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Organization of the mouse and human DC network

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Dendritic cells (DCs) are the most potent antigen sensing and presenting cells in the body and are able to both initiate and fine-tune complex immune responses on a multitude of levels. In this review, we outline recent advances in our understanding of the organization of the DC network in mice and humans, the functional specialization of the DC subsets that compose these networks, and how this has enabled us to begin to elucidate cross-species parallels. Understanding the inter-relationships between DC populations in both man and mouse will ultimately allow us to exploit our knowledge of DC biology for effective therapeutic strategies.

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Introduction

Dendritic cells (DCs) are functionally specialized antigen sensing and presenting cells that initiate and orchestrate immunity. DCs are optimally equipped to recognize pathogens, vaccines and self-antigens, and to simultaneously instruct the type, magnitude and specificity of immune responses.

Subsets within the heterogeneous DC population have traditionally been defined by characteristic anatomical location and phenotype. The broadest division separates DCs resident in lymphoid tissue (LT) from migratory non-lymphoid tissue (NLT) DCs, which migrate to the lymph nodes (LNs) through the lymphatics. In mice, resident LT DCs are historically termed ''conventional DCs'' (cDCs) to distinguish them from migratory DCs and plasmacytoid DCs (pDCs). cDCs themselves are further divided into two major subsets: $CD8\alpha^+$ DCs and $CD4^+CD11b^+$ DCs, based on the expression of these cell surface molecules (for review [1]). Similarly, migratory DC populations are largely distinguished by mutually exclusive surface expression of the integrins CD103 and CD11b, except in the lamina propria, where DCs co-expressing CD103 and CD11b exist [2••,3••]. DCs that populate the outer epidermal layer of stratified epithelia are called Langerhans cells (LCs) [4]. In addition, inflammation induces the generation of inflammatory DCs (iDCs) with specific phenotypic and functional characteristics [5].

In human peripheral blood, there are three DC subsets within the $HLA\text{-}DR^+lineage^-$ cell population and distinct from $CD14^+$ and $CD16^+$ monocytes. pDCs are detected alongside two myeloid DC subsets characterized by surface expression of the non-classical MHC class I molecule CD1c (BDCA-1) and thrombomodulin (CD141, BDCA-3) [6,7]. In human LT and NLT, similar subsets are described, with an additional subset expressing the receptor CD14 [8] and LCs in the epidermis, characterized by the high expression of the non-classical MHC class I molecule CD1a [9].

While early findings of similarities between human and mouse pDCs and LCs supported the notion of conserved organization of the DC system in the two species, translational efforts were limited by an absence of shared expression of important subset-discriminatory DC markers. For example, CD1c and CD1a, commonly used for the discrimination of human DC subsets, are non-existent in the mouse. Similarly, CD4 is expressed across human DC subsets, but in mice is only present on splenic $CD11b^+$ DCs. Despite the apparent imperfections in the alignment of the DC systems in the two species, it is only through a more complete understanding of the organization of both systems that we can begin to leverage the knowledge gained in mice into an ability to manipulate the human DC compartment for therapeutic benefit.

