The pathophysiology of anaphylaxis

Laurent L. Reber, PhD,[a,b,c,e] Joseph D. Hernandez, MD, PhD,[d] and Stephen J. Galli, MD[c,e,f] *Paris, France, and Stanford, Calif*

Anaphylaxis is a severe systemic hypersensitivity reaction that is rapid in onset; characterized by life-threatening airway, breathing, and/or circulatory problems; and usually associated with skin and mucosal changes. Because it can be triggered in some persons by minute amounts of antigen (eg, certain foods or single insect stings), anaphylaxis can be considered the most aberrant example of an imbalance between the cost and benefit of an immune response. This review will describe current understanding of the immunopathogenesis and pathophysiology of anaphylaxis, focusing on the roles of IgE and IgG antibodies, immune effector cells, and mediators thought to contribute to examples of the disorder. Evidence from studies of anaphylaxis in human subjects will be discussed, as well as insights gained from analyses of animal models, including mice genetically deficient in the antibodies, antibody receptors, effector cells, or mediators implicated in anaphylaxis and mice that have been "humanized" for some of these elements. We also review possible host factors that might influence the occurrence or severity of anaphylaxis. Finally, we will speculate about anaphylaxis from an evolutionary perspective and argue that, in the context of severe envenomation by arthropods or reptiles, anaphylaxis might even provide a survival advantage. (J Allergy Clin Immunol 2017;140:335-48.)

Key words: *Anaphylaxis, basophils, cysteinyl leukotrienes, epinephrine, food allergy, histamine, IgE, mast cells, platelet-activating factor, urticaria*

The recent International Consensus on Anaphylaxis described anaphylaxis as "a serious, generalized or systemic, allergic or hypersensitivity reaction that can be life-threatening or fatal."[1] This definition is intentionally "generic" in that it does not mention any of the specific immune elements that might be involved in particular instances of the disorder because these can vary depending on individual circumstances. In this review we will describe the key immune elements, such as antibody isotypes, effector cells, and biological mediators, that can contribute to the development and pathophysiologic manifestations of anaphylaxis. In particular, we will note the extent of evidence implicating these immune components in anaphylaxis in human subjects versus that induced in mouse models of the disorder, focusing especially on forms of anaphylaxis induced by reactions of allergens with antigen-specific antibodies. We will not extensively review forms of anaphylaxis induced by the antibody-independent activation of effector cells, such as mast cells and basophils, topics that have been reviewed elsewhere.[2,3]

CLINICAL ANAPHYLAXIS

The clinical definition, classification, nomenclature, and treatment of anaphylaxis have been points of controversy, varying among different medical subspecialties and in different countries, and it became clear that an important goal for the field would be to achieve a true international consensus on these important points.[4] Subsequently, multinational multidisciplinary symposia were convened to agree on the definition of anaphylaxis, the clinical criteria for its diagnosis, and its management.[5] Participants agreed on a description of anaphylaxis as "a serious allergic reaction that is rapid in onset and may cause death," as well as on 3 sets of clinical criteria to diagnose anaphylaxis.[5] These criteria were reaffirmed in the recent International Consensus on Anaphylaxis article[1] and are more extensively reviewed elsewhere in this issue of the *Journal*.[6]

A minority of patients exhibit biphasic allergic reactions, in which signs and symptoms of anaphylaxis recur hours after the early phase of the reaction has waned, and in some patients late-phase reactions occur without initial hypotension or airway obstruction.[7,8] In addition to the biphasic reactions observed in some patients with anaphylaxis induced by a variety of causes, patients who have IgE reactive with the oligosaccharide galactose-alpha-1,3-galactose, which is present in mammalian meat and in some therapeutic antibodies, can exhibit anaphylaxis

From [a]the Department of Immunology, Unit of Antibodies in Therapy and Pathology, Institut Pasteur, Paris; [b]Institut National de la Santé et de la Recherche Médicale, Paris; and [c]the Department of Pathology, [d]the Department of Pediatrics, Division of Allergy, Immunology and Rheumatology, [f]the Department of Microbiology and Immunology, and [e]the Sean N. Parker Center for Allergy and Asthma Research, Stanford University School of Medicine.

L.L.R. is supported by the European Commission (Marie Skłodowska-Curie Individual Fellowship H2020-MSCA-IF-2014 656086) and the Institut National de la Santé et de la Recherche Médicale (INSERM). S.J.G. is supported by National Institutes of Health grants U19 AI104209, NS 080062, and R01 AR067145 and the Department of Pathology, Stanford University School of Medicine.

Disclosure of potential conflict of interest: L. L. Reber has received a grant from the Marie Skłodowska-Curie Individual Fellowship (H2020-MSCA-IF-2014 656086). J. D. Hernandez has received a grant from the American Academy of Allergy, Asthma & Immunology. S. J. Galli has received grants from the National Institutes of Health (NIH; 5U19AI104209 and R01AR067145); is a member of the National Institute of Allergy and Infectious Diseases Advisory Board; and has additional grants under consideration with the NIH.

Received for publication May 9, 2017; revised June 12, 2017; accepted for publication June 14, 2017.

Corresponding author: Stephen J. Galli, MD, Department of Pathology, Stanford University School of Medicine, Center for Clinical Sciences Research, 269 Campus Dr, Rm 3255b, Stanford, CA 94305-5176. E-mail: sgalli@stanford.edu.

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

0091-6749/$36.00

© 2017 American Academy of Allergy, Asthma & Immunology

http://dx.doi.org/10.1016/j.jaci.2017.06.003

Terms in boldface and italics are defined in the glossary on page 336.

Abbreviations used
ASA: Active systemic anaphylaxis
BV: Honeybee venom
CysLT: Cysteinyl leukotriene
LT: Leukotriene
MPO: Myeloperoxidase
PAF: Platelet-activating factor
PAF-AH: Platelet-activating factor acetylhydrolase
PSA: Passive systemic anaphylaxis

after a delay of several hours during which no signs or symptoms are apparent.[9]

Although there is broad consensus on many aspects of the treatment of anaphylaxis,[6,10-12] such recommendations are based largely on observational studies, extrapolation from retrospective case reviews, and a few clinical trials.[10,11] Injectable epinephrine is universally agreed upon as the first-line therapy for anaphylaxis[10-12] and can counteract many pathophysiologic changes in patients with anaphylaxis by acting through α_1-adrenergic receptors to induce vasoconstriction, which prevents or diminishes tissue/airway edema, hypotension, and distributive shock; β_1-adrenergic receptors to increase heart rate and cardiac contractility; and β_2-adrenergic receptors to dilate the airways.[11] In addition, epinephrine's action on β_2-adrenergic receptors might potentially block further release of mediators (histamine and eicosanoids) by mast cells and perhaps other effector cells.[13,14]

Other therapies should be considered second-line therapies and not a substitute for epinephrine. Guidelines generally agree that patients should be placed in a supine position and given crystalloid to maintain perfusion, and oxygen.[10,12] H_1- and H_2-antihistamines might be helpful in treating cutaneous and upper respiratory signs and symptoms, and corticosteroids might help prevent biphasic reactions but neither prevent nor treat airway obstruction or circulatory collapse and therefore cannot be considered alternatives to epinephrine.[10-12] Development of novel therapies for anaphylaxis is likely to be guided mainly by limited data from human subjects and by observations made using animal models.

IMMUNOLOGIC MECHANISMS OF ANAPHYLAXIS

Only limited data on immunologic mechanisms of anaphylaxis from human subjects are available because of the life-threatening nature of anaphylaxis and obvious ethical concerns. Human studies of anaphylaxis have included inducing anaphylaxis in volunteers (most often through Hymenoptera sting challenge) and collecting samples from patients presenting for emergency management of anaphylaxis. Data obtained in such studies, as well as key findings obtained by using mouse models of anaphylaxis, are summarized in Fig 1 and Table I.[15-106] The major pathophysiologic changes observed during anaphylaxis and some of the mediators that are thought to contribute to them are shown in Fig 2.

EFFECTOR MOLECULES AND RECEPTORS

IgE-dependent anaphylaxis

IgE antibodies can play an important role in conferring immunologic specificity to effector cell activation in patients with anaphylaxis and other allergic diseases.[15,106-108] IgE is the isotype found at by far the lowest concentrations in the circulation (50-200 ng/mL total circulating IgE in healthy subjects vs approximately 10 mg/mL for IgG)[107]; however, IgE can be found at much higher levels in patients with allergic diseases.[15,16] IgE binds to the high-affinity receptor FcεRI on the surfaces of blood basophils and tissue-resident mast cells[17] and (in human subjects to a greater extent than in mice) other cell types, including

GLOSSARY

ACTIVE SYSTEMIC ANAPHYLAXIS (ASA): Anaphylaxis induced by means of active immunization (induction of antibodies involved in anaphylaxis through antigen sensitization of naive hosts).

ANGIOTENSINOGEN: Primarily synthesized in the liver, angiotensinogen is an α_2-globulin that is converted into angiotensin I by renin. Angiotensin I is converted into angiotensin II by angiotensin-converting enzyme. Angiotensin II, in addition to promoting vasoconstriction, also mediates thirst, sodium retention, and aldosterone secretion.

c-*KIT* D816V MUTATION: *c-KIT* is the gene for KIT, a transmembrane tyrosine kinase receptor whose ligand is stem cell factor. The D816V mutation is the most commonly detected mutation in mastocytosis and occurs in codon 816. It consists of the substitution of valine for aspartate (Asp816Val). This activating mutation results in ligand-independent autophosphorylation of KIT.

DISSEMINATED INTRAVASCULAR COAGULATION (DIC): A coagulopathy that occurs as a secondary complication to many different disorders. Key features are microthrombi leading to tissue hypoxia and infarction, as well as hemorrhages caused by depletion of coagulation factors and platelets and activation of fibrinolysis. Trauma, sepsis, and malignancy are common triggers.

MASS SPECTROMETRY: A laboratory tool that can be used to detect and quantify the protein composition of a biological sample. Proteins are ionized, followed by separation of the ions by mass/charge ratio. Ions then pass through a tuned field and generate an electric current that can be analyzed.

MYELOPEROXIDASE (MPO): An enzyme that mediates the conversion of H_2O_2 to HOCl, which can contribute to the killing of phagocytosed bacteria, fungi, and viruses, as well as to oxidative damage to host tissues.

PASSIVE SYSTEMIC ANAPHYLAXIS (PSA): A model in which the adoptive transfer of IgE or IgG antibodies to normal mice permits them to exhibit anaphylaxis on subsequent challenge with antigens recognized by such antibodies.

TRYPTASE: A serine esterase with both mature and immature forms and the most abundant serine protease of mast cells. Basophils have about 500-fold lower levels of tryptase than mast cells. The immature form is released constitutively by unstimulated mast cells, whereas the mature form is released on mast cell activation, such as in anaphylaxis. In human subjects there are 4 different tryptases (α, β, γ, and δ), of which the α and β tryptases are thought to be medically important. Tryptases can act locally, as well as remotely, on release. Tryptase's biological functions are not entirely understood, but it is thought to have proinflammatory effects, including promotion of tissue edema and remodeling, chemokine secretion, and neutrophil recruitment. Anti-inflammatory effects include degradation of proteins, such as allergens and neuropeptides.

The Editors wish to acknowledge Daniel Searing, MS, for preparing this glossary.

