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Recent Insights into the Mechanisms of Anaphylaxis

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Abstract

Anaphylaxis is an acute life threatening systemic allergic reaction that can have a wide range of clinical manifestations. The most common triggers for anaphylaxis include food, medication, and venom. What is curious regarding anaphylaxis is how so many different agents can induce a severe systemic clinical response but only in a select subgroup of patients. Over the past decade, several important advances have been made in understanding the underlying cellular and molecular mechanisms contributing to anaphylaxis, with mast cells being an essential component. Classically, crosslinked IgE bound to its high affinity receptor induces mast cell mediator release. However, toll-like, complement, or Mas-related G protein-coupled receptors also activate mouse and human mast cells. While anaphylaxis secondary to foods historically has been more extensively characterized clinically and mechanistically, more recent studies have shifted focus towards understanding drug-induced anaphylaxis. The focus of this review is to highlight recent basic science developments and compare what is currently known regarding anaphylaxis to food, medications, and venom.

Keywords

Anaphylaxis; Food Allergy; Venom Allergy; Drug Allergy; Mast cell; IgE; MRGPRX2; Complement

Introduction

Anaphylaxis is an acute life threatening systemic allergic reaction that can have a wide range of clinical manifestations including urticaria, respiratory distress, nausea, vomiting, diarrhea, and/or hypotension[1]. In children, the most common causes of anaphylaxis are

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Conflict of Interest Disclosure:

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foods including egg, cow's milk, wheat, peanut, tree nut, fish, shellfish, and soy, yet it is possible that the induction and effector mechanism induced by each of these food allergens differs. While some food allergies can persist into adulthood, the most common triggers of anaphylaxis in adults are instead medications and venom[2]. Medications accounted for more than half of severe fatal anaphylaxis in the US over a 12-year period[3]. While the culprit drug was not specified in the vast majority of these cases, antibiotics, radiocontrast media, neuromuscular blocker agents (NMBAs), and antineoplastic agents were implicated at the highest frequencies[3]. In regard to venom-induced anaphylaxis, Hymenoptera (bee and wasp) stings are the most prominent causes in North America and Europe, however, reactions to the venoms of snakes, other invertebrates, and cold-blooded vertebrates have also been described[4]. Mast cells (MCs) are essential mediators of anaphylaxis, likely for all of these classes of triggers, although other cell types can contribute. Classically, crosslinked IgE bound to its high affinity receptor induces MC mediator release. However, toll-like, complement or Mas-related G protein-coupled (MRG) receptors and even non-IgE antibodies also activate mouse and human MCs[5]. This review will highlight basic science developments over the past five years regarding our evolving understanding of anaphylaxis to food, medications, and venom.

Food-Induced Anaphylaxis

Recent work has uncovered mechanistic aspects of how MCs are activated by food-specific antibodies and the lymphocytes that regulate this antibody response. Kita and colleagues recently confirmed numerous older studies that anaphylaxis in murine food allergy models can also be induced by activating MCs via both IgE and IgG Fc receptors[6]. An important link between gut mast cell numbers and skin inflammation has also been elucidated[7] to explain a well-established clinical association between eczema and food allergies. Skin tape stripping results in release of systemic IL-33 that acts on gut ILC2s to make IL-4 and IL-13 and MC expansion[7]. Subsequently, mucosal MCs are triggered by allergens but how luminal antigens reach MCs remained unclear. Elegant work using mouse models demonstrated that particular types of gut epithelium transport food allergens to submucosal MCs thereby promoting anaphylaxis[8].