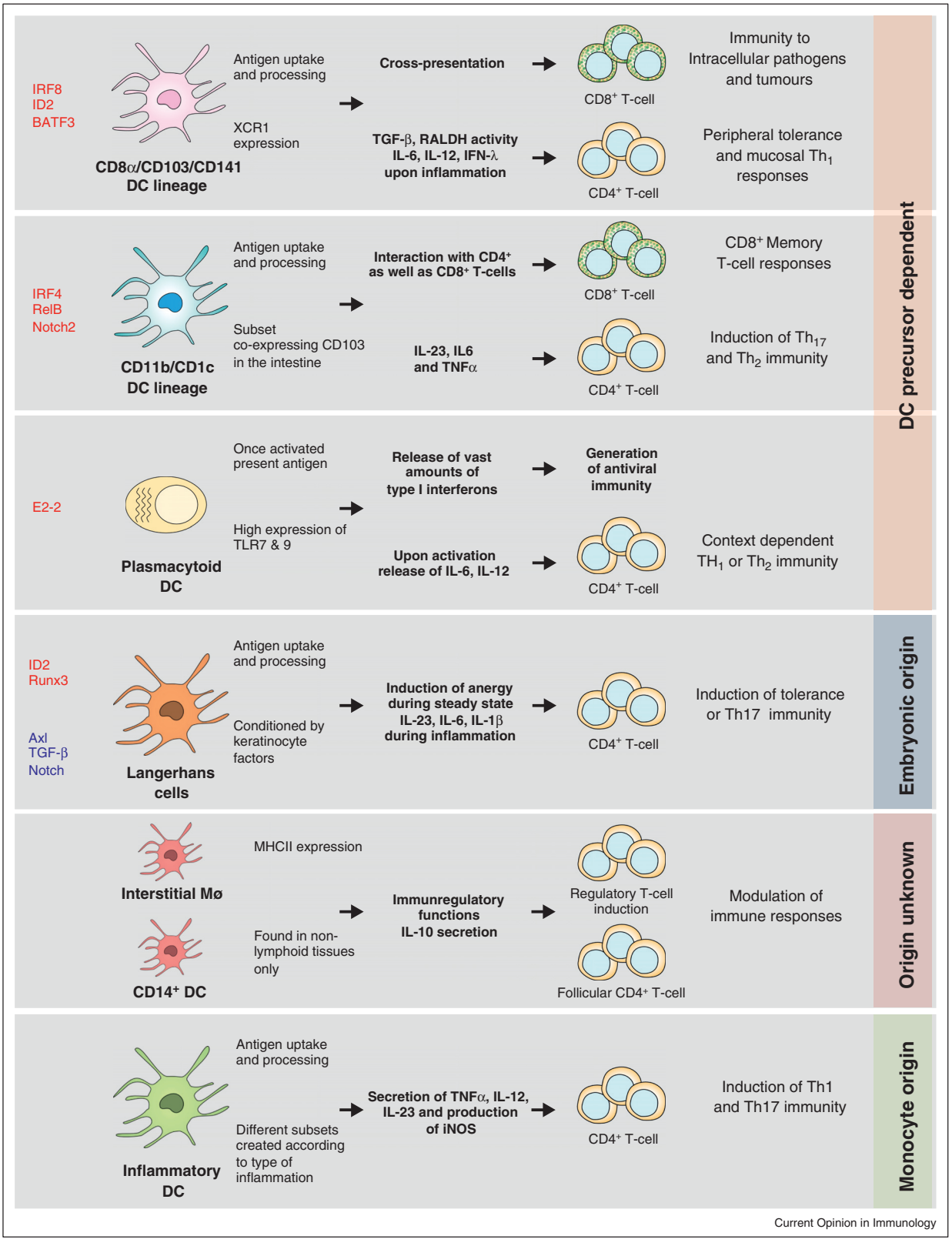
In this review, we present recent advances in knowledge of mouse and human DC subtypes and functional properties, leading us to propose a framework that aligns human and mouse DC networks, highlighting the parallel organization of DCs in both species (Figure 1).

Mouse dendritic cells

Ontogeny

Recent studies have shed new light on the organization and inter-relationships of murine DC subsets, as well as on their relationship to monocytes and macrophages. Identification of DC progenitors has enabled tracing of the lineage that originates from the bone marrow (BM) to give rise to all DCs (for review [10]), with the exception of LCs, which derive from embryonic precursors [11]. Two studies have also identified Zbtb46 as the transcription

Figure 1



Different subsets of dendritic cells shape distinct types of immune responses. This figure depicts the differential transcription factor requirements (human: blue; mouse: red), origin and functional properties of mouse and human dendritic cell subsets.

factor marking DC-committed progenitors, such as pre-DCs, as well as mature DCs [12••,13••]. Alongside, a recent study employing a DC fate-mapping model successfully identified CD8α$^+$, CD103$^+$ and CD11b$^+$ DCs as deriving from DC-restricted progenitors. This study constitutes the first genetic model that provides an ontogenic perspective to define *bona fide* DCs [14••]. The human equivalents of these murine DC progenitors remain unidentified.

