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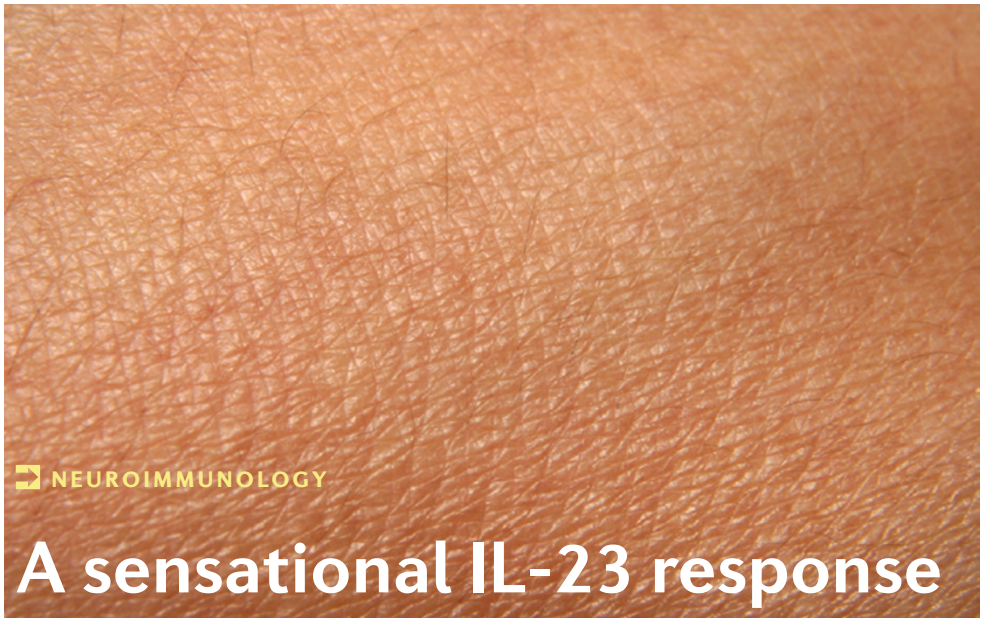

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NEUROIMMUNOLOGY

A sensational IL-23 response

Patients with psoriasis develop prominent skin lesions and frequently report associated symptoms of pain, itching and discomfort. There is evidence that local anaesthetics or surgical denervation can not only alleviate these pain sensations but can also decrease inflammation in psoriatic skin. This suggests that the peripheral nervous system may contribute to the development of skin inflammation in this disease. In support of this idea, Riol-Blanco, Ordovas-Montanes *et al.* now report that a subset of sensory neurons in the skin is essential for interleukin-23 (IL-23) production and local inflammation in a mouse model of psoriasis.

Pain sensations in the skin are transmitted by sensory fibres that express the cation channel TRPV1 and most of these nociceptors also express the sodium channel Nav1.8 (also known as SCN10A). The authors treated mice with different neurotoxins to deplete either TRPV1$^+$ nociceptors or sympathetic neurons and then induced psoriasis-like inflammation by applying imiquimod to the ear skin. They found that sympathetic denervation reduced ear swelling in this model but had no marked effect on skin inflammation. By contrast, depletion of TRPV1$^+$ sensory nerves markedly reduced both tissue swelling and inflammatory cell infiltration in response to imiquimod. Further experiments showed that these effects are independent of T cell responses in the draining lymph nodes, which suggests that sensory TRPV1$^+$ nociceptors promote local immune responses directly in the skin.

> “sensory nerves interpret environmental signals in order to shape local immune responses”

As imiquimod-induced skin inflammation is known to be IL-23-dependent, the authors examined how TRPV1$^+$ nociceptor ablation affects the production of this cytokine. Following imiquimod treatment, the skin of control mice showed an upregulation of mRNA encoding IL-23p19 (*Il23a*) but not of mRNA encoding IL-12p35 (*Il12a*). In addition, both mRNA and protein levels of the IL-12p40 subunit — which is shared by IL-12 and IL-23 — were increased in these mice. Notably, upregulation of *Il23a* mRNA and of the p40 protein was almost completely abolished if TRPV1$^+$ nociceptors were depleted before imiquimod application. However, mice in which nociceptors had been depleted developed a psoriasis-like inflammation following intradermal injection of IL-23. Thus, TRPV1$^+$ nociceptors seem to promote skin inflammation by stimulating the production of IL-23.

The authors found that neutrophils and inflammatory monocytes were not required for IL-12p40 production in response to imiquimod. By contrast, depletion of dermal dendritic cells (DCs) led to reduced *Il23a* expression in the skin of imiquimod-treated mice. Confocal microscopy imaging of the steady-state skin showed that approximately 75% of dermal DCs are in direct contact with, or in close proximity to, sensory nerves. Furthermore, real-time imaging of Nav1.8-reporter mice that had been reconstituted with fluorescently labelled bone marrow cells indicated that dermal DCs interact with local nociceptors in diverse ways — some dermal DCs were imaged attaching to nerve fibres and extending protrusions into the surrounding tissue, whereas other DCs seemed to be using the nerve fibres as a scaffold for their migration through the tissue.

The authors propose that TRPV1$^+$Nav1.8$^+$ nociceptors can promote inflammatory responses in the skin by inducing IL-23 production by local DCs. This IL-23 can then stimulate other local immune cells to produce cytokines — such as IL-17 and IL-22 — that drive psoriasiform skin inflammation. The molecular basis of the nociceptor–DC interaction that is involved here remains to be determined, but the study suggests that sensory nerves interpret environmental signals in order to shape local immune responses.

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ORIGINAL RESEARCH PAPER Riol-Blanco, L. *et al.* Nociceptive sensory neurons drive interleukin-23-mediated psoriasiform skin inflammation. *Nature* http://dx.doi.org/10.1038/nature13199 (2014)