

Animal models of anaphylaxis

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Purpose of review

In this review we will focus on recent advances in the role of mast cells in the pathophysiology of insect allergy and the possible mechanisms of mast cell activation in anaphylaxis.

Recent findings

Anaphylactic reactions in the mouse can be induced by several independent pathways involving immunoglobulin E, immunoglobulin free light chains, or immunoglobulin G. There is considerable evidence that mast cells play a central role in anaphylactic reactions to insect stings. Mast cells can be directly activated by components of insect venom or after allergic sensitization. Of interest is the observation that mast cells are not only effector cells in insect allergy, but may also play a protective role in preventing the development of severe anaphylactic responses or by controlling inflammatory reactions by modulation of antigen-specific T-cell responses.

Summary

The contribution of mast cells in anaphylactic responses to insect venom may be heterogeneous. On the one hand, activation of mast cells contributes to the pathology by the release of bioactive and tissue-damaging mediators. However, mast cell activation may neutralize constituents in insect venom and defend against the adverse effects of these toxins or they may modulate inflammation through downregulation of antigen-specific immune responses.

Keywords

anaphylaxis, hypersensitivity, immunoglobulin free light chains, insect allergy, insect venom, mast cells

Introduction

Foods and insect stings are the most common causes of anaphylactic reactions. To explore the mechanisms underlying the development of allergy and to identify new prophylactic and therapeutic intervention strategies, animal models are being developed that mimic allergic responses in humans. Furthermore, increasing interest in animal models to assess the potential allergenicity of proteins has been generated by the introduction of novel proteins by modern biotechnology [1].

In this review, current insights into the mechanism of anaphylactic reactions in animal models of anaphylaxis will be discussed. We will focus on the role of mast cells in the pathophysiology of insect allergy and the possible mechanisms of mast cell activation in anaphylaxis.

Animal models of anaphylaxis

Stinging insects are members of the order Hymenoptera and include bees (honeybees, bumblebees), vespids (Vespidae family – yellow jackets, hornets, wasps), and formicids (fire ants, *Solenopsis* genus). Today immunotherapy is the only curative treatment against these allergies. To examine new treatment concepts, animal models for insect venom allergy are being developed. At present, only a limited number of animal models for insect allergy have been described. General mechanisms of immunization and elicitation of type I or IV hypersensitivity reactions may also apply for insect allergens, but differences compared with other allergens may also be expected due to the specific nature of the stinging insect venoms. At this point further research into models for insect allergy is needed.

Winkler *et al.* [2] described the development of a murine model of yellow jacket venom allergy that mimics the natural mode of sensitization. Intraperitoneal immunization with yellow jacket venom in BALB/c mice, with or without the use of the adjuvant aluminum hydroxide, led to the development of allergen-specific antibodies with an immunoglobulin (Ig)-E-binding profile comparable to that of wasp venom allergic human individuals. In another model, BALB/c mice were exposed to at least 16 mosquito (*Aedes aegypti*) bites, twice a week for 4 weeks. Mosquito-exposed animals developed a positive immediate wheal reaction, positive passive cutaneous anaphylaxis response and positive delayed papule upon exposure to mosquito antigens. Sensitization was accompanied by increased levels of antigen-specific IgE and IgG₁ [3]. In other models, venom components of stinging

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Abbreviations

Ig immunoglobulin
IL interleukin

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insects are introduced into the animals to determine their potential to induce acute effects on immune effector cells (e.g. mast cells) or active sensitization and production of antigen-specific immunoglobulins [4,5].

