Bee sting allergy could be a defense response gone haywire, scientists finds

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For most people, a bee sting causes temporary pain and discomfort, but for those with a bee venom allergy, the consequences can be devastating: They experience anaphylactic shock, including a drop in blood pressure, itchy hives and breathing problems, and may die if not promptly treated.

New findings by Stanford University School of Medicine scientists may provide an evolutionary explanation for severe allergic reactions. In a paper to be published online Oct. 24 in *Immunity*, the researchers show that mice injected with a small dose of bee venom were later resistant to a potentially lethal dose of the same venom. The study is the first experimental evidence that the same immune response involved in allergies may have evolved to serve a protective role against toxins.

The study builds on earlier work by the researchers, characterizing the innate immune response to snake venom and honeybee venom. Innate immune responses occur in subjects exposed to a foreign substance, such as a pathogen or a toxic material like venom, for the first time. Immune cells called mast cells, which reside in most of the body's tissues, are poised to unleash signals that turn on defense responses when a pathogen or toxin intrudes. In a previous study, the researchers found that mast cells produce enzymes that can detoxify components of snake venom, and that mast cells can also enhance innate resistance to honeybee venom.

Such innate immune responses do not require prior immunization or the development of specific antibodies. By contrast, during an adaptive immune response, the immune system generates antibodies that recognize the invading pathogen or toxin; this process makes it possible to vaccinate against infectious diseases. Adaptive immunity is usually a faster, more specific and more effective form of defense than innate immunity.

In allergic reactions, a type of antibody called IgE binds to the surface of mast cells and prompts them to initiate an adaptive immune response when exposed to the antigen recognized by that IgE. "The functions of IgE and mast cells are mostly known in the context of allergies," said Thomas Marichal, DVM, PhD, a postdoctoral scholar and co-lead author of the study.

"It was kind of a dogma that most IgE-related responses are detrimental," said postdoctoral scholar Philipp Starkl, PhD, the other lead author. "We and others speculated that there should be some very positive evolutionary pressure to keep these cells and these antibodies, because if they were just bad and deleterious, they would have been eliminated."

The researchers hypothesized that IgE might be required for protection against a lethal sting, and that allergies are an extreme, and maladaptive, example of this type of defense. This idea, known as the toxin hypothesis of allergy, was first proposed by Margie Profet in 1991, but was largely ignored by immunologists until recently.

To find out whether adaptive immune responses could help mice resist bee venom, Marichal and Starkl first injected mice with a low dose of venom equivalent to one or two stings. The mice developed more venom-specific immune cells, and higher levels of IgE antibodies against the venom, than control mice injected with a salt solution.

Three weeks later, they injected both groups of mice with a potentially lethal dose of venom, similar to five bee stings. The immunized mice had less hypothermia and were three times more likely to survive than the control mice. Moreover, they did not develop the anaphylactic reactions characteristic of severe allergies.

To determine whether IgE antibodies were required for this protection, the team tested mice with three types of mutations: mice without IgE, mice without functional IgE receptors on their mast cells, and mice without mast cells. The IgE-deficient mutant mice were previously developed by Hans Oettgen, MD, PhD, associate professor of pediatric immunology at Harvard Medical School and a co-author of the study.

In all three groups of mutant mice, pre-immunization with a low dose of bee venom did not confer protection against a lethal dose, suggesting that the protection depends on IgE signaling and mast cell activation. "That was pretty exciting for us," said Marichal. "It was the first time we could see a beneficial function for these IgE antibodies."

Pre-immunization with a low dose of venom from the Russell's viper also protected mice from a higher dose of venom from this snake, which

is one of the "big four" species responsible for most snakebite deaths in India. So the researchers believe the response could be generalized to different types of toxic venoms.

"Our findings support the hypothesis that this kind of venom-specific, IgE-associated, adaptive immune response developed, at least in evolutionary terms, to protect the host against potentially toxic amounts of venom, such as would happen if the animal encountered a whole nest of bees, or in the event of a snakebite," said Stephen Galli, MD, professor and chair of pathology and the co-senior author of the study. "Anaphylaxis probably represents the extreme end of a spectrum of IgE-associated reactivity, which in some unfortunate individuals is either poorly regulated or excessively robust, so the reaction itself can become dangerous to them."

Galli cautioned that it's not yet known whether IgE responses also protect humans from the toxic effects of arthropod or reptile venom, but it would be unthinkable to test lethal doses of venom in humans. Reptile and arthropod venoms are complex chemical cocktails. Some venom components have evolved to mimic chemicals made by the human body, such as endothelin-1, which causes blood vessels to constrict during bacterial infections. At the same time, mammals have evolved immune responses to venom, which in some cases escalate into maladaptive allergic reactions.

"We experience allergies in a much cleaner world, where we don't have the same threats of venomous creatures and potentially toxic food that existed for much of our evolutionary history," said Galli. "And so we're left with this residual type of reactivity that seems completely mysterious and pointless and harmful. This is the first evidence, that we know of, indicating that IgE-associated 'allergic-type' immune responses can actually reduce the toxicity of naturally occurring venoms."

More information: *Immunity*, Marichal et al.: "A Beneficial Role for Immunoglobulin E in Host Defense against Honeybee Venom." dx.doi.org/10.1016/j.immuni.2013.10.005

Immunity, Palm et al.: "Bee venom phospholipase A2 induces an ST2-dependent type 2 response and Immunoglobulin E-mediated protective immunity." dx.doi.org/10.1016/j.immuni.2013.10.006

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