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ANTIBODIES

Taking the sting out

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Complementary studies in *Immunity* by Palm, Rosenstein *et al.* and Marichal, Starkl *et al.* address two long-standing immunological questions — does IgE have beneficial roles in non-parasitic settings and how are such type 2 immune responses initiated?

Marichal, Starkl *et al.* were inspired by Profet's 'toxin hypothesis', which proposes that a common feature of allergens is their origin from sources that are likely to contain toxins, such as foods or venoms, and that IgE responses can protect the host from the toxic effects of such noxious substances. Therefore, key symptoms of allergy (such as sneezing or diarrhoea) could be viewed as protective mechanisms for expelling toxins, rather than as maladaptive immune behaviours. To investigate this idea, they immunized mice with doses of honey bee venom that were designed to mimic the amount of bee venom delivered by 1–10 honey bee stings. Primary immunization of mice with increasing doses of venom led to increased lethality. However, if mice were initially exposed to a sublethal dose of the venom (for example, doses mimicking 1–2 stings), they showed increased resistance to secondary challenge with high doses of venom.

> "venoms can induce IgE-associated immune responses that protect animals against subsequent exposure to lethal doses of the venom"

The authors found that acquired resistance to bee venom was dependent on the development of a type 2 immune response. Generation of bee venom-specific IgE antibodies was crucial for acquired resistance to the venom, as immunization of IgE-deficient mice (or mice unable to signal through the high-affinity Fc receptor for IgE (FcεRI)) with low doses of venom did not promote resistance to subsequent high doses of venom. Furthermore, passive transfer of bee venom-specific IgE was as effective as active immunization in protecting mice against high doses of venom. Mast cell-deficient mice failed to show IgE-mediated resistance to bee venom, which thereby implicates mast cells in the IgE-mediated protective effect. Finally, the authors showed that acquired IgE-associated immune responses also protect mice against Russell's viper venom.

The study by Palm, Rosenstein *et al.* focused on how bee venom initiates a type 2 immune response. They immunized mice with bee venom or with purified proteins from the venom and found that bee venom phospholipase A2 (PLA2), which is the major allergen in the venom, induced the most potent type 2 immune response. PLA2 purified from a rattlesnake also induced type 2 responses in mice, which suggests that PLA2 may be a conserved type 2 response-inducing component of venoms. The enzymatic activity of bee venom PLA2 was necessary to induce a type 2 response, which indicates that bee venom PLA2 may initiate such responses by hydrolysing membrane phospholipids.

Damage to cell membranes has been suggested to lead to the release of interleukin-33 (IL-33), which is known to drive type 2 immune responses. The authors found that bee venom-derived PLA2 and its enzymatic product lysophosphatidylcholine could induce IL-33 production and activation of type 2 innate lymphoid cells *in vivo*. They also showed that the ability of bee venom-derived PLA2 to induce type 2 immune responses depended on ST2 (also known as IL-1RL1), which is a component of the IL-33 receptor. In keeping with the study by Marichal, Starkl *et al.*, Palm, Rosenstein *et al.* found that immunization of mice with a low dose of bee venom-derived PLA2 induced protection against subsequent high doses of this venom component, and that acquired resistance depended on FcεRI. Surprisingly though, when ST2-deficient mice were immunized with bee venom PLA2, they did not show any apparent defect in IgE induction or in acquired resistance to PLA2.

In summary, these studies show that venoms can induce IgE-associated immune responses that protect animals against subsequent exposure to lethal doses of the venom — but the exact mechanisms by which the venoms induce IgE antibody production remain to be determined.

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ORIGINAL RESEARCH PAPERS Marichal, T. *et al.* A beneficial role for immunoglobulin E in host defense against honeybee venom. *Immunity* http://dx.doi.org/10.1016/j.immuni.2013.10.005 (2013) | Palm, N. W. *et al.* Bee venom phospholipase A2 induces a primary type 2 response that is dependent on the receptor ST2 and confers protective immunity. *Immunity* http://dx.doi.org/10.1016/j.immuni.2013.10.006 (2013)

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