Other models for anaphylaxis include animal models for food allergy, which have been successfully used for immunological research. These models have been established in mouse [6], rat [7] and guinea pig [8]. The normal immune response to dietary proteins is oral tolerance and therefore animal models of food allergy require nonphysiological routes of allergen presentation and the use of adjuvants to bypass this state of tolerance and to obtain clinical responses that mimic human IgE-mediated food allergy. The degree of sensitization is affected by several parameters that are well described by Helm [9], including the concentration of the antigen, the route of protein administration, and a genetic predisposition. To obtain a successful sensitization protocol, high-immunoglobulin (especially IgE) responder strains are used, which resemble atopic humans in their genetic predisposition to respond with an overproduction of IgE to antigens. The Brown Norway rat food allergy model is known to be a high IgE responder strain and has been used for oral sensitization to food proteins without the use of an adjuvant [10]. DBA/2 mice respond with both IgE and IgG production against cow's milk casein by casein feeding, indicating that these mice can be naturally sensitized [11,12]. Alternatively, sensitization can be achieved with the help of adjuvants, for example with cholera toxin. Mouse models for cow's milk allergy and peanut allergy have been established in C3H/HeJ mice [6,12].

An approach to determine the allergenicity of proteins has been developed by Dearman and Kimber [13] in BALB/c mice by intraperitoneal administration of various food antigens (peanut agglutinin, ovalbumin and potato protein extract). Much more robust IgE responses were provoked by intraperitoneal administration compared with gavage exposure of the same proteins. During the last couple of years, nonmurine animal models in dogs [14] and swine [15], which more closely mimic allergic diseases in humans, have been used for investigations involving food allergy.

Investigating the role of mast cells

Mast cells are widely distributed throughout the body and abundant numbers can be found at strategic sites facing the exterior, for example in skin, gastrointestinal tract and mucosal barriers. Mast cells arise from bone marrow progenitor cells and maturation from these progenitor cells occurs in the peripheral tissues where they ultimately reside as mature cells [16–18]. At sites of local inflammation, the number of mast cells can increase due to attraction of mast cell progenitors and increased growth

factor production, for example interleukin (IL)-3, 4, 9, and stem cell factor [18–20]. The local environment also determines the phenotype of the mast cells, resulting in differences in, for example, mast cell protease expression, heparin content and responses to certain stimuli. Mast cells resident in mucosal tissue (mucosal mast cells; MMCs) or in connective or submucosal layers (connective tissue mast cells; CTMCs) represent two distinct populations with different characteristics. Mast cells can be activated by many immunologic and nonimmunologic triggers such as IgE, IgG₁, immunoglobulin free light chains, anaphylatoxins, neuropeptides, lipopolysaccharide, stem cell factor, superantigens and many more [21•]. Activation of mast cells leads to release of preformed mediators stored in mast cell granules and active synthesis of lipid mediators and cytokines. Certain stimuli such as stem cell factor [22], substance P [23] and heat shock protein 70 [24] can stimulate selective release of mediators from mast cells [21•].

Different approaches can be used to study the role of mast cells in immune effector responses. In-vitro cultured primary rodent or human mast cells can be useful in investigating the direct effects of stimulating agents on mast cells, including mediator release, receptor expression and involved signal transduction pathways. Various protocols have been described to culture mast cells with MMC or CTMC-like characteristics from different cell sources [18,20,25–30].

Human mast cells can be cultured from CD34⁺ progenitor cells in, for example, human cord blood, peripheral blood or buffy coats [31–34,35•]. Importantly, because of the limited availability of primary human mast cell cultures, most in-vitro data are derived from murine mast cells that do not always reflect the human situation [35•].

To investigate the role of mast cells in the pathophysiology of anaphylaxis, genetically mast cell-deficient mice are very useful animal models. Different mouse strains virtually devoid of mast cells in all tissues are available. In most studies, WBB6F₁-*Ki*^{W/W^v} mice were used as a mast cell-deficient animal model, but one has to be aware that these mice also have other phenotypic alterations, including anemia, lack of fertility, and a deficiency in melanocytes [36,37•]. Systemic or local engraftment with primary cultured mast cells allows specific reconstitution of the mast cell population (to create so-called 'mast cell knock in animals') to indisputably assess the role of mast cells in altered biological responses in deficient animals. Another mast cell-deficient strain, C57BL6-*Ki*^{W-sh/W-sh}, has received increased popularity in recent years. This strain, similar to the W/W^v mice, virtually lacks mast cells in all tissue, but has the advantage that it is not infertile and can be

crossed with other knockout or transgenic strains to obtain specific genetic changes [36,37[•]].

