFα *in vitro* equivalents of dermal $CD1a^+$ and $CD14^+$ DCs [30]. In the presence of Flt3-ligand and thrombopoietin, $CD34^+$ precursors give rise to *in vitro* equivalents of $CD1c^+$ cDCs, $Clec9A^+CD141^+$ cDCs and pDCs, but the yield of these cultures is low [39].

3. Cross-presentation by human DC subsets

In addition to the conventional MHC class II presentation pathway to activate $CD4^+$ T cells, DCs have developed an alternative pathway for the MHC class I-restricted presentation of internalized antigens to $CD8^+$ T cells: the cross-presentation pathway. It has been known for a long time that human *in vitro*-generated monocyte-derived DCs, but not macrophages, can cross-present antigens [40]. However, numerous studies in the mouse have shown that only some murine DC subsets, namely the CD8-like DCs and inflammatory DCs, cross-present efficiently due to specific features of their endocytic pathway [12]. However, after activation or targeting through specific surface receptors such as CD205, CD11b-like DCs have also been shown to cross-present antigen [41,42].