

Nipping cat allergy with fusion proteins

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Immunotherapy for allergies can be an imperfect and unpredictable exercise; immunization with allergens can even lead to an acute allergic response. A new approach, involving fusing the allergen to a protein that modulates the immune response, could provide a more effective and safer alternative (pages 446–449).

When a person with a severe allergy to cats enters a friend's home for the first time, he or she does not have to be told whether there is a cat in residence. The runny eyes, itchy nose, tightening chest and other symptoms begin within minutes—shortly before the rush for the door.

In this issue, Zhu *et al.* introduce a new potential treatment for such misery. Their work establishes proof of principle for a general approach that might be applied not only to severe cat allergy but to a wide range of allergies to specific agents.

The authors administer to mice a fusion protein comprised of a cat allergen (Feld1) linked to part of the constant (Fc γ) portion of IgG. This approach suppresses Feld1 allergen- and IgE-dependent activation of mast cells and basophils, the key effector cells that produce the mediators of allergic reactions^{1,2}. This approach is appealing because it cleverly exploits a well-established mechanism for such suppression³. In addition, because the fusion protein cannot accidentally activate mast cells and basophils as can a large dose of conventional allergen, this represents a potentially safer way to administer allergen for immunotherapy.

Mast cells reside in virtually all vascularized tissues, especially near surfaces exposed to the environment, whereas basophils are circulating granulocytes that can be recruited to tissues at sites of allergen exposure^{1,2}. Acute exposure to allergens provokes an allergic response in sensitized individuals whose immune systems contain IgE specific for these allergens; the allergens induce activation and release of proinflammatory mediators from mast cells and basophils, which bear such IgE on their surface (Fig. 1a). IgE antibodies also can increase the expression of the IgE receptor, Fc ϵ RI, on the surface of these cells^{1,4}. The increased expression of Fc ϵ RI increases the

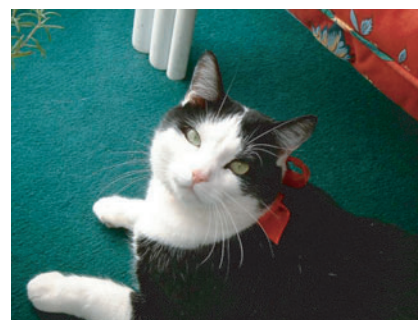
cells' sensitivity to allergen stimulation and the intensity of the mediator release elicited during the ensuing allergen-induced secretory response^{1,4}.

It is now clear that a number of molecules expressed on the cell surface, or within mast cells and basophils, can downregulate signaling initiated at Fc ϵ RI^{1,3}. Although several of these may be amenable to therapeutic manipulation, an attractive candidate is the inhibitory protein Fc γ RIIb, which binds the Fc γ portion of the IgG antibody. Fc γ RIIb is expressed on the surface of both mast cells and basophils in humans³.

It is well established that co-ligation of Fc ϵ RI with Fc γ RIIb can dramatically diminish both the extent of effector cell activation by allergen *in vitro*^{1,3} and the allergic response *in vivo*^{5,6}. Zhu *et al.*⁷ have advanced the field by creating a chimeric protein that co-ligates Fc ϵ RI with Fc γ RIIb in an allergen-specific manner. The chimeric protein contains the cat allergen recognized by IgE Fel d1 thereby targeting the molecule to mast cells and basophils bearing IgE with specificity for that allergen. The protein also contains enough of the Fc γ portion of IgG to engage Fc γ RIIb—thereby suppressing Fc ϵ RI-dependent activation of these effector cells (Fig. 1b).

The new approach was successful on several fronts. First, the Fc γ -allergen fusion protein did not activate effector cells sensitized with IgE against Fel d1, showing that the fusion protein did not act as a conventional allergen and trigger an acute response. Secondly, the fusion protein markedly suppressed IgE- and allergen-induced human mast cell or basophil activation and downstream signaling events *in vitro* (Fig. 1b). Finally, the approach suppressed IgE-dependent acute responses to Fel d1 in mice *in vivo*.

Fc γ -allergen fusion proteins, if proven safe and effective in humans (the usual 'big if' at this stage of drug development), may offer significant advantages over existing approaches for manipulating the immune system to treat patients with severe allergies. In the 1950s, Mary Hewitt Loveless pioneered the use of purified venom from wasps and



Irene Check

Armed and dangerous.

bees (*Hymenoptera*) for the allergen-specific immunotherapy of patients susceptible to anaphylaxis induced by the stings of these insects; although this approach is still considered the standard of care for such patients, it has not been possible to generalize this approach to other agents that can provoke anaphylaxis⁸. Moreover, inadvertent administration of too much allergen during immunotherapy can provoke a severe acute allergic response.

At the opposite end of the spectrum of specificity, IgE itself has been targeted—an approach that, in principle, can be used to treat all IgE-associated allergies simultaneously. Treatment with humanized antibodies to IgE can ameliorate signs and symptoms of allergic asthma in some patients⁹ and may also benefit patients with severe allergies to peanuts¹⁰. Unfortunately, the response to anti-IgE treatment in many patients with asthma, while measurable, does not amount to a 'cure.'