CD8α/CD103$^+$ dendritic cells

In recent years, genetic and functional studies have shown that the LT CD8α$^+$ and NLT CD103$^+$ DC subsets constitute a distinct DC lineage with unique properties, despite their different phenotypes. This illustrates the value of analyses of growth and transcription factor requirements (genetic approach) of DC subsets in understanding their inter-relationships.

CD103$^+$ DCs and CD8α$^+$ DCs are dependent on the receptor Fms-like tyrosine kinase 3 (Flt3) and also require the transcription factors inhibitor of DNA binding 2 (ID2), Basic Leucine Zipper Transcription Factor, ATF-Like 3 (BATF3) and interferon regulatory factor (IRF) 8 for their full differentiation [15•]. Phenotypically, both subsets express the chemokine receptor XCR1, the necrotic cell receptor DNGR1 (CLEC9A) and Toll-like receptors (TLR) 3, 4, 11 and 13 [15•,16••,17••].

Recent studies identified CD8α$^+$ DCs in the spleen and in the LNs as well as NLT CD103$^+$ DCs as the essential subtype to efficiently cross-present antigen and stimulate CD8$^+$ T-cell immunity through secretion of IL-12, promoting Th1 differentiation [16••,17••,18,19]. In the case of CD8$^+$ T cell induction, the importance of cross-presentation by CD8α$^+$/CD103$^+$ DCs has been convincingly illustrated following challenge with immunogenic tumors and during infection with West Nile, murine Cytomegalovirus, Influenza virus, Herpes simplex virus (HSV) and Toxoplasma gondii [17••,19,20•]. Furthermore, CD103$^+$ DCs have been shown to constantly acquire and present apoptotic antigens during steady state, possibly to induce cross-tolerance [21–23]. We are just beginning to uncover the particular features of these two cell subsets that underlie their superior cross-presentation ability. As mentioned before, both CD8α$^+$ and CD103$^+$ DCs express DNGR1 (CLEC9A), a receptor for necrotic material which binds and then diverts these antigens towards the cross-presentation pathway, hence coupling dead cell recognition to cross-priming [24]. Additionally, in the case of influenza infection, lung CD103$^+$ DCs adopt an antiviral state driven by the type I interferon pathway, inhibiting viral replication as well as favoring cross-presentation of viral antigens [25].

NLTs CD103$^+$ DCs are also mediators of mucosal tolerance. In the non-inflamed intestine, CD103$^+$CD11b$^-$ DCs present in the lamina propria (LP), interact closely with goblet cells, acquire luminal antigen, and express high levels of TGF-β and retinaldehyde dehydrogenase, which confers a gut-homing phenotype to T-cells as well as inducing regulatory T-cells [26–28]. Interestingly, inflammation abolishes this pro-tolerance phenotype of CD103$^+$CD11b$^-$ DCs and leads to secretion of IL-6 and IL-12 [26,29]. Thus the CD103/CD8α lineage responds to its local microenvironment in order to induce either mucosal tolerance or cross-presentation-dependent CD8$^+$ T-cell immunity. Finally, CD8α$^+$ DCs are the major producers of IFN-λ (also termed IL-28/29), a potent immune-modulatory and antiviral cytokine in response to dsRNA poly I:C [30••].

CD11b$^+$ dendritic cells

CD11b$^+$ DCs are present in all major lymphoid and non-lymphoid organs. In contrast to NLT CD11b$^+$ DCs, CD11b$^+$ DCs in the spleen also express CD4, and can be subdivided further according to expression of the endothelial cell-selective adhesion molecule, ESAM [31].

