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Title: Investigating the critical roles of mast cells and IgE in innate and adaptive defenses against venoms

Abstract: Mast cells and IgE antibodies are thought to promote health by contributing to host responses to certain parasites, but other beneficial functions have remained obscure. Venoms provoke innate inflammatory responses and pathology reflecting the activities of the contained toxins. Venoms also can induce allergic sensitization and the development of venom-specific IgE antibodies, which can predispose some subjects to exhibit anaphylaxis upon subsequent exposure to the relevant venom. We found that *innate* functions of mast cells, including the degradation of venom toxins by mast-cell-derived proteases, can enhance survival in mice injected with venoms from the honeybee, two species of scorpion, four species of poisonous snakes, or the Gila monster. We also found that mice injected with sub-lethal amounts of honeybee or Russell's viper venom exhibited enhanced survival after subsequent challenge with potentially lethal amounts of that venom, and that IgE antibodies, FcεRI, and probably mast cells contributed to such acquired resistance. While there are many other mechanisms that can contribute to host defense against a variety of venoms, our findings in mice suggest that mast cells, and IgE-dependent mast cell activation, can participate substantially in defense against the morbidity and mortality induced by certain insect and snake venoms. This ability to reduce the toxicity of certain venoms may represent an ancient, and beneficial, role of mast cells and IgE-dependent mast cell activation.

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