Role of mast cells in insect allergy: effector or inhibitor cell?

The role of mast cells in anaphylaxis is well established [38]. Allergic reactions to insect stings can be established by direct activation of mast cells by peptide/protein components of the insect venoms such as phospholipase A₂ and mastoparan or the induction of type I hypersensitivity responses due to the presence of venom-specific IgE [4,5,39,40]. Patients suffering from mastocytosis, a rare disease characterized by increased numbers of mast cells in skin and other organs, are at greater risk of developing severe sting anaphylaxis [41,42].

Interestingly, in a recent study by Metz and coworkers [43^{••}], it was shown that mast cells can also play a protective role in reactions to snake and bee venom. Mast cell-deficient animals showed a much greater drop in rectal temperature and increased mortality upon exposure to snake and honeybee venom. Mast cells confer this protection possibly through the release of carboxypeptidase A, a proteolytic enzyme capable of degrading endothelin-1 (like) proteins in the venom [44]. It has been shown in earlier studies that mast cells express endothelin-A (ET_A) receptors and can produce endothelin-1 upon activation. However, activated mast cells can also diminish endothelin levels and reduce endothelin-induced pathology [44]. It remains to be investigated whether human mast cells can confer a similar protection against insect venoms and whether such toxins are present in all insect venoms.

In a murine model to study mosquito bite-induced allergic itch-associated responses, no effect of mast cell deficiency was found on itch induced after intradermal injection of salivary gland extract of mosquitos [45]. Exposure of mice to mosquito bites, however, activates dermal mast cells and induces a local influx of inflammatory cells. Mast cells were found to be responsible for macrophage inflammatory protein-2 (MIP-2) production in the skin and IL-10 in draining lymph nodes. The induction of IL-10 in the lymph nodes can ultimately lead to a downregulation of antigen-specific immune responses [46[•]]. Indeed, mast cells have been shown to play an essential role in the induction of CD4⁺CD25⁺Foxp3⁺ regulatory T cell-dependent peripheral tolerance [47^{••}].

Role of IgE, IgG and immunoglobulin free light chains in hypersensitivity responses

Studies in murine models have identified two distinct pathways of systemic anaphylaxis [48]. The first is the

classical IgE-mediated hypersensitivity reaction that is characterized by the presence of antigen-specific IgE antibodies that can bind to FcεRI receptors on cell membranes of mast cells and basophils. Cross linking of IgE antibodies stimulates mast cell degranulation and release of mediators, including histamine and serotonin, and the synthesis and secretion of platelet-activating factor (PAF) and leukotrienes. These mediators cause the symptoms of anaphylaxis by inducing smooth muscle contraction and increasing vascular permeability. An alternative pathway of murine anaphylaxis is IgE independent. In contrast to the classical allergic reaction, antigen-challenged mice can exhibit anaphylaxis despite the absence of mast cells, FcεRI, and IgE. Systemic anaphylaxis is induced by antigen binding to IgGs that cross link the low-affinity receptors for IgG (FcγRIII) on macrophages, stimulating PAF release. Both pathways of systemic anaphylaxis can be induced by select antigen immunization and challenge protocols. The critical factor that determines whether IgE-dependent anaphylaxis is induced is the quantity of antigen-specific IgG antibody produced and the quantity of antigen used to challenge immunized mice. Recently, murine studies have demonstrated that IgG antibodies can block IgE-dependent anaphylaxis under conditions of high IgG antibody concentration and low allergen dose without causing anaphylaxis through the alternative pathway [49[•]]. Of note, IgG-mediated anaphylaxis has not been demonstrated in humans, although anaphylaxis has been described in the absence of IgE antibodies or mast cell degranulation products. The difficulty to demonstrate FcγRIII-mediated anaphylaxis is probably related to the quantity of antigen and IgG antibody that are required to trigger FcγRIII-dependent anaphylaxis [38].

