

Molecular mechanisms in allergy and clinical immunology

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Anaphylaxis: Lessons from mouse models

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Studies with mouse models demonstrate 2 pathways of systemic anaphylaxis: a *classic pathway* mediated by IgE, FcεRI, mast cells, histamine, and platelet-activating factor (PAF) and an *alternative pathway* mediated by IgG, FcγRIII, macrophages, and PAF. The former pathway requires much less antigen and antibody than the latter. This is modified, however, by IgG antibodies that prevent IgE-mediated anaphylaxis by intercepting antigen before it binds to mast cell-associated IgE. Consequently, IgG antibodies block systemic anaphylaxis induced by small quantities of antigen but mediate systemic anaphylaxis induced by larger quantities. The importance of the alternative pathway in human subjects is unknown, but human IgG, IgG receptors, macrophages, mediators, and mediator receptors have appropriate properties to support this pathway if sufficient IgG and antigen are present. The severity of systemic anaphylaxis is increased by nitric oxide produced by the enzyme endothelial nitric oxide synthase and by the cytokines IL-4 and IL-13 and decreased by endogenous β-adrenergic stimulation and receptors that contain ITIM that bind tyrosine phosphatases. Anaphylaxis is also suppressed by other receptors and ion channels that function through distinct mechanisms. Unlike systemic anaphylaxis, intestinal anaphylaxis (allergic diarrhea) is almost totally IgE and mast cell dependent and is mediated predominantly by PAF and serotonin. Some potent food allergens, including peanuts and tree nuts, can directly enhance anaphylaxis by stimulating an anaphylactoid response through the innate immune system. Results of these studies suggest novel prophylactic agents, including nonstimulatory anti-IgE mAbs, IL-4 receptor antagonists, PAF antagonists, and agents that cross-link FcεRI

or FcγRIII to an ITIM-containing inhibitory receptor. (*J Allergy Clin Immunol* 2007;120:506-15.)

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Anaphylactic responses to insect stings, injected medications, foods, and other agents remain substantial problems and are increasing in frequency.^{1,2} Unfortunately, prophylaxis and treatment have advanced little in recent years and remain limited to avoidance, allergen desensitization therapy, and medications, including antihistamines, epinephrine, and intravenous fluids. In response, considerable effort is being made to better understand the mechanisms responsible for anaphylaxis and test potential novel therapies. Much of this effort has been directed toward the development and analysis of models in laboratory animals, especially mice. Such approaches have tremendous advantages, including economy and the availability of genetically inbred strains, animals that overexpress or delete a specific gene, and mAbs that promote or suppress a specific molecular pathway. Results obtained with animal models, however, are not necessarily applicable to human subjects. This article will review the results of studies of anaphylaxis with mouse models and provide a framework for considering their applicability to human disease. Key concepts of this review are listed in Table I.

TWO PATHWAYS OF MURINE SYSTEMIC ANAPHYLAXIS

Central to all studies of anaphylaxis in the mouse is the observation that systemic anaphylaxis (rapid and potentially reversible hypotension, hypothermia, decreased mobility, and scratching) can be mediated by 2 independent mechanisms.³ One, which I refer to as the *classic pathway*, involves mast cells sensitized by IgE antibodies bound to FcεRI. Antigen-induced cross-linking of mast cell-associated IgE leads rapidly to mast cell degranulation with release of mediators and enzymes, such as the mucosal mast cell granule-specific β-chymase mouse mast cell protease 1 (MMCP1).³⁻⁶ Histamine is primarily responsible for the development of shock (detected as

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Abbreviations used

gp49B1:	Glycoprotein 49B1
ITAM:	Intracellular immunoreceptor tyrosine-based activation motifs
ITIM:	Intracellular immunoreceptor tyrosine-based inhibition motif
MAFA:	Mast cell function-associated antigen
MMCP1:	Mouse mast cell protease 1
OVA:	Chicken ovalbumin
PAF:	Platelet-activating factor
PCA:	Passive cutaneous anaphylaxis
PECAM-1:	Platelet/endothelial cell adhesion molecule-1
PIR:	Paired immunoglobulin-like receptor
SHIP:	Src homology 2-containing inositol phosphatase
SHP:	Src homology 2-containing tyrosine phosphatase
STAT:	Signal transducer and activator of transcription
TRPM4:	Transient receptor potential cation channel, subfamily M, member 4

hypothermia), although platelet-activating factor (PAF) also contributes.³ This mechanism of anaphylaxis can be modeled by injecting mice with an mAb, such as EM-95, that cross-links mast cell-associated IgE.³

Systemic anaphylaxis that closely resembles IgE/FcεRI/mast cell-mediated shock is also induced in mice through an *alternative pathway* that is mediated by IgG antibodies, the activating low-affinity IgG receptor FcγRIII, and macrophages.^{3,7-10} PAF, rather than histamine, is primarily responsible for the development of shock in this system.¹¹ Although IgG antibody-dependent complement activation can produce anaphylatoxins, including C3a and C5a, these do not appear to be important in the IgG-mediated alternative pathway.^{3,12} The alternative pathway can be modeled by injecting mice with an mAb, 2.4G2, that cross-links FcγRIII on macrophages.³ Although 2.4G2 also binds to an inhibitory IgG receptor, FcγRIIb, 2.4G2-induced inhibitory effects on macrophages are outweighed by the stimulatory effects, presumably because mouse macrophages generally express considerably more FcγRIII than FcγRIIb.¹³⁻¹⁵