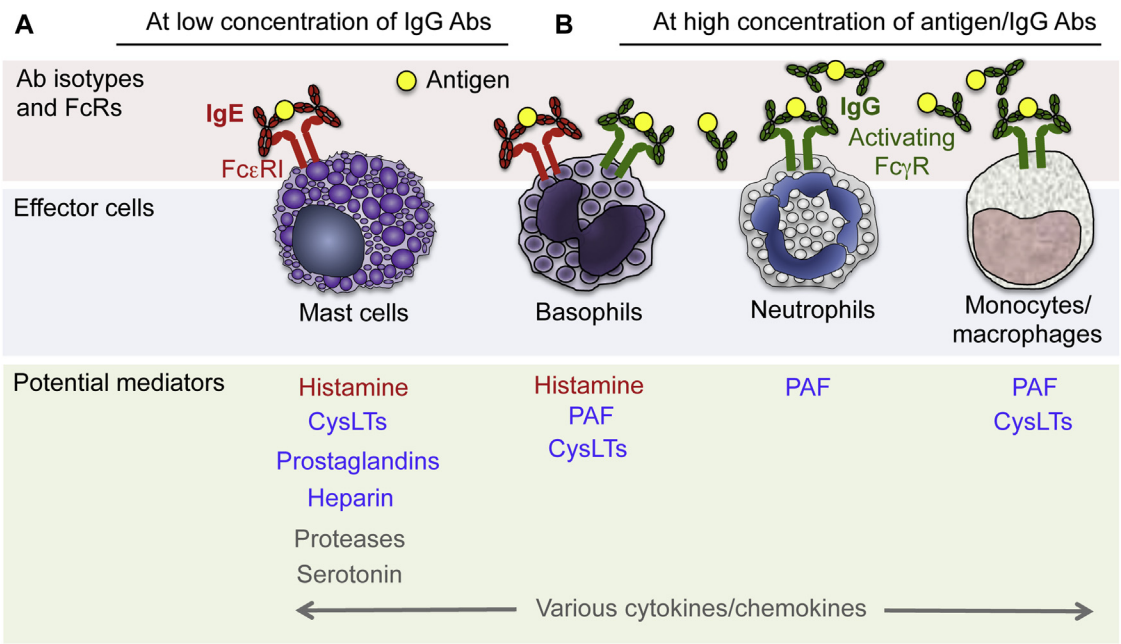

FIG 1. Multiple potential pathways in antibody *(Ab)*–mediated anaphylaxis. **A,** Antigen-specific IgE antibodies and FcεRI-bearing effector cells (eg, mast cells and basophils) play a dominant role in anaphylaxis induced (sometimes by very small amounts of bi- or multi-valent antigen) when concentrations of IgG antibodies are low. **B,** Mouse models of anaphylaxis suggest that IgG antibodies and FcγR-bearing effector cells (eg, basophils, macrophages, neutrophils, and mast cells) can be important effectors of anaphylaxis induced by large amounts of antigen that forms immune complexes in the presence of high concentrations of IgG antibodies. Some examples of anaphylaxis likely involve both pathways (A and B). Note that coengagement of immunoreceptor tyrosine-based activation motif (ITAM)-containing activating FcγRs or FcεRI with the immunoreceptor tyrosine-based inhibitory motif (ITIM)-bearing FcγRIIB (on mast cells [in mice, but perhaps not, or at lower levels, in human subjects] or basophils [in human subjects and mice]) can act to diminish effector cell activation. Red indicates strong evidence for the importance of these mediators in human anaphylaxis induced by antigen. Blue indicates that these elements can participate in models of anaphylaxis in mice, but their importance in human anaphylaxis is not yet clear. Gray indicates elements with the potential to influence anaphylaxis, but their importance in human or mouse anaphylaxis is not yet clear (eg, human mast cells are thought to make little or no serotonin).

neutrophils, eosinophils, monocytes and dendritic cells, and platelets.[17] On exposure to a bivalent or multivalent allergen, cross-linking of FcεRI-bound IgE induces activation of mast cells and basophils and the immediate release of preformed mediators, such as histamine and various proteases, as well as *de novo* synthesis of many inflammatory mediators, such as certain leukotrienes (LTs), prostaglandins, and cytokines.[15,17] The importance of that reaction was demonstrated 50 years ago, when different groups realized that purified IgE was capable of transferring skin reactivity from sensitized human subjects to naive hosts.[18-20,106] Similarly, transfer of antigen-specific IgE into naive mice sensitizes the animals to have anaphylaxis on subsequent exposure to that allergen.[21,22] Such IgE-mediated anaphylaxis is abrogated in mice lacking the high-affinity IgE receptor FcεRI,[22] as well as in mast cell–deficient mice,[23-25] highlighting the importance of IgE-mediated mast cell activation in such models of anaphylaxis.

Ever since the discovery that IgE can transfer allergen reactivity, antigen-specific IgE antibodies have been regarded as a key risk factor for the development of allergy, anaphylaxis, or both on subsequent antigen exposure. Indeed, quantification of specific IgE levels is used as part of the diagnostic evaluation of those thought to have allergic diseases and to identify potential triggers of anaphylaxis in patients with a history of anaphylaxis.[109] Several trials have concluded that the use of the anti-IgE therapeutic antibody omalizumab as an adjunctive treatment during food or venom immunotherapy can decrease the risks of severe allergic reactions, including anaphylaxis, and in some but not all trials has been reported to improve the rapidity and efficacy of immunotherapy in achieving desensitization.[26-30] In addition, limited clinical data also suggest that omalizumab might prevent spontaneous episodes of anaphylaxis in patients with systemic mastocytosis, a disease characterized by marked increases in mast cell numbers and activity[31] (also see the review by Akin[110] in this issue of the *Journal*).

Clearly, however, IgE levels alone do not explain a subject's susceptibility to anaphylaxis. Some patients can experience near-fatal anaphylaxis despite having low or undetectable levels of circulating allergen-specific IgE.[111] Conversely, allergen-specific IgE can be detected in the plasma of many subjects who do not have clinical symptoms when exposed to that allergen.[112] This is particularly true for Hymenoptera venom, with the vast majority (approximately 80%) of patients with IgE antibodies specific for Hymenoptera venoms having no history of systemic reactions to such venoms.[113-116] Therefore, taken in isolation, the presence of antigen-specific IgE antibodies does not indicate that the person necessarily will exhibit any, let alone severe, clinical reactivity to the recognized antigens.[117-123]

TABLE I. Roles (or potential roles) of various antibodies, effector cells, and mediators in anaphylaxis in human subjects and mice

Effector mechanisms	Human subjects	Mice
Antibody isotypes		
IgE	• Increased IgE levels are present in patients with allergic diseases.[15,16] • Purified IgE can transfer skin reactivity from a sensitized human subject to a naive host.[18-20,106] • The anti-IgE antibody omalizumab can decrease the risks of anaphylaxis.[26-31]	• PCA and PSA are induced by transfer of antigen-specific IgE into naive mice and antigen challenge.[21,22] • IgE-mediated PCA and PSA are abrogated in mice lacking the high-affinity IgE receptor FcεRI.[22] • ASA is reduced partially in IgE-deficient or *FcεR1*$^{-/-}$ mice in some models but not in others.[35,56,60,66,90,91]
IgG	• No definitive evidence is present to date. • Cases of anaphylaxis were reported after treatment with therapeutic mAbs without detectable levels of anti-drug IgE.[40,92-94]	• IgG_1, IgG_{2a}, and IgG_{2b} (but not IgG_3) can induce PSA.[32-42] • IgG-PSA is reduced in *FcγRIII*$^{-/-}$ mice.[33,34] • IgG_1 and IgG_{2b} (but not IgG_{2a}) PSA is enhanced in *FcγRIIB*$^{-/-}$ mice.[34] • Mice deficient in FcεRIα exhibit enhanced systemic anaphylaxis on challenge with 2.4G2 anti-FcγRII/III antibodies.[17] • Mice deficient for IgG_1 or FcγRIII are largely protected in several ASA models.[56,65,66] • Humanized mice expressing human FcεRI or FcγRIIA can have IgG-mediated anaphylaxis.[85-87]
Complement		
Anaphylatoxins	• Injection of low doses of C3a, C4a, or C5a in the skin of healthy volunteers induces immediate wheal-and-flare reactions.[44-47] • Blood levels of C3a, C4a, and C5a correlate with the severity of anaphylaxis in human subjects.[43]	• Reduced peanut-induced anaphylaxis is seen in *C4*$^{-/-}$ mice.[95] • Reduced IgE PCA is seen in mice in which mast cells lack C3aR or C5aR.[96] • Anaphylaxis was induced by direct activation of complement by peanut extract in one model.[88] • *C3*$^{-/-}$ mice can fully develop the IgG-PSA model.[97] • ASA is not affected in C2-, C5- and C5aR-deficient mice or after depletion of complement by using cobra venom factor.[90,98]
Effector cells		
Mast cells	• Increased tryptase levels have been detected during acute anaphylaxis in human subjects.[43,48-51] • There is a high occurrence of anaphylaxis in patients with mastocytosis.[52-54]	• IgE PCA and PSA were reduced markedly in various strains of mast cell–deficient mice.[23-25,40,55] • ASA is reduced in mast cell–deficient mice in some studies but not in others.[33,36,56-60,66,90,99]
Basophils	• There is no definitive evidence to date. • Basophil activation tests were used to diagnose or confirm allergen sensitization.[61-64]	• Controversial: some reports indicate a contribution of basophils to IgG PSA[34,36,38] or ASA,[35,56,58] whereas others found no significant role for basophils.[34,59,66,97,100]
Neutrophils	• MPO levels are increased in patients with anaphylaxis compared with healthy donors.[67]	• Antibody-mediated neutrophil depletion reduces IgG PSA and ASA in some[34,35,38] but not all[58,66] models.
Monocytes/ macrophages	• Not yet determined	• Depletion of monocytes/macrophages using clodronate liposomes can reduce IgG PSA and ASA.[34,56,59,65,66]
Platelets	• There is no definitive evidence to date. • Anaphylaxis in human subjects is associated with platelet activation.[68]	• There is no definitive evidence to date. • Depletion of platelets with anti-platelet antibodies (daily for 3 d) or neuraminidase does not reduce ASA.[65]
Mediators		
Histamine	• Aerosol administration of histamine induces bronchoconstriction in healthy volunteers.[69,70] • Intravenous administration of histamine in volunteers can reproduce many of the symptoms of anaphylaxis.[71,72] • H_1-antihistamines are commonly used as adjunctive therapy for acute anaphylaxis and anaphylactoid reactions.[73]	• Histamine injection induces anaphylaxis.[101,102] • H_1-antihistamine reduces IgE PSA.[101] • IgG PSA and ASA are reduced in mice pretreated with H_1-antihistamine in some models[34,66,103] but not in others.[35,65] • Mice deficient for the histidine decarboxylase gene are protected from IgE PSA.[101] • H1 and H2 receptor–deficient mice are partially protected from IgE PSA.[102]
CysLTs	• Levels of some CysLTs are increased during anaphylaxis onset.[79-81] • Intradermal injection of LTB_4, LTC_4, and LTD_4 induces a wheal-and-flare reaction in healthy volunteers.[82] • Aerosol administration of LTC_4 and LTD_4 in healthy subjects induces bronchoconstriction.[69,70,78]	• There is reduced IgE PSA in mice deficient for LTC_4 synthase.[83] • Mice deficient for CysLT receptor type 1 also have significantly reduced IgE PCA.[84]

(Continued)

TABLE I. *(Continued)*

Effector mechanisms	Human subjects	Mice
PAF	• Injection of PAF in the skin of healthy volunteers induces wheal-and-flare reactions.[74-76] • Circulating PAF levels increase and circulating PAF-AH activity decreases in proportion to the severity of anaphylaxis.[43,51,77]	• PAF is released during IgG PSA and ASA.[35,58] • Injection of PAF induces anaphylaxis.[104] • Reduced ASA in mice deficient for the PAF receptor.[105] • PAF receptor antagonists can partially reduce anaphylaxis in IgG PSA and ASA models.[34,35,39,40,58,65,66]
Others	• Anaphylaxis induces increases in levels of many mediators that could contribute (positively or negatively) to the clinical signs and symptoms. This includes various cytokines and chemokines, prostaglandins, tryptase, bradykinin, and serotonin, for example.	• Mast cell–derived prostaglandin D_2 can limit IgE PCA and IgE PSA.[89]

PCA, Passive cutaneous anaphylaxis.

IgE-independent anaphylaxis

The fact that some patients experience anaphylaxis despite having undetectable levels of circulating allergen-specific IgE[111] suggests the existence of IgE-independent pathways of anaphylaxis. However, it should be noted that a lack of detection of free IgE does not mean that such patients do not have enough FcεRI-bound IgE to experience IgE-mediated anaphylaxis. More definitive evidence for IgE-independent anaphylaxis has been obtained by using mouse models (Table I).

Role of IgG and FcγRs

In addition to IgE, we now know that mouse IgG also can induce ***passive systemic anaphylaxis (PSA)*** reactions, with physiologic manifestations similar to those seen in patients with IgE-dependent PSA (mainly hypothermia, vasodilatation, and cardiopulmonary changes).[32-42] Whether IgG antibodies also mediate anaphylaxis in human subjects still remains to be proved and is the topic of a recent review.[2] As demonstrated in mice, IgG-mediated anaphylaxis typically requires a much larger dose of antigen than does IgE-mediated anaphylaxis,[124] and systemic anaphylaxis also requires systemic absorption of ingested antigen.[125] Such conditions could be encountered in the case of anaphylaxis occurring in response to infusion of large quantities of a drug or a therapeutic mAb (Table I).[2]

Role of complement

Activation of the complement cascade occurs in response to many stimuli and leads to generation of the small polypeptides C3a, C4a, and C5a, also named anaphylatoxins, which are potent inflammatory mediators.[126] Multiple lines of evidence suggest that anaphylatoxins might be involved in anaphylaxis. Depletion of complement levels and production of C3a and C5a is observed in human anaphylaxis.[43,127] Anaphylatoxins can activate various myeloid cells, including mast cells and basophils.[126] Injection of low doses of C3a, C4a, or C5a into the skin of healthy volunteers induces immediate wheal-and-flare reactions.[44-47] In addition, one study showed that blood levels of C3a, C4a, and C5a correlated with the severity of anaphylaxis in human subjects.[43] Several transgenic mouse models have been used to study the importance of the complement pathway in anaphylaxis. Data obtained by using these transgenic models are reviewed in Table I and suggest that in mice the effect of complement components on anaphylaxis can be in most cases largely redundant with that of other mediators and might depend on the specific model used.