In the past few years, our group [50,51] described a novel mechanism for the elicitation of immediate hypersensitivity-like reaction via immunoglobulin free light chains. Transfer of antigen-specific immunoglobulin free light chains into naïve mice sensitized them to the respective antigen. Local challenge of the sensitized animals with the proper antigen resulted in the induction of mast cell activation, leading to vascular leakage and edema formation after skin challenge or acute bronchoconstriction after intranasal challenge [50,52]. The importance of mast cells in this response was demonstrated in mast cell-deficient animals in which these changes were absent, while reconstitution of the mast cell population restored the response. The immunoglobulin free light chain-elicited hypersensitivity responses could be inhibited by local or systemic application of a specific antagonist F991 [50,52,53]. Using F991 it was further shown that immunoglobulin free light chains play a crucial role in the induction of delayed hypersensitivity responses in skin and airways of hapten-sensitized animals. Normal values for human serum κ free light chain range from 1.2

to 21 mg/l and λ free light chains from 3.0 to 42 mg/l, while significant increases in serum levels of immunoglobulin free light chains have been reported for various diseases [51,54^{*}]. For example, in nonatopic asthma patients it was found that serum free light chain concentrations were increased compared with those in nonatopic asthma patients [52]. Further research is needed to evaluate whether immunoglobulin free light chains could drive anaphylactic sting reactions in 'nonatopic' insect allergy patients.

Conclusion

Anaphylactic reactions in the mouse can be induced by several independent pathways involving IgE and mast cells, immunoglobulin free light chains and mast cells, or IgG and macrophages. There is considerable evidence that mast cells play a central role in anaphylactic reactions to insect stings. Mast cells can be directly activated by components of insect venom or after allergic sensitization. Specific IgE is produced in mice when exposed to venom extracts, while the role of immunoglobulin free light chains remains to be determined. Anaphylaxis induced via macrophages is not likely to occur in insect allergy because this pathway is dependent on large quantities of allergen. Of interest is the observation that mast cells are not only effector cells in insect allergy, but could play a protective role by destroying endothelin-like constituents in insect venom, thereby preventing the development of severe anaphylactic responses. In addition, by the release of immunosuppressive mediators, activated mast cells could also downregulate further immunological responses elicited by antigen-specific T lymphocytes.

The number of available animal models to investigate insect allergy is limited, but other models for anaphylaxis may increase the insights into insect allergy considering the numerous parallels with allergic reactions elicited by other allergens.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 361).

