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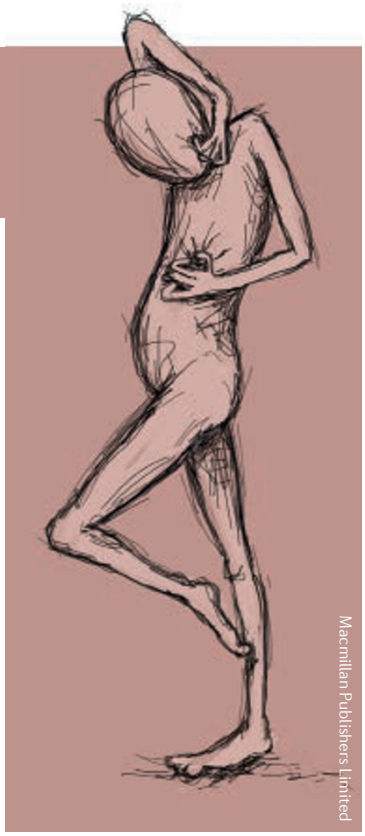
NEUROIMMUNOLOGICAL DISORDERS

JAK in the itch

Reflexes such as coughing and scratching help to expel pathogens and other potentially harmful substances. These reflex responses are also associated with chronic inflammatory diseases, such as asthma and atopic dermatitis, but the mechanisms involved are not well understood. Oetjen *et al.* now show that IL-4 and IL-13 can directly activate sensory neurons, and that IL-4 receptor-α (IL-4Rα) and Janus kinase 1 (JAK1) signalling in sensory neurons drives chronic itch.

> “blockade of IL-4Rα and JAK1 could be used to treat chronic itch”

It is well established that type 2 cytokines drive skin inflammation in diseases such as atopic dermatitis, but it has not been clear how they contribute to itch behaviour. The authors found that dorsal root ganglia (DRG), which contain sensory neurons that innervate the skin, express receptors for IL-4 and IL-13, as well as for the known pruritogen IL-31. Stimulation of mouse DRG neurons with IL-4 or IL-13 activated a subset of sensory neurons, and similar observations were made in IL-4-stimulated sensory neurons from humans. The neurons that responded to IL-4 and IL-13 were predominantly small-diameter neurons, similar to histamine-responsive neurons, suggesting that these neurons may mediate itch. Further studies showed that IL-4 and IL-13 directly activate sensory neurons via transient receptor potential channels. However, in contrast to IL-31, administration of high doses of IL-4 or IL-13 intradermally did not induce acute itch in mice. To test whether these cytokines instead alter the responsiveness of sensory neurons to other pruritogens, the authors exposed mice to a variety of pruritogens, including histamine, before and after exposure to IL-4. These studies confirmed that pretreatment with IL-4 sensitizes DRG neurons to previously sub-threshold levels of pruritogens.



This suggested that, rather than contributing to acute itch, type 2 cytokines may promote chronic itching. To test this, the authors generated mice that specifically lack IL-4Rα expression on sensory neurons (IL-4Rα$^{\Delta neuron}$ mice). Preliminary experiments showed that sensory neurons from these mice did not respond to IL-4 and IL-13, but responded normally to other pruritogens. Notably, in a mouse model of atopic dermatitis induced by the topical irritant MC903, IL-4Rα$^{\Delta neuron}$ mice showed markedly reduced scratching behaviour compared with controls, as well as reduced skin inflammation. Further analyses showed that IL-4 induces JAK1 phosphorylation in sensory neurons, so the authors generated mice specifically lacking JAK1 in sensory neurons (JAK1$^{\Delta neuron}$ mice). Development and function of DRG neurons appeared to be normal in these mice and they responded normally to a range of pruritogens. However, in the MC903 model, JAK1$^{\Delta neuron}$ mice showed markedly reduced scratching, despite developing control levels of skin inflammation. Intraperitoneal treatment of wild-type mice with the JAK inhibitor ruxolitinib also significantly reduced scratching behaviour in the MC903 model. Finally, JAK1$^{\Delta neuron}$ mice showed reduced scratching behaviour in a distinct non-inflammatory model of chronic itch. Together, these findings suggest that JAK1 signalling in sensory neurons drives chronic itching even in the absence of overt skin inflammation.

Recent studies have shown that JAK inhibitors can reduce itch symptoms in patients with atopic dermatitis. The authors' findings in mice suggested that blocking neuronal JAK1 signalling also limits itching in non-inflammatory settings. They therefore tested whether JAK inhibition can be used to treat patients with chronic idiopathic pruritus (CIP), a disease characterized by chronic itch but minimal skin inflammation. Five patients with severe CIP were treated off-label with the JAK inhibitor tofacitinib; all showed reduced itch scores, despite having failed to respond to multiple other treatments.

The authors suggest that blockade of IL-4Rα and JAK1 could be used to treat chronic itch, a condition that affects up to 15% of the population but has no specific medications. They propose that the same type 2 cytokine signals that amplify immunity at barrier surfaces may have been co-opted by the sensory nervous system to heighten potentially protective behavioural responses.

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