Expert Review of Vaccines

ISSN: 1476-0584 (Print) 1744-8395 (Online) Journal homepage: informahealthcare.com/journals/ierv20

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To cite this article: Florent Ginhoux & Andreas Schlitzer (2014) CD11b$^+$ DCs rediscovered: implications for vaccination, Expert Review of Vaccines, 13:4, 445-447, DOI: 10.1586/14760584.2014.893196

To link to this article: https://doi.org/10.1586/14760584.2014.893196

CD11b$^+$ DCs rediscovered: implications for vaccination

Expert Rev. Vaccines 13(4), 445–447 (2014)

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Dendritic cells (DCs) are potent antigen sensing and presenting cells, able to both initiate and orchestrate complex immune responses. DCs are optimally equipped to recognize pathogens, as well as self-antigens and vaccine components, and instruct the type, magnitude and specificity of the ensuing immunity. However, the DC population is remarkably heterogeneous and consists of multiple subsets with different ontogeny, differentiation and functional specializations. Therefore, a deeper understanding of DC subset biology is fundamental for the development and implementation of innovative vaccination strategies.

Subsets of dendritic cells (DCs) have traditionally been defined by characteristic anatomical location and surface phenotype. The broadest division separates DCs resident in lymphoid tissue (LT) from migratory non-LT (NLT) DCs that migrate to the lymph nodes through the lymphatics. In mice, resident LT DCs are termed 'conventional DCs' (cDCs), distinct from migratory DCs. cDCs are divided into two major subsets based on surface molecule expression patterns: CD8α^+ DCs and CD4$^+$CD11b$^+$ DCs [1]. Similarly, migratory DC populations are distinguished by mutually exclusive surface expression of the integrins CD103 and CD11b, with the exception of a DC population in the intestinal lamina propria that expresses both [2,3]. Recent studies (see below) have established that migratory NLT DC populations are in fact related to LT DC populations by common ontogeny and shared dependence on the Fms-like tyrosine kinase 3 ligand receptor (FLT3) for differentiation. Therefore, the term 'cDCs' now includes both LT and NLT DCs. In contrast, epidermal Langerhans cells that arise from embryonic progenitors [4] and inflammatory DCs (iDCs), which are generated during inflammation and arise from monocytes, have been shown to be FLT3-independent and have different ontogeny, phenotype and function [5]. Hence, these populations are no longer considered *bona fide* DCs.

Until recently, CD8α^+/CD103$^+$ DCs have been the center of interest of the DC community, while study of CD11b$^+$ DCs has been hampered by an overlapping phenotype with monocytes, macrophages and iDCs, which made them difficult to isolate for experimentation. Genetic and functional studies have revealed that LT CD8α^+ and NLT CD103$^+$ DC subsets constitute a unified DC lineage with unique properties despite their different phenotypes. CD8α^+/CD103$^+$ DCs are required to efficiently cross-present antigen and stimulate CD8$^+$ T cell immunity through secretion of IL-12, thereby also promoting Th1 differentiation and underlining their crucial role in the defense against intracellular pathogens [1]. In contrast, dissecting the relationship between NLT and LT CD11b$^+$ DC populations has proven difficult: phenotypically, while spleen CD11b$^+$ DCs express CD4 and endothelial cell-selective adhesion molecule (ESAM) [6], NLT CD11b$^+$ DCs do not. Ontogenetically, NLT CD11b$^+$ DCs (expressing MHC-II, CD11c and CD11b) were thought to arise from both bone marrow

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KEYWORDS: CD103$^+$ DCs CD11b$^+$ DCs • CD1c$^+$ DCs CD141$^+$ DCs • CD8$^+$ DCs • DC targeting • dendritic cell subset • dendritic cells • human dendritic cells • immune function • Th17 • Th2 • vaccine

 10.1586/14760584.2014.893196 ISSN 1476-0584

(BM) DC-specific progenitors and monocytes, with partial dependence on both FLT3 and the macrophage/monocyte lineage growth factor receptor, CSF-1R, for their differentiation [7]. However, reanalysis of the CD11b$^+$ DC compartment using CD24 (DC marker) and CD64/MerTK (macrophage markers) improved discrimination of DCs and macrophages, revealing the true *bona fide* DC nature of the CD24$^+$CD11b$^+$ population, which is purely dependent on FLT3 for its differentiation [8,9]. CD11b$^+$ DCs were also found to depend on various other transcription factors (TFs) such as NOTCH2, RELB and IRF4 [6,8–10]. These recent developments illustrate the importance of analyses of growth factor and TF requirements of DC subsets in advancing our understanding of their inter-relationships.

Significant progress has also been made in our comprehension of CD11b$^+$ DC function. Splenic CD11b$^+$ DCs were shown to be potent inducers of CD4$^+$ T cell proliferation [11], and efficient induction of CD8$^+$ memory T cell responses was attributed to CD11b$^+$ DCs in the dermis [12] (although a possible contribution by iDCs cannot be excluded in this study). However, a single unifying function for all NLT CD11b$^+$ DC populations has yet to be discovered. Recent studies suggest now a crucial role for murine CD11b$^+$ DCs in the induction of Th2 and Th17 responses to allergens and extracellular pathogens. Lung CD11b$^+$ DCs are the major inducers of Th2 immunity in a model of allergic airway inflammation [13,14]. Similarly, the intestine-specific DC population co-expressing CD11b and CD103 is involved in priming Th2 responses during *Nippostrongylus brasiliensis* infection. Alongside, cutaneous CD11b$^+$ DCs induce polarization of Th2 cells after subcutaneous immunization with ovalbumin along with papain or alum, as well as in a model of contact hypersensitivity [14–16]. In two of these studies [15,16], the macrophage galactose-type C-type lectin 2 (MGL2/CD301b) was used as a surrogate marker for CD11b$^+$ DCs. In particular, Kumamoto *et al.* employed an *in vivo* DC depletion approach using a MGL2-DTR model [16] and Murakami *et al.* targeted CD11b$^+$ DCs using a rat monoclonal antibody against MGL2. While these data are certainly of interest, the specificity of such approaches is somewhat unproven as MGL2 is not exclusively expressed by DCs, but also by some macrophages, monocytes and Langerhans cells in the skin [Schlitzer and Ginhoux, Unpublished Data].