Dissecting the relationship between NLT and LT CD11b$^+$ DC populations has proven difficult and exemplifies the challenges in understanding DC populations in general. NLT CD11b$^+$ DCs, identified as MHC-II$^+$CD11c$^+$CD11b$^+$ cells, were initially shown to arise from both BM DC-specific progenitors and monocytes, and to be partially dependent on both Flt3 and colony stimulating factor 1 receptor (CSF-1R) for their differentiation [15•]. However, this was recently shown to be due to monocyte/macrophage contamination in the MHC-II$^+$CD11c$^+$CD11b$^+$ cells [32•,33•,34•,35•]. Identification of new markers of DCs (CD24) and macrophages (CD64 and MerTK) alongside re-analysis of the growth factor requirements of CD11b$^+$ DCs has revealed that these cells are only dependent on Flt3, and not CSF-1R.

CD11b$^+$ DCs were found to depend on various transcription factors including neurogenic locus notch homolog protein 2 (Notch2), V-Rel Avian Reticuloendotheliosis Viral Oncogene Homolog B (Relb) and IRF4. Interestingly, requirements differ according to DC tissue location: while spleen CD11b$^+$ESAM$^+$ DCs are dependent on Notch2, Relb as well as on lymphotoxin β receptor (LtβR) [31,36,37] but not on IRF4 [32•], the CD11b$^+$CD103$^+$ DCs in the gut lamina propria are Notch2, Relb, IRF4 as well as LtβR dependent [32•,34•,38]. In contrast, lung CD11b$^+$ DCs are independent of Notch2 and Relb, but do require IRF4 [32•]. Such tissue-dependence in transcription factor requirements either suggests that tissue CD11b$^+$ DCs are independent populations arising from different types of progenitors, or reflects distinct differentiation conditions imposed by the local microenvironment. In conclusion, although clearly

related, whether LT and NLT CD11b$^+$ DCs represent a homogeneous lineage or divergent branches of the same ontogenic tree remains unclear.

Functionally, splenic CD11b$^+$ DCs are potent inducers of CD4$^+$ T-cell proliferation [39••] and are equipped with a comprehensive set of TLRs–expressing TLRs 5, 6, 7, 9 and 13, as well as the intracellular pattern-recognition receptor, RIG-I [1]. However, a unifying function for all NLT CD11b$^+$ DC populations is yet to be uncovered. Dermal CD11b$^+$ DCs were found to be crucial for the induction of efficient CD8$^+$ memory T-cell responses [40], although discrimination between *bona fide* tissue-resident CD11b$^+$ DCs and inflammatory DCs was not made in this particular study as markers for their discrimination only became available recently. Nevertheless, a specialized role of CD11b$^+$ DCs in the induction of Th2 and Th17 responses is emerging. Lung CD11b$^+$ DCs were the major inducers of Th2 responses in a model of allergic inflammation induced by house dust mite [33•]. Additionally, recent studies showed that lung CD11b$^+$ DCs are potent stimulators of Th17 immunity through release of IL-23 in both steady state and after Aspergillus fumigatus infection [32•].

Similarly, intestinal CD11b$^+$ DCs control Th17 immunity. Intestinal CD11b$^+$ DCs can be separated in two subsets according to the expression of CD103. CD11b$^+$CD103$^+$ DCs, unique to this tissue, constitutively expressed IL-23, IL-6 and were the major producers of Th17-inducing cytokines during infection with Citrobacter rodentium or following immunization with a TLR5 ligand [32•,34•,41]. The CD11b$^+$CD103$^+$ DC population also contributes to intestinal homeostasis through production of IL-22BP [42]. The intestinal CD11b$^+$ population that lacks CD103$^-$ is substantially smaller, and was found to migrate to the mesenteric LN where it induced IFN-γ/IL-17-secreting CD4$^+$ T-cells [43]. Altogether, these studies illustrate the versatile role of CD11b$^+$ DCs in the induction and regulation of CD4$^+$ T-cell immunity across a range of tissues.