Regulatory T cells (Tregs) have a clear role in tolerance to food antigens[9]; recent work using tetramers in mice tracked the early induction of food-specific anergic T cells showing that with oral tolerance these cells ultimately transform into Tregs and suppress other T effector populations[10]. The microbiome regulates the functionality of Tregs to food. Clostridial species activate Tregs through innate immune pathways that promote tolerance to food allergens[11]. Feehley et al. identified changes also in Clostridial species in children sensitized to milk and, using a mouse model, showed that gut microbiota from these children predispose to oral anaphylaxis and alter the transcriptional profiles of intestinal epithelial cells[12]. However, both IL-4 and particular microbiota can overcome the protective effects of TGFb produced by Tregs to food, thus predisposing to anaphylaxis[13], highlighting the interplay between immune cells and the gut environment for food allergy.

Work over the past five years has advanced our understanding of the T cells that guide IgE induction; these studies demonstrate that Tfh cells, not Th2, are required for allergen

specific IgE induction[14 15]. We demonstrated that a subset of Tfh cells, marked by expression of GATA3 and IL-13 (termed “Tfh13”), is responsible for induction of high affinity IgE that potently induces anaphylaxis[14]; where these cells act in the follicle to promote IgE, and the specific role of IL-13 remains unknown. Oral tolerance to allergens induced during early life prevents the induction of *Il4*-expressing Tfh cells in mice through a CTLA-4 dependent mechanism[16]. However, oral immunotherapy of patients with peanut allergy suppressed multiple T effector cell populations without altering allergen specific Tfh cells[17] raising questions about how difficult Tfh cell repression might be in patients. Blocking the interaction of Tfh and B cells through PD1 blockade inhibits IgE production while promoting low affinity IgG, possibly by deregulating the germinal center reaction in mouse models and was associated with reduced anaphylaxis[6, 18]. Finally, the timing of adjuvant and allergen exposure in a mouse food allergy model was essential for induction of food specific IgE by promoting IgE+ B cell survival and expansion[19]. These insights into the nature and timing of T-B cell interactions driving food-reactive antibodies provide new mechanistic approaches to redirecting the allergic response in patients with food allergy while highlighting the challenges of doing so.

Alpha-gal syndrome is a novel form of food-induced anaphylaxis where, in contrast to other foods, clinical symptoms typically develop 2–6 hours following ingestion of a product containing the polysaccharide galactose alpha 1,3 galactose (alpha-gal)[20]. Alpha-gal is present on cells and tissues of non-primate mammals and patients with alpha-gal syndrome typically experience delayed reactions after ingestion of mammalian meats including beef, pork, and lamb. In the US, sensitization to alpha-gal is thought to occur through lone star tick bites which in part explains the geographical variation observed in disease prevalence[21]. However, there are many unanswered questions regarding alpha-gal syndrome including the underlying mechanisms by which tick bites induce alpha-gal specific IgE and why clinical symptoms are delayed following ingestion[22]. In regard to the latter, Román-Carrasco and colleagues found that alpha-gal can only pass through an intestinal epithelial monolayer *in vitro* when bound to lipids and not proteins. They suggest that alpha-gal may be entering the circulation mainly in the form of chylomicrons, and the slow release of the allergen from these structures may in turn be responsible for the delayed presentation of clinical symptoms following ingestion[23].

Medication-Induced Anaphylaxis

Similar to food, IgE-mediated MC degranulation has also been associated with medication-induced anaphylaxis. However, unlike food, most drugs are too small by themselves to be recognized by IgE. Instead, some drugs are haptens, small molecules that are recognized by adaptive immune cells only when attached to a larger protein. Penicillin is one of the most well-characterized haptens and penicilloyl, the major hapten-carrier complex, is responsible for more than half of IgE-mediated reactions to the drug[24]. However, it is unclear how penicillin (or hapten)-specific IgE is generated and whether Tfh cells or Tregs, for example, play a similar role as in food-induced anaphylaxis. Identifying and quantifying drug specific IgE is also more limited than in food allergy as clinically validated skin testing and immunoassays are not available for most medications.

