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NEUROIMMUNOLOGY

Scratching the surface of chronic itch

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Neuroimmune interactions at barrier surfaces drive protective responses, such as coughing or scratching, that act to expel potentially noxious substances or pathogens. However, dysregulation of these responses can result in undesirable conditions, such as chronic itch. Kim and colleagues now show that direct activation of sensory neurons by the type 2 cytokine interleukin-4 (IL-4) plays a key part in the establishment of chronic itch.

The contribution of type 2 cytokines to inflammatory skin conditions that are associated with chronic itch, such as atopic dermatitis, is well established; however, the mechanisms by which these immune-signalling molecules drive itch are unclear. The authors here showed that a small subset of sensory neurons in the dorsal root ganglia (DRG) of mice and humans express the IL-4 receptor and exhibit calcium responses when treated with IL-4 in culture. The transcriptional profile and morphological properties of these neurons suggested that they are likely to be itch-mediating neurons, and this was confirmed by their responsiveness to known pruritogens such as histamine.

These findings demonstrated that IL-4 can directly activate itch-mediating sensory neurons; however, when the authors injected IL-4 into the skin of mice they did not elicit acute scratching. Instead, the authors found that treatment of DRG neurons with IL-4 caused them to respond to otherwise subthreshold amounts of other pruritogens and that a skin injection with IL-4 elevated scratching responses in the mice. Similar sensitization is observed in human patients with atopic dermatitis, which prompted the authors to speculate that IL-4 might contribute to chronic itch.

To examine this possibility, the authors took advantage of a mouse model of atopic dermatitis in which topical application of MC903 drives skin inflammation and chronic itch. They discovered that mice in which the IL-4 receptor gene was deleted from sensory neurons exhibited less scratching after MC903 application than did wild-type mice, revealing a crucial role for IL-4 in chronic itch in this model.

In immune cells, IL-4 acts via Janus kinase (JAK)-dependent pathways, and clinical studies have suggested that targeting this pathway might be a way to reduce chronic inflammatory itch; however, whether JAK signalling also functions within neurons to drive itch is unknown. Here, the authors revealed that deletion of *Jak1* in mouse DRG neurons reduced responses to IL-4. Furthermore, conditional deletion of *Jak1*, or treatment with a JAK inhibitor *in vivo,* reduced scratching in response to both MC903 and a topical application of a mixture of acetone, ether and water, which induces chronic itch in the absence of skin inflammation.

The contribution of JAK signalling to chronic itch in both inflammatory and non-inflammatory conditions suggests that targeting this pathway might also alleviate symptoms in patients in whom chronic itch is not associated with inflammation. Indeed, the authors showed that off-label treatment of patients with chronic idiopathic pruritus with a JAK inhibitor used for the treatment of rheumatoid arthritis reduced symptoms of itch.

These findings show that IL-4 acts a neuromodulator that alters the responsiveness of sensory neurons to skin irritants and reveal a potential new target for the treatment of various chronic itch conditions.

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ORIGINAL ARTICLE Oetjen, L. K. *et al.* Sensory neurons co-opt classical immune signaling pathways to mediate chronic itch. *Cell* **171**, 217–228 (2017)