Evidence for the existence of these 2 independent pathways of anaphylaxis comes from multiple studies performed over several years by many investigators. Demonstration of anaphylaxis in mice that lacked mast cells (c-kit-deficient W/W^v mice),¹⁶ FcεRI,¹⁷ or IgE¹² provided evidence for the existence of an alternative pathway. Studies with FcγRIII-deficient,¹⁴ FcRγ-deficient,¹⁸ and FcεRIα-deficient¹⁷ mice demonstrated that FcγRIII is required for the alternative pathway but not the classic pathway, that FcεRIα is required for the classic pathway but not the alternative pathway, and that FcRγ (which combines with both FcεRIα and FcγRIII and is required for signaling by ligands bound to both receptors) is required for both pathways.^{14,17,18} Studies with 2.4G2 and anti-IgE mAb (EM-95) demonstrated that the former mAb blocks antigen induction of the alternative, but not the classic, pathway, whereas EM-95 has the opposite

effect.³ The importance of mast cells in the classic, but not the alternative, pathway was demonstrated by studies with W/W^v mice,^{16,19} whereas the importance of macrophages in the alternative, but not the classic, pathway was demonstrated by studies that killed or desensitized macrophages with gadolinium, a rare earth metal that is used at a lower dose as a contrast agent for magnetic resonance imaging.^{3,7,8} Differences in mediator involvement in the 2 pathways were established by studies that demonstrated partial suppression of anti-IgE mAb-induced anaphylaxis with an antihistamine, more complete suppression of anti-IgE mAb-induced anaphylaxis with a combination of antihistamine plus PAF antagonist, and nearly complete inhibition of 2.4G2-induced anaphylaxis with a PAF antagonist.³ The 2 pathways of anaphylaxis and some of the receptors that regulate mast cell and macrophage participation in anaphylaxis (see below) are diagrammed in Fig 1.

Although clinical features of the 2 pathways of murine anaphylaxis closely resemble each other, and anaphylaxis induced by one pathway desensitizes the induction of shock through the other pathway for a few hours,³ there are some important differences. Tachycardia is more prominent when anaphylaxis is induced in mast cell-sufficient than in mast cell-deficient mice^{14,19} and hence is most likely dependent on IgE and histamine. This might reflect the ability of PAF, the primary mediator of the alternative pathway, to decrease myocardial function.²⁰ The classic and alternative pathways differ even more importantly in the antibody and antigen concentrations that are required to induce anaphylaxis. Induction of hypothermia through the alternative pathway requires approximately 100-fold more antigen than induction of a similar response through the classic pathway.⁴ Anaphylaxis mediated through the alternative pathway also appears to require much more antibody than anaphylaxis mediated through the classic pathway. IgE-mediated anaphylaxis can be seen when IgE levels are so low that IgE, although present on mast cells, is undetectable in serum.²¹ In contrast, relatively high levels of serum IgG antibody are required for antigen induction of anaphylaxis through the IgG/FcγRIII/macrophage pathway.⁴ These differences are consistent with the much higher affinity of FcεRI for IgE than FcγRIII for IgG^{22,23} and with the direct binding of antigen to mast cell-associated IgE, whereas antigen/IgG complexes presumably form in blood and lymph before binding to FcγRIII.

These differences in required antigen and antibody concentrations and the tendency to generate much larger IgG than IgE responses have important consequences for the induction and prevention of systemic anaphylaxis. Although much less antigen is required to trigger the classic pathway in the presence of antigen-specific IgE and the absence of antigen-specific IgG than is required to trigger the alternative pathway when antigen-specific IgG is present, responses are dramatically altered in the common situation when antigen-specific IgE and IgG are both present and there is more IgG than IgE. In this latter situation, antigen is likely to encounter IgG in blood or lymph before it can bind to mast cell-associated IgE.

TABLE I. Key concepts

1. Anaphylaxis in the mouse can occur through 2 independent pathways: one that involves IgE, FcεRI, mast cells, PAF, and histamine and the other that involves IgG, FcγRIII, macrophages, and PAF.
2. Considerably less antibody and antigen are required to trigger IgE-dependent anaphylaxis than IgG-mediated anaphylaxis, provided that IgG antibodies are insufficient to block antigen binding to mast cell-associated IgE.
3. Most human anaphylaxis is probably IgE dependent because it involves small quantities of antigen, but there is some evidence that human anaphylaxis can be IgG mediated when induced by large quantities of antigen.
4. Mast cell degranulation can be inhibited by cross-linking FcεRI to an ITIM-containing cell membrane receptor.
5. Anaphylaxis is promoted by endogenously produced IL-4, IL-13, and nitric oxide and inhibited by endogenously produced β-adrenergic agonists. These agents act distally to mast cell and macrophage activation.
6. Gastrointestinal anaphylaxis is induced by an IgE/FcεRI/mast cell/PAF plus serotonin pathway.
7. Peanut and tree nut proteins can induce a C3-dependent anaphylactoid response that can synergize with IgE-induced mast cell activation to exacerbate anaphylaxis.
8. The murine and human immune systems are sufficiently similar that these observations about murine anaphylaxis are likely to apply to human subjects.

