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EDITORIAL

Synovial fluid CD1c$^+$ myeloid dendritic cells – the inflammatory picture emerges

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Abstract

Dendritic cells (DCs) comprise a heterogeneous group of antigen-presenting cells with many specialized functions, including essential constitutive roles in priming immune and autoimmune responses and in the maintenance of peripheral self-tolerance. At the interface of the innate and adaptive immune systems, they contribute considerably to the production of inflammatory and anti-inflammatory mediators with diverse functions. Emerging evidence suggests that the wide involvement of DCs in immunity and tolerance reflects the function of specialized DC subsets.

In the previous issue of *Arthritis Research & Therapy*, Moret and colleagues [1] studied the CD1c$^+$ subset of myeloid dendritic cells (DCs) in rheumatoid arthritis (RA) synovial fluid (SF) and peripheral blood (PB). Recent articles have identified species-specific phenotypic markers of mouse and human DC subsets, which have equivalent functional specialization. Accumulated understanding derived from murine systems is increasingly becoming more translatable to human immunology and disease pathology. In human PB, three DC subsets (initially identified by the BDCA monoclonal antibodies) can be identified among antigen-presenting cells expressing HLA-DR but lacking monocyte or lymphocyte lineage markers. These include CD123$^+$ BDCA-2$^+$ plasmacytoid DCs, CD1c (BDCA-1)$^+$ myeloid DCs, and CD141 (BDCA-3)$^+$ myeloid cross-presenting DCs [2–4]. Both CD1c$^+$ and CD141$^+$ DCs express the myeloid markers CD13 and CD33. Only a small fraction of CD1c$^+$ DCs expresses CD14. Among CD14$^+$ monocytes, three subsets include CD14^{++}CD16$^-$ classical, CD14^{++}CD16$^+$ intermediate, and CD14$^+$CD16^{++} non-classical monocytes. These are developmentally related subsets: classical transition to non-classical monocytes during the course of an infection [4].

In mice and humans, plasmacytoid DCs are identifiable by their strong capacity to secrete IFN-α. Developmentally, plasmacytoid DCs depend on the transcription factor E2-2. The human PB CD141$^+$ DC subset was shown to be functionally equivalent to murine CD8$^+$CD103$^+$CD11b$^-$ DCs in that both had unique capacity to cross-present protein antigen to CD8$^+$ T cells and depend on the transcription factor Batf3. CD141$^+$ DCs have not yet been studied in the synovium but were found to have a regulatory role in the skin [5]. In contrast, the CD1c$^+$ PB DC subset was shown by microarray and functional analysis to be an equivalent human population to the murine CD103$^-$CD11b$^+$ myeloid (possibly monocyte-derived) DCs [3]. In the mouse, CD103$^-$CD11b$^+$CD4$^+$ DCs do not develop in the absence of IRF4 or RelB transcription factors [3,6]. IRF4-dependent myeloid DCs were identified in lung and gut, where they specifically produced IL-23 and induced T helper (Th)-17 cells after fungal infection [3]. PB CD1c$^+$ DCs from healthy human donors promoted Th17 and Th1 T-cell differentiation *in vitro* in the presence of fungal hyphae but secreted IL-10 and suppressed T-cell proliferation after *Escherichia coli* [3,7]. Thus, their capacity to activate T cells is likely to be stimulus-dependent. Recently, CD1c$^+$CD11c$^+$HLA-DR$^+$CD16$^-$CD14$^+$ DCs were identified in human inflammatory fluids, including ascites and SF [8]. In view of their low levels of CD14 expression, their lack of CD16 expression distinguished them from non-classical inflammatory monocytes/macrophages [8]. PB CD1c$^+$ DCs and inflammatory CD1c$^+$ DCs expressed high levels of *IRF4*, *FLT3*, and *ZBTB46* mRNA, suggesting common developmental pathways with murine CD103$^-$CD11b$^+$ myeloid and human monocyte-derived DCs. Stimulated ascites fluid CD1c$^+$ DCs secreted high levels of IL-23 and induced high levels of IL-17, IFN-γ, IL-5, and IL-13 [8].

The DCs in the article by Moret and colleagues were identified from RA SF on the basis of the expression of CD1c and lack of CD19. This enriched an activated DC

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population expressing high levels of HLA-DR, with only a small proportion expressing CD14. SF CD1c$^+$ DCs were considerably more activated, as previously described [9], and expressed higher levels of chemokines, including IL-16, TARC, MIG, and IP-10, than their counterparts in PB from patients with RA. In autologous mixed lymphocyte cultures, SF CD1c$^+$ DCs were much more efficient stimulators of CD4$^+$ T-cell proliferation and Th1, Th17, and Th2 cytokine production than PB CD1c$^+$ DCs. Thus, the CD1c$^+$ SF DCs resemble inflammatory CD1c$^+$ DCs described in SF and ascites [8] and appear to overlap considerably with the myeloid CD33$^+$CD14$^+$ SF DC population described to strongly stimulate autologous T cells and to express intracellular RelB, before the discovery of the CD1c$^+$ myeloid DC subset marker [10,11]. While SF DCs were previously described to express low levels of CD14, the lack of CD14 expression by the CD1c$^+$ DCs isolated by Moret and colleagues very likely relates to poor discrimination of CD14$^-$, CD14$^+$, and CD14^{++} cells by the monoclonal antibody and isotype used.

In summary, CD1c$^+$ SF DCs clearly are highly constitutively activated and capable of strongly chemo-attracting effector T cells producing various cytokines. MIG and IP-10 are strongly IFN-γ-dependent, suggesting a positive feedback loop with Th1 cells stimulated by synovial CD1c$^+$ DCs. Similar to their monocyte-derived DC counterparts in the mouse, these DCs appear to be highly responsive to their environment, including suppression in response to various Toll-like receptor ligands, making them potentially interesting targets in RA.

Abbreviations

DC: Dendritic cell; IFN: Interferon; IL: Interleukin; PB: Peripheral blood; RA: Rheumatoid arthritis; SF: Synovial fluid; Th: T helper.

Competing interests

The author is director of Dendright Pty Ltd, a company that is commercializing vaccines to suppress autoimmune diseases.

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