POTENTIAL EFFECTOR CELLS OF ANAPHYLAXIS

Mast cells

Mast cells are viewed as key players in IgE-dependent allergies and anaphylaxis.[15,128] Mast cells ordinarily express large numbers of the high-affinity IgE receptor FcεRI. During IgE-dependent immune responses, the antigen-dependent cross-linking of antigen-specific IgE bound to FcεRI induces aggregation of FcεRI, promoting the activation of downstream signaling events that lead to secretion of several biologically active products thought to be implicated in allergic reactions, such as histamine and various cysteinyl leukotrienes (CysLTs).[15,129-131] The molecular mechanisms of such IgE-dependent stimulation of mast cells have been extensively reviewed.[15,129,131-133] There is compelling evidence of activation of mast cells during acute anaphylaxis. Although histamine detection can be used to diagnose anaphylaxis, detection of histamine in clinical blood specimens is difficult because of its extremely short half-life, and histamine is not a mast cell–specific product because it can also be released by other cells, including basophils[134] and neutrophils.[135,136] ***Tryptase*** is much more stable than histamine and is considered a largely mast cell–derived product.[48] Mature β-tryptase is stored in mast cell granules and released on activation, such as in anaphylaxis, whereas α- and β-protryptases are secreted constitutively by mast cells, and therefore increased blood levels might indicate increased mast cell burden rather than anaphylaxis.[48] Increased levels of tryptase have been detected during acute anaphylaxis in human subjects.[43,48-51] However, the roles of tryptase or other mast cell–derived proteases in anaphylaxis remain unknown. Moreover, in some patients with anaphylaxis, such as children with food allergen–induced anaphylaxis, increased blood levels of tryptase have not been detected.[137] Additional evidence for a role of mast cells in anaphylaxis comes from the observation that patients with mastocytosis, a disease characterized by the presence of high numbers of mast cells in various organs,[138] have a high occurrence of anaphylaxis.[52] In children with mastocytosis, increased serum tryptase levels, which are used as an indicator of mast cell burden, are a risk factor for anaphylaxis and for the severity of anaphylactic episodes.[53,54]

Studies with various strains of mast cell–deficient mice also confirmed the key role of mast cells in IgE-mediated anaphylaxis.[23-25,40,55] Several reports now demonstrate that mast cell–deficient mice also have reduced peanut-induced anaphylaxis in active systemic anaphylaxis (ASA) models.[56-60] However, the role of mast cells in ASA models using other

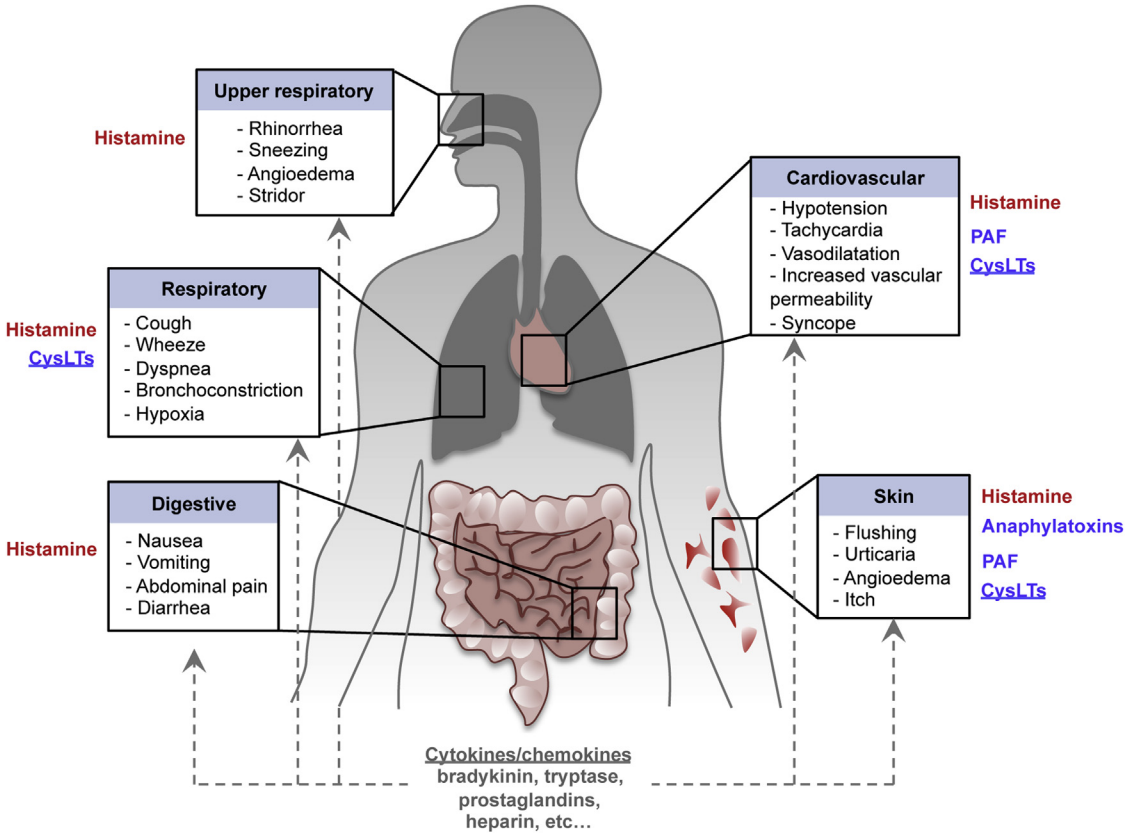

FIG 2. Pathophysiologic changes in anaphylaxis and mediators that have been implicated in these processes. Note: As mentioned in the text, first-line treatment of anaphylaxis consists of rapid administration of epinephrine (see Castells[6]). Although there is evidence that the mediators shown in the figure, particularly histamine and CysLTs, contribute to some of the various signs and symptoms of anaphylaxis and antihistamines are routinely administered to patients with anaphylaxis, pharmacologic targeting of such mediators represents second-line treatment and should not be considered an alternative to epinephrine. Red indicates strong evidence for the importance of that mediator in human subjects in the development of some of the signs and symptoms listed in the adjacent box. Blue indicates that these elements can be important in mouse models of anaphylaxis, but their importance in human anaphylaxis is not yet clear (studies in human subjects suggest that CysLTs can contribute importantly to the bronchoconstriction and enhanced vascular permeability associated with anaphylaxis [see text]). Gray indicates elements with the potential to influence anaphylaxis, but their importance in human or mouse anaphylaxis is not yet clear. Note that some mediators *(underlined)* are likely to contribute to development of late consequences of anaphylaxis.

antigens/allergens is more controversial (Table I). Therefore it is likely that mast cells can play either dominant or largely redundant roles in anaphylaxis and that the mast cell's role can be enhanced or masked depending on factors such as the exact model, adjuvant, and allergen used.

Basophils

Human basophils also express high levels of the high-affinity IgE receptor FcεRI[139] and express the activating IgG receptor FcγRIIA and inhibitory IgG receptor FcγRIIB.[140] Several lines of evidence suggest that basophils participate in anaphylaxis.[134] For example, IgE-dependent activation of human basophils is associated with increased levels of certain basophil cell-surface markers, such as CD203c or CD63, and this forms the basis of basophil activation tests, which can be used to diagnose or confirm allergen sensitization and monitor the effects of efforts to treat these conditions with immunotherapy.[61-64] However, it is difficult to ascertain how important a contribution basophils make to the pathology of anaphylaxis in human subjects, given the concomitant mast cell activation that occurs in this setting. Even in mice, the role of basophils in anaphylaxis is unsettled and appears to be model-dependent (Table I).

Monocytes/macrophages

Monocytes and macrophages express high levels of activating FcγRs[141] and can also respond to anaphylatoxins.[142] Studies in mice have shown that depletion of monocytes/macrophages by using clodronate liposomes can reduce anaphylaxis in both IgG-mediated passive models and active models (Table I).[34,56,59,65,66] These data suggest that monocytes/macrophages might play an important role in anaphylaxis. However, to the best of our knowledge, the extent to which monocytes/macrophages can contribute to anaphylaxis in human subjects has not yet been determined.

Neutrophils

The potential functions of neutrophils in patients with anaphylaxis have been recently reviewed in detail.[143] Human

and mouse neutrophils express several activating FcγRs,[143] can produce histamine,[135,136] and can release platelet-activating factor (PAF; please see below for details on the role of PAF in anaphylaxis) in response to stimulation with immune complexes *in vitro*.[35] Moreover, human neutrophils reportedly can express FcεRI, particularly in some patients with asthma.[144] The major enzyme stored in neutrophils is ***myeloperoxidase (MPO)***. A recent report shows that circulating MPO levels are increased in patients with anaphylaxis compared with those in healthy donors.[67] Consistent with this, increased MPO activity can also be detected as soon as 2 minutes after antigen challenge in an active mouse model of anaphylaxis.[35] However, it should be noted that these results do not provide definitive proof of neutrophil activation in anaphylaxis because MPO could also be potentially released by other cell populations, including macrophages.[145] Reduced expression of the activating IgG receptors FcγRIII and FcγRIV on mouse neutrophils occurs after IgG-mediated PSA, which suggests more definitely that neutrophils could be directly activated by IgG immune complexes during anaphylaxis.[34,37] Antibody-mediated neutrophil depletion can reduce anaphylaxis in mice exhibiting IgG-mediated PSA[34,35,38] or mast cell–independent ASA models.[35,66] However, neutrophil-depleting antibodies had no effect in a mast cell–dependent ASA model induced without artificial adjuvants.[66] This suggests that neutrophils might be particularly prominent in ASA models induced with adjuvants and that such models might not require any nonredundant contributions of mast cells (Table I).

Platelets

Anaphylaxis in human subjects is associated with platelet activation,[68] presumably in response to PAF and/or other mechanisms, and activated platelets can release mediators, such as platelet factor 4 and serotonin,[68] which can contribute to the pathophysiology of anaphylaxis. Moreover, human (but not mouse) platelets can express FcεRI, FcεRII, and FcγRIIA,[140,146,147] and platelets can be activated *ex vivo* after incubation with serum from allergic patients and subsequent exposure to the relevant allergen.[148] Two recent reports have shown that during basophil activation tests performed in blood specimens *ex vivo*, basophils (a potential source of PAF) can form associations with platelets,[149,150] identifying this interaction as one that should be investigated further in the context of anaphylaxis.

POTENTIAL MEDIATORS OF ANAPHYLAXIS

Histamine

Histamine has long been considered an important mediator of anaphylaxis. Weiss et al[69,70] showed that aerosol administration of histamine induces bronchoconstriction in healthy volunteers, although the effect of histamine was much less potent than that of LTs. Intravenous administration of histamine in volunteers can reproduce many of the signs and symptoms of anaphylaxis, including cutaneous flushing, headache, airway obstruction, and transient hemodynamic changes, mainly represented by systemic hypotension, tachycardia, and increased left ventricular performance.[71,72] There are 4 known histamine receptors, named H1 to H4.[151] Studies with receptor antagonists suggest that some of the systemic effects of histamine, including airway obstruction and tachycardia, are mainly mediated through the H1 receptor, whereas some others, including cutaneous flushing and headaches, seem to be mediated through both H1 and H2 receptors.[71] H_1-antihistamines are commonly used as adjunctive treatment for acute anaphylaxis and anaphylactoid reactions.[73] The contribution of histamine to anaphylaxis has also been confirmed by using mouse models (Table I). Mast cells and basophils likely represent the main sources of histamine in patients with anaphylaxis. In agreement with this, histamine release is abrogated in mast cell–deficient mice in a model of IgE-mediated PSA,[24] and increases in plasma histamine levels are also abrogated in 2 models of ASA in mice deficient for both mast cells and basophils.[58,66]

PAF

PAF is a potent phospholipid-derived mediator implicated in platelet aggregation and thought to play an important role in a variety of immune and inflammatory responses. The biology of PAF and its potential role in anaphylaxis have been recently reviewed in detail.[152] PAF can be released by a variety of human cells, including purified lung mast cells and blood basophils after *ex vivo* stimulation with anti-IgE antibodies[153] and purified neutrophils after incubation *in vitro* with heat-aggregated human IgG.[154] Many of the cell populations that produce PAF can also respond to PAF, including platelets, mast cells, neutrophils, and macrophages.[152] Injection of PAF in the skin of healthy volunteers induces wheal-and-flare reactions.[74-76] Because these reactions could be blocked by H_1-antihistamines, it was first proposed that PAF induced wheals through secondary histamine release by dermal mast cells.[75,76] However, unlike human lung mast cells and peripheral blood–derived mast cells, skin mast cells do not degranulate in response to PAF stimulation *ex vivo*.[155] In addition, Krause et al[156] showed that intradermal injection of PAF, unlike histamine and codeine, did not cause a statistically significant increase in dermal histamine levels in healthy volunteers.

