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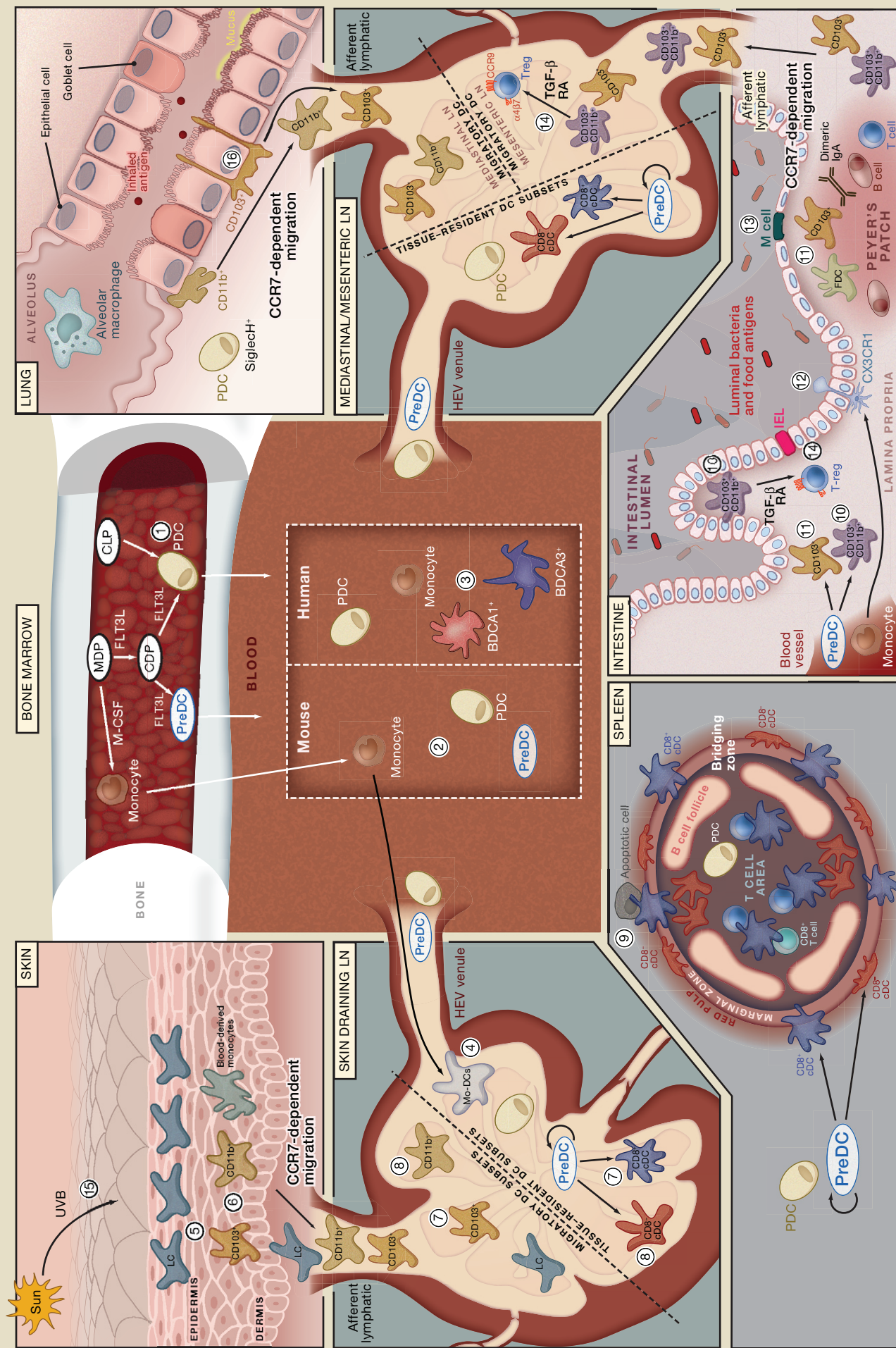
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SnapShot: Dendritic Cells

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Cell



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Dendritic cells (DCs) are specialized antigen-presenting cells that are found in most tissues. They initiate immunity, including responses to many different pathogens, and link innate responses to pathogens to the development of adaptive immunity. DCs also mediate tolerance or silencing, which is required to prevent unwanted immune reactions to self and environmental antigens. DCs are comprised of several subpopulations, or subsets, which are the focus of this SnapShot.