Plasmacytoid dendritic cells

Mouse pDCs are characterized by expression of the cell surface markers CD11c, BST2, Siglec-H and B220, and depend on the transcription factor E2-2 for their development [44]. In the steady state, pDCs are found in the BM and other lymphoid organs, including the spleen and LNs, while upon infection/inflammation, they also colonize NLTs at the inflamed site [45,46]. pDCs express high levels of TLR7 and 9, which when ligated by viral products stimulate secretion of vast amounts of type I interferon, IL-12 and IL-6 [47–49]. Furthermore, pDCs secrete the anti-viral cytokine IFN-λ following exposure to parapoxviruses or HSV-1 [30••]. Stimulated pDCs also upregulate MHC-II, the costimulatory molecules CD40, CD69, CD80 and CD86, and acquire the ability to cross-present antigen, thereby inducing context-dependent Th1 and Th2 immunity [50,51].

Epidermal Langerhans cells

Epidermal Langerhans cells (LCs) are an atypical antigen presenting cell subset that, unlike any other DC population, derives from embryonic precursors, mainly fetal liver monocytes [11,52], and is self-renewing [52,53]. Their development is dependent on ID2 as well as runt-related transcription factor 3 (RUNX3) proteins [54,55]. This subset characteristically expresses the epithelial cell adhesion molecule (Epcam) and langerin, a C type lectin that localizes in LC-specific organelles called Birbeck granules. LCs constantly migrate to the skin-draining LN where they present dermal and epidermal antigens to CD4$^+$ T-cells [56,57], inducing anergy and thereby promoting peripheral tolerance [58]. However, in the context of Candida albicans or Staphylococcus aureus skin infections, LCs drive Th17 immunity through secretion of IL-23, IL-6 and IL-1β [59•]. In contrast to other DC subsets, immune responses driven by LCs seem to be highly adaptable, being dictated by environmental and pathogenic cues, rather than pre-imprinted functional specializations.

Inflammatory dendritic cells

Inflammatory dendritic cells (iDCs) arise during tissue inflammation that may be caused by pathogen invasion or autoimmune disorders, such as intestinal inflammation. iDCs derive from monocytes [60] and express CD11b, CD11c, MHC-II, CD64, FcγRε alongside varying levels of Ly6C [33•,61•]. Consistent with their monocytic origin, iDC generation is dependent on CSF-1R [62]. Functionally, iDCs capture antigen and migrate to the draining LN, where they predominantly drive Th1 immunity [63,64], through the production of vast quantities of IL-12 [60,63]. Furthermore, iDCs release substantial amounts of IL-23 upon adequate stimulation [65] and promote Th17 immunity. iDCs arising in the spleen during Listeria monocytogenes infection are characterized by their high secretion of tumor necrosis factor a (TNFα) and iNOS, leading to their denomination TipDC (TNF/iNOS-producing DC) [61•]. Interestingly, it would appear that there is marked plasticity within the iDC population. During infection with gram-positive bacteria, Flt3L-dependent CD209α$^+$ iDCs expressing the DC-specific marker Zbtb46 were reported and are distinct from the classical CSF-1R-dependent iDCs. Furthermore CD209α$^+$ iDCs have been found to be potent cross-presenters *in vivo* [66]. Such a wide spectrum of immune specializations suggests heterogeneity in the iDC population, though it remains to be determined whether this is imprinted by the type of inflammatory challenge or by the different nature of iDC progenitors.