A limited number of reports have assessed concentrations of PAF or platelet-activating factor acetylhydrolase (PAF-AH), an enzyme responsible for the rapid degradation of PAF, after anaphylaxis in human subjects. In these reports circulating PAF levels were increased, and circulating PAF-AH activity was inversely correlated with the severity of anaphylaxis.[43,51,77]

The contribution of PAF to anaphylaxis has been studied in more detail using pharmacologic and genetic approaches in mouse models (Table I). In most models combined inhibition of histamine and PAF almost entirely blocked anaphylaxis, suggesting additive or synergistic effects of histamine and PAF. The main cellular source of PAF in these reports likely depends on the exact anaphylaxis model used. Using an adjuvant-free active anaphylaxis model, we recently reported that the PAF receptor antagonist CV-6209 can reduce anaphylaxis in wild-type mice but has no effect on the residual anaphylaxis observed in monocyte/macrophage-depleted mice, suggesting that monocytes/macrophages represent the major source of PAF in this model.[66]

CysLTs

A third class of potential mediators of anaphylaxis was originally termed slow-reacting substance of anaphylaxis and

consists of 3 bioactive CysLTs: LTB_4, LTC_4, and LTD_4.[78] CysLTs are synthesized from arachidonic acid by a variety of cells, including mast cells, basophils, and macrophages.[157] CysLTs and their metabolites can be measured by using ***mass spectrometry***, and several reports show that levels of some of these products, namely LTE_4, 2,3-dinor-9α,11β-PGF_2, and 9α,11β-PGF_2, are increased during the onset of anaphylaxis.[79-81] Although these reports indicate that CysLTs and their metabolites might be good biomarkers of anaphylaxis, they do not prove that these compounds make an important contribution to the clinical manifestations of anaphylaxis. However, multiple observations suggest that CysLTs can promote acute allergic reactions. When injected intradermally in healthy volunteers, each of the 3 CysLTs elicited a wheal-and-flare reaction.[82] In addition, aerosol administration of LTC_4 and LTD_4 in healthy subjects induced bronchoconstriction with 1,000-fold more potency than histamine (Table I).[69,70,78]

More definitive evidence for a role of CysLTs in anaphylaxis comes from studies in mice. Mice deficient for LTC_4 synthase (an enzyme responsible for biosynthesis of LTC_4) or for the CysLT receptor CysLT receptor type 1 have markedly reduced IgE-mediated passive cutaneous anaphylaxis.[83,84]

Other potential mediators

Anaphylaxis induces changes in levels of many other mediators, which could contribute (positively or negatively) to the clinical signs and symptoms (Table I). This includes tryptase,[49,127,158-160] prostaglandins,[80,158] and cytokines/chemokines.[43,159] Depletion of the bradykinin precursor high-molecular-weight kininogen has been observed in patients with anaphylaxis, likely through activation of the plasma contact system and kallakrein.[127,161,162] Patients with anaphylaxis can also experience depletion of clotting factors, including Factors V and VIII, and in extreme cases experience ***disseminated intravascular coagulation***.[127,163] Although most patients promptly treated for anaphylaxis recover without obvious sequelae, some have recurrent signs and symptoms that require continued treatment with epinephrine and for which corticosteroids are administered.[10,164] Such sequelae are thought to reflect the "late" consequences of some of the mediators released by effectors of anaphylaxis, such as CysLTs, cytokines, and chemokines, or by structural cells activated in this setting.[164] Finally, mast cells can release adenosine on IgE-dependent activation, and adenosine can have complex effects mediated through various adenosine receptors with distinct functions, which have the potential to influence the pathophysiology of anaphylaxis.[165] However, more work is needed to define the importance of most of these mediators in anaphylaxis, particularly in human subjects.

INSIGHTS FROM HUMANIZED MODELS OF ANAPHYLAXIS

Several humanized mouse models of anaphylaxis have been developed to investigate the functions of human antibodies, Fc receptors, and effector cells in anaphylaxis. Transgenic mice expressing human FcεRI instead of the mouse protein ($hFc\varepsilon RI^{Tg}$ mice) were generated, and the expression profile of the human FcεRI transgene is very similar to that found in humans.[166-169] $hFc\varepsilon RI^{Tg}$ mice can have systemic anaphylaxis in response to intravenous sensitization with mouse or human IgE (mouse IgE can bind to human FcεRI, whereas human IgE cannot bind to the mouse receptor) followed by systemic antigen challenge,[166,169] and also can exhibit cutaneous anaphylaxis when they are sensitized intradermally with serum from patients with peanut allergy and then intravenously challenged with peanut extract.[170] $hFc\gamma RI^{Tg}$ and $hFc\gamma RIIA^{Tg}$ mice have also been generated, and the expression of human FcγRI or FcγRIIA in such transgenic mice recapitulates that found in humans.[85,86] Each of these transgenic models can exhibit IgG-mediated anaphylaxis though a mechanism involving monocytes/macrophages and neutrophils.[154,171]

More recently, Gillis et al[87] developed a novel mouse strain in which the human low-affinity IgG receptor locus, comprising both activating (human FcγRIIA, FcγRIIIA, and FcγRIIIB) and inhibitory (human FcγRIIB) human FcγR genes, has been knocked in into the equivalent mouse locus. These knock-in mice are susceptible to PSA induced by injection of heat-aggregated human intravenous immunoglobulin. The contribution of human FcγRIIA to anaphylaxis is predominant in these mice, as revealed in experiments using an anti-FcγRIIA blocking antibody.[87] Antibody-mediated depletion of neutrophils and, to a lesser extent, basophils also ameliorated signs of anaphylaxis. Finally, such anaphylaxis could be partially inhibited by using either a PAF receptor antagonist or a histamine receptor 1 antagonist.[87]

Recently, 3 groups independently attempted to generate humanized models of anaphylaxis using different strains of highly immunodeficient NOD-SCID γ (NSG) mice engrafted with human stem cells.[172-174] Bryce et al[174] used NSG mice expressing human stem cell factor, IL-3, and GM-CSF transgenes (NSG-SGM3 mice) and engrafted them with human thymus, liver, and hematopoietic stem cells. Such engraftment resulted in the development of large numbers of human mast cells in NSG-SGM3 mice in the peritoneal cavity and peripheral tissues. The authors induced both passive cutaneous anaphylaxis and PSA reactions on sensitization with a chimeric IgE containing the human constant region and challenge with the relevant antigen.

Burton et al[172] used NSG mice carrying a human stem cell factor transgene and engrafted them with human hematopoietic stem cells. The authors demonstrated that such engrafted mice also develop large numbers of human mast cells, produce human IgE in response to gavage with peanut extract, and have anaphylaxis on subsequent oral challenge with peanut. Importantly, anaphylaxis in this model could be blocked in mice treated with the anti-human IgE antibody omalizumab (which does not recognize mouse IgE).

Pagovich et al[173] also developed a humanized model of peanut anaphylaxis in NSG mice engrafted with blood mononuclear cells from patients with peanut allergy with a clinical history of anaphylaxis. These mice produced human IgE and IgG antibodies in response to intraperitoneal sensitization with peanut and had anaphylaxis on subsequent oral challenge with peanut. Again, anaphylaxis was reduced in mice treated with omalizumab, as well as in mice that had received an adeno-associated virus coding for omalizumab.

Altogether, results from such humanized models of anaphylaxis suggest that both human IgE and human IgG have the potential to induce anaphylaxis through their respective Fc receptors and also suggest that peanut anaphylaxis is highly dependent on IgE.

TABLE II. Key concepts and therapeutic implications

- Although mice can exhibit both IgE- and IgG-dependent anaphylaxis, the existence of IgG-mediated anaphylaxis in human subjects has not been conclusively demonstrated.
- In addition to mast cells and basophils, macrophages, neutrophils, and perhaps other leukocytes and platelets also might produce a diverse array of inflammatory mediators during anaphylaxis, and such products have the potential to contribute to reactions that might be difficult to treat, protracted in nature, or biphasic.
- Genetic modifiers and other host factors, as well as gene-environment interactions, can influence the development of anaphylactic reactivity, as well as the presentation, severity, or both, of anaphylaxis.
- Although the potential evolutionary benefit of anaphylaxis remains uncertain, recent evidence in mice suggests that anaphylaxis can have effects that can reduce the toxic effects of certain arthropod or reptile venoms.

GENETIC DIVERSITY/HOST FACTORS INFLUENCING ANAPHYLAXIS

Genetic modifiers can influence mast cell activation and the development of anaphylaxis, as demonstrated in differences observed between the 129/Sv and C57BL/6 strains of mice.[175] 129/Sv mice demonstrated higher levels of plasma histamine than did C57BL/6 mice after anaphylaxis induced by anti-IgE. Although higher numbers of mast cells and serum IgE levels in the 129/Sv mice could potentially explain these differences, the authors also demonstrated that bone marrow–derived cultured mast cells from 129/Sv mice degranulated more robustly than those from C57BL/6 while synthesizing similar quantities of cytokines.[175] However, the specific genetic modifiers responsible for these observed differences between the 2 strains of mice remain unknown.

Ethnic differences in rates of food allergy and anaphylaxis suggest that genetic modifiers can exist also in human populations.[176,177] Reasons for these ethnic disparities remain unclear but might reflect true genetic differences; environmental factors, including socioeconomic status; or a combination of factors. Nevertheless, a handful of genetic polymorphisms have been described that might influence development of anaphylaxis. Genetic polymorphisms in the genes encoding IL-4 receptor α, IL-10, and IL-13 have been linked to the development of anaphylaxis to drugs and latex[178-180] but theoretically might influence allergen sensitization more than (or in addition to) effector mechanisms during anaphylaxis.

Polymorphisms affecting metabolism of mediators of anaphylaxis also can influence anaphylaxis severity. As mentioned above, PAF-AH activity levels inversely correlated with severity of anaphylaxis.[43,51,77] A loss-of-function mutation in PAF-AH, V279F, has been linked to asthma but not yet to anaphylaxis.[181] Subjects with variants in ***angiotensinogen*** (ie, the MM genotype associated with decreased levels of angiotensinogen) were reported to have increased rates of Hymenoptera venom allergy and more severe reactions during venom immunotherapy.[182] Similarly, among patients with tree nut and peanut allergies, lower serum angiotensin-converting enzyme levels were associated with more severe pharyngeal edema, presumably through decreased bradykinin metabolism.[183]

A few mutations have been described that might influence the development and severity of anaphylaxis. An activating mutation in ***c-KIT D816V*** promotes mast cell proliferation in patients with clonal mast cell disorders, including mastocytosis (also see Akin[110] in this issue of the *Journal*).[184,185] D816V mutations are also found in some patients with recurrent anaphylaxis who do not have increased mast cell numbers on pathology and therefore do not meet the criteria for mastocytosis[186]; although this suggests that their mast cells are hyperresponsive, this has not yet been substantiated. In autosomal dominant hyper-IgE syndrome caused by loss-of-function mutations in signal transducer and activator of transcription 3, patients have increased levels of total and allergen-specific IgE but clinically lower rates of anaphylaxis.[187] This clinical observation can be explained, at least in part, by decreased mast cell degranulation[187] and/or by inhibition of enhanced vascular permeability through increased resilience of adherens junctions in patients and cells with signal transducer and activator of transcription 3 loss-of-function mutations.[188]

The role of sex hormones in patients with anaphylaxis is unclear. Anaphylaxis occurs more commonly in women than men.[189,190] Moreover, in a model of PSA, female mice exhibited a greater decrease in body temperature than did male mice, and this sex difference could be abrogated by ovariectomy or administration of estrogen antagonist to female mice.[191] However, analysis of patients in an anaphylaxis registry revealed increased severity of anaphylaxis in male versus female patients of 13 to 56 years of age but no sex differences in anaphylaxis severity for prepubescent patients or those older than 56 years.[192]

RECOVERY FROM ANAPHYLAXIS

Many of those who have experienced anaphylaxis and were not treated have survived the episode, particularly those with less severe presentations. What is the basis of such recovery? Variations in metabolism of mediators, including PAF and bradykinin, can influence manifestations of anaphylaxis[43,51,77,183] and theoretically the ability to recover from these manifestations. In animal models of anaphylaxis and in human subjects undergoing insect sting challenge, levels of substances with endogenous vasopressor activity, including epinephrine, norepinephrine, and angiotensin II, are increased within minutes after development of anaphylaxis,[193,194] which is likely to compensate for the vasodilation and fluid extravasation occurring during anaphylaxis. Observations that β-adrenergic blockade can exacerbate systemic anaphylaxis in mouse and rat models[88,195] and in patients with severe anaphylaxis caused by multiple causes,[196-199] particularly when combined with angiotensin-converting enzyme inhibitors,[200] support a role for endogenous vasopressors in limiting the severity of pathophysiologic changes in the setting of anaphylaxis. Mast cell degranulation releases chymase, which can convert angiotensin I to angiotensin II[201] and thereby directly contribute to increased angiotensin II levels observed after anaphylaxis. In a recent article Nakamura et al[89] showed that mice in which mast cells cannot produce prostaglandin D_2 have enhanced

manifestations of IgE-mediated anaphylaxis. Therefore it appears that mast cells also can secrete antianaphylactic mediators, which might help to limit anaphylactic responses.[89] Evidence in mice indicates that sphingosine-1-phosphate can both enhance features of anaphylaxis via effects on mast cells[202] and also, via effects on other cell types, enhance histamine clearance, thus contributing to recovery from anaphylaxis.[203] Finally, it is possible that genetically determined or other differences in mast cell activation or mediator release profiles, or in the tissue responses to such mediators, might contribute to differences in the manifestations of or recovery from anaphylaxis.

