DENDRITIC CELLS

Tracing the origins of cDCs

The classification of macrophages and dendritic cells (DCs) has mainly been based on cell morphology, phenotype and/or select functional attributes. However, many of these markers are not unique to a specific cell type, which has resulted in much debate as to whether a given mononuclear phagocyte should be classified as a DC or a macrophage. Reporting in *Cell*, Reis e Sousa and colleagues show that the precursors of conventional DCs (cDCs) in mice are marked by dendritic cell natural killer lectin group receptor 1 (DNDR1; encoded by *CLEC9A*), and they describe a model in which these cells and their progeny are genetically labelled, which facilitates the identification of cDCs in mice on the basis of ontogeny rather than phenotype or function.

Previous studies have shown that plasmacytoid DCs (pDCs) and specific cDC subsets express DNDR1. Now the authors show that DNDR1 is also expressed by bone marrow progenitor cells that phenotypically resemble

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common DC precursors (CDPs). To test the differentiation potential of these cells, lineage-negative CD115⁺DNDR1⁺ bone marrow cells were transferred to congenic mice. In contrast with unfractionated bone marrow, which gave rise to a variety of lymphoid and myeloid lineages, lineage-negative CD115⁺DNDR1⁺ bone marrow cells almost exclusively generated CD11c⁺MHC class II⁺ cDCs, but not pDCs. This suggests that DNDR1 expression marks precursor cells that have a cDC-restricted differentiation potential. Of note, on the basis of the data in the paper, the authors suggested that the acronym CDPs should therefore be defined as conventional DC precursors.

Next, the authors generated mice in which DNDR1-expressing cells and their progeny are indelibly marked with enhanced yellow fluorescent protein (YFP), termed *Clec9a^{+/cre}Rosa^{+/EYFP}* mice. As expected, the expression of YFP in these mice was restricted to CDPs, to resident CD8α⁺ and CD11b⁺ cDC subsets in the spleen and skin-draining lymph nodes, and to migratory CD103⁺ cDCs in the skin. No YFP expression was observed in CD169⁺ metallophilic macrophages, in Langerhans cells, or in LY6C^{hi} and LY6C^{low} monocytes. Of note, pDCs (SIGLEC-H⁺B220⁺) expressed only low levels of YFP, which, together with the results of the transfer study described above, suggests that these cells arise from a distinct pDC-specific precursor cell. However, CD8α⁺CD205⁺ cells, which have previously been reported to resemble pDCs, expressed high levels of YFP, which suggests that they arise from CDPs.

Further investigation of these mice showed that cDCs in non-lymphoid tissues, including the lungs, intestines and kidneys, can be specifically identified by their DNDR1 expression history. In the lungs, CD103⁺ cells, CD103⁺CD11b⁺ cells and CD11b⁺ cells were labelled with YFP, even though the CD103⁺CD11b⁺ and CD11b⁺ cell subsets lacked DNDR1 expression. By contrast, pDCs and CD64⁺ cells (which have been argued to represent monocyte progeny) were inefficiently labelled with YFP. Similarly, in the small intestine, CD11b⁺CD103⁺ cells, CD11b⁺CD103⁺ cells and CD11b⁺CD103⁺ cells (a cell subset which has previously been suggested to arise from monocytes) all expressed YFP, which indicates that they descend from CDPs. By contrast, monocyte-derived CD11c^{low}CD64⁺ cells were poorly labelled with YFP. Interestingly, CD64⁺ cells specifically in the kidneys were also labelled with YFP, which suggests that the expression of CD64 does not differentiate between CDP-derived and monocyte-derived cells in this tissue site. Further analysis showed that CD64⁺CD11b^{low}F4/80^{hi} kidney cells had phenotypic and functional properties that are typical of cDCs.

Finally, *Clec9a^{+/cre}Rosa^{+/EYFP}* mice were shown to faithfully trace CDP-derived cells, but not monocyte-derived cells that resemble cDCs, during inflammation following infection with *Listeria monocytogenes* or following dextran sulphate sodium treatment to induce colitis.

So, *Clec9a^{+/cre}Rosa^{+/EYFP}* mice represent an *in vivo* model to identify cDCs on the basis of their ontogenetic descent from a committed precursor cell and have been used in this study to confirm that cDCs are an independent leukocyte lineage.

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ORIGINAL RESEARCH PAPER Schraml, B. U. et al. Genetic tracing via DNDR-1 expression history defines dendritic cells as a hematopoietic lineage. *Cell* **154**, 843–858 (2013)