- 1 Matsuda T, Matsubara T, Hino S. Immunogenic and allergenic potentials of natural and recombinant innocuous proteins. *J Biosci Bioeng* 2006; 101:203–211.
- 2 Winkler B, Bolwig C, Seppala U, *et al.* Allergen-specific immunosuppression by mucosal treatment with recombinant Ves v 5, a major allergen of *Vespa vulgaris* venom, in a murine model of wasp venom allergy. *Immunology* 2003; 110:376–385.
- 3 Chen YL, Simons FE, Peng Z. A mouse model of mosquito allergy for study of antigen-specific IgE and IgG subclass responses, lymphocyte proliferation, and IL-4 and IFN- γ production. *Int Arch Allergy Immunol* 1998; 116:269–277.
- 4 Dudler T, Machado DC, Kolbe L, *et al.* A link between catalytic activity, IgE-independent mast cell activation, and allergenicity of bee venom phospholipase A2. *J Immunol* 1995; 155:2605–2613.
- 5 King TP, Jim SY, Wittkowski KM. Inflammatory role of two venom components of yellow jackets (*Vespa vulgaris*): a mast cell degranulating peptide mastoparan and phospholipase A1. *Int Arch Allergy Immunol* 2003; 131:25–32.
- 6 Li XM, Serebrisky D, Lee SY, *et al.* A murine model of peanut anaphylaxis: T- and B-cell responses to a major peanut allergen mimic human responses. *J Allergy Clin Immunol* 2000; 106:150–158.
- 7 Knippels LM, Penninks AH, Spanhaak S, *et al.* Oral sensitization to food proteins: a Brown Norway rat model. *Clin Exp Allergy* 1998; 28:368–375.
- 8 Piacentini GL, Bertolini A, Spezia E, *et al.* Ability of a new infant formula prepared from partially hydrolyzed bovine whey to induce anaphylactic sensitization: evaluation in a guinea pig model. *Allergy* 1994; 49:361–364.
- 9 Helm RM. Food allergy animal models: an overview. *Ann N Y Acad Sci* 2002; 964:139–150.
- 10 Knippels LM, Penninks AH, van Meeteren M, *et al.* Humoral and cellular immune responses in different rat strains on oral exposure to ovalbumin. *Food Chem Toxicol* 1999; 37:881–888.
- 11 Ito K, Inagaki-Ohara K, Murosaki S, *et al.* Murine model of IgE production with a predominant Th2-response by feeding protein antigen without adjuvants. *Eur J Immunol* 1997; 27:3427–3437.
- 12 Li XM, Schofield BH, Huang CK, *et al.* A murine model of IgE-mediated cow's milk hypersensitivity. *J Allergy Clin Immunol* 1999; 103:206–214.
- 13 Dearman RJ, Kimber I. A mouse model for food allergy using intraperitoneal sensitization. *Methods* 2007; 41:91–98.
- 14 Buchanan BB, Frick OL. The dog as a model for food allergy. *Ann N Y Acad Sci* 2002; 964:173–183.
- 15 Helm RM, Furuta GT, Stanley JS, *et al.* A neonatal swine model for peanut allergy. *J Allergy Clin Immunol* 2002; 109:136–142.
- 16 Chen CC, Grimbaldston MA, Tsai M, *et al.* Identification of mast cell progenitors in adult mice. *Proc Natl Acad Sci U S A* 2005; 102:11408–11413.