This SnapShot emphasizes five types of DCs: plasmacytoid DCs (PDCs), classic or tissue-resident DC (cDCs), migratory DCs, monocyte-derived DCs (Mo-DCs), and Langerhans cells (LS). PDCs produce large amounts of type I IFN (interferon) in response to viruses through the nucleic acid sensors Toll-like receptor 7 (TLR7) and TLR9. The cDCs are found in lymphoid organs (i.e., spleen and lymph nodes), whereas migratory DCs are found in nonlymphoid organs (e.g., skin, lung, and intestine). The migratory DCs sample their environment and subsequently migrate to draining lymph nodes, where they act as sentinels presenting tissue-derived antigens to T cells for the induction of immunity or tolerance. Monocytes can convert to DCs, generating Mo-DCs, but this subset of DCs is still being defined in various tissues. Finally, LCs are DCs found within stratified squamous epithelia, like the skin and analogous epithelia at oral and genital surfaces.

Different subsets of DCs have different innate properties. This means that each subset can quantitatively or qualitatively express particular surface receptors, especially lectins involved in antigen uptake and presentation; signaling receptors, like certain Toll-like receptors; and cytokines/chemokines. All subsets link innate immunity to adaptive immunity, but more research is required to determine whether different subsets are specialized to induce different forms of tolerance.

The localization of these different subsets of DCs and a few special features and markers are outlined. (For more information on DCs classes, see the collection of Reviews in Immunological Reviews, Volume 234, 2010).

DCs are derived from hematopoietic progenitors. Recent studies have elucidated the successive commitment steps in DC differentiation in the bone marrow. However, the immediate precursor for PDCs in the bone marrow has not been resolved (1).

Classic DC-restricted precursors (preDC) and PDCs arise from a common DC progenitor (CDP) in the bone marrow, which has lost the potential to form monocytes. Both preDCs and PDCs leave the bone marrow and circulate through the blood to lymphoid organs (e.g., spleen and lymph nodes) (2). In mice, preDCs express low levels of major histocompatibility complex II (MHC II) and terminally differentiate into classical, or tissue-resident, CD8 α^+ and CD8 α^- DCs. In contrast, human blood has two forms of DCs expressing high MHCII: BDCA-1/CD1c⁺ and BDCA-3/CD141⁺ (3). In both human and mouse blood, monocytes are abundant, but they are not depicted here.

Monocytes from blood can differentiate into DCs (Mo-DCs) (4) with a high capacity to present antigen to CD4⁺ and CD8⁺ T cells. Few Mo-DCs are found in draining lymph nodes of the skin in steady state, but this population increases substantially after stimulation with a TLR4 agonist, such as lipopolysaccharide (LPS).

In the skin (5), epidermal Langerhans cells (LCs) and dermal DCs expressing CD103 (CD103⁻) each can express the lectin Langerin and migrate to skin-draining lymph nodes. However, epidermal LCs derive originally from a progenitor in the fetal liver or yolk sac, which depends on macrophage colony-stimulating factor (M-CSF). Once LCs are in the epidermis, they are irradiation resistant. In contrast, CD103⁺ dermal DCs derive from blood preDCs; they are dependent on fms-like tyrosine kinase 3 ligand (FLT3L) and are irradiation sensitive. Other LC markers include epithelial cell adhesion molecule (EpCAM), F4/80, E-cadherin, and CD11b. Both LCs and CD103⁺ dermal DCs express DEC-205/CD205. In the dermis (6), CD103⁺ CD11b⁻ and CD103⁻ CD11b⁺ dermal DCs can be further subdivided into other subsets using additional markers.