CAN ANAPHYLAXIS BE BENEFICIAL?

Using mouse models, we recently reported that the development of a type 2 immune response to honeybee venom (BV) could increase the survival of mice challenged with whole BV.[204] Also, others have shown in mice that a type 2 immune response to BV phospholipase A_2 (which is considered to be the major BV allergen in human subjects) could diminish the decrease in body temperature induced by challenge with a "near-lethal" dose of BV phospholipase A_2.[205] Importantly, these effects were dependent on IgE[204] and on the high-affinity IgE receptor FcεRI.[204,205] In a follow-up study we also provided evidence that IgE, FcεRI, and mast cells can enhance the survival of mice injected with Russell's viper venom.[206]

One of the mechanisms by which innate activation of mouse mast cells can enhance the survival of naive mice on their first exposure to various arthropod[207] or reptile[206-208] venoms is the proteolytic reduction of the toxicity of venom components by mast cell–derived carboxypeptidase 3A[208-209] or mouse mast cell protease 4 (chymase).[207] Given that snake (or arthropod) envenomation in the field can result in systemic distribution of the venom, one could argue that systemic IgE-dependent mast cell activation in this setting could both produce the clinical picture of anaphylaxis and also result in the systemic release of mediators (ie, mast cell proteases) that can degrade toxic components of the venom. In such settings anaphylaxis could be beneficial if it prevents death by envenomation and the unfortunate subject also survives the anaphylaxis. Although we do not know whether human IgE also can enhance resistance to venoms (and we imagine that we would have some trouble enlisting volunteers for such a study), it is tempting to speculate that anaphylaxis induced by small amounts of venom (eg, a single or wasp bee sting) represents only the most extreme and maladaptive end of a spectrum of acquired IgE-mediated immune responses to venom that includes, at the other end of the spectrum, appropriately regulated immune responses that can enhance resistance to such venoms.

CONCLUDING REMARKS

Anaphylaxis represents one of the most urgent of medical emergencies, in which rapid diagnosis and prompt and appropriate treatment can mean the difference between life and death. Although there has been steady progress in our understanding of the antibodies, effector cells, and mediators that can contribute to the development and manifestations of anaphylaxis, especially in the context of mouse models of the disorder, the basic clinical management of anaphylaxis has changed little in decades (see Castells[6] in this issue of the *Journal* and Table II). In a report published in 2005, Sampson et al[5] identified as major research needs both the development of "universally accepted diagnostic criteria" and the importance of identifying "reliable laboratory biomarkers to confirm the clinical impression." As noted in our introduction, the first need largely has been addressed by international and interdisciplinary efforts to forge consensus. However, the second need remains essentially unfulfilled. It is our hope that further progress in understanding the immunopathogenesis and pathophysiology of anaphylaxis in all of its various forms will help to guide efforts to devise more effective strategies for preventing this disorder and also to provide more effective options for rapidly diagnosing and effectively treating anaphylaxis when it occurs.

REFERENCES

1. Simons FE, Ardusso LR, Bilo MB, Cardona V, Ebisawa M, El-Gamal YM, et al. International consensus on (ICON) anaphylaxis. World Allergy Organ J 2014;7:9.
2. Finkelman FD, Khodoun MV, Strait R. Human IgE-independent systemic anaphylaxis. J Allergy Clin Immunol 2016;137:1674-80.
3. Subramanian H, Gupta K, Ali H. Roles of Mas-related G protein-coupled receptor X2 on mast cell-mediated host defense, pseudoallergic drug reactions, and chronic inflammatory diseases. J Allergy Clin Immunol 2016;138:700-10.
4. Bock G, Goode J, editors. Final discussion, in anaphylaxis: Novartis Foundation Symposium 257. Chichester (UK): John Wiley & Sons, Ltd; 2004; http://dx.doi.org/10.1002/0470861193.ch22.
5. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391-7.
6. Castells M. The diagnosis and management of anaphylaxis in precision medicine. J Allergy Clin Immunol 2017;140:321-33.
7. Golden DB. Patterns of anaphylaxis: acute and late phase features of allergic reactions. Novartis Found Symp 2004;257:101-15, 157-60, 276-85.
8. Lee S, Sadosty AT, Campbell RL. Update on biphasic anaphylaxis. Curr Opin Allergy Clin Immunol 2016;16:346-51.
9. Commins SP, Jerath MR, Cox K, Erickson LD, Platts-Mills T. Delayed anaphylaxis to alpha-gal, an oligosaccharide in mammalian meat. Allergol Int 2016;65:16-20.
10. Lieberman P, Nicklas RA, Randolph C, Oppenheimer J, Bernstein D, Bernstein J, et al. Anaphylaxis—a practice parameter update 2015. Ann Allergy Asthma Immunol 2015;115:341-84.
11. Simons FE, Ebisawa M, Sanchez-Borges M, Thong BY, Worm M, Tanno LK, et al. 2015 update of the evidence base: World Allergy Organization anaphylaxis guidelines. World Allergy Organ J 2015;8:32.
12. Muraro A, Roberts G, Worm M, Bilo MB, Brockow K, Fernandez Rivas M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy 2014;69:1026-45.
13. Broder I, Baumal R. Studies of reversed anaphylaxis in the perfused guinea-pig lung. Immunology 1972;22:651-61.
14. Peachell P. Regulation of mast cells by beta-agonists. Clin Rev Allergy Immunol 2006;31:131-42.
15. Galli SJ, Tsai M. IgE and mast cells in allergic disease. Nat Med 2012;18:693-704.
16. Platts-Mills TA, Schuyler AJ, Erwin EA, Commins SP, Woodfolk JA. IgE in the diagnosis and treatment of allergic disease. J Allergy Clin Immunol 2016;137:1662-70.
17. Kraft S, Kinet JP. New developments in FcepsilonRI regulation, function and inhibition. Nat Rev Immunol 2007;7:365-78.
18. Stanworth DR, Humphrey JH, Bennich H, Johansson SG. Specific inhibition of the Prausnitz-Kustner reaction by an atypical human myeloma protein. Lancet 1967;2:330-2.
19. Ishizaka K, Ishizaka T, Richter M. Effect of reduction and alkylation on allergen-combining properties of reaginic antibody. J Allergy 1966;37:135-44.
20. Ribatti D. The discovery of immunoglobulin E. Immunol Lett 2016;171:1-4.
21. Wershil BK, Mekori YA, Murakami T, Galli SJ. 125I-fibrin deposition in IgE-dependent immediate hypersensitivity reactions in mouse skin. Demonstration of the role of mast cells using genetically mast cell-deficient mice locally reconstituted with cultured mast cells. J Immunol 1987;139:2605-14.