- 17 Arinobu Y, Iwasaki H, Gurish MF, *et al.* Developmental checkpoints of the basophil/mast cell lineages in adult murine hematopoiesis. *Proc Natl Acad Sci U S A* 2005; 102:18105–18110.
- 18 Okayama Y, Kawakami T. Development, migration, and survival of mast cells. *Immunol Res* 2006; 34:97–115.
- 19 Rottem M, Hull G, Metcalfe DD. Demonstration of differential effects of cytokines on mast cells derived from murine bone marrow and peripheral blood mononuclear cells. *Exp Hematol* 1994; 22:1147–1155.
- 20 Ryan JJ, Kashyap M, Bailey D, *et al.* Mast cell homeostasis: a fundamental aspect of allergic disease. *Crit Rev Immunol* 2007; 27:15–32.
- 21 Theoharides TC, Kalogeromitos D. The critical role of mast cells in allergy and inflammation. *Ann N Y Acad Sci* 2006; 1088:78–99.
Concise review describing the triggers for mast cell activation, mediators released by mast cells and the role of mast cells in different pathologies.
- 22 Oliveira SH, Hogaboam CM, Berlin A, *et al.* SCF-induced airway hyperreactivity is dependent on leukotriene production. *Am J Physiol Lung Cell Mol Physiol* 2001; 280:L1242–L1249.
- 23 Karimi K, Kool M, Nijkamp FP, *et al.* Substance P can stimulate prostaglandin D2 and leukotriene C4 generation without granule exocytosis in murine mast cells. *Eur J Pharmacol* 2004; 489:49–54.
- 24 Mortaz E, Redegeld FA, Dunsmore K, *et al.* Stimulation of cysteinyl leukotriene production in mast cells by heat shock and acetylsalicylic acid. *Eur J Pharmacol* 2007; 561:214–219.
- 25 Ihle JN, Keller J, Oroszlan S, *et al.* Biologic properties of homogeneous interleukin 3. I: Demonstration of WEHI-3 growth factor activity, mast cell growth factor activity, p cell-stimulating factor activity, colony-stimulating factor activity, and histamine-producing cell-stimulating factor activity. *J Immunol* 1983; 131:282–287.
- 26 Malbec O, Roget K, Schiffer C, *et al.* Peritoneal cell-derived mast cells: an in vitro model of mature serosal-type mouse mast cells. *J Immunol* 2007; 178:6465–6475.
- 27 Sur R, Cavender D, Malaviya R. Different approaches to study mast cell functions. *Int Immunopharmacol* 2007; 7:555–567.
- 28 Karimi K, Redegeld FA, Heijdra B, *et al.* Stem cell factor and interleukin-4 induce murine bone marrow cells to develop into mast cells with connective tissue type characteristics in vitro. *Exp Hematol* 1999; 27:654–662.
- 29 Tsuji K, Zsebo KM, Ogawa M. Murine mast cell colony formation supported by IL-3, IL-4, and recombinant rat stem cell factor, ligand for c-kit. *J Cell Physiol* 1991; 148:362–369.
- 30 Yamada N, Matsushima H, Tagaya Y, *et al.* Generation of a large number of connective tissue type mast cells by culture of murine fetal skin cells. *J Invest Dermatol* 2003; 121:1425–1432.

