An itching paradox—a molecule that triggers the urge to scratch also turns down inflammation in the skin

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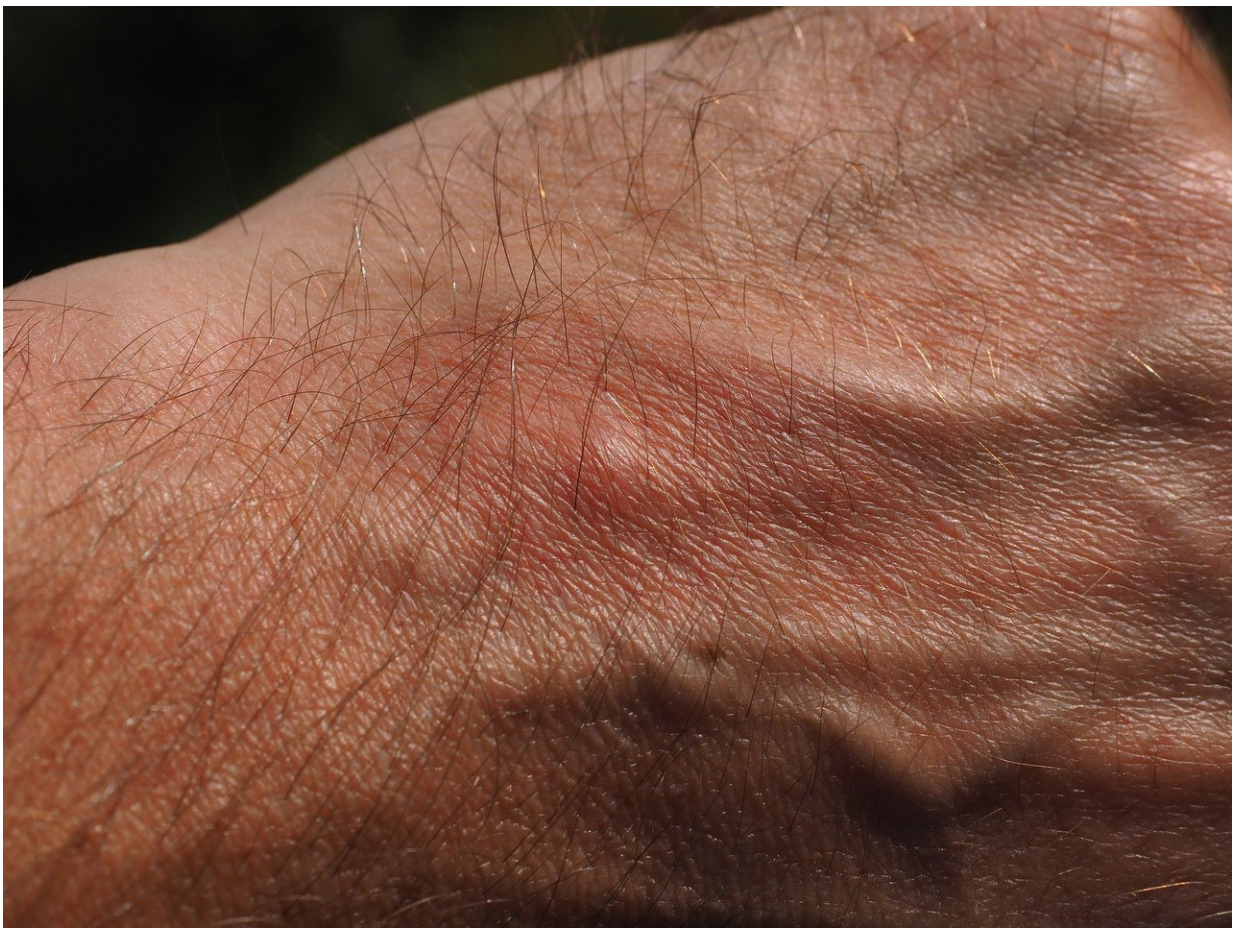

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Itching can be uncomfortable, but it's a normal part of your skin's immune response to external threats. When you're itching from an encounter with poison ivy or mosquitoes, consider that your urge to scratch may have evolved to get you to swat away disease-carrying pests.

