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DENDRITIC CELLS

The true face of migratory DCs


George Marshall/NPG

> a paradigm shift whereby skin-resident DCs dampen rather than promote immune responses

Vaccine development has traditionally focused on targeting antigen to skin dendritic cells (DCs), which are thought to migrate to lymph nodes to initiate an immune response. However, new research suggests that these migratory skin DCs actually have an inhibitory role and instead that it is lymphoid-resident classical DCs (cDCs) activated by FMS-like tyrosine kinase 3 ligand (FLT3L) that drive vaccination-triggered immune responses.

FLT3L is a haematopoietin that is secreted during infection and is known to maintain DC numbers. Anandasabapathy *et al.* found that FLT3L levels increased following subcutaneous DC-targeted immunization with an HIV-derived peptide (gag p24) and adjuvant in mice. FLT3L treatment led to enhanced immunity, including increased expansion of $CD4^+$ T cell populations and higher production of interferon-γ and IgG. Notably, FLT3-deficient mice had lower vaccination-triggered immune responses than wild-type mice, confirming the importance of FLT3–FLT3L interactions in this process.

To determine the mechanism underlying enhanced FLT3L-mediated immunity upon subcutaneous immunization, the authors assessed the effects of FLT3L treatment on DC subsets in mouse skin-draining lymph nodes. They observed a substantial expansion of cDC populations, in particular $CD205^+CD8\alpha^+$ DCs, which became enriched to 73% of the total lymph node-resident DCs. An expansion of total migratory DCs, including the $langerin^+$ skin DCs, was also seen. Furthermore, FLT3L treatment increased antigen uptake by the DC subsets *in vivo*, which probably drives the enhanced responses following immunization.

Surprisingly, the depletion of $langerin^+$ skin DCs did not diminish vaccine-driven immune responses in untreated and FLT3L-treated mice; in fact, *ex vivo* effector and humoral immune responses to the HIV gag p24 peptide were enhanced, suggesting that these DCs suppress vaccine-driven immunity. Consistent with this, blocking the migration of all skin DC subsets to lymph nodes through the deletion of CC-chemokine receptor 7 (CCR7) resulted in higher *ex vivo* responses to gag p24 following immunization, irrespective of FLT3L treatment.

Instead, the authors found that ZBTB46-dependent cDCs are required to drive effector immune responses following gag p24 immunization. ZBTB46 is a recently described transcription factor that is specifically required in cDCs. Indeed, *ex vivo* immune responses to gag p24 were impaired in mice lacking ZBTB46 or CD11c (which is expressed at high levels by DCs).

These findings suggest a paradigm shift whereby skin-resident DCs dampen rather than promote immune responses following subcutaneous immunization with a peptide such as gag p24. The authors show that independent of FLT3L treatment, migratory DCs upregulate genes associated with immune suppression, including those encoding suppressor of cytokine signalling 2, interleukin-15 and programmed cell death 1 ligand 1, which block DC and T cell activation. Similar observations were made in human cells.

On the basis of their findings, the authors suggest that future protein vaccine development efforts might consider shifting the focus from targeting migratory skin DCs, including $langerin^+$ DCs, and instead focus on enhancing antigen capture by ZBTB46-dependent cDCs through protein immunization and FLT3L treatment.

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ORIGINAL RESEARCH PAPER Anandasabapathy, N. *et al.* Classical Flt3L-dependent dendritic cells control immunity to protein vaccine. *J. Exp. Med.* **211**, 1875–1891 (2014)

FURTHER READING Kastenmüller, W. *et al.* Dendritic cell-targeted vaccines — hope or hype? *Nature Rev. Immunol.* http://dx.doi.org/10.1038/nri3727 (2014)