



Food allergens, such as peanuts, can cause anaphylaxis.

PERSPECTIVES

IMMUNOLOGY

Dangerous liaisons in anaphylaxis

Dendritic cells deliver allergens to mast cells in the skin via microvesicles

By **Francesca Levi-Schaffer**¹
and **Jörg Scheffell**²

In 1902, Richet and Portier tried to immunize a dog with a toxic sea anemone (*Actinia*) extract. However, to their surprise, the dog died 25 minutes after the second injection. They named the harmful effect anaphylaxis (from Greek, lack of protection) (1). Awarded with the Nobel Prize in 1913, Richet explained that the two necessary and sufficient features for anaphylaxis to develop are an incubation time in between injections and two injections of the same “poison.” Thereafter, the often-life-threatening phenomenon of systemic anaphylaxis (or anaphylactic shock) was found to be caused rapidly after exposure to several environmental antigens (allergens) that enter the circulation and are usually derived from certain foods, drugs, insect venoms, latex, and immunotherapy injections. Similar to all allergic reactions, anaphylaxis is induced by rapid, immunoglobulin E (IgE) antibody-mediated release of immune mediators, such as histamine and platelet-activating factor (PAF) from tissue-resident mast cells (MCs) and presumably from peripheral blood basophils (2, 3). However, in contrast with other forms of allergy such as asthma, allergic rhinitis, and atopic dermatitis, anaphylaxis is systemic and life-threatening owing to cardiovascular and respiratory symptoms (2). Allergic and anaphylactic reactions imply that allergens from the circulation cross

epithelial and/or endothelial (the vascular lining) barriers to interact with IgE bound to MCs. However, the mechanisms were unknown. On page 656 of this issue, Choi *et al.* (4) elegantly demonstrate that such allergens are trapped by dendritic cells (DCs) that produce microvesicles (MVs) to interact with MC-IgE in the skin.

MCs are the cardinal cells of allergy, strategically present perivascularly throughout the body in both connective and mucosal tissues (5). Importantly, MCs are highly granulated, containing several preformed proinflammatory mediators [such as histamine, tryptase, and tumor necrosis factor (TNF)] and express FcεRI, the high affinity receptor for IgE. When MC-bound IgEs encounter a specific allergen, FcεRIs are cross-linked, leading to immediate cell activation, degranulation, and production and release of lipid metabolites. Subsequently, several cytokines and chemokines are released in a second wave, which, together with the activation of infiltrated inflammatory cells, cause symptoms similar to the immediate response.

In the model proposed by Choi *et al.*, conventional DCs (cDCs) of the cDC2 subset, and to a lesser extent cDC1s, are pivotal in anaphylaxis by shuttling allergens to IgE-bearing MCs. DCs are members of the professional antigen-presenting cell (APC) family, which also includes Langerhans cells and macrophages in the skin. Various phenotypical and functionally distinguishable dermal DC subsets have been identified in humans and mice (6), with cDC2 being the most abundant subset in the dermis. DCs originate from the bone marrow and engraft all nonlymphoid tissues, where they “sample” their environment by taking up foreign- or host-derived material (antigens). The ingested material is

processed and presented as small peptides via major histocompatibility complex (MHC) class II molecules to CD4⁺ T cells in lymphoid tissues, such as the lymph nodes.

Choi *et al.* found that allergen-sensitized, cDC2-deficient mice had significantly less-severe anaphylaxis when challenged intravenously with allergen. They discovered that cDC2s continuously probe adjacent blood vessels for allergens, with extensions projecting through the endothelial wall. Importantly, perivascular MCs were unable to probe the cutaneous circulation for allergens by themselves, as has been described for their acquisition of IgE (7). In contrast to the usual antigen-presentation process, a major portion of the allergens were not internalized by the cDC2s but were instead passed on to allergen-specific IgE bound to MCs via MVs (see the figure). MVs originate from the plasma membrane, range between 40 and 1000 nm in size, and are frequently shed from the membrane of cDC2s and other cells (8). In their experiments, the process of MV shedding was extremely rapid, reflecting the fast onset of symptoms during anaphylaxis. Direct cell-cell contact between MCs and DCs may also occur despite not being essential and thus not the primary means of MC activation in their models. Notably, MVs were also used to distribute allergens to neighboring macrophages and DCs, thereby spreading the antigens in the tissue. Choi *et al.* further showed that MV budding from the plasma membrane was dependent on the adenosine triphosphatase activity of vacuolar protein sorting-associated protein 4 (VPS4). Consequently, mice deficient for VPS4 in DCs exhibited much milder anaphylaxis when challenged with allergen. Choi *et al.* suggest that promiscuous scavenger or man-