As a result, antigen-specific IgG can block IgE-mediated anaphylaxis.⁴ Consequently, when antigen levels are insufficient to induce IgG-mediated anaphylaxis, high levels of IgG antibodies can prevent the development of any anaphylactic response.⁴ For a similar reason, larger amounts of antigen trigger anaphylaxis predominantly through the alternative pathway when antigen-specific IgG antibody levels are high, even though antigen-specific IgE is present.⁴ In this situation the 2 anaphylaxis pathways will be triggered simultaneously only when the amount of challenge antigen exceeds the capacity of IgG antibody to block antigen binding to mast cell-associated IgE.⁴

Differences in the reported relative importance of IgE-dependent and independent pathways of anaphylaxis, which abound in the literature, thus likely result from differences in the characteristics and relative amounts of antigen used to induce an antibody response and the amounts of antigen used to trigger anaphylaxis. A very potent antigen, such as goat anti-IgD antiserum, primes for anaphylaxis that is induced almost entirely through the alternative pathway unless milligram quantities of the relevant allergen (goat IgG) are used for the challenge.⁴ In contrast, mice primed with penicillin conjugated to ovalbumin have an IgE-dependent anaphylactic response to penicillin,²⁴ and mice primed by multiple injections of an insulin-derived peptide exhibit evidence of both the classic and alternative pathways of anaphylaxis.²⁵

PHYSIOLOGIC AND PHARMACOLOGIC MODULATORS OF SYSTEMIC ANAPHYLAXIS

The most direct determinants of anaphylaxis induction and severity are the extent and rapidity of cross-linking of mast cell FcεRI and macrophage FcγRIII. These are influenced by antigen dose, speed of antigen access to the circulation (ie, route of antigen administration), concentration of IgE and IgG antibody, antibody affinity, number and activation state of mast cells and macrophages, and density of mast cell FcεRI and macrophage FcγRIII. Multiple additional factors, however, can act at several levels to modulate anaphylaxis induction. FcεRI and

FcγRIII stimulate mast cells and macrophages, respectively, by activating cell-associated tyrosine kinases (which activate signaling proteins by phosphorylating their tyrosine residues) through ITAMs that are located on intracytoplasmic domains of the FcRs (to increase readability, acronyms are used in place of the full names of several protein motifs, signaling molecules, receptors, and protein channels throughout this paper; the full names are provided in the abbreviations list).^{15,22} Because this FcR-induced activation of mast cells and macrophages is mediated by tyrosine phosphorylation, other receptors that include intracellular immunoreceptor tyrosine-based inhibition motifs (ITIMs) that activate the SHP1 and SHP2 (which inactivate signaling proteins by dephosphorylating their tyrosine residues), SHIP (which inactivates inositol-based signaling molecules by dephosphorylating them), or both can suppress both pathways of anaphylaxis. The best studied of these is the ITIM-containing inhibitory IgG receptor FcγRIIb, which is present on both mast cells and macrophages and has some capacity to bind both IgE and IgG.^{13,26} Both pathways of anaphylaxis are exacerbated in mice deficient in FcγRIIb, regardless of whether anaphylaxis is induced by means of active immunization (induction of antibody through antigen stimulation) or passive immunization (injection of mice with antigen-specific IgE or IgG antibodies before antigen challenge).¹³ As a result, agents such as cytokines and immune complexes, which modify the ratio of FcγRIIb to FcγRIII or FcεRI, can influence anaphylaxis severity and development.

FcγRIIb is only one example of an ITIM-associated receptor that can negatively regulate cellular activation; others that appear to regulate mast cell activation include CD300a,²⁷ PIR-B,²⁸ PECAM-1,²⁹ the c-lectin MAFA,³⁰ and gp49B1.³¹ Some of these receptors, such as PIR-B, which binds to MHC class I molecules,³² appear to regulate basal levels of mast cell activation,²⁸ whereas others might act like FcγRIIb to downmodulate antigen-induced mast cell activation. PIR-B is also expressed on macrophages, where it also appears to regulate basal activation.³² Better understanding of how some of these receptors regulate mast cell activation awaits identification of their natural ligands.