Human dendritic cells

CD141$^+$ dendritic cells

CD141$^+$ DCs are present in human blood, tonsil and LN, as well as some NLTs including the lung, liver and skin [67••,68,69]. Skin-resident CD141$^+$ DCs have been shown to migrate to the draining LN, where both resident and migratory CD141$^+$ DCs are also found [67••,70]. Recent studies looking at functional and phenotypic comparisons have suggested that CD141$^+$ DCs most closely resemble murine CD8α$^+$/CD103$^+$ DC populations. For example, both cell subsets specifically express XCR1 and DNGR1 (CLEC9A) [23,71,72,73,74••,75,76••], as well as TLRs 1, 2, 3, 6, 7, 8 [68,77] and possess high antigen cross-presentation capacities [23,67••,78,79••]. CD141$^+$ DCs similarly take up and process apoptotic, as well as necrotic, material *in vitro* [77••], and upon stimulation release TNFα, CXCL10, and varying amounts of IL-12p70 [30••,67••]. Finally, similar to murine CD8α$^+$ splenic DCs, human blood and liver CD141$^+$ DCs produce high levels of IFN-λ upon exposure to poly I:C [30••] or hepatitis C virus [80].

Such pairing of phenotypically different mouse and human subsets constituted an important step in the alignment of mouse and human DC networks. However, certain differences between these subsets remain. Murine CD8α$^+$/CD103$^+$ DCs are the main producers of IL-12 while in the human IL-12 production is not limited to the CD141$^+$ subset [67••,69]. Moreover, IL-12 was not detected when skin DCs were cultured with a wide range of stimuli including TLR3 and TLR7/8 agonists [67••].

CD1c$^+$ dendritic cells

The major DC subset in human blood, LNs, spleen and NLTs is characterized by the expression of CD1c, CD11c, CD11b and Sirpα [6,69,81], a phenotype reminiscent of murine CD11b$^+$ DCs. CD1c$^+$ DCs express TLRs 1-10, as well as various other pattern recognition receptors including the fungal uptake receptors Dectin 1 and 2 [9,82]. Skin CD1c$^+$ DCs secrete TNFα, IL-8, IL-10 and IL-23 upon stimulation [67••,83]. Recently lung-resident CD1c$^+$ DCs were shown to be the major Th17 inducing cell type likely through release of IL-23 upon Aspergillus fumigatus challenge, similarly to murine lung CD11b$^+$ DCs [32•]. This functional parallel between human CD1c$^+$ and murine CD11b$^+$ DCs is further supported by transcriptomic analysis, suggesting homology between them [32•]. Finally, in the context of Influenza virus infection, lung CD1c$^+$ DCs express membrane bound transforming growth factor β (TGF-β), that in turn imprints intraepithelial homing to CD8$^+$ T-cells [84]. This points to a major role for CD1c$^+$ DCs in the modulation of mucosal T-cell responses as well as crucial inducers of immunity towards extracellular pathogens.

CD14$^+$ dendritic cells

CD14$^+$ DCs are unique to the human immune system and are found in LNs as well as NLTs. Skin CD14$^+$ DCs express low levels of CD1c and can also be induced to express CD141 [85], but are distinct from CD141^{hi} cross-presenting DCs, which do not express CD14 or macrophage [67••]. In fact, CD14$^+$ DCs are phenotypically similar to blood CD14$^+$ monocytes, but express higher levels of MHC-II and CD11c. CD14$^+$ DCs have a transcriptome and phenotype that overlaps with that of monocytes/macrophages, expressing an array of macrophage-related molecules including CD163 and CX3CR1 [67••,86,87]. Alongside this atypical phenotype, it is currently unclear whether CD14$^+$ DCs migrate to the draining LN, as they do not appear to express the homing receptor CCR7 [88], and are comparatively weak stimulators of naïve T-cell responses. In contrast, CD14$^+$ DCs are potent activators of follicular helper T-cells as well as antibody-secreting B-cells [88–90], they also express TLRs 1-9, and release IL-1β, IL-6, IL-8 and IL-10 upon stimulation [89]. In addition, there is some evidence that dermal CD14$^+$ DCs can induce regulatory T cells [85]. The murine counterpart of human CD14$^+$ DCs is currently unknown, but their phenotypic, transcriptomic and functional resemblance to monocytes/macrophages suggest that these cells could be monocytes that have extravasated during steady state, as recently described in murine tissues [91•].