Cetuximab is a chimeric monoclonal antibody which targets the epidermal growth factor receptor and is associated with a unique form of IgE-mediated anaphylaxis. In this instance, specific IgE is not directed against an epitope of the drug itself but instead to the sugar glycosylating a portion of the cetuximab heavy chain, galactose alpha 1,3 galactose (alpha-gal)[25]. This is the first known instance of a specific IgE directed to a polysaccharide in a medication and is also related to the alpha-gal syndrome as discussed above.

In addition to IgE and mast cells, IgG and neutrophils may also play a role in certain forms of drug-induced anaphylaxis. Recently, Jonsson and colleagues found those patients with severe anaphylaxis to NMBA had elevated concentrations of anti-NMBA IgG as well as higher levels of neutrophil activation and platelet activating factor (PAF) compared to controls who did not develop anaphylaxis[26]. They propose that the anti-NMBA IgG complexes primarily engage FcγRIIA (CD32a) and FcγRIII (CD16) on the surface of neutrophils leading to their activation and downstream release of PAF, a potent mediator of anaphylaxis associated with smooth muscle contraction and vasodilation. Importantly, in this cohort, 31% of patients lacked biomarkers consistent with IgE-mediated anaphylaxis, which illustrates that IgG (and neutrophil) mediated anaphylaxis can occur with or without an IgE mediated hypersensitivity reaction. It is likely that other drugs can also induce IgG-mediated anaphylaxis, but an exhaustive list of these agents is not currently known.

Complement is another pathway that has been associated with drug-induced anaphylaxis. C3a and C5a, aptly named anaphylatoxins, are products of complement activation that can induce mast cell and basophil degranulation. Cremophor, a diluent commonly found in the chemotherapy agent, paclitaxel, can directly activate the complement system[27]. A recent study found that paclitaxel (independent of Cremophor) can also directly engage the C5aR1 to elicit anaphylaxis in murine models[28].

Finally, the Mas-related G protein-coupled receptor X2 (MRGPRX2) is predominantly expressed on mast cells in the skin but can be found at lower levels in the lungs and gut. While the natural ligand for MRGPRX2 is not known, small molecules that carry a net positive charge have been identified that can bind to this receptor which in turns leads to direct mast cell activation, release of tryptase, histamine, and prostaglandins[29]. Numerous drugs including fluroquinolones, vancomycin, certain neuromuscular blockers, and certain anti-depressants have been shown to activate MRGPRX2 in human and murine mast cells *in vitro*[29–32]. In contrast to IgE-mediated reactions, activation of MRGPRX2 does not require prior exposure to the drug, can occur on the first administration, and requires high enough concentrations of the inciting drug to trigger receptor activation. This, in addition to the receptor mainly being expressed in the skin, raises questions as to the precise role MRGPRX2 has in the development of anaphylaxis (a systemic response) versus a cutaneous reaction (a local response) and warrants further investigation.

While outside the scope of this review, there are countless other medications that have been associated with anaphylaxis in select individuals and the underlying mechanisms by which this anaphylaxis occurs is likely to vary. Notably, during the COVID-19 pandemic, episodes of anaphylaxis following administration of COVID mRNA vaccines were reported albeit the exact component of the vaccine responsible for inducing anaphylaxis remains

unclear[33]. Interestingly, in a recent study of patients with a history of a severe reaction to their first COVID vaccine (including 19 with anaphylaxis), all tolerated their second dose of the vaccine[34]. This would suggest against a traditional IgE-mediated driven mechanism for anaphylaxis but complement instead may be playing a role. Further studies exploring this phenomena are thus indicated.

Venom Induced Anaphylaxis

Systemic venom reactions occur more often in middle-aged and elderly patients and are more commonly associated with cardiovascular and mast cell diseases compared with food-induced anaphylaxis[35]. In particular, clonal mast cell disorders, mainly systemic mastocytosis, predisposes patients to severe venom-induced anaphylaxis. However, recently, hereditary α-tryptasemia, which is a non-clonal mast cell disease caused by increased germline copies of *TPSAB1* that encodes α-tryptase (one of the major proteases secreted by mast cells)[36], has been identified as a risk factor for severe venom-induced anaphylaxis[37]. The mechanism of how this increased α-tryptase expression contributes to or is associated with venom-induced anaphylaxis remains unknown.