Notable overlaps have been found between CD8 α^+ cDCs and CD103⁺ CD11b⁻ migratory DCs (7); both share dependence on the transcription factors basic leucine zipper transcription factor ATF-like 3 (Batf3), inhibitor of DNA binding 2 (Id2), and interferon regulatory factor 8 (IRF8). Also, CD8 α^+ cDCs and CD103⁺ DCs show a superior ability to cross-present antigen and prime CD8⁺ T cells. On the other hand, CD8 α^- cDCs resemble CD103⁻ CD11b⁺ migratory DC (8), although there are fewer markers to identify these subsets at the current time. cDCs in lymphoid organs express more CD11c and less MHC II than migratory DCs derived from other tissues, such as the lung, skin, and intestine.

In the spleen (9), CD8 α^+ cDCs capture dying cells from the blood stream and selectively, by and large, express several receptors that have been implicated in the uptake of dying cells, including CD36, α v β 5, triggering receptor expressed on myeloid cells-like 4 (Trem4), CLEC9A or DNGR1, and CLEC12A. CD8 α is the main marker for this DC subset in mouse lymphoid organs, but not in other species.

A subset of migratory DCs, which coexpresses CD11b and CD103, has been reported in intestinal lamina propria, localized centrally within the villous core (10). Both CD103⁺ CD11b⁺ (10) and CD103⁺ CD11b⁻ (11) intestinal DC subsets derive from preDCs, and they appear able to migrate to the mesenteric lymph node in a C-C chemokine receptor type 7 (CCR7)-dependent fashion.

CX3CR1^{high} CD11c⁺ MHC II⁺ cells (12) express several tissue macrophage markers, including F4/80, and they are selectively reduced when the M-CSF receptor is disrupted in mice. This population of cells can extend processes between the columnar epithelial cells into the intestinal lumen to sample antigens, but they appear unable to migrate to lymph nodes in the steady state.

The epithelium over the Peyer's patch (13) and other mucosal-associated lymphoid organs (not shown) have specialized epithelial cells called M, or microfold, cells. M cells transport antigens into the underlying tissue, where they are taken up by local DCs. DCs that receive antigen through M cells then migrate to the gut-associated lymphoid tissue (GALT) and present it to T cells.

Small intestine CD103⁺ DC (14) produce the vitamin A metabolite retinoic acid (RA), which synergizes with TGF- β to promote the differentiation of Foxp3⁺ regulatory T cells (Treg). RA also induces the expression of gut homing receptor CCR9 and α 4 β 7 on T cells.

Similarly to the diet-derived Vitamin A (RA) in the intestine, the sun's ultraviolet B (UVB) radiation in the skin (15) also promotes tissue homing of T cells. Vitamin D3 generated locally in the skin by UVB can be metabolized by DCs to its active compound 1,23(OH)₂D3, which subsequently induces the upregulation of CCR10 in T cells and their homing to the skin.

In the lungs, the conducting airways are lined with CD103⁺ intraepithelial DC (16), which can sample antigens from the airway lumen by extending their dendrites between epithelial cells.

Abbreviations

BDCA, blood dendritic cell antigen; CCR7, C-C chemokine receptor type 7; CD103, α E integrin or integrin α IEL; cDC, classic dendritic cells; CDP, common dendritic cell precursor; CLP, common lymphoid progenitor; LC, Langerhans cells; cDC, classic dendritic cells; FDC, follicular dendritic cell; FLT3L, fms-like tyrosine kinase 3 ligand; GM-CSF, granulocyte-macrophage colony-stimulating factor; HEV, high endothelial venules; IEL, intestinal intraepithelial lymphocytes; M-CSF, macrophage colony-stimulating factor; MDP, macrophage and dendritic cell precursor; PDC, plasmacytoid dendritic cells; preDC, classic dendritic cells precursor; SiglecH, sialic acid binding immunoglobulin-like Lectin H; RA, retinoic acid; TGF- β , transforming growth factor β ; UVB, ultraviolet B radiation.

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