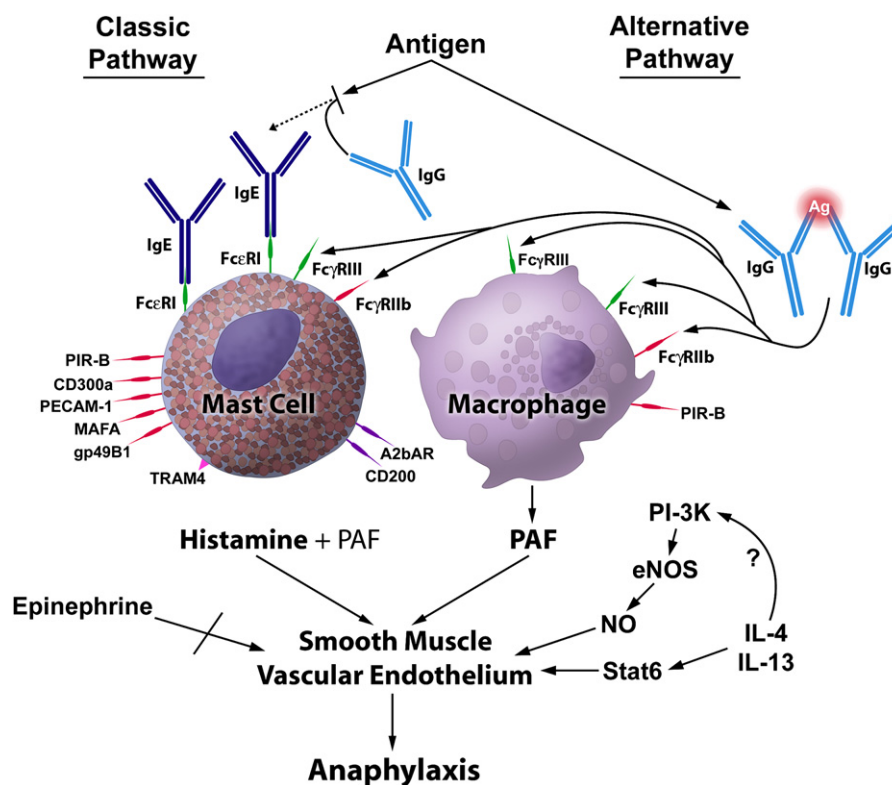


FIG 1. Mechanisms of murine anaphylaxis. Antigen (Ag) can cause systemic anaphylaxis in mice through (1) the classic pathway by cross-linking IgE bound to mast cell FcεRI, stimulating histamine and PAF release, or (2) the alternative pathway by forming complexes with IgG that cross-link macrophage FcγRIII, stimulating PAF release. PAF and histamine cause the symptoms of anaphylaxis predominantly by inducing smooth muscle contraction and increased vascular permeability. Stimuli that induce mast cell and macrophage activation are mediated by receptors (shown in *green*) that include ITAMs, and receptors (shown in *red*) that contain ITIMs can suppress mast cell and macrophage activation. Suppressive receptors that do not work through ITIMs are shown in *purple*, and a suppressive ion channel is shown in *pink*. Anaphylaxis can be exacerbated at the target cell level by nitric oxide (NO) produced by the enzyme endothelial nitric oxide synthase (eNOS) and by IL-4 and IL-13, which act through a signal transducer and activator of transcription 6 (STAT6)-dependent pathway to increase the sensitivity of target cells to vasoactive mediators and might act through a phosphatidyl inositol-3 kinase (PI-3K)-dependent pathway to induce endothelial nitric oxide synthase. Figure adapted and updated from Finkelman et al⁶¹ with permission.

Not all inhibitory receptors on mast cells or macrophages contain ITIMs. The mast cell receptor for the glycoprotein CD200, for example, is still able to inhibit FcεRI-mediated mast cell activation by binding SHIP1 and inhibiting the Ras/mitogen-activated protein kinase pathways of cellular activation.³³ Other mast cell-associated negative modulations of degranulation include the A2b adenosine receptor³⁴ and the TRPM4 ion channel.³⁵ Undoubtedly, further studies of mast cell and macrophage activation by immunoglobulin receptors will reveal additional regulatory receptors and pathways.

Both the classic and alternative pathways of anaphylaxis are also regulated by agents that modify responsiveness to the mediators released by macrophages and mast cells. Nitric oxide, produced by endothelial nitric oxide synthase activated through the phosphatidyl inositol-3 kinase/Akt pathway,³⁶ increases susceptibility to anaphylaxis by promoting vasodilatation and increasing vascular

permeability.³⁷ IL-4 and IL-13, which are produced by T cells and basophils³⁸ and activate phosphatidyl inositol-3 kinase in several cell types through the type 1 and type 2 IL-4 receptors,³⁹ also act through IL-4 receptors to activate the transcription factor STAT6,⁴⁰ which increase responsiveness to several mast cell- and macrophage-generated mediators, including histamine, PAF, serotonin, and leukotriene C₄.⁴¹ Both endothelial nitric oxide synthase and IL-4/IL-13 exacerbation of anaphylaxis occur under physiologic conditions.^{37,41} The response to vasoactive mediators is also regulated through cardiovascular β-adrenergic receptors, which normally increase myocardial contractility and vascular tone to compensate for the decreased intravascular volume, vasodilatation, and myocardial depression that are induced by PAF and histamine.⁴² Consequently, physiologic and pharmacologic β-adrenergic agonists ameliorate anaphylaxis,⁴³ whereas β-adrenergic blockers can exacerbate this disorder.⁴⁴ The severity of anaphylaxis might similarly be modified

by expression of different β -adrenergic receptor alleles, which encode receptors that vary in their response to β -adrenergic agonists.⁴⁵