The role of the adaptive immune system, including IgE, is less clear in venom-induced anaphylaxis than in food-induced anaphylaxis. Venom-specific IgE is detectable in almost all patients with a history of venom-induced anaphylaxis, and it enhances MC degranulation upon venom exposure[38]. Conversely, the majority of people with IgE to venom do not react with anaphylaxis[39]. Like drugs but unlike most food allergens, venom components can directly induce MC degranulation without specific IgE[40]. In addition, Elst and colleagues showed that bone marrow mast cells from patients with a clonal mast cell disorder and history of venom anaphylaxis overexpress FcεRI (but not MRGPRX2), emphasizing the complexity of the interactions between IgE and mast cells in venom-induced anaphylaxis[41]. Interestingly, in mice the ultimate result of MC degranulation has shown beneficial, detoxifying effects on venoms and thus the development of an IgE response to venom has been proposed to be a protective, rather than pathogenic, response to venoms[40, 42].

The mechanism leading to venom sensitization also remains largely unknown. Foundational mechanistic studies in mice were performed by Palm et al. a decade ago, which revealed that enzymatically active phospholipase A2 (PLA2) - one of the main allergens in bee venom - induced release of interleukin-33 and the Th2 response but not sIgE[42]. Melittin, which is the major component of bee venom, induces inflammation via the inflammasome/caspase1/IL1β pathway[43]. Ogden et al. confirmed that enzymatically active PLA2 is a potent adjuvant that shifts the immune response toward Th2 cells[44]. Bruni et al. reported that the IgE-immune response to the venom of Thalassophryne nattereri (venomous fish from South America) was IL-4-dependent[45] and that the main component of this venom, natterin, induced NLRP6 and NLRC4 inflammasome-dependent neutrophilic inflammation in the lung[46]. The relative roles of pro-type 2 signals such as IL-33 and IL-4 versus the IL-1beta/inflammasome pathways in protection from envenoming remain unclear and likely are complementary rather than directly linked[43].

Unmet Needs and Future Directions

Anaphylaxis is a markedly heterogenous condition and therefore we and others[47] have emphasized the need to interpret data in the context of specific triggers and patient populations rather than applying anaphylaxis mechanisms broadly to clinically related syndromes. Patients can present with a myriad of cutaneous, respiratory, cardiovascular, or gastrointestinal symptoms (*i.e.*, phenotypes) that fulfill the clinical definition. Additionally, as discussed above, there are multiple different cellular and molecular mechanisms (*i.e.*, endotypes) that can be involved. Two major endotypes of anaphylaxis have been recognized based on whether the response is IgE-dependent or IgE-independent. While the former endotype is more uniform, involving the classical activation of mast cells and basophils, the latter endotype is diverse and includes direct mast cell activation via MRGPRX2, IgG-mediated activation of mast cells, basophils, and neutrophils through the FcγRs, and complement activation. More mechanistic studies of anaphylaxis have been completed in murine models and translation to human models and clinical disease is needed.

