International Immunopharmacology 34 (2016) 1–15

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Review

Tissue-resident dendritic cells and diseases involving dendritic cell malfunction☆

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ARTICLE INFO

Article history:
Received 25 November 2015
Accepted 5 February 2016
Available online 22 February 2016

Keywords:
Dendritic cells
Resident DCs
DC-related diseases
Autoimmunity
Cancer

ABSTRACT

Dendritic cells (DCs) control immune responses and are central to the development of immune memory and tolerance. DCs initiate and orchestrate immune responses in a manner that depends on signals they receive from microbes and cellular environment. Although DCs consist mainly of bone marrow-derived and resident populations, a third tissue-derived population resides the spleen and lymph nodes (LNs), different subsets of tissue-derived DCs have been identified in the blood, spleen, lymph nodes, skin, lung, liver, gut and kidney to maintain the tolerance and control immune responses. Tissue-resident DCs express different receptors for microbe-associated molecular patterns (MAMPs) and damage-associated molecular patterns (DAMPs), which were activated to promote the production of pro- or anti-inflammatory cytokines. Malfunction of DCs contributes to diseases such as autoimmunity, allergy, and cancer. It is therefore important to update the knowledge about resident DC subsets and diseases associated with DC malfunction.

Published by Elsevier B.V.

Contents

☆ This project was funded in part by federal funds from the National Cancer Institute, National Institutes of Health, under Contract No. HHSN261200800001E and was supported in part by the Intramural Research Program of the NCI, NIH. This project was also supported in part by the grants from the National Natural Science Foundation of China (31470844).
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http://dx.doi.org/10.1016/j.intimp.2016.02.007
1567-5769/Published by Elsevier B.V.

1. Introduction

DC development takes place in the bone marrow and is a continuous process due to the requirement for replenishment of mature DCs in peripheral tissues. DCs can be divided into at least five broad groups based on phenotypic, functional and developmental criteria (Table 1). These groups include plasmacytoid DCs (pDCs), migratory and lymphoid tissue-resident $CD8^+$ DC-like DCs, migratory and lymphoid tissue-resident $CD11b^+$ DCs, Langerhans cells and monocyte-derived DCs, which are derived from a range of progenitors [1–4]. Langerhans cells are generated from fetal liver and yolk sac during embryonic development [5,6], whereas common DC progenitors (CDPs) give rise to plasmacytoid DCs and other conventional DC subsets. Pre-DCs are downstream of CDPs and have lost the capacity to generate pDCs, but are capable of generating lymphoid tissue-resident $CD8^+$ DCs and $CD11b^+$ DCs [7] possibly with their migratory counterparts referred as to $CD103^+$ and $CD11b^+$ DCs, respectively, found in many tissues [8,9]. pDCs can also be derived from lymphoid-primed multipotent progenitors (LMPPs) of bone marrow origin [10].

The capacity of DCs to capture antigens from the environment is increased even when there is no overt infection or inflammation, probably allowing for silencing the immune system in the presence of harmless environmental antigens. In response to danger signals such as bacterial and viral PAMPs, DCs rapidly promote T cell-mediated immunity to selectively eliminate infected cells. After capturing antigens, DCs migrate through lymphatics to reach secondary lymphoid organs, where DCs present processed antigenic peptides to stimulate naïve T cells in the context of MHC molecule. There also is evidence showing steady-state migration of DCs into lymph nodes under physiological conditions, which may serve to generate tolerant T cells to self and non-dangerous antigens.

Viewing the complexity of DC system accumulated during the past decades, the aim of this review is to provide an overview of the recent developments in the understanding of the distribution of tissue resident DC subsets in different organs and the relevance of resident DCs to the pathogenesis of human diseases, including auto-immunity, inflammation, allergic diseases, and cancer.

