Mapping the human dendritic cell lineage

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Conventional dendritic cells (cDC) are professional antigen-presenting cells that orchestrate immune responses and can be classified into two functionally distinct lineages named cDC1 and cDC2. Important questions on the origins and differentiation paths of human DC populations remain elusive. Here we combine two high-dimensional technologies, single-cell mRNA sequencing and Cytometry by Time-of-Flight (CyTOF) to define and characterize DC precursors (pre-DC) present in human blood. We show that a previously underestimated pre-DC population shares surface markers with plasmacytoid DC (pDC) but has distinct functional properties that were previously attributed to pDC. Finally, we trace the origin of DCs from BM to peripheral blood and reveal that pre-DC comprise three distinct sub-populations consisting of uncommitted preDC and pre-DC subpopulations committed to the cDC1 lineage or cDC2 lineage. The discovery of multiple committed pre-DC populations present in human peripheral blood confirms the existence of DCs as a distinct hematopoietic lineage and opens promising new avenues for the therapeutic exploitation of DC subset-specific targeting.