MOUSE MODELS OF INTESTINAL ANAPHYLAXIS

Allergen ingestion can induce the shock syndrome characterized as systemic anaphylaxis but more commonly induces gastrointestinal symptoms, such as diarrhea.^{1,46,47} Three experimental mouse models of intestinal anaphylaxis have been described: one in which mice are sensitized by ingestion of an allergen, such as peanut extract, with cholera toxin⁴⁸; one in which mice are sensitized by means of intraperitoneal injection of chicken ovalbumin (OVA) with the adjuvant alum (aluminum hydroxide)⁴⁹; and one in which mice are sensitized by means of transdermal immunization with a hazelnut extract.⁵⁰ Oral challenge with the appropriate allergen induces diarrhea in the OVA/alum model and can induce both diarrhea and shock in the peanut extract/cholera toxin and transdermal hazelnut models, although systemic symptoms can be mouse strain dependent.⁴⁸⁻⁵⁰ Studies in the OVA/alum and peanut extract/cholera toxin models indicate almost complete dependence on IgE and mast cells, although PAF and serotonin, rather than histamine, are the primary mediators involved in allergic diarrhea.^{48,49}

It is currently unclear why systemic anaphylaxis is a characteristic of the peanut extract/cholera toxin and transdermal hazelnut models but not the OVA/alum model. Possible explanations include different ratios of IgE/IgG antibody production (higher in the peanut/cholera toxin model than the OVA/alum model) or greater systemic absorption of intact peanut allergen epitopes than OVA epitopes. In this regard studies have demonstrated resistance of major peanut allergens, such as Ara h 1, to digestion, as well as the presence of IgE antibodies that recognize short linear Ara h 1 amino acid sequences, as opposed to the longer, conformation-dependent epitopes that are often required for IgE antibody binding and are more easily destroyed by digestion.^{51,52} It is likely that quantitative, rather than qualitative, differences among the 3 models of food-induced anaphylaxis are responsible for the difference in systemic features because shock develops in the OVA/alum model in mice that have been further sensitized to mast cell–released mediators by treatment before allergen challenge with IL-4 and a β -adrenergic antagonist (R. Strait and F. D. Finkelman, unpublished data).

Studies of intestinal anaphylaxis have also explored additional possible reasons why peanuts are such a common cause of food allergy in the United States and Europe and, unlike most other food allergens aside from tree nuts, a cause of lethal anaphylaxis and anaphylaxis that persists into adulthood.^{53,54} One intriguing observation is the finding that Ara h 1 is a ligand of the dendritic cell receptor dendritic cell–specific intercellular adhesion molecule–grabbing nonintegrin and can activate dendritic cells through this receptor to present antigen in a way that

is more likely to stimulate a T_H2 cytokine response.⁵⁵ Even more recently, we have found that injection of mice with an extract of peanuts or tree nuts can directly induce an anaphylactoid (antibody-independent shock/hypothermia) response. This appears to result primarily from activation of the innate immune system, inasmuch as it is induced in B cell– and T cell–deficient mice with severe combined immune deficiency and appears to depend to a great extent on complement activation (it is considerably reduced in C3-deficient mice), although it might be partially dependent on activation of immunoglobulin receptors (it is reduced somewhat in FcR γ -deficient mice).

The peanut protein or proteins important in the response to peanut extract have not yet been identified. Two leading candidates, however, Ara h 1 and peanut agglutinin, have been eliminated, and preliminary data suggest involvement of a low-molecular-weight protein. This is consistent with a report that purified major peanut allergens are much less immunogenic than the crude extract (ie, peanut molecules that do not elicit a strong IgE response act as adjuvants that promote antibody production to the major allergens).⁵⁶ The anaphylactoid reaction to peanut extract is primarily macrophage dependent, although mast cell activation also occurs, as shown by an increase in serum MMCP1 levels. Consistent with this cellular involvement, both PAF and histamine are involved in the response, with PAF more important than histamine in shock pathogenesis. Peanut extract injection also causes a substantial TNF response, with smaller but significant IL-6, IL-4, and IL-13 responses but no increase in IFN- γ production.

Taken together, these observations suggest that peanuts have 4 characteristics that make them the “perfect allergen:” (1) they contain large concentrations of immunogenic proteins that resist digestion; (2) they contain a protein that stimulates dendritic cells to present antigen in a way that promotes a T_H2 response; (3) they contain 1 or more proteins that induce the production of cytokines that promote a T_H2 response; and (4) they activate complement to produce complement breakdown products (presumably the anaphylatoxins C3a and/or C5a) that stimulate mast cell and macrophage activation and lead to release of PAF and histamine. This activation of macrophages and mast cells through the innate immune system can interact synergistically with antibody-mediated mast cell activation to turn mild anaphylaxis into lethal anaphylaxis (M. Khodoun, R. Strait, and F. D. Finkelman, manuscript in preparation).

