DENDRITIC CELLS

DC family welcomes a new arrival

Just when you thought that the dendritic cell (DC) family could not get any larger, two reports published in *Nature Medicine* characterize a new member of the DC family in mice. These cells — which express natural killer (NK)-cell markers, produce type I and type II interferons (IFNs) after stimulation and mediate cell lysis — are known as IFN-producing killer DCs (IKDCs).

Recent studies indicate that there is substantial crosstalk between DCs and NK cells. So, both groups set out to investigate further the relationship between these two cells types. Taieb *et al.* studied a mouse model of antitumour immunity in which C57BL/6 mice treated with imatinib mesylate (Gleevec; Novartis) generate an antitumour response that is mediated by NK1.1$^+$ cells. In this study, combining imatinib mesylate with interleukin-2 (IL-2) increased this antitumour response, and this was associated with a large number of CD11c$^+$ cells infiltrating the tumours. Most of the tumour-infiltrating CD11c$^+$ cells expressed B220, NK1.1 and other NK-cell markers (such as CD49b and NK group 2, member D (NKG2D)) but not Gr1, which is expressed by plasmacytoid DCs (pDCs). Consistent with these cells being a new subset of DCs, ~50% of the CD11c$^+$B220$^+$NK1.1$^+$ cells also expressed MHC class II molecules, and cells with this phenotype could be detected in mice lacking lymphocytes and NK cells (that is, mice lacking recombination-activating gene 2 (RAG2) and the common cytokine-receptor γ-chain (γ_c)).

B220$^+$NK1.1$^+$ DCs isolated from mice treated with imatinib mesylate and IL-2 mediated TRAIL (TNF-related apoptosis-inducing ligand)-dependent tumour-cell lysis. Expression of TRAIL is induced by IFNγ, and when stimulated with either tumour cells or imatinib mesylate and IL-2, these DCs produced large amounts of IFNγ. Importantly, these IKDCs controlled tumour-cell growth when transferred to mice lacking RAG2 and γ_c, indicating that IKDCs induce an effective antitumour response *in vivo*.

Independently, Chan *et al.* identified CD11c$^+$CD49b$^+$B220$^+$Gr1$^-$ DC populations in all the mouse strains that they analysed. These cells also expressed many NK-cell-related genes and were molecularly distinct from conventional DCs and pDCs. They called these cells IKDCs because of their functional characteristics. When freshly isolated, these cells were unable to lyse typical NK-cell target cells, but following stimulation with CpG-containing oligodeoxynucleotides (CpG ODNs), they lysed these target cells efficiently and produced IL-12 and IFNα. By contrast, when stimulated with IL-12 and IL-15, they produced IFNγ.

However, stimulation of IKDCs with CpG ODNs only transiently enabled these cells to mediate target-cell lysis, and cell-surface expression of NKG2D began to decrease 14 hours after stimulation. This was associated with upregulation of MHC class II expression and an increased ability to induce CD4$^+$ T-cell proliferation. Consistent with these observations, when freshly isolated IKDCs were injected into the spleens of naive mice that were then infected with *Listeria monocytogenes*, IKDCs that remained in the spleen were NKG2D^{hi} MHC class II^{low} and were poor stimulators of CD4$^+$ T-cell proliferation, whereas IKDCs that had migrated to the lymph nodes were NKG2D^{low}MHC class II^{hi} and were good stimulators of CD4$^+$ T-cell proliferation.

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Although these two studies use different approaches to study immune responses in mice, both identify a new population of IFN-producing DCs with cytolytic activity. Both groups suggest that these cells might be an important link between innate and adaptive immunity.

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ORIGINAL RESEARCH PAPERS Taieb, J. *et al.* A novel dendritic cell subset involved in tumor immunosurveillance. *Nature Med.* **12**, 214–219 (2006) | Chan, C. W. *et al.* Interferon-producing killer dendritic cells provide a link between innate and adaptive immunity. *Nature Med.* **12**, 207–213 (2006)