¹Pharmacology and Experimental Therapeutics Unit, School of Pharmacy, Institute for Drug Research, Faculty of Medicine, The Hebrew University of Jerusalem, Post Office Box 12065, Jerusalem 91120, Israel. ²Department of Dermatology and Allergy, Charité Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany. Email: francescal@ekmd.huji.ac.il

nose receptors facilitate allergen binding to the plasma membrane of the cDC2s. In their model, blocking or depleting the mannose receptor in DCs reduced their capacity to activate MCs via MVs.

The global incidence of anaphylaxis is increasing, particularly in response to food-derived allergens. The study of Choi *et al.* strengthens the role of skin MCs in anaphylaxis, but the role of blood basophils (which are the first to encounter allergens) remains unclear (2, 3). A number of other open questions also remain. Notably, the human and the mouse systems might work differently. In mice, IgG can also induce systemic anaphylaxis. In addition, the nature of the allergen might influence the mechanism. Moreover, besides mannose receptors, which other receptors facilitate allergen binding? Do DCs discriminate between internalization, processing, and MHC presentation versus antigen spreading via MVs? The described mechanism also suggests a high turnover rate of membrane lipids and proteins in DCs to sustain the permanent shedding of MVs from the plasma membrane. How do these cells keep up with the production of new plasma membrane? How specific are MVs in their cellular interactions? What happens to the allergen-loaded MVs in the tissue, do nonimmune cells interact with them, and what are the consequences? Much still remains unknown about MV biology.

The work of Choi *et al.* adds an important piece to the puzzle of how allergens become distributed to MCs in the tissues to start the

dangerous chain reaction that leads to anaphylaxis. MCs are spread out in the body. Are similar pathways triggered in other tissues involving other DC subsets? Is this newly discovered mechanism a possible target for therapeutic intervention in anaphylaxis? Probably not. Sentinel functions of DCs and other APCs fulfill an important role in protecting the host from pathogens and internal threats (9). Therefore, interference bears the risk of serious side effects. Current options for anaphylaxis include avoidance, immunotherapy, and immediate epinephrine injection followed by antihistamines and corticosteroids (10). In the future, directly targeting MCs or IgE might be the best prophylactic strategy for anaphylaxis (5). ■

REFERENCES AND NOTES

1. C. Richet, Nobel lecture: Anaphylaxis, 11 December 1913; www.nobelprize.org/prizes/medicine/1913/richet/lecture/.
2. L. L. Reber *et al.*, *J. Allergy Clin. Immunol.* **140**, 335 (2017).
3. H. Karasuyama, K. Miyake, S. Yoshikawa, Y. Yamanishi, *J. Allergy Clin. Immunol.* **142**, 370 (2018).
4. H. W. Choi *et al.*, *Science* **362**, eaao0666 (2018).
5. R. S. Gangwar, N. Landolina, L. Arpinati, F. Levi-Schaffer, *Pharmacol. Ther.* **170**, 37 (2017).
6. S. W. Kashem, M. Haniffa, D. H. Kaplan, *Annu. Rev. Immunol.* **35**, 469 (2017).
7. L. E. Cheng *et al.*, *Immunity* **38**, 166 (2013).
8. G. Raposo, W. Stoorvogel, *J. Cell. Biol.* **200**, 373 (2013).
9. P. Matzinger, *Annu. Rev. Immunol.* **12**, 991 (1994).
10. F. E. Simons *et al.*, *World Allergy Organ. J.* **8**, 32 (2015).

