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Reclassification of plasmacytoid dendritic cells as innate lymphocytes is premature

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In a recent Comment article, Ziegler-Heitbrock and colleagues[1] challenge the current definition of plasmacytoid dendritic cells (pDCs) as a sublineage of dendritic cells (DCs), and instead propose to reclassify them as innate lymphocytes. That proposal represents an important discussion regarding the complex nature and lineage affiliation of pDCs in view of the emerging new data in the field. At the same time, we believe that the proposed reclassification of pDCs is not warranted by the currently available information, as discussed here.

Ontogeny of pDCs

As correctly noted by Ziegler-Heitbrock et al.[1], the progenitors of pDCs encompass a variety of phenotypes and may indeed comprise cells with predominantly myeloid or lymphoid potentials. We also agree that all approaches to define these progenitors, from adoptive transfers to clonal barcoding, are subject to caveats whose discussion goes beyond the scope of this Correspondence. Recent studies cited by the authors delineated the development of mouse pDCs from progenitors that are distinct from the progenitors of conventional DCs (cDCs) and that express lymphoid markers such as IL-7 receptor (also known as CD127) and Ly6D. The expression of these markers and several other 'lymphoid' genes indeed distinguishes pDCs from cDCs and suggests that pDCs have similarities with immature lymphocytes, particularly B cells. However, these shared transcriptomic and phenotypic features of pDCs and immature lymphocytes do not necessarily imply their common origin. Instead, the shared features may result from the reliance of pDCs and early B cells on distinct but homologous E protein transcription factors – E2-2 (also known as TCF4) and E2A (also known as TCF3), respectively – which are known to share target genes. Indeed, global gene expression profiling showed a closer proximity of pDCs at steady state to cDCs than to natural killer (NK) cells or B cells, in both mice and humans[2].

Irrespective of their transcriptional regulation, several considerations regarding the development of pDCs are relevant. First, pDCs and cDCs – and only these cells – can develop from bone marrow progenitors cultured with the growth factor FLT3 ligand (FLT3L). By contrast, FLT3L is not sufficient for commitment to or development of any lymphoid cells. Conversely, the development of pDCs requires neither the common cytokine receptor γ-chain[3] nor the transcription factor JAK3 (Ref. [4]), which are both required for the development of all lymphocytes. Second, both pDCs and cDCs are very short lived; thus, their developmental kinetics must, by definition, be different from those of long-lived lymphocytes. Third, pDCs develop normally even when lymphoid progenitors have been depleted, for example by oestrogen treatment[5]. Fourth, as cited by Ziegler-Heitbrock et al.[1], a recent study showed that mature peripheral pDCs and cDCs emerge with similar kinetics and efficiency from progenitors expressing the 'myeloid' marker CX3CR1. Although these studies do not rule out the development of some pDCs from lymphoid progenitors, they point to a close developmental affiliation of the pDC and cDC lineages.

Functions of pDCs

Ziegler-Heitbrock et al.[1] are correct in outlining that the patterns of pDC migration and recirculation in the steady state are more similar to those of lymphocytes than of cDCs. They also correctly note that steady-state pDCs, unlike cDCs, have little capacity for antigen presentation and T cell priming in the absence of activation. However, activated pDCs undergo transcriptional remodelling towards cDC-like cells[6]. Accordingly, they upregulate CCR7 and acquire antigen-presentation capacity, as shown by the tracing of pDCs that have produced interferon in vivo[7]. Importantly, this acquisition of antigen-presentation capacity is observed even after the potentially contaminating pDC-like DCs (also known as transitional DCs, Axl^{+} DCs or pre-DCs) have been removed[8,9]. Activated pDCs also acquire capacity for cross-presentation[10], which is typically restricted to only a few myeloid cell types such as cDC1s. Notwithstanding the capacity of activated pDCs for T cell priming and cross-priming in vitro, the relevance of these events in vivo remains to be established. Overall, pDCs do not fit the definition of a DC as a cell that is capable of T cell priming in the steady state; that is, indeed, a distinguishing feature of cDCs. Nevertheless, the acquisition of cDC-like features and of cDC-like capacity for antigen presentation and cross-presentation by activated pDCs further highlights their close affiliation with the DC lineage.

pDCs as cytokine-producing cells

We agree with Ziegler-Heitbrock et al.[1] that the capacity for rapid and large-scale production of all subtypes of type I interferon is the most salient, defining property of pDCs. However, one key difference between cytokine production by pDCs and lymphocytes is the nature of the stimulus. Lymphocytes are typically triggered for cytokine production by a surface receptor recognizing antigen (in the case of T cells and B cells), cell-associated molecules (in the case of NK cells) or other cytokines (in the case of innate lymphoid cells). By contrast, pDCs are triggered by innate pattern recognition receptors (PRRs), specifically by endosomal Toll-like receptors (TLRs) for pathogen-derived nucleic acids. This mode of direct pathogen recognition is characteristic of myeloid cells, including cDCs. For example, cDC1s directly recognize protozoan profilin and viral double-stranded RNA through endosomal TLRs to trigger the production of IL-12 and type III interferon, respectively; these unique cytokine responses are a salient feature of this cell type. Moreover, interferon production by pDCs is important for optimal antiviral T cell responses, which links the direct recognition of a pathogen through TLRs to adaptive immune responses in a manner that is similar to cDCs. Thus, the primary role of pDCs as cytokine-producing cells does not necessarily define them as innate lymphoid cells and is equally compatible with affiliation to the DC lineage.

Conclusions

As highlighted by Ziegler-Heitbrock et al.[1], the lineage identity of pDCs is complex and eludes simple definitions based on either ontogeny or function. Without doubt, pDCs differ from cDCs in their inferior antigen-presentation

capacity at steady state, and they resemble lymphocytes in many aspects of their transcriptome and homeostasis. By contrast, pDCs seem to be closely affiliated with the DC lineage in terms of their ontogeny, gene expression programme and ultimate role as a bridge between innate PRR-mediated pathogen recognition and adaptive immunity. In view of this complex and unique nature of pDCs, their radical reclassification as a lymphoid cell type seems to be premature. Future studies may add important new pieces to the puzzle of pDC identity and warrant its further discussion and possible nomenclature changes.

There is a reply to this letter by Ziegler-Heitbrock, L., Ohteki, T., Ginhoux, F., Shortman, K. & Spits, H. *Nat. Rev. Immunol.* https://doi.org/10.1038/s41577-023-00866-w (2023).

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Competing interests

The authors declare no competing financial interests.