22. Dombrowicz D, Flamand V, Brigman KK, Koller BH, Kinet JP. Abolition of anaphylaxis by targeted disruption of the high affinity immunoglobulin E receptor alpha chain gene. Cell 1993;75:969-76.
23. Feyerabend TB, Weiser A, Tietz A, Stassen M, Harris N, Kopf M, et al. Cre-mediated cell ablation contests mast cell contribution in models of antibody- and T cell-mediated autoimmunity. Immunity 2011;35:832-44.
24. Oka T, Kalesnikoff J, Starkl P, Tsai M, Galli SJ. Evidence questioning cromolyn's effectiveness and selectivity as a 'mast cell stabilizer' in mice. Lab Invest 2012; 92:1472-82.
25. Lilla JN, Chen CC, Mukai K, BenBarak MJ, Franco CB, Kalesnikoff J, et al. Reduced mast cell and basophil numbers and function in Cpa3-Cre; Mcl-1fl/fl mice. Blood 2011;118:6930-8.
26. Nadeau KC, Kohli A, Iyengar S, DeKruyff RH, Umetsu DT. Oral immunotherapy and anti-IgE antibody-adjunctive treatment for food allergy. Immunol Allergy Clin North Am 2012;32:111-33.
27. MacGinnitie AJ, Rachid R, Gragg H, Little SV, Lakin P, Cianferoni A, et al. Omalizumab facilitates rapid oral desensitization for peanut allergy. J Allergy Clin Immunol 2017;139:873-81.e8.
28. Wood RA, Kim JS, Lindblad R, Nadeau K, Henning AK, Dawson P, et al. A randomized, double-blind, placebo-controlled study of omalizumab combined with oral immunotherapy for the treatment of cow's milk allergy. J Allergy Clin Immunol 2016;137:1103-10, e1-11.
29. Boni E, Incorvaia C, Mauro M. Dose-dependence of protection from systemic reactions to venom immunotherapy by omalizumab. Clin Mol Allergy 2016;14:14.
30. Ricciardi L. Omalizumab: a useful tool for inducing tolerance to bee venom immunotherapy. Int J Immunopathol Pharmacol 2016;29:726-8.
31. Carter MC, Robyn JA, Bressler PB, Walker JC, Shapiro GG, Metcalfe DD. Omalizumab for the treatment of unprovoked anaphylaxis in patients with systemic mastocytosis. J Allergy Clin Immunol 2007;119:1550-1.
32. Harada M, Nagata M, Takeuchi M, Ohara T, Makino S, Watanabe A. Age-dependent difference in susceptibility to IgE antibody- and IgG1 antibody-mediated passive anaphylactic shock in the mouse. Immunol Invest 1991;20:515-23.
33. Miyajima I, Dombrowicz D, Martin TR, Ravetch JV, Kinet JP, Galli SJ. Systemic anaphylaxis in the mouse can be mediated largely through IgG1 and Fc gammaR-III. Assessment of the cardiopulmonary changes, mast cell degranulation, and death associated with active or IgE- or IgG1-dependent passive anaphylaxis. J Clin Invest 1997;99:901-14.
34. Beutier H, Gillis CM, Iannascoli B, Godon O, England P, Sibilano R, et al. IgG subclasses determine pathways of anaphylaxis in mice. J Allergy Clin Immunol 2017;139:269-80.e7.
35. Jonsson F, Mancardi DA, Kita Y, Karasuyama H, Iannascoli B, Van Rooijen N, et al. Mouse and human neutrophils induce anaphylaxis. J Clin Invest 2011; 121:1484-96.
36. Tsujimura Y, Obata K, Mukai K, Shindou H, Yoshida M, Nishikado H, et al. Basophils play a pivotal role in immunoglobulin-G-mediated but not immunoglobulin-E-mediated systemic anaphylaxis. Immunity 2008;28:581-9.
37. Khodoun MV, Strait R, Armstrong L, Yanase N, Finkelman FD. Identification of markers that distinguish IgE- from IgG-mediated anaphylaxis. Proc Natl Acad Sci U S A 2011;108:12413-8.
38. Khodoun MV, Kucuk ZY, Strait RT, Krishnamurthy D, Janek K, Clay CD, et al. Rapid desensitization of mice with anti-FcgammaRIIb/FcgammaRIII mAb safely prevents IgG-mediated anaphylaxis. J Allergy Clin Immunol 2013;132:1375-87.
39. Finkelman FD, Rothenberg ME, Brandt EB, Morris SC, Strait RT. Molecular mechanisms of anaphylaxis: lessons from studies with murine models. J Allergy Clin Immunol 2005;115:449-58.
40. Finkelman FD. Anaphylaxis: lessons from mouse models. J Allergy Clin Immunol 2007;120:506-17.
41. Hirayama N, Hirano T, Kohler G, Kurata A, Okumura K, Ovary Z. Biological activities of antitrinitrophenyl and antidinitrophenyl mouse monoclonal antibodies. Proc Natl Acad Sci U S A 1982;79:613-5.
42. Grey HM, Hirst JW, Cohn M. A new mouse immunoglobulin: IgG3. J Exp Med 1971;133:289-304.
43. Brown SG, Stone SF, Fatovich DM, Burrows SA, Holdgate A, Celenza A, et al. Anaphylaxis: clinical patterns, mediator release, and severity. J Allergy Clin Immunol 2013;132:1141-9.e5.
44. Lepow IH, Willms-Kretschmer K, Patrick RA, Rosen FS. Gross and ultrastructural observations on lesions produced by intradermal injection of human C3a in man. Am J Pathol 1970;61:13-23.
45. Wuepper KD, Bokisch VA, Muller-Eberhard HJ, Stoughton RB. Cutaneous responses to human C 3 anaphylatoxin in man. Clin Exp Immunol 1972;11:13-20.
46. Yancey KB, Hammer CH, Harvath L, Renfer L, Frank MM, Lawley TJ. Studies of human C5a as a mediator of inflammation in normal human skin. J Clin Invest 1985;75:486-95.
47. Gorski JP, Hugli TE, Muller-Eberhard HJ. C4a: the third anaphylatoxin of the human complement system. Proc Natl Acad Sci U S A 1979;76:5299-302.
48. Schwartz LB. Diagnostic value of tryptase in anaphylaxis and mastocytosis. Immunol Allergy Clin North Am 2006;26:451-63.
49. Schwartz LB, Metcalfe DD, Miller JS, Earl H, Sullivan T. Tryptase levels as an indicator of mast-cell activation in systemic anaphylaxis and mastocytosis. N Engl J Med 1987;316:1622-6.
50. Stone SF, Cotterell C, Isbister GK, Holdgate A, Brown SG. Emergency Department Anaphylaxis Investigators. Elevated serum cytokines during human anaphylaxis: identification of potential mediators of acute allergic reactions. J Allergy Clin Immunol 2009;124:786-92.e4.
51. Vadas P, Perelman B, Liss G. Platelet-activating factor, histamine, and tryptase levels in human anaphylaxis. J Allergy Clin Immunol 2013;131:144-9.
52. Schuch A, Brockow K. Mastocytosis and Anaphylaxis. Immunol Allergy Clin North Am 2017;37:153-64.
53. Brockow K, Jofer C, Behrendt H, Ring J. Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. Allergy 2008;63:226-32.
54. Alvarez-Twose I, Vano-Galvan S, Sanchez-Munoz L, Morgado JM, Matito A, Torrelo A, et al. Increased serum baseline tryptase levels and extensive skin involvement are predictors for the severity of mast cell activation episodes in children with mastocytosis. Allergy 2012;67:813-21.
55. Sawaguchi M, Tanaka S, Nakatani Y, Harada Y, Mukai K, Matsunaga Y, et al. Role of mast cells and basophils in IgE responses and in allergic airway hyperresponsiveness. J Immunol 2012;188:1809-18.
56. Arias K, Chu DK, Flader K, Botelho F, Walker T, Arias N, et al. Distinct immune effector pathways contribute to the full expression of peanut-induced anaphylactic reactions in mice. J Allergy Clin Immunol 2011;127:1552-61.e1.
57. Burton OT, Noval Rivas M, Zhou JS, Logsdon SL, Darling AR, Koleoglou KJ, et al. Immunoglobulin E signal inhibition during allergen ingestion leads to reversal of established food allergy and induction of regulatory T cells. Immunity 2014;41:141-51.
58. Reber LL, Marichal T, Mukai K, Kita Y, Tokuoka SM, Roers A, et al. Selective ablation of mast cells or basophils reduces peanut-induced anaphylaxis in mice. J Allergy Clin Immunol 2013;132:881-8, e1-11.
59. Smit JJ, Willemsen K, Hassing I, Fiechter D, Storm G, van Bloois L, et al. Contribution of classic and alternative effector pathways in peanut-induced anaphylactic responses. PLoS One 2011;6:e28917.
60. Sun J, Arias K, Alvarez D, Fattouh R, Walker T, Goncharova S, et al. Impact of CD40 ligand, B cells, and mast cells in peanut-induced anaphylactic responses. J Immunol 2007;179:6696-703.
61. Jones SM, Pons L, Roberts JL, Scurlock AM, Perry TT, Kulis M, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. J Allergy Clin Immunol 2009;124:292-300, e1-97.
62. Giavina-Bianchi P, Galvao VR, Picard M, Caiado J, Castells MC. Basophil activation test is a relevant biomarker of the outcome of rapid desensitization in platinum compounds-allergy. J Allergy Clin Immunol Pract 2017;5:728-36.
63. Kim SY, Kim JH, Jang YS, Choi JH, Park S, Hwang YI, et al. The basophil activation test is safe and useful for confirming drug-induced anaphylaxis. Allergy Asthma Immunol Res 2016;8:541-4.
64. Santos AF, Du Toit G, Douiri A, Radulovic S, Stephens A, Turcanu V, et al. Distinct parameters of the basophil activation test reflect the severity and threshold of allergic reactions to peanut. J Allergy Clin Immunol 2015;135: 179-86.
65. Strait RT, Morris SC, Yang M, Qu XW, Finkelman FD. Pathways of anaphylaxis in the mouse. J Allergy Clin Immunol 2002;109:658-68.
66. Balbino B, Sibilano R, Starkl P, Marichal T, Gaudenzio N, Karasuyama H, et al. Pathways of immediate hypothermia and leukocyte infiltration in an adjuvant-free mouse model of anaphylaxis. J Allergy Clin Immunol 2017;139:584-96.e10.
67. Francis A, Bosio E, Stone SF, Fatovich DM, Arendts G, Nagree Y, et al. Neutrophil activation during acute human anaphylaxis: analysis of MPO and sCD62L. Clin Exp Allergy 2017;47:361-70.
68. Kasperska-Zajac A, Rogala B. Platelet function in anaphylaxis. J Investig Allergol Clin Immunol 2006;16:1-4.
69. Weiss JW, Drazen JM, Coles N, McFadden ER Jr, Weller PF, Corey EJ, et al. Bronchoconstrictor effects of leukotriene C in humans. Science 1982;216:196-8.
70. Weiss JW, Drazen JM, McFadden ER Jr, Weller P, Corey EJ, Lewis RA, et al. Airway constriction in normal humans produced by inhalation of leukotriene D. Potency, time course, and effect of aspirin therapy. JAMA 1983;249:2814-7.
71. Kaliner M, Sigler R, Summers R, Shelhamer JH. Effects of infused histamine: analysis of the effects of H-1 and H-2 histamine receptor antagonists on cardiovascular and pulmonary responses. J Allergy Clin Immunol 1981;68:365-71.
72. Vigorito C, Russo P, Picotti GB, Chiariello M, Poto S, Marone G. Cardiovascular effects of histamine infusion in man. J Cardiovasc Pharmacol 1983;5:531-7.

73. Sheikh A, Ten Broek V, Brown SG, Simons FE. H1-antihistamines for the treatment of anaphylaxis: Cochrane systematic review. Allergy 2007;62:830-7.
74. Archer CB, Page CP, Paul W, Morley J, MacDonald DM. Inflammatory characteristics of platelet activating factor (PAF-acether) in human skin. Br J Dermatol 1984;110:45-50.
75. Lai CK, Ollier S, Lau CK, Holgate ST. Effect of azelastine and ketotifen on the bronchial and skin responses to platelet-activating factor in humans. Clin Exp Allergy 1991;21:489-96.
76. Juhlin L, Pihl-Lundin I. Effects of antihistamines on cutaneous reactions and influx of eosinophils after local injection of PAF, kallikrein, compound 48/80 and histamine in patients with chronic urticaria and healthy subjects. Acta Derm Venereol 1992;72:197-200.
77. Vadas P, Gold M, Perelman B, Liss GM, Lack G, Blyth T, et al. Platelet-activating factor, PAF acetylhydrolase, and severe anaphylaxis. N Engl J Med 2008;358:28-35.
78. Austen KF. The cysteinyl leukotrienes: where do they come from? What are they? Where are they going? Nat Immunol 2008;9:113-5.
79. Higashi N, Mita H, Ono E, Fukutomi Y, Yamaguchi H, Kajiwara K, et al. Profile of eicosanoid generation in aspirin-intolerant asthma and anaphylaxis assessed by new biomarkers. J Allergy Clin Immunol 2010;125:1084-91.e6.
80. Ono E, Taniguchi M, Mita H, Fukutomi Y, Higashi N, Miyazaki E, et al. Increased production of cysteinyl leukotrienes and prostaglandin D2 during human anaphylaxis. Clin Exp Allergy 2009;39:72-80.
81. Denzlinger C, Haberl C, Wilmanns W. Cysteinyl leukotriene production in anaphylactic reactions. Int Arch Allergy Immunol 1995;108:158-64.
82. Soter NA, Lewis RA, Corey EJ, Austen KF. Local effects of synthetic leukotrienes (LTC4, LTD4, LTE4, and LTB4) in human skin. J Invest Dermatol 1983;80:115-9.
83. Kanaoka Y, Maekawa A, Penrose JF, Austen KF, Lam BK. Attenuated zymosan-induced peritoneal vascular permeability and IgE-dependent passive cutaneous anaphylaxis in mice lacking leukotriene C4 synthase. J Biol Chem 2001;276:22608-13.
84. Maekawa A, Austen KF, Kanaoka Y. Targeted gene disruption reveals the role of cysteinyl leukotriene 1 receptor in the enhanced vascular permeability of mice undergoing acute inflammatory responses. J Biol Chem 2002;277:20820-4.
85. Heijnen IA, van Vugt MJ, Fanger NA, Graziano RF, de Wit TP, Hofhuis FM, et al. Antigen targeting to myeloid-specific human Fc gamma RI/CD64 triggers enhanced antibody responses in transgenic mice. J Clin Invest 1996;97:331-8.
86. McKenzie SE, Taylor SM, Malladi P, Yuhan H, Cassel DL, Chien P, et al. The role of the human Fc receptor Fc gamma RIIA in the immune clearance of platelets: a transgenic mouse model. J Immunol 1999;162:4311-8.
87. Gillis CM, Jonsson F, Mancardi DA, Tu N, Beutier H, Van Rooijen N, et al. Mechanisms of anaphylaxis in human low-affinity IgG receptor locus knock-in mice. J Allergy Clin Immunol 2017;139:1253-65.e14.
88. Khodoun M, Strait R, Orekov T, Hogan S, Karasuyama H, Herbert DR, et al. Peanuts can contribute to anaphylactic shock by activating complement. J Allergy Clin Immunol 2009;123:342-51.
89. Nakamura T, Fujiwara Y, Yamada R, Fujii W, Hamabata T, Lee MY, et al. Mast cell–derived prostaglandin D2 attenuates anaphylactic reactions in mice. J Allergy Clin Immunol 2017 [Epub ahead of print].
90. Oettgen HC, Martin TR, Wynshaw-Boris A, Deng C, Drazen JM, Leder P. Active anaphylaxis in IgE-deficient mice. Nature 1994;370:367-70.
91. Dombrowicz D, Flamand V, Miyajima I, Ravetch JV, Galli SJ, Kinet JP. Absence of Fc epsilonRI alpha chain results in upregulation of Fc gammaRIII-dependent mast cell degranulation and anaphylaxis. Evidence of competition between Fc epsilonRI and Fc gammaRIII for limiting amounts of FcR beta and gamma chains. J Clin Invest 1997;99:915-25.
92. Cheifetz A, Smedley M, Martin S, Reiter M, Leone G, Mayer L, et al. The incidence and management of infusion reactions to infliximab: a large center experience. Am J Gastroenterol 2003;98:1315-24.
93. Baker DL, Nakamura GR, Lowman HB, Fischer SK. Evaluation of IgE antibodies to omalizumab (Xolair(R)) and their potential correlation to anaphylaxis. AAPS J 2016;18:115-23.
94. Price KS, Hamilton RG. Anaphylactoid reactions in two patients after omalizumab administration after successful long-term therapy. Allergy Asthma Proc 2007;28:313-9.
95. Kodama T, Sekine H, Takahashi M, Iwaki D, Machida T, Kanno K, et al. Role of complement in a murine model of peanut-induced anaphylaxis. Immunobiology 2013;218:844-50.
96. Schäfer B, Piliponsky AM, Oka T, Song CH, Gerard NP, Gerard C, et al. Mast cell anaphylatoxin receptor expression can enhance IgE-dependent skin inflammation in mice. J Allergy Clin Immunol 2013;131:541-8, e1-9.
97. Jiao D, Liu Y, Lu X, Liu B, Pan Q, Liu Y, et al. Macrophages are the dominant effector cells responsible for IgG-mediated passive systemic anaphylaxis challenged by natural protein antigen in BALB/c and C57BL/6 mice. Cell Immunol 2014;289:97-105.
98. Windbichler M, Echtenacher B, Takahashi K, Ezekowitz RA, Schwaeble WJ, Jenseniuis JC, et al. Investigations on the involvement of the lectin pathway of complement activation in anaphylaxis. Int Arch Allergy Immunol 2006;141:11-23.
99. Takeishi T, Martin TR, Katona IM, Finkelman FD, Galli SJ. Differences in the expression of the cardiopulmonary alterations associated with anti-immunoglobulin E-induced or active anaphylaxis in mast cell-deficient and normal mice. Mast cells are not required for the cardiopulmonary changes associated with certain fatal anaphylactic responses. J Clin Invest 1991;88:598-608.
100. Ohnmacht C, Schwartz C, Panzer M, Schiedewitz I, Naumann R, Voehringer D. Basophils orchestrate chronic allergic dermatitis and protective immunity against helminths. Immunity 2010;33:364-74.
101. Makabe-Kobayashi Y, Hori Y, Adachi T, Ishigaki-Suzuki S, Kikuchi Y, Kagaya Y, et al. The control effect of histamine on body temperature and respiratory function in IgE-dependent systemic anaphylaxis. J Allergy Clin Immunol 2002;110:298-303.
102. Wechsler JB, Schroeder HA, Byrne AJ, Chien KB, Bryce PJ. Anaphylactic responses to histamine in mice utilize both histamine receptors 1 and 2. Allergy 2013;68:1338-40.
103. Arias K, Baig M, Colangelo M, Chu D, Walker T, Goncharova S, et al. Concurrent blockade of platelet-activating factor and histamine prevents life-threatening peanut-induced anaphylactic reactions. J Allergy Clin Immunol 2009;124:307-14, e1-2.
104. Kelefiotis D, Vakirtzi-Lemonias C. In vivo responses of mouse blood cells to platelet-activating factor (PAF): role of the mediators of anaphylaxis. Agents Actions 1993;40:150-6.
105. Ishii S, Kuwaki T, Nagase T, Maki K, Tashiro F, Sunaga S, et al. Impaired anaphylactic responses with intact sensitivity to endotoxin in mice lacking a platelet-activating factor receptor. J Exp Med 1998;187:1779-88.
106. Oettgen HC. Fifty years later: Emerging functions of IgE antibodies in host defense, immune regulation, and allergic diseases. J Allergy Clin Immunol 2016;137:1631-45.
107. Dullaers M, De Bruyne R, Ramadani F, Gould HJ, Gevaert P, Lambrecht BN. The who, where, and when of IgE in allergic airway disease. J Allergy Clin Immunol 2012;129:635-45.
108. Gould HJ, Sutton BJ. IgE in allergy and asthma today. Nat Rev Immunol 2008;8:205-17.
109. Hamilton RG, MacGlashan DW Jr, Saini SS. IgE antibody-specific activity in human allergic disease. Immunol Res 2010;47:273-84.
110. Akin C. Mast cell activation syndromes. J Allergy Clin Immunol 2017;140:349-55.
111. Simons FE, Frew AJ, Ansotegui IJ, Bochner BS, Golden DB, Finkelman FD, et al. Risk assessment in anaphylaxis: current and future approaches. J Allergy Clin Immunol 2007;120(suppl):S2-24.
112. Sicherer SH, Sampson HA. Food allergy. J Allergy Clin Immunol 2010;125(suppl):S116-25.
113. Bilo BM, Bonifazi F. Epidemiology of insect-venom anaphylaxis. Curr Opin Allergy Clin Immunol 2008;8:330-7.
114. Sturm GJ, Heinemann A, Schuster C, Wiednig M, Groselj-Strele A, Sturm EM, et al. Influence of total IgE levels on the severity of sting reactions in Hymenoptera venom allergy. Allergy 2007;62:884-9.
115. Haftenberger M, Laussmann D, Ellert U, Kalcklosch M, Langen U, Schlaud M, et al. [Prevalence of sensitisation to aeraoallergens and food allergens: results of the German Health Interview and Examination Survey for Adults (DEGS1)]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2013;56:687-97.
116. Langen U, Schmitz R, Steppuhn H. [Prevalence of allergic diseases in Germany: results of the German Health Interview and Examination Survey for Adults (DEGS1)]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2013;56:698-706.
117. Bousquet J, Anto JM, Bachert C, Bousquet PJ, Colombo P, Crameri R, et al. Factors responsible for differences between asymptomatic subjects and patients presenting an IgE sensitization to allergens. A GA2LEN project. Allergy 2006;61:671-80.
118. Golden DB, Marsh DG, Kagey-Sobotka A, Freidhoff L, Szklo M, Valentine MD, et al. Epidemiology of insect venom sensitivity. JAMA 1989;262:240-4.
119. Nicolaou N, Poorafshar M, Murray C, Simpson A, Winell H, Kerry G, et al. Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics. J Allergy Clin Immunol 2010;125:191-7, e1-13.