ADDITIONAL MOUSE MODELS OF ANAPHYLAXIS

Passive cutaneous anaphylaxis

Although passive cutaneous anaphylaxis (PCA) is more useful as a model for probing mechanisms of anaphylaxis than a model of human allergy, it has played an historically important role in dissection of the mechanisms of anaphylaxis.⁵⁷ Unlike systemic anaphylaxis in the mouse, PCA mediated by autologous antibody appears to be entirely mast cell dependent and is primarily dependent on

IgE.⁵⁸ PCA can also be mediated, however, by a fraction of IgG1 molecules, called anaphylactic IgG1. These IgG1 molecules bind to mast cells, and binding appears to be influenced by a glycosylated determinant that is promoted by IL-4 and inhibited by IL-10, IL-12, and IFN- γ .^{23,59} IgG1-mediated PCA is dependent on Fc γ RIII (it is absent in Fc γ RIII-deficient mice and blocked by pretreatment with 2.4G2⁹). It is not known whether an interaction between IgG1 and mast cell Fc ϵ RI is also required, and it is not clear whether PCA can also be induced by mouse IgG2a and IgG2b, which also bind to Fc γ RIII.²³ It is possible that cytokine-dependent glycosylation increases the affinity of IgG1 for Fc γ RIII, decreases its affinity for Fc γ RIIb, or both; however, there is presently no experimental support for this speculation. It is also important to note that IgG1 has never been shown to induce mast cell-mediated systemic anaphylaxis; indeed, Fc γ RIII cross-linking by 2.4G2 fails to induce an increase in serum MMCP1 levels *in vivo* or to desensitize mice to mast cell stimulation by anti-IgE mAb.^{3,38}

Penicillin-induced anaphylaxis

The results of most studies of systemic and local anaphylaxis are consistent with all general conclusions that have been presented up to this point, including conclusions about the relative roles of IgG versus IgE, IgG receptors versus Fc ϵ RI, mast cells versus macrophages, and histamine versus PAF. A series of well-documented studies with a mouse model of penicillin allergy, however, are an apparent exception to these conclusions. Studies with this system, in which mice are sensitized with a penicillin-OVA conjugate plus adjuvant and challenged with penicillin conjugated to a different protein, suggested that systemic anaphylaxis was IgE dependent because it was blocked by anti-IL-4 mAb but mast cell independent (present in W/W^v mice) and primarily PAF dependent.²⁴ A separate study of passive systemic anaphylaxis with this system more directly demonstrated IgE, but not IgG, involvement (the sensitizing serum factor was heat labile and absorbed by an anti-IgE antibody column but not by an anti-IgG antibody column) but did not investigate mast cell dependence.⁶⁰ The results of the latter study are not difficult to explain; IgE-dependent, mast cell-dependent systemic anaphylaxis has been shown in several mouse models, as described earlier. Explanation of the former studies is more difficult because anti-IgE mAb fails to induce systemic anaphylaxis in mast cell-deficient W/W^v mice.^{3,14} This makes the authors' suggestion that the putative IgE-dependent, mast cell-independent anaphylaxis was mediated primarily by basophils, the only cells in the mouse beside mast cells that express Fc ϵ RI,³⁸ unlikely.⁶⁰ It also seems unlikely that IgE mediates anaphylaxis in the penicillin model by binding to macrophage Fc γ RIII; if this were the case, the IgG anti-penicillin antibodies that are produced in this model should make any requirement for IgE redundant. My favored interpretation is that the penicillin model induces both IgE/mast cell-dependent and IgG/macrophage-dependent anaphylaxis, and anti-IL-4 mAb suppresses

anaphylaxis in this model for reasons other than or in addition to its suppression of the IgE response, such as inhibition of IL-4's effects on target cells that enhance the response to mediators released by mast cells and macrophages.⁴¹ In this regard it is pertinent that the active immunization study of penicillin-induced anaphylaxis used mortality as its only read-out.²⁴ As a result, it would not detect the possibility that suppression of IL-4 exacerbation of anaphylaxis blocked mortality but did not fully prevent the disease. An additional related possibility is that anti-IL-4 mAb inhibits penicillin-induced anaphylaxis by suppressing the IgE response required to mediate basophil secretion of IL-4 and IL-13³⁸ and thus exacerbation of anaphylaxis by both cytokines.

RELEVANCE OF MOUSE MODELS TO HUMAN ANAPHYLAXIS

The focus of this article on specifics of mouse models of anaphylaxis, including the effects of specific mouse IgG isotypes and immunoglobulin receptors, raises questions about the human relevance of these studies. The many similarities and few differences between the mouse and human immune systems that are germane to the relevance of mouse models to human anaphylaxis have been previously summarized (reproduced here as Table II).⁶¹ There are no precise homologies between mouse and human IgG subclasses, and Fc ϵ RI is expressed by more cell types in human subjects (eg, macrophages) than in mice, where it is only expressed on mast cells and basophils.⁶² Both considerations suggest that systemic anaphylaxis might be more IgE dependent in human subjects than in mice and are consistent with the strong evidence for IgE-dependent anaphylaxis and relatively little evidence for IgG-dependent anaphylaxis in human subjects.