Plasmacytoid dendritic cells

pDCs can be found in human blood as well as lymphoid tissues and are characterized by the expression of CD123, CD303 and CD304 [81]. During inflammation or infection, pDCs are rapidly recruited to the site of insult [92]. Human pDC development, similar to the mouse, is dependent on E2-2, as revealed by Pitts-Hopkins syndrome [44]. pDCs express high levels of TLRs 7 and 9, and produce high amounts of type 1 interferons upon stimulation [93,94]. Hepatitis C virus RNA, in particular, also stimulates pDC IFN-λ production [95]. Unstimulated pDCs are poor inducers of T-cell proliferation; however after maturation pDCs prime both Th1 and Th2 immunity, and efficiently cross-present antigen, at least *in vitro* [93,96–98], similarly to their murine homologues.

Langerhans cells

Human LCs are identified by high CD1a and low CD11c expression, which distinguishes them from CD14$^+$ and CD1c$^+$ DC subsets also found in the skin. Paralleling the unique homeostasis of murine LCs, there is evidence from limb-transplant studies that the LC population is similarly self-sustaining in humans [99,100]. Human LC development, at least *in vitro*, is dependent on Axl, Notch and TGF-β [101,102]. *Ex vivo* LCs express a wide array of TLRs, though not TLR2, 4 or 5. Freshly isolated LCs exhibit only a fraction of the cross-presentation capacity of their *in vitro*-generated LC counterparts

[89], highlighting the caution with which such data must be interpreted. Functionally, co-culture of autologous LCs and memory T-cells results in induction of regulatory T-cells, dependent on MHC-II [103]. However, in the same culture conditions in the context of Candida albicans infection, LCs induce a potent Th17 response [103]. Thus, similar to murine LCs, the skin microenvironment and type of stimulus/inflammation are key drivers of the response of LCs in humans.

Inflammatory dendritic cells

Different types of human inflammatory DCs have been identified, varying by phenotype and condition studied. All subsets of human iDCs express high levels of MHC-II, CD11c, CD11b, CD1a and CD206, but differ in levels of CD1c and CD14 [104–106]. Human TipDCs are characterized by their lack of CD1c and CD14 expression and production of TNFα and iNOS. Human TipDCs functionally resemble their mouse counterparts [105], potently priming Th17 and Th1 immunity [105–107]. In ascites or in synovial fluid from inflamed joints, a $CD1c^+CD14^+$ iDC subset was identified with high expression of IRF4 and abundant production of IL-23 upon stimulation. However it is unclear whether these cells represent a *bona fide* iDC population or are simply activated tissue-resident $CD1c^+$ DCs [106]. Study of the auto-inflammatory condition psoriasis has also revealed the existence of a distinct subset of iDCs characterized by expression of SLAN (6-sulfo LacNAc) [104]. The phenotypic and functional versatility of human iDC subsets underlines the need for further clarification of their interrelationships *in vivo*.

Concluding remarks

Major advances have been made in the alignment of human and mouse DC subsets, supporting the notion of a parallel organization of the DC system in the two species. Both murine and human tissues contain two major DC subsets: mouse $CD8\alpha^+/CD103^+$ DCs, which are related to human $CD141^+$ DCs, with conserved expression of markers that transcend species differences such as CLEC9A and XCR1 as well as abilities for cross-presentation and Th1-polarization, underlining their crucial role against intracellular pathogens. There is substantial evidence that murine $CD11b^+$ DCs are related to human $CD1c^+$ DCs, both exhibiting Th2-polarizing and Th17-polarizing capabilities, underlining their crucial role against extracellular pathogens. In addition, human tissues contain $CD14^+$ DCs with monocyte and/or macrophage characteristics. The murine counterpart of human $CD14^+$ DCs, if one exists, is currently undefined.

Functional alignment of mouse and human DC subsets will facilitate the translation of knowledge from mouse models that can only be gained by *in vivo* experimentation, into the human setting. Combining functional, genetic and transcriptomic studies holds considerable promise for the unification of the human and mouse DC systems, and so holds the key to advancing the field of human DC immunotherapy.

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