120. Schafer T, Przybilla B. IgE antibodies to Hymenoptera venoms in the serum are common in the general population and are related to indications of atopy. Allergy 1996;51:372-7.
121. Sturm GJ, Kranzelbinder B, Schuster C, Sturm EM, Bokanovic D, Vollmann J, et al. Sensitization to Hymenoptera venoms is common, but systemic sting reactions are rare. J Allergy Clin Immunol 2014;133:1635-43.e1.
122. Hamilton RG. Allergic sensitization is a key risk factor for but not synonymous with allergic disease. J Allergy Clin Immunol 2014;134:360-1.
123. Warrington R. Lack of correlation between severity of clinical symptoms, skin test reactivity, and radioallergosorbent test results in venom-allergic patients. Allergy Asthma Clin Immunol 2006;2:62-7.
124. Strait RT, Morris SC, Finkelman FD. IgG-blocking antibodies inhibit IgE-mediated anaphylaxis in vivo through both antigen interception and Fc gamma RIIb cross-linking. J Clin Invest 2006;116:833-41.
125. Strait RT, Mahler A, Hogan S, Khodoun M, Shibuya A, Finkelman FD. Ingested allergens must be absorbed systemically to induce systemic anaphylaxis. J Allergy Clin Immunol 2011;127:982-9.e1.
126. Klos A, Tenner AJ, Johswich KO, Ager RR, Reis ES, Kohl J. The role of the anaphylatoxins in health and disease. Mol Immunol 2009;46:2753-66.
127. Smith PL, Kagey-Sobotka A, Bleecker ER, Traystman R, Kaplan AP, Gralnick H, et al. Physiologic manifestations of human anaphylaxis. J Clin Invest 1980;66:1072-80.
128. Voehringer D. Protective and pathological roles of mast cells and basophils. Nat Rev Immunol 2013;13:362-75.
129. Kalesnikoff J, Galli SJ. New developments in mast cell biology. Nat Immunol 2008;9:1215-23.
130. Abramson J, Pecht I. Regulation of the mast cell response to the type 1 Fc epsilon receptor. Immunol Rev 2007;217:231-54.
131. Reber LL, Frossard N. Targeting mast cells in inflammatory diseases. Pharmacol Ther 2014;142:416-35.
132. Turner H, Kinet JP. Signalling through the high-affinity IgE receptor Fc epsilonRI. Nature 1999;402:B24-30.
133. Rivera J, Fierro NA, Olivera A, Suzuki R. New insights on mast cell activation via the high affinity receptor for IgE. Adv Immunol 2008;98:85-120.
134. Schroeder JT. Basophils: emerging roles in the pathogenesis of allergic disease. Immunol Rev 2011;242:144-60.
135. Alcaniz L, Vega A, Chacon P, El Bekay R, Ventura I, Aroca R, et al. Histamine production by human neutrophils. FASEB J 2013;27:2902-10.
136. Xu X, Zhang D, Zhang H, Wolters PJ, Killeen NP, Sullivan BM, et al. Neutrophil histamine contributes to inflammation in mycoplasma pneumonia. J Exp Med 2006;203:2907-17.
137. De Schryver S, Halbrich M, Clarke A, La Vieille S, Eisman H, Alizadehfar R, et al. Tryptase levels in children presenting with anaphylaxis: temporal trends and associated factors. J Allergy Clin Immunol 2016;137:1138-42.
138. Valent P, Akin C, Hartmann K, Nilsson G, Reiter A, Hermine O, et al. Advances in the classification and treatment of mastocytosis: current status and outlook toward the future. Cancer Res 2017;77:1261-70.
139. Karasuyama H, Mukai K, Obata K, Tsujimura Y, Wada T. Nonredundant roles of basophils in immunity. Annu Rev Immunol 2011;29:45-69.
140. Bruhns P, Jonsson F. Mouse and human FcR effector functions. Immunol Rev 2015;268:25-51.
141. Guilliams M, Bruhns P, Saeys Y, Hammad H, Lambrecht BN. The function of Fcgamma receptors in dendritic cells and macrophages. Nat Rev Immunol 2014;14:94-108.
142. Bohlson SS, O'Conner SD, Hulsebus HJ, Ho MM, Fraser DA. Complement, c1q, and c1q-related molecules regulate macrophage polarization. Front Immunol 2014;5:402.
143. Jonsson F, Mancardi DA, Albanesi M, Bruhns P. Neutrophils in local and systemic antibody-dependent inflammatory and anaphylactic reactions. J Leukoc Biol 2013;94:643-56.
144. Gounni AS, Lamkhioued B, Koussih L, Ra C, Renzi PM, Hamid Q. Human neutrophils express the high-affinity receptor for immunoglobulin E (Fc epsilon RI): role in asthma. FASEB J 2001;15:940-9.
145. Klebanoff SJ. Myeloperoxidase: friend and foe. J Leukoc Biol 2005;77:598-625.
146. Joseph M, Gounni AS, Kusnierz JP, Vorng H, Sarfati M, Kinet JP, et al. Expression and functions of the high-affinity IgE receptor on human platelets and megakaryocyte precursors. Eur J Immunol 1997;27:2212-8.
147. Hasegawa S, Pawankar R, Suzuki K, Nakahata T, Furukawa S, Okumura K, et al. Functional expression of the high affinity receptor for IgE (FcepsilonRI) in human platelets and its' intracellular expression in human megakaryocytes. Blood 1999;93:2543-51.
148. Capron A, Joseph M, Ameisen JC, Capron M, Pancre V, Auriault C. Platelets as effectors in immune and hypersensitivity reactions. Int Arch Allergy Appl Immunol 1987;82:307-12.
149. Mukai K, Gaudenzio N, Gupta S, Vivanco N, Bendall SC, Maecker HT, et al. Assessing basophil activation by using flow cytometry and mass cytometry in blood stored 24 hours before analysis. J Allergy Clin Immunol 2017;139:889-99.e11.
150. Tordesillas L, Rahman AH, Hartmann BM, Sampson HA, Berin MC. Mass cytometry profiling the response of basophils and the complete peripheral blood compartment to peanut. J Allergy Clin Immunol 2016;138:1741-4.e9.
151. MacGlashan D Jr. Histamine: a mediator of inflammation. J Allergy Clin Immunol 2003;112(suppl):S53-9.
152. Gill P, Jindal NL, Jagdis A, Vadas P. Platelets in the immune response: revisiting platelet-activating factor in anaphylaxis. J Allergy Clin Immunol 2015;135:1424-32.
153. Triggiani M, Schleimer RP, Warner JA, Chilton FH. Differential synthesis of 1-acyl-2-acetyl-sn-glycero-3-phosphocholine and platelet-activating factor by human inflammatory cells. J Immunol 1991;147:660-6.
154. Jonsson F, Mancardi DA, Zhao W, Kita Y, Iannascoli B, Khun H, et al. Human FcgammaRIIA induces anaphylactic and allergic reactions. Blood 2012;119:2533-44.
155. Kajiwara N, Sasaki T, Bradding P, Cruse G, Sagara H, Ohmori K, et al. Activation of human mast cells through the platelet-activating factor receptor. J Allergy Clin Immunol 2010;125:1137-45.e6.
156. Krause K, Gimenez-Arnau A, Martinez-Escala E, Farre-Albadalejo M, Abajian M, Church MK, et al. Platelet-activating factor (PAF) induces wheal and flare skin reactions independent of mast cell degranulation. Allergy 2013;68:256-8.
157. Peters-Golden M, Gleason MM, Togias A. Cysteinyl leukotrienes: multifunctional mediators in allergic rhinitis. Clin Exp Allergy 2006;36:689-703.
158. Lessof MH, Youlten LJ, Heavey D, Kemeny DM, Dollery C. Local mediator release in bee venom anaphylaxis. Clin Exp Allergy 1989;19:231-2.
159. Korosec P, Turner PJ, Silar M, Kopac P, Kosnik M, Gibbs BF, et al. Basophils, high-affinity IgE receptors, and CCL2 in human anaphylaxis. J Allergy Clin Immunol 2017 [Epub ahead of print].
160. van der Linden PW, Hack CE, Poortman J, Vivie-Kipp YC, Struyvenberg A, van der Zwan JK. Insect-sting challenge in 138 patients: relation between clinical severity of anaphylaxis and mast cell activation. J Allergy Clin Immunol 1992;90:110-8.
161. van der Linden PW, Hack CE, Eerenberg AJ, Struyvenberg A, van der Zwan JK. Activation of the contact system in insect-sting anaphylaxis: association with the development of angioedema and shock. Blood 1993;82:1732-9.
162. Sala-Cunill A, Bjorkqvist J, Senter R, Guilarte M, Cardona V, Labrador M, et al. Plasma contact system activation drives anaphylaxis in severe mast cell-mediated allergic reactions. J Allergy Clin Immunol 2015;135:1031-43.e6.
163. Pumphrey RS. Fatal anaphylaxis in the UK, 1992-2001. Novartis Found Symp 2004;257:116-28, discussion 28-32, 57-60, 276-85.
164. Lieberman P. Biphasic anaphylactic reactions. Ann Allergy Asthma Immunol 2005;95:217-26, 258.
165. Kalesnikoff J, Galli SJ. Anaphylaxis: mechanisms of mast cell activation. Chem Immunol Allergy 2010;95:45-66.
166. Dombrowicz D, Brini AT, Flamand V, Hicks E, Snouwaert JN, Kinet JP, et al. Anaphylaxis mediated through a humanized high affinity IgE receptor. J Immunol 1996;157:1645-51.
167. Dombrowicz D, Lin S, Flamand V, Brini AT, Koller BH, Kinet JP. Allergy-associated FcRbeta is a molecular amplifier of IgE- and IgG-mediated in vivo responses. Immunity 1998;8:517-29.
168. Mancardi DA, Iannascoli B, Hoos S, England P, Daeron M, Bruhns P. FcgammaRIV is a mouse IgE receptor that resembles macrophage FcepsilonRI in humans and promotes IgE-induced lung inflammation. J Clin Invest 2008;118:3738-50.
169. Fung-Leung WP, De Sousa-Hitzler J, Ishaque A, Zhou L, Pang J, Ngo K, et al. Transgenic mice expressing the human high-affinity immunoglobulin (Ig) E receptor alpha chain respond to human IgE in mast cell degranulation and in allergic reactions. J Exp Med 1996;183:49-56.
170. Liu Y, Sun Y, Chang LJ, Li N, Li H, Yu Y, et al. Blockade of peanut allergy with a novel Ara h 2-Fcgamma fusion protein in mice. J Allergy Clin Immunol 2013;131:213-21, e1-5.
171. Mancardi DA, Albanesi M, Jonsson F, Iannascoli B, Van Rooijen N, Kang X, et al. The high-affinity human IgG receptor FcgammaRI (CD64) promotes IgG-mediated inflammation, anaphylaxis, and antitumor immunotherapy. Blood 2013;121:1563-73.
172. Burton OT, Stranks AJ, Tamayo JM, Koleoglou KJ, Schwartz LB, Oettgen HC. A humanized mouse model of anaphylactic peanut allergy. J Allergy Clin Immunol 2017;139:314-22.e9.
173. Pagovich OE, Wang B, Chiuchiolo MJ, Kaminsky SM, Sondhi D, Jose CL, et al. Anti-hIgE gene therapy of peanut-induced anaphylaxis in a humanized murine model of peanut allergy. J Allergy Clin Immunol 2016;138:1652-62.e7.