Another unmet need in anaphylaxis is the identification of a factor that could reliably and quickly link a particular clinical phenotype with an underlying inflammatory endotype. In patients with chemotherapy-induced reactions, serum levels of IL-6 may be associated more specifically with cardiovascular and neuromuscular symptoms as opposed to cutaneous or respiratory symptoms[48]. Tryptase is a granule protein released by mast cells upon activation that clinically can be used as an indicator for anaphylaxis. However, not all cases of anaphylaxis are associated with elevated tryptase levels and vice versa. Additionally, elevated serum tryptase levels cannot discern if the mast cell was activated by an IgE-mediated, MRGPRX2-mediated or another pathway. Histamine metabolites N-methylhistamine and N-methylimidazole acetic acid, the prostaglandin D_2 metabolite 2,3-dinor-11-beta-$PGF_{2\alpha}$, and leukotriene (LT) E_4 may also be elevated in the urine during and for a period of time after anaphylaxis. However, these mediators cannot distinguish which mechanism induced anaphylaxis and the clinical specificity and sensitivity of these markers has not been well established. Recently, hsa-miR-451a, a miRNA expressed mostly by neutrophils, was identified as a novel potential biomarker of acute anaphylaxis but further work is needed to evaluate its clinical utility[49]. Thus, while progress has been made, additional studies are still needed to identify biomarkers unique to specific mechanisms of anaphylaxis. By identifying the immunologic pathway contributing to a specific clinical reaction, the ideal goal would be to then initiate a more tailored and effective treatment.

While the acute treatment of anaphylaxis (epinephrine) is well established, the long-term management of these patients historically has been avoidance of the inciting agent. The exception being in patients with venom-induced anaphylaxis where venom immunotherapy has been shown to be highly effective and immune modulating[50]. Recently, oral immunotherapy to peanut has been FDA approved in children. However, to date, this therapy has not been shown to permanently modify the immune response to peanut but instead can potentially raise the threshold for which anaphylaxis to peanut is induced[51]. Likewise, drug desensitizations can be successfully performed to allow a patient to temporarily receive a drug that caused anaphylaxis in the past[52]. However, outside of the desensitization, the risk of anaphylaxis to that drug remains. A novel way of preventing

anaphylaxis in mice was reported through the inhibition of FcεRI-mediated signaling with acalabrutinib, a BTK inhibitor[53]. Evaluation of the effects of acalabrutinib in humans is needed as is the development of other therapies for the chronic management of patients with anaphylaxis.

In addition to managing anaphylaxis after it has occurred, it is also important to focus on understanding why it develops in the first place. It is unclear why only certain patients develop anaphylaxis and not others. For MRGPRX2, elevated expression on mast cells has been observed in certain patient populations such as chronic spontaneous urticaria[54] and maculopapular cutaneous mastocytosis[55]. Variants in MRGPRX2 associated with a loss of function have also been identified[56]. However, there is not yet an assay able to predict who is at high risk of developing a reaction.

Genetic factors likely play a role in anaphylaxis as, for example, increased copies of *TPSAB1* have been associated with significantly higher frequency of anaphylaxis among patients with mastocytosis[57] and are more common in patients with a history of idiopathic anaphylaxis compared to the general population 37. Regarding food-induced anaphylaxis, the HLADPB1*02:01:02 allele was associated with a significantly increased risk of wheat-dependent exercise-induced anaphylaxis[58] and specific loci in the HLA-DR/DQ region have been associated with self-reported reactions to shrimp and peach in Japanese populations[59]. Additionally, the *SERPINB* gene cluster at 18q21.3 was identified as a susceptibility locus for food allergy[60]. Together these studies highlight the continued need to investigate genetic factors that could predict susceptibility of developing anaphylaxis.

Finally, while food, medication, and venom represent some of the most common triggers of anaphylaxis, as many as 14–59% of cases report no identifiable cause[61]. These cases of exclusion are diagnosed as having idiopathic anaphylaxis and even less known about the underlying mechanisms by which this form of anaphylaxis occurs. Some of the cases classified decades ago as idiopathic have now been demystified due to recognition of novel mechanisms involved in anaphylaxis with alpha-gal syndrome being a prime example. However, there are many cases of anaphylaxis that remain unresolved, and it is that hope that as more is understood about other underlying mechanisms important in causing anaphylaxis, less clinical cases will remain idiopathic.

In conclusion, these observations highlight the overall complexity inherent in studying the mechanisms of anaphylaxis but also the incredible impact research in this area could have on the lives of a wide spectrum of patients.

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