Aside from this, recent studies have indicated that lung CD11b$^+$ DCs are potent stimulators of Th17 immunity through release of IL-23 in both steady state and upon *Aspergillus fumigatus* infection [8]. Similarly, intestinal CD11b$^+$CD103$^+$ DCs, unique to the intestine, control the induction of Th17 immunity [8,9]. They are constitutively expressing IL-23 and IL-6 and were the major producers of Th17-inducing cytokines during infection with *Citrobacter rodentium* or following immunization with a TLR5 ligand [17,18]. Altogether, these studies highlight the versatile role of CD11b$^+$ DCs in the induction and regulation of CD4$^+$ T cell immunity across a range of tissues. In contrast to CD8α^+/CD103$^+$ DCs, which exhibit superior cross-presentation abilities and induce Th1 polarization, CD11b$^+$ DCs are specialized in the induction of Th2 and Th17 responses, underlining their crucial role in defense against extracellular pathogens and highlighting the concept of division of labor through functional specialization of DC subsets.

While much progress has been made in understanding the origin and function of CD11b$^+$ DCs, many questions remain unanswered. Do CD11b$^+$ DCs arise from dedicated precursors? Are CD11b$^+$ DCs a homogeneous lineage? Are there specialized subsets for induction of Th2 or Th17 immunity within the CD11b$^+$ subset? And, perhaps most importantly, does a related DC subset with similar function exist in humans?

Identification of DC progenitors and precursors has enabled fate mapping of the DC lineage, which originates in the BM and subsequently gives rise to all DCs (for review [1]). Using a DC progenitor fate-mapping strategy based on the expression of CLEC9A, a receptor for necrotic material that is expressed by DC-restricted progenitors called common DC progenitors and pre-DCs led to the finding that CD8α^+, CD103$^+$ and CD11b$^+$ DCs are derived from such DC-restricted progenitors [19]. However, genetic labeling of CD11b$^+$ DCs was incomplete and uneven compared with CD8α^+/CD103$^+$ DCs in this model, which could reflect a contribution from different DC progenitors that do not give rise to the CD8α^+/CD103$^+$ lineage. Such discrepancies raise the question of whether DC precursors could either be intrinsically primed to give rise to a specific DC subset or are responding to extrinsic cues from the BM milieu or organ microenvironment. The latter hypothesis is supported by the fact that CD11b$^+$ DCs show tissue-dependent TF requirements, which may reflect a certain degree of genetic imprinting on DC precursors by the host tissue. In fact, splenic CD11b$^+$ESAM$^+$ DCs are dependent on NOTCH2 and RELB, but not on IRF4, while the CD11b$^+$CD103$^+$ DCs in the gut lamina propria are dependent on NOTCH2, RELB and IRF4 [6,8,10]. In contrast, lung CD11b$^+$ DCs differentiate independently of NOTCH2 and RELB but do require IRF4 [8]. IRF4-dependent CD11b$^+$ DCs have only been identified in the lung and the small intestine, implying the existence of a mucosal CD11b$^+$ DC lineage with unique immune-stimulatory abilities. This heterogeneity of the CD11b$^+$ DC population between mucosal and non-mucosal tissues suggests that CD11b$^+$ DCs may not be as homogeneous and conserved as the CD8α^+/CD103$^+$ lineage. Nevertheless, the level at which the specificity of this mucosal lineage is controlled, and the underlying molecular mechanisms, remains to be discovered: perhaps at the level of the tissue with a common DC precursor, such as the pre-DC, which is recruited and differentiated in response to microenvironmental cues. Or at the level of a specific DC precursor with mucosal DC potential already imprinted in the BM. At this stage, we must conclude that although clearly related, whether LT and NLT CD11b$^+$ DCs represent a homogeneous lineage or divergent branches of the same ontogenic tree remains unclear.

Finally, 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. Recent work showed that murine CD11b$^+$ DCs are phenotypically and

functionally related to human CD1c$^+$ DCs, the major DC subset in blood and tissue. Human lung-resident CD1c$^+$ DCs were shown to be the major Th17-inducing cell type, likely through release of IL-23, upon *A. fumigatus* challenge, similarly to murine lung CD11b$^+$ DCs. Such functional parallels between human CD1c$^+$ and murine CD11b$^+$ DCs appear to be further supported by transcriptomic analysis [8]. Lastly, CD1c$^+$ DCs in human were shown to imprint intraepithelial homing capabilities to CD8$^+$ T cells through a TGF-β-dependent mechanism [20]. These data identify CD1c$^+$ DCs as crucial contributors to the modulation of mucosal T cell responses as well as inducers of immunity to extracellular pathogens.

Taken together, there is now substantial evidence that murine CD11b$^+$ DCs are related to human CD1c$^+$ DCs, with both exhibiting Th2- and Th17-polarizing capabilities, making them attractive candidates for targeted vaccinations against extracellular pathogens such as parasites or bacteria. Further functional alignment of mouse and human DC subsets will also facilitate translation of knowledge from mouse *in vivo* experimentation models to the human setting, enabling new and innovative vaccination strategies to be tested such as DC subset antibody targeting.

Financial & competing interests disclosure

This work was supported by the Singapore Immunology Network core grant. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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