174. Bryce PJ, Falahati R, Kenney LL, Leung J, Bebbington C, Tomasevic N, et al. Humanized mouse model of mast cell-mediated passive cutaneous anaphylaxis and passive systemic anaphylaxis. J Allergy Clin Immunol 2016; 138:769-79.
175. Yamashita Y, Charles N, Furumoto Y, Odom S, Yamashita T, Gilfillan AM, et al. Cutting edge: genetic variation influences Fc epsilonRI-induced mast cell activation and allergic responses. J Immunol 2007;179:740-3.
176. Mahdavinia M, Fox SR, Smith BM, James C, Palmisano EL, Mohammed A, et al. Racial differences in food allergy phenotype and health care utilization among US children. J Allergy Clin Immunol Pract 2017;5:352-7.e1.
177. Buka RJ, Crossman RJ, Melchior CL, Huissoon AP, Hackett S, Dorrian S, et al. Anaphylaxis and ethnicity: higher incidence in British South Asians. Allergy 2015;70:1580-7.
178. Apter AJ, Schelleman H, Walker A, Addya K, Rebbeck T. Clinical and genetic risk factors of self-reported penicillin allergy. J Allergy Clin Immunol 2008; 122:152-8.
179. Guglielmi L, Fontaine C, Gougat C, Avinens O, Eliaou JF, Guglielmi P, et al. IL-10 promoter and IL4-Ralpha gene SNPs are associated with immediate beta-lactam allergy in atopic women. Allergy 2006;61:921-7.
180. Brown RH, Hamilton RG, Mintz M, Jedlicka AE, Scott AL, Kleeberger SR. Genetic predisposition to latex allergy: role of interleukin 13 and interleukin 18. Anesthesiology 2005;102:496-502.
181. Karasawa K, Harada A, Satoh N, Inoue K, Setaka M. Plasma platelet activating factor-acetylhydrolase (PAF-AH). Prog Lipid Res 2003;42:93-114.
182. Niedoszytko M, Ratajska M, Chelminska M, Makowiecki M, Malek E, Sieminska A, et al. The angiotensinogen AGT p.M235T gene polymorphism may be responsible for the development of severe anaphylactic reactions to insect venom allergens. Int Arch Allergy Immunol 2010;153:166-72.
183. Summers CW, Pumphrey RS, Woods CN, McDowell G, Pemberton PW Arkwright PD. Factors predicting anaphylaxis to peanuts and tree nuts in patients referred to a specialist center. J Allergy Clin Immunol 2008;121:632-8.e2.
184. Nagata H, Worobec AS, Oh CK, Chowdhury BA, Tannenbaum S, Suzuki Y, et al. Identification of a point mutation in the catalytic domain of the protooncogene c-kit in peripheral blood mononuclear cells of patients who have mastocytosis with an associated hematologic disorder. Proc Natl Acad Sci U S A 1995;92:10560-4.
185. Gulen T, Ljung C, Nilsson G, Akin C. Risk factor analysis of anaphylactic reactions in patients with systemic mastocytosis. J Allergy Clin Immunol Pract 2017 [Epub ahead of print].
186. Akin C, Scott LM, Kocabas CN, Kushnir-Sukhov N, Brittain E, Noel P, et al. Demonstration of an aberrant mast-cell population with clonal markers in a subset of patients with "idiopathic" anaphylaxis. Blood 2007;110:2331-3.
187. Siegel AM, Stone KD, Cruse G, Lawrence MG, Olivera A, Jung MY, et al. Diminished allergic disease in patients with STAT3 mutations reveals a role for STAT3 signaling in mast cell degranulation. J Allergy Clin Immunol 2013;132: 1388-96.
188. Hox V, O'Connell MP, Lyons JJ, Sackstein P, Dimaggio T, Jones N, et al. Diminution of signal transducer and activator of transcription 3 signaling inhibits vascular permeability and anaphylaxis. J Allergy Clin Immunol 2016;138:187-99.
189. Webb LM, Lieberman P. Anaphylaxis: a review of 601 cases. Ann Allergy Asthma Immunol 2006;97:39-43.
190. Worm M, Edenharter G, Ruëff F, Scherer K, Pföhler C, Mahler V, et al. Symptom profile and risk factors of anaphylaxis in Central Europe. Allergy 2012;67:691-8.
191. Hox V, Desai A, Bandara G, Gilfillan AM, Metcalfe DD, Olivera A. Estrogen increases the severity of anaphylaxis in female mice through enhanced endothelial nitric oxide synthase expression and nitric oxide production. J Allergy Clin Immunol 2015;135:729-36.e5.
192. Francuzik W, Nassiri M, Babina M, Worm M. Impact of sex on anaphylaxis severity—data from the Anaphylaxis Registry. J Allergy Clin Immunol 2015; 136:1425-6.
193. Piper PJ, Collier HO. Release of catecholamines in the guinea-pig by substances involved in anaphylaxis. Nature 1967;213:838-40.
194. van der Linden PW, Struyvenberg A, Kraaijenhagen RJ, Hack CE, van der Zwan JK. Anaphylactic shock after insect-sting challenge in 138 persons with a previous insect-sting reaction. Ann Intern Med 1993;118:161-8.
195. Zhang W, Shibamoto T, Kurata Y, Kohno H. Effects of β-adrenoceptor antagonists on anaphylactic hypotension in conscious rats. Eur J Pharmacol 2011;650: 303-8.
196. Awai LE, Mekori YA. Insect sting anaphylaxis and beta-adrenergic blockade: a relative contraindication. Ann Allergy 1984;53:48-9.
197. Jacobs RL, Rake GW Jr, Fournier DC, Chilton RJ, Culver WG, Beckmann CH. Potentiated anaphylaxis in patients with drug-induced beta-adrenergic blockade. J Allergy Clin Immunol 1981;68:125-7.
198. Lang DM. Anaphylactoid and anaphylactic reactions. Hazards of beta-blockers. Drug Safety 1995;12:299-304.
199. Lee S, Hess EP, Nestler DM, Bellamkonda Athmaram VR, Bellolio MR, Decker WW, et al. Antihypertensive medication use is associated with increased organ system involvement and hospitalization in emergency department patients with anaphylaxis. J Clin Allergy Immunol 2013;131:1103-8.
200. Nassiri M, Babina M, Dölle S, Edenharter G, Ruëff F, Worm M. Ramipril and metoprolol intake aggravate human and murine anaphylaxis: evidence for direct mast cell priming. J Allergy Clin Immunol 2015;135:491-9.
201. Li M, Liu K, Michalicek J, Angus JA, Hunt JE, Dell'Italia LJ, et al. Involvement of chymase-mediated angiotensin II generation in blood pressure regulation. J Clin Invest 2004;114:112-20.
202. Olivera A, Mizugishi K, Tikhonova A, Ciaccia L, Odom S, Proia RL, Rivera J. The sphingosine kinase-sphingosine-1-phosphate axis is a determinant of mast cell function and anaphylaxis. Immunity 2007;26:287-97.
203. Olivera A, Eisner C, Kitamura Y, Dillahunt S, Allende L, Tuymetova G, et al. Sphingosine kinase 1 and sphingosine-1 phosphate receptor 2 are vital to recovery from anaphylactic shock in mice. J Clin Invest 2010;120:1429-40.
204. Marichal T, Starkl P, Reber LL, Kalesnikoff J, Oettgen HC, Tsai M, et al. A beneficial role for immunoglobulin E in host defense against honeybee venom. Immunity 2013;39:963-75.
205. Palm NW, Rosenstein RK, Yu S, Schenten DD, Florsheim E, Medzhitov R. Bee venom phospholipase A2 induces a primary type 2 response that is dependent on the receptor ST2 and confers protective immunity. Immunity 2013;39:976-85.
206. Starkl P, Marichal T, Gaudenzio N, Reber LL, Sibilano R, Tsai M, et al. IgE antibodies, FcepsilonRIalpha, and IgE-mediated local anaphylaxis can limit snake venom toxicity. J Allergy Clin Immunol 2016;137:246-57.e11.
207. Akahoshi M, Song CH, Piliponsky AM, Metz M, Guzzetta A, Abrink M, et al. Mast cell chymase reduces the toxicity of Gila monster venom, scorpion venom, and vasoactive intestinal polypeptide in mice. J Clin Invest 2011;121:4180-91.
208. Metz M, Piliponsky AM, Chen CC, Lammel V, Abrink M, Pejler G, et al. Mast cells can enhance resistance to snake and honeybee venoms. Science 2006;313: 526-30.
209. Schneider LA, Schlenner SM, Feyerabend TB, Wunderlin M, Rodewald HR. Molecular mechanism of mast cell mediated innate defense against endothelin and snake venom sarafotoxin. J Exp Med 2007;204:2629-39.