My own view is that most human anaphylaxis is probably IgE dependent; however, I suspect that the reasons for this apparent interspecies difference have more to do with the specific mouse models used to study systemic anaphylaxis than with differences between the murine and human immune systems. Mice and human subjects both express stimulatory and inhibitory IgG receptors on macrophages, including Fc γ RIIb and Fc γ RIII,¹⁵ and human IgG1 and IgG3, which are produced in a large amount in protein-induced immune responses, bind to and activate these receptors.⁶³ PAF is produced by human, as well as mouse, macrophages and increases vascular permeability in both species.^{20,64} Consequently, it is reasonable to hypothesize that antigen/IgG complexes can induce the same syndrome in human subjects that they induce in mice. However, although mouse models of systemic anaphylaxis typically immunize mice with large amounts of antigen and/or potent adjuvants that induce large IgG, as well as IgE, responses, human systemic anaphylaxis usually occurs in individuals who have been accidentally immunized with small amounts of antigen (eg, the small amounts of venom injected by stinging insects). It would be unlikely for human subjects immunized in this

TABLE II. Anaphylaxis-relevant similarities and differences between the mouse and human immune systems⁶¹

Characteristic	Mouse	Human
Presence of IgE	+	+
Presence of FcεRI on mast cells and basophils	+	+
Presence of FcεRI on macrophages and Langerhans cells	—	+
Presence of FcγRIIb on mast cells	+	+
Presence of FcγRIII on macrophages	+	+
Presence of FcγRIIA, FcγRIIA, and FcγRIIC	—	+
Mast cell production of histamine	+	+
Macrophage production of PAF	+	+
Activation of mast cells by IgG	+ (weak)	—
IgE binding to FcγRIIb and FcγRIII	+	+

way to have and maintain the large IgG antibody responses that are a feature of the mouse models, whereas low-dose antigen immunization might actually favor an IgE response.⁶⁵ Similarly, antigen challenges that induce human anaphylaxis tend to be smaller than those used to challenge mice, especially when the size difference between the 2 species is taken into account. The much lower antigen and antibody requirements for IgE- than IgG-mediated anaphylaxis noted earlier⁴ thus favor the IgE/FcεRI/mast cell pathway of anaphylaxis in human subjects.

Despite this, it is important to consider that human anaphylaxis has been described in the absence of detectable allergen-specific IgE antibody in serum and in the absence of detectable evidence of mast cell degranulation (ie, no increase in serum tryptase levels).⁶⁶⁻⁶⁸ The best evidence for IgG-mediated human anaphylaxis comes from observations made in patients with Crohn's disease, who, like goat anti-mouse IgD-primed and challenged mice, were immunized (unintentionally) and challenged intravenously with large doses of a foreign immunoglobulin, the chimeric mouse/human anti-TNF mAb infliximab. The 11 patients in this study rapidly experienced hyperemia, palpitations, diaphoresis, nausea, dizziness, and, in some cases, dyspnea and hypotension; all had IgG antibodies to the mouse immunoglobulin determinants on infliximab; none had increased serum IgE levels; and none had increased tryptase levels in blood that was drawn 20 minutes after the onset of the reaction.⁶⁹ Although it is risky to base an argument for IgG-mediated anaphylaxis predominantly on absent evidence for IgE-mediated anaphylaxis, these observations suggest that it would be worthwhile to look for evidence of macrophage activation and PAF secretion in human subjects with anaphylaxis after a large dose of antigen.^{70,71}

IMPLICATIONS FOR PROPHYLAXIS AND TREATMENT

Regardless of the importance of IgG-mediated anaphylaxis in human subjects, studies with mouse models have

TABLE III. Novel approaches to prevention of anaphylaxis suggested by studies with mouse models

1. Nonactivating anti-IgE mAbs
2. IL-4 receptor α chain antagonists (blocking mAbs and IL-4 mutants that bind but do not signal)
3. Ligands and antibodies that cross-link FcεRI or FcγRIII with an ITIM-containing inhibitory receptor
4. PAF antagonists
5. Tyrosine phosphatase activators
6. Encapsulated IL-12 (for food allergy)

suggested several approaches that might be useful for anaphylaxis prophylaxis (Table III) but few or none that might be useful for treatment. The possible prophylactic closest to the clinic is an anti-IgE mAb that binds to an IgE epitope blocked by FcεRI, so that it can prevent IgE binding to mast cell FcεRI but cannot induce anaphylaxis by cross-linking IgE already bound to FcεRI on mast cells. One such anti-IgE mAb has been shown to increase tolerance for ingested peanuts in patients with severe peanut allergy.⁷² Interestingly, some patients treated with a humanized anti-IgE mAb have had anaphylaxis in response to treatment; it is not clear whether this was IgE mediated and resulted from insufficient neutralization of IgE or whether it was IgG mediated.⁷³

The importance of PAF in murine IgE- and IgG-mediated anaphylaxis makes the use of PAF antagonists, in combination with an antihistamine, a promising agent for prevention of anaphylaxis. Several PAF antagonists have been developed,^{74,75} but none have been marketed, and I am aware of no human trials of these drugs for anaphylaxis prevention or therapy.