Table 1
Mouse DC subtypes.[a]

DC subsets	Phenotype
Plasmacytoid DCs	$CD11c^{int}$, $B220^+$
$CD8^+$ DC-like DCs	$CD8\alpha^+$, $CD11b^{lo/-}$, $CD103^{+/-}$, $Langerin^{+/-}$, $DEC205^+$, $Sirp\alpha^-$, $Clec9A^+$, $XCR1^+$
$CD11b^+$ DCs	$CD4^{+/-}$, $CD8^-$, $CD11b^+$, $Sirp\alpha^+$, $DEC205^-$
Langerhans cells	$CD11b^{int}$, $EpCAM^{hi}$, $Langerin^+$, $DEC205^+$, $CD103^-$
Monocyte-derived DCs	$CD11b^+$, $DEC205^+$

[a] Ref. [1].

2. Tissue-resident dendritic cells (DCs)

2.1. Skin-resident DCs

DCs in the epidermis and dermis recognize invading pathogens and are dedicated antigen-presenting cells (APCs) to initiate both innate and adaptive immunity. Early studies revealed two main populations of DCs present in the normal skin: epidermal Langerhans' cells (LCs) and dermal (or interstitial) DCs (DDCs). They both express CD11c, MHC-class I, MHC II, CD1b, CD45, CCR6, IFN-γR, IL-1R1, IL-1R2, TNFR-2 and CD32. LCs also are CD324-, Birbeck granule- and CD207-positive; while DDCs do not express CD324, Birbeck granule and CD207, but CD11b, CD1d, CCR2, IL-2R2a, IL-7R, IL4R, CD64, CD206, CD209 and Factor XIII. However, DDCs were recently further divided into $CD11b^+$ and $CD103^+$ subsets (Or $XCR1^+$ DCs). Mouse $CD11b^+$ DCs are further divided into monocyte-derived counterpart ($CD14^+$ DCs in humans) and pre-DC-derived counterpart ($CD1c^+$ DCs in humans). In human skin, DCs comprise up to four different subsets: Langerhans cells, $CD1c^+$ DCs, $CD14^+$ DCs and a newly identified $CD141^+$ subset [11]. Therefore, Langerhans cells are found in human and mouse: human $CD141^+$ DCs match mouse $CD103^+$ dermal DCs and human $CD1c^+$ DCs of pre-DC origin (blood borne precursor) and $CD14^+$ DCs of monocyte origin combine to correspond to mouse $CD11b^+$ dermal subset DCs. Mouse dermis additionally contains a minor population of cDCs known as double-negative DCs that are $XCR1^-CD207^-$ and express very low levels of CD11b [12,13]. This population expresses a DC lineage-specific transcription factor, ZBTB46, and the development depends on IFN-regulatory factor 4 (IRF4) and FLT3L. In mouse, migratory counterpart of double-negative DCs is found in the skin-draining lymph nodes under both steady-state and inflammatory conditions with unknown specific functions. No human equivalent of mouse double-negative dermal DCs has been identified as yet (Table 2).

2.2. Blood-resident DCs

Two main DC precursor subtypes are identified in human blood: DCs and pDCs. They are relatively immature and express only low levels of adhesion and costimulatory molecules. Blood DCs (0.26% in leukocytes) descend from the myeloid lineage and express blood DC antigen (BDCA)-1, CD11c, and Toll-like receptors TLR2, TLR4, TLR5, and TLR3. The cells secrete mainly IL-12 in response to bacterial components. pDCs (0.2% in leukocytes) express BDCA-2 (or CD303) and CD123, and are specialized in antiviral innate immune responses by producing copious amounts of type I interferons (IFN-γ) upon exposure of intracellular TLR9 and TLR7 to DNA and RNA viruses. In addition, a small third population (0.02% of leukocytes) of blood DCs are distinguishable based on the expression of CD11c and BDCA-3 (or CD141), but not BDCA-1, CD123 and BDCA-2 [14]. Mouse blood DCs are less well characterized with a majority of circulating MHC class II^+CD11c^+ as pDCs and low