

Mast cells as regulators and effectors

Stephen J. Galli, M.D.

Mast cell degranulation is important in the pathogenesis of anaphylaxis and allergic disorders, but it is unlikely that these cells evolved in order to cause death or disease. Moreover, while many of the secreted products of mast cells can have pro-inflammatory functions that contribute to pathology, some mast cell-derived molecules can also have effects that can restrain or diminish inflammation and tissue damage. We recently provided evidence for a particular setting in which extensive mast cell degranulation, instead of enhancing morbidity and mortality, can enhance survival: the innate responses of mice to the venoms of certain poisonous reptiles or arthropods.

It has been known for some time that many animal venoms contain components that can induce mast cell degranulation, and this has been thought to contribute to the pathology and mortality caused by envenomation. However, we showed that mast cells can enhance the resistance of mice to the venoms of three snakes (*Atractaspis engaddensis* [the Israeli mole viper], *Crotalus atrox* [the western diamondback rattlesnake] and *Agkistrodon contortrix contortrix* [the southern copperhead]), and the honeybee (*Apis mellifera*), as well as to a specific component of *Atractaspis engaddensis* venom, sarafotoxin 6b (that is structurally similar to the mammalian peptide, endothelin-1 [ET-1]), and reported evidence that mouse mast cell-derived carboxypeptidase A3 (CPA3) can contribute to the detoxification of sarafotoxin 6b, ET-1, and the unfractionated snake venoms (Metz M, Piliponsky AM, Chen C-C, Lammel V, Åbrink M, Pejler G, Tsai M, Galli SJ. *Science*. 2006; **313**:526-30). The molecular mechanism by which mouse CPA3 degrades and detoxifies sarafotoxin 6b and ET-1 was elegantly demonstrated by the group of Hans-Reimer Rodewald (Schneider LA, Schlenner SM, Feyerabend TB, Wunderlin M, Rodewald HR. *J. Exp. Med.* 2007; **204**:2629-39).

More recently, using both mast cell-engrafted genetically mast cell-deficient mice and mice deficient in individual mast cell-associated proteases, we showed that mast cells, and the mast cell-associated chymase mouse mast cell protease-4 (MCPT4), can enhance resistance of mice to the venom of the Gila monster lizard (*Heloderma suspectum*), a toxic component of that venom (helodermin), and the structurally similar mammalian peptide, vasoactive intestinal polypeptide (VIP), as well as to the venoms of two species of scorpions (Akahoshi M, Song CH, Piliponsky AM, Metz M, Guzzetta A, Åbrink M, Schlenner S, Feyerabend TB, Rodewald HR, Pejler G, Tsai M, Galli SJ. *J. Clin. Invest.* 2011; **121**:4180-91).

These and other findings indicate that the expression by mast cells of receptors for VIP, ET-1, neurotensin, and additional endogenous peptides that can trigger mast cell degranulation, when combined with the mast cell's ability to produce enzymes that can degrade these and related peptides, permits mast cells to contribute to health in two different contexts: reducing the toxicity associated with high concentrations of the endogenous peptides and limiting the pathology induced by structurally and functionally similar peptides contained in animal venoms. It is tempting to speculate further that the occurrence of large numbers of mast cells in the skin, a frequent site of envenomation, in part reflects evolutionary pressure to position these cells where they can rapidly respond

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to, and thereby help to limit the toxicity of, the venoms of poisonous invertebrates and reptiles. Finally, the development of IgE antibodies to venom components has been reported for snake, honeybee and scorpion venoms. It is well known that exposure of highly sensitized subjects to such venoms can result in anaphylaxis. However, the possibility should be considered that the presence of anti-venom IgE may further increase the ability of mast cell degranulation to enhance resistance to such venoms, at least in those subjects whose antibody-dependent reactions stop short of anaphylaxis.