- 31 Valent P, Spanblochl E, Sperr WR, *et al.* Induction of differentiation of human mast cells from bone marrow and peripheral blood mononuclear cells by recombinant human stem cell factor/kil-ligand in long-term culture. *Blood* 1992; 80:2237–2245.
- 32 Wang XS, Lau HY. Histamine release from human buffy coat-derived mast cells. *Int Immunopharmacol* 2007; 7:541–546.
- 33 Wang XS, Yip KH, Sam SW, *et al.* Buffy coat preparation is a convenient source of progenitors for culturing mature human mast cells. *J Immunol Methods* 2006; 309:69–74.
- 34 Theoharides TC, Kempuraj D, Tagen M, *et al.* Human umbilical cord blood-derived mast cells: a unique model for the study of neuro-immuno-endocrine interactions. *Stem Cell Rev* 2006; 2:143–154.
- 35 Bischoff SC. Role of mast cells in allergic and nonallergic immune responses:
 - comparison of human and murine data. *Nat Rev Immunol* 2007; 7:93–104.
 Review describing the recent advances in human mast cell biology and comparing the findings made with human and murine mast cells.
- 36 Grimaldeston MA, Chen CC, Piliponsky AM, *et al.* Mast cell-deficient W-sash c-kit mutant Kit W-sh/W-sh mice as a model for investigating mast cell biology in vivo. *Am J Pathol* 2005; 167:835–848.
- 37 Grimaldeston MA, Metz M, Yu M, *et al.* Effector and potential immunoregulatory roles of mast cells in IgE-associated acquired immune responses. *Curr Opin Immunol* 2006; 18:751–760.
 This article focuses on the role of mast cells in the sensitization phase of an allergic response, the effector phase, late phase reaction and its role during chronic inflammation.
- 38 Finkelman FD, Rothenberg ME, Brandt EB, *et al.* Molecular mechanisms of anaphylaxis: lessons from studies with murine models. *J Allergy Clin Immunol* 2005; 115:449–457.
- 39 Peng Z, Yang M, Simons FE. Immunologic mechanisms in mosquito allergy: correlation of skin reactions with specific IgE and IgG antibodies and lymphocyte proliferation response to mosquito antigens. *Ann Allergy Asthma Immunol* 1996; 77:238–244.
- 40 Xu X, Yang H, Yu H, *et al.* The mastoparanogen from wasp. *Peptides* 2006; 27:3053–3057.
- 41 Dubois AE. Mastocytosis and Hymenoptera allergy. *Curr Opin Allergy Clin Immunol* 2004; 4:291–295.
- 42 Rueff F, Placzek M, Przybilla B. Mastocytosis and Hymenoptera venom allergy. *Curr Opin Allergy Clin Immunol* 2006; 6:284–288.
- 43 Metz M, Piliponsky AM, Chen CC, *et al.* Mast cells can enhance resistance to
 - snake and honeybee venoms. *Science* 2006; 313:526–530.
 This study describes that mast cells can significantly reduce the morbidity and mortality induced by honeybee venom. It was found that the release of carboxypeptidase A is likely responsible for the breakdown of venom components such as endothelin-like proteins.
- 44 Maurer M, Wedemeyer J, Metz M, *et al.* Mast cells promote homeostasis by limiting endothelin-1-induced toxicity. *Nature* 2004; 432:512–516.
- 45 Ohtsuka E, Kawai S, Ichikawa T, *et al.* Roles of mast cells and histamine in mosquito bite-induced allergic itch-associated responses in mice. *Jpn J Pharmacol* 2001; 86:97–105.
- 46 Depinay N, Hacini F, Beghdadi W, *et al.* Mast cell-dependent down-regulation
 - of antigen-specific immune responses by mosquito bites. *J Immunol* 2006; 176:4141–4146.
 In this study it is shown that mosquito bites can activate mast cells and results in local production of MIP-2 in the skin and IL-10 in the draining lymph nodes. The IL-10 production ultimately leads to the downregulation of antigen-specific T cell responses.
- 47 Lu LF, Lind EF, Gondek DC, *et al.* Mast cells are essential intermediaries in
 - regulatory T-cell tolerance. *Nature* 2006; 442:997–1002.
 This study describes that mast cells are crucial in the induction of Treg-induced peripheral tolerance. Activated CD4⁺CD25⁺Foxp3⁺ produce the mast cell growth and activating factor IL-9, resulting in recruitment and activation of mast cells in tolerant tissue. In turn, mast cells seem responsible for the release of immunosuppressive mediators.
- 48 Strait RT, Morris SC, Yang M, *et al.* Pathways of anaphylaxis in the mouse. *J Allergy Clin Immunol* 2002; 109:658–668.
- 49 Strait RT, Morris SC, Finkelman FD. IgG-blocking antibodies inhibit IgE-mediated anaphylaxis in vivo through both antigen interception and Fc gamma R1b cross-linking. *J Clin Invest* 2006; 116:833–841.
 This study shows that IgG blocking antibodies can completely downregulate IgE-mediated anaphylaxis without the induction of anaphylaxis through an alternative pathway (FcγRIII) provided that the IgG antibody concentration is high and the allergen dose is low.
- 50 Redegeld FA, van der Heijden MW, Kool M, *et al.* Immunoglobulin-free light chains elicit immediate hypersensitivity-like responses. *Nat Med* 2002; 8:694–701.
- 51 Redegeld FA, Nijkamp FP. Immunoglobulin free light chains and mast cells: pivotal role in T-cell-mediated immune reactions? *Trends Immunol* 2003; 24:181–185.
- 52 Kraneveld AD, Kool M, van Houwelingen AH, *et al.* Elicitation of allergic asthma by immunoglobulin free light chains. *Proc Natl Acad Sci U S A* 2005; 102:1578–1583.
- 53 van Houwelingen AH, Kaczynska K, Kraneveld AD, *et al.* Topical application of F991, an immunoglobulin free light chain antagonist, prevents development of contact sensitivity in mice. *Clin Exp Allergy* 2007; 37:270–275.
- 54 van der Heijden M, Kraneveld A, Redegeld F. Free immunoglobulin light chains
 - as target in the treatment of chronic inflammatory diseases. *Eur J Pharmacol* 2006; 533:319–326.
 Review of the various biological properties of immunoglobulin free light chains with a special focus on their possible role in inflammatory diseases.