However, for many people who suffer from chronic skin diseases like eczema, the sensation of itch can fuel a vicious cycle of scratching that interrupts sleep, reduces productivity and prevents them from enjoying daily life. This cycle is caused by sensory neurons and skin immune cells working together to promote itching and skin inflammation.

But, paradoxically, some of the mechanisms behind this feedback loop also stop inflammation from getting worse. In our newly published research, my team of immunologists and neuroscientists and I discovered that a specific type of itch-sensing neuron can push back on the itch-scratch-inflammation cycle in the presence of a small protein. This protein, called interleukin-31, or IL-31, is typically involved in triggering itching.

This negative feedback loop—like the vicious cycle—is only possible because the itch-sensing nerve endings in your skin are closely intertwined with the millions of cells that make up your skin's immune system.

An itchy molecule

The protein IL-31 is key to the connection between the nervous and immune systems. This molecule is produced by some immune cells, and like other members of this molecule family, it specializes in helping immune cells communicate with each other.

IL-31 is rarely present in the skin or blood of people who don't have a history of eczema, allergies, asthma or related conditions. But those with

conditions like eczema that cause chronic itch have significantly increased skin production of IL-31. There is strong evidence that IL-31 is one of a small set of proteins that immune cells produce that can bind directly to sensory neurons and trigger itching. Small amounts of purified IL-31 injected directly into skin or spinal fluid leads to impressively rapid-onset itching and scratching.

However, when my colleagues and I induced rashes in mice by exposing them to dust mites, we found that itch-sensing neurons turned down the dial on inflammation at the site of itching instead of promoting it. They did so by secreting small molecules called neuropeptides that, in this context, directed immune cells to respond less enthusiastically. In sum, we had discovered an inverse relationship between itching and skin inflammation, tethered by a single molecule.

But if IL-31 triggers itching, which can worsen inflammation by making patients scratch their skin, how does it reduce inflammation?

We found the answer to this paradox in a little-known function of sensory neurons called neurogenic inflammation. This nerve reflex triggers sensory neurons to release various signaling molecules directly into tissues, including specific neuropeptides that promote signs of inflammation like increased blood flow to the skin. Neurogenic inflammation acts within the same nerves that transmit sensory information like itch, pain, touch and temperature, but differs by the path it takes: away from the brain rather than toward it.

We discovered that IL-31 can induce neurogenic inflammation, mapping a direct pathway going from IL-31 through sensory neurons to repress immune cells in the skin. When we engineered mice to be unresponsive to IL-31, we similarly found that they had more activated skin immune cells that produced more inflammation. This means the net effect of IL-31 is to blunt overall inflammation.

IL-31 as potential treatment

Our study shows that IL-31 causes sensory neurons in the skin to perform two very different functions: They signal inward to the spinal cord and brain to stimulate an itching sensation that typically leads to more inflammation, but they also signal back out to the skin and quell inflammation by inhibiting certain immune cells.

Although paradoxical, this makes evolutionary sense. Scratching an itch can feel very satisfying but doesn't have much utility in the modern world where we're more likely to suffer from compulsive scratching than encounter stinging nettles. In contrast, unchecked inflammation underlies many chronic autoimmune diseases. Therefore, turning off an immune response in inflamed tissue can be as important as turning it on.

Our discoveries raise important questions about the implications of modifying IL-31 to treat different diseases. For one, it isn't clear how IL-31-sensing neurons interface with other neuronal circuits that also regulate skin inflammation. Furthermore, some patients have higher levels of allergic proteins in their blood or develop asthma flares when taking existing drugs that target IL-31. IL-31 is also found in some lung and gut cells—how and why would an itch-inducing molecule be present in internal organs?

Anatomical niches where sensory neurons and immune cells converge are present throughout the human body. If an itchy molecule like IL-31 can use neuronal circuitry to dampen an immune response in the skin, similar molecules like those used in migraine drugs could be repurposed to treat skin conditions, too.

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