IL-4 receptor antagonists (both blocking antibodies and a mutant form of IL-4 that binds to IL-4R α but does not signal^{76,77}), which are currently being developed for the treatment of asthma, also have appeal as possible anaphylaxis therapeutics. These agents could work in multiple ways: suppressing IgE production, inhibiting T_H2 cell differentiation, decreasing mast cell differentiation, and blocking the enhancing effects of IL-4 and IL-13 on responsiveness to mediators released by mast cells and macrophages. Other potential cytokine-based therapeutics for the treatment of food allergy include ingestible encapsulated IL-12, which stimulates intestinal production of IFN- γ and suppresses intestinal T_H2 responses,⁷⁸ and IL-10, which has a general anti-inflammatory effect.⁷⁹

Agents that activate tyrosine phosphatases and cross-link them with mast cell FcεRI to prevent the tyrosine phosphorylation required to induce mast cell degranulation are also promising. An IgE Fc-IgG Fc fusion protein, which would prevent mast cell activation by cross-linking mast cell FcεRI with FcγRIIb, is already in clinical development.^{80,81} A bifunctional antibody that cross-links the ITIM-containing molecule CD300a with IgE (and indirectly with FcεRI) also prevents mast cell degranulation in mice and is an attractive candidate for treatment of mast cell-mediated disease.⁸² The same is true for bifunctional

antibodies or ligands that could cross-link FcεRI with any of the other ITIM-associated mast cell proteins or ITIM-independent activators of mast cell tyrosine phosphatases that were mentioned earlier in this article. Small molecule activators of tyrosine phosphatases, such as SHIP1,⁸³ also hold promise as inhibitors of mast cell degranulation, although the multiple functions of these molecules in many cell types might make their activation on all cell types more problematic than activation limited to mast cells, basophils, and FcεRI.

It is also worth considering that many of these approaches might be used along with antigen-specific desensitization through either an oral or a parenteral route. Antigen-specific desensitization has been considered too dangerous for the treatment of food-induced anaphylaxis,⁸⁰ although recent oral immunotherapy trials of patients with less severe food allergy appear promising.^{84,85} Inhibition of mast cell activation with any of the several approaches mentioned in this review might provide a safer opening for the use of desensitization therapy, which could then provide a more long-lasting prophylactic effect. In this regard treatment with the nonactivating anti-IgE mAb omalizumab has already been shown to increase the safety of rush desensitization to ragweed.⁸¹ Mast cell-inhibiting therapies might even allow for treatment with an otherwise activating anti-IgE mAb, which could theoretically eliminate mast cell-associated IgE and desensitize mast cells to provide more effective long-term prophylaxis than treatment with a nonactivating anti-IgE antibody.

In contrast to these multiple promising prophylactic approaches, studies with mouse models currently provide little hope for novel anaphylaxis therapies, with the possible exception of injectable PAF antagonists, which have not been well evaluated in a therapeutic model. The rapid progression of anaphylaxis makes it difficult to think of possible therapies that will reverse the established effects of mast cell- and macrophage-released mediators better than β-adrenergic agonists and intravenous fluids. The EpiPen (Dey, L.P., Napa, Calif) will probably be around for a long time.

FUTURE GOALS OF RODENT STUDIES IN ANAPHYLAXIS

Many goals for future research in this area are obvious continuations of present studies, including (1) determination of the requirements for IL-4 and IL-13 in maintaining allergen sensitization once it has been induced, (2) identification of the ligands of each mast cell- and macrophage-associated ITIM-containing receptor, (3) evaluation of the relative importance of the classic and alternative pathways of anaphylaxis in response to different allergens, (4) identification of better footprints of mast cell and macrophage activation that can be used to diagnose anaphylaxis, (5) identification of the precise antigen characteristics that promote allergenicity, and (6) determination of the mechanisms that promote TH2 responses. Other important goals that are less directly related

to current studies include determination of the extent to which ingested allergens must be absorbed to induce allergic diarrhea and systemic anaphylaxis; determination of whether systemic responses to ingested allergens are mediated by the classic or the alternative pathway; development of safer, easier, longer-lasting and more general methods of desensitization; and development of models that can be optimally used to test small molecule inhibitors of mast cell degranulation, macrophage activation, and mediator effects on target organs. Ultimately, research should aim at identifying improved ways to rapidly reverse anaphylactic responses that have already begun.

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Correction

With regard to the June 2007 article entitled "Eosinophilic disorders" (*J Allergy Clin Immunol* 2007;119:1291-300), the citations of Table I and Table II in the text were reversed. The reference to Table I in the text of the article actually refers to Table II, and the reference to Table II actually refers to Table I.