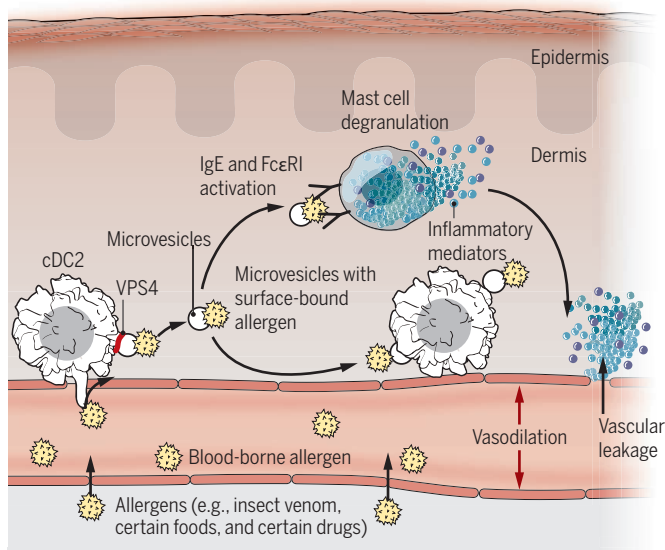
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The allergen shuttle

cDC2s in the skin continuously sample allergens from the circulation and distribute them via microvesicles to APCs or IgE-coated mast cells. This results in mast cell degranulation and immediate release of various proinflammatory mediators. The simultaneous degranulation of mast cells in different body locations leads within minutes to systemic symptoms and may cause death of the individual.



Systemic anaphylaxis can be fatal.

Cardiovascular
Hypotension
Slowing or rapid heartbeat

Central nervous system
Headache
Confusion
Anxiety
Loss of consciousness

Respiratory
Shortness of breath
Coughing

Skin
Itching
Urticaria
Angioedema

Gastrointestinal
Incontinence
Diarrhea
Pain

IMMUNOLOGY

A key ingredient for priming killer T cells

WDFY4 protein controls the generation of antiviral and antitumor CD8⁺ T cell immunity

By Gaëtan Barbet and J. Magarian Blander

For the adaptive immune system to detect intracellular infection, microbial protein fragments (antigens) must be presented by major histocompatibility complex class I (MHC-I) molecules. This entails an elaborate intracellular folding of MHC-I molecules with peptides from the infecting pathogen, followed by their display on the cell surface for surveillance by CD8⁺ T cells (1). In a variation of this classical pathway of MHC-I antigen presentation, a subset of professional antigen-presenting cells called dendritic cells (DCs) conduct cross-presentation, whereby MHC-I molecules are directed to present exogenous peptides from internalized microbes and dying infected cells or cancer cells (2). Because of the potential to prime cytotoxic CD8⁺ T cells against intracellular pathogens and cancer cells, cross-presentation has preoccupied immunologists for decades. But how this process is orchestrated remains poorly understood. On page 694 of this issue, Theisen *et al.* (3) reveal a critical role for the protein WDFY4 (WD repeat- and FYVE domain-containing protein 4) in cross-presentation and not in classical MHC-I antigen presentation. The authors show that WDFY4 works specifically in the conventional DC1 (cDC1) subset and is responsible for their specialization at cross-presentation (4). This revelation identifies WDFY4 as a therapeutic target to mobilize cytotoxic CD8⁺ T cells against tumors and infected cells.

WDFY4 is a large transmembrane protein and member of the BDCP (BEACH domain-

Jill Roberts Institute for Research in Inflammatory Bowel Disease; Gastroenterology and Hepatology Division, Joan and Sanford I. Weill Department of Medicine; Department of Microbiology and Immunology; Sandra and Edward Meyer Cancer Center; and Immunology and Microbial Pathogenesis Program, Weill Cornell Graduate School of Medical Sciences, Weill Cornell Medicine, Cornell University, New York, NY, USA. Email: jmblander@med.cornell.edu

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