

Suffering from skin allergies? TRPA1 may be the key to skin relief

By Sheila Yong

As one of the first recipients of an Outstanding New Environmental Scientist (ONES) grant award, when they were first offered by NIEHS in 2006, [Sven-Eric Jordt, Ph.D.](#)

(http://medicine.yale.edu/pharm/people/sven_jordt-2.profile)

, has come a long way in studying how certain airborne pollutants interact with sensory nerve cells to cause eye, nose, and throat irritation. His research, thus far, has yielded exciting findings on the role of the transient receptor potential (TRP) ion channel TRPA1 in driving asthmatic airway inflammation, as well as hypersensitivity caused by a wide range of irritants (see [story](#)).

The associate professor in the Department of Pharmacology at Yale University has now taken this research a step further, to investigate how TRPA1 may also be involved in triggering the inflammatory responses in allergic contact dermatitis (ACD). Funded in part by NIEHS, the [study](#)

(<http://www.ncbi.nlm.nih.gov/pubmed/23722916>)

was published in the May 30 online edition of The FASEB Journal.

What do ACD and asthma have in common?

ACD is a skin condition that often presents with red rash and blisters, as well as itching and burning skin. “ACD and asthma share similar etiologies, in that they are both triggered by initial exposures to allergens and produce a local Th2-driven inflammatory response at the site of challenge,” Jordt explained. “We began our study on ACD in 2009, while completing our experiments on the asthma model, because we were curious to find out whether the sensory neurons in the skin and their TRP channels would also be involved in maintaining inflammation in ACD.”

ACD is triggered by small reactive chemicals called haptens, which react with proteins in the skin to form strongly immunogenic epitopes, parts of an antigen molecule that sensitize the immune system to respond to subsequent challenges. Haptens are present in a variety of natural, industrial, and consumer products, including detergents, fragrances, and food additives. The most commonly encountered hapten is urushiol, which is produced by poison ivy, oak, and sumac. ACD resulting from urushiol exposure affects more than 10 million patients a year, in the United States alone.

Jordt’s team used both urushiol and oxazolone as their model haptens in this study. They showed that while wild-type mice exhibited skin inflammation upon allergen challenge, the response in TRPA1-deficient mice was significantly reduced. Naturally, the use of HC-030031, a well-established TRPA1 antagonist, diminished the skin inflammation in wild-type mice. Using antibody-based and immunofluorescence-based techniques, the researchers also detected an increase in levels of inflammatory cytokines and skin infiltration by T cells at ACD-affected sites, both of which could be subdued by HC-030031. On the other hand, mice lacking TRPV1, a TRP family member that is structurally related to TRPA1, suffered the same extent of skin irritation as the wild-type mice, indicating that TRPV1 is not involved in the inflammatory responses in ACD.

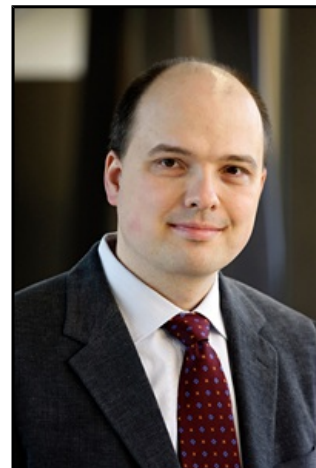
Jordt also described a fascinating phenomenon known as the atopic march, where patients suffering from ACD, particularly atopic dermatitis, often develop asthma. “It is speculated that the inflammatory signals from the skin eventually trigger sensitization of the airways, leading to asthma attacks in these patients,” he noted. Whether or not TRPA1 is the missing link between ACD and asthma remains to be determined.

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TRPA1 controls inflammation and pruritogen responses in allergic contact dermatitis. FASEB J; doi:10.1096/fj.13-229948 [Online 30 May 2013].

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Jordt is grateful for the support he receives from NIEHS. “Funding from NIEHS has continued to allow my team to discover novel and unexpected findings, which may lead to new approaches for treating and preventing ACD.” (Photo courtesy of Steve McCaw)

Overcoming the hurdle in treating ACD

One major complication of ACD is pruritus, more commonly known as itching. However, since ACD-associated pruritus is resistant to antihistamines, there are few treatment options for chronic sufferers whose quality of life is severely impacted. “We decided that our ACD mouse model is ideal for studying histamine-independent pruritus, since TRPV1 has been reported to induce histamine-mediated pruritus, but has no effect on the inflammatory responses in ACD,” Jordt commented.

To this end, his study revealed TRPA1 as a critical mediator of histamine-independent itching, since TRPA1-deficient mice exhibited reduced ACD-associated scratching behavior compared to wild-type and TRPV1-deficient mice. More importantly, his team also discovered several downstream signaling pathways crucial for histamine-independent pruritus that are facilitated by several peptide mediators. These include Substance P, a neuropeptide expressed in the inflamed skin; endothelin-1, a peptide secreted by cells lining the interior surface of blood vessels; and neurotransmitter serotonin.

Jordt hopes that his findings will advance the field of ACD treatment. “In addition to TRPA1, these downstream pathways are also suitable drug targets for novel anti-itch medications that are effective for treating ACD,” he concluded.

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