There are a number of possible reasons for less-than-complete responsiveness to IgE therapy and some of these may also apply to the new approach proposed by Zhu *et al.* There is no longer any reasonable doubt that mast cells, and probably also basophils, are major sources of the mediators that produce acute allergic reactions, including those seen in individuals with atopic asthma^{1,2,9}. But human asthma is now understood to be a chronic disorder, associated with long-term changes in the

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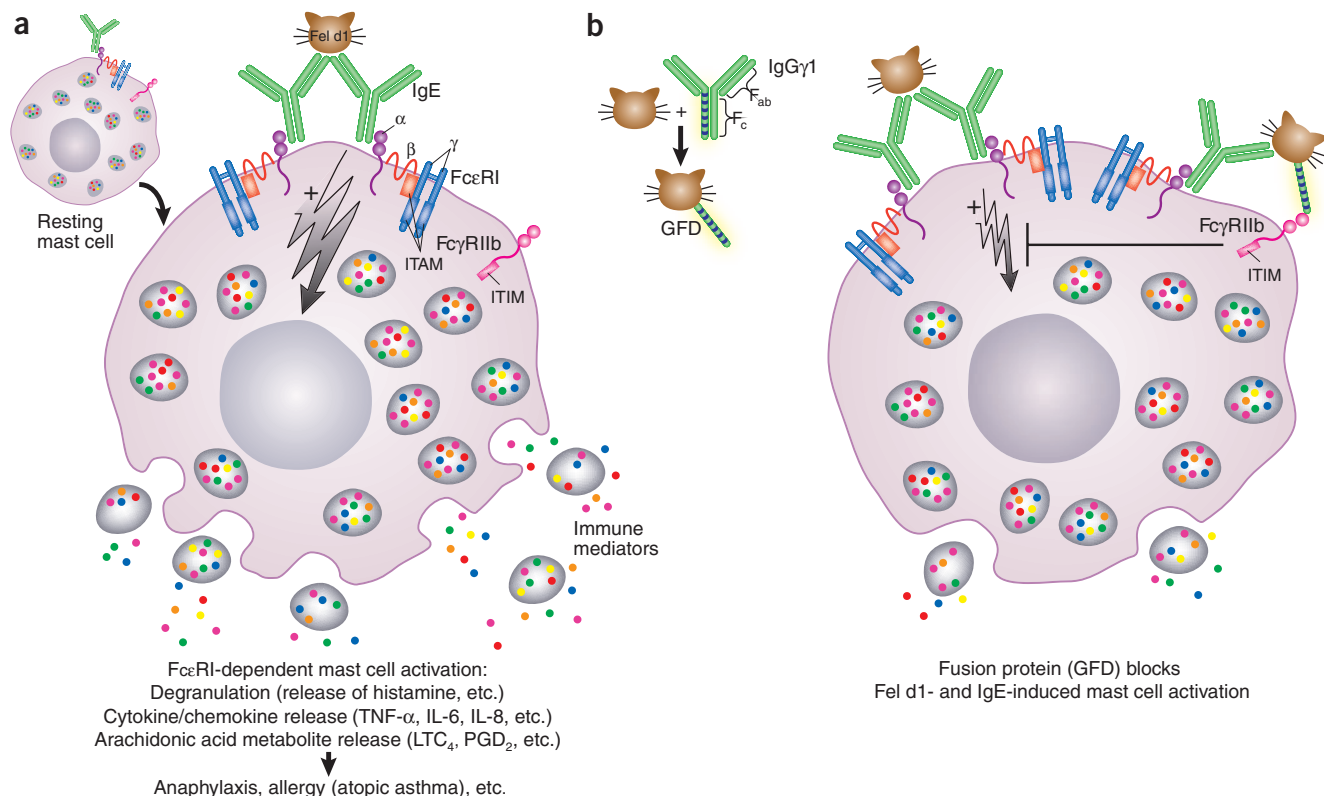


Figure 1 Here, kitty, kitty. **(a)** How mast cells and basophils initiate an allergic response. Subjects sensitized to specific allergens, such as the cat allergen Fel d1, produce IgE antibodies specific to these allergens. These IgE antibodies bind to high-affinity receptors (FcεRI), expressed on the surface of mast cells and basophils. Aggregation of FcεRI, typically by the binding of di- or multivalent allergen recognized by the IgE, induces mast cell and basophil activation. These cells degranulate and release preformed mediators (such as histamine) stored in the granules, synthesize and release leukotrienes and prostaglandins, and secrete a variety of cytokines and chemokines; these molecules collectively produce the clinical features of acute allergic reactions^{1,2,12–14}. **(b)** The Fcγ-Fel d1 fusion protein (GFD) generated by Zhu *et al.*⁷ blocks cat-induced acute allergic reactions. It probably does so by co-ligating FcεRI (bound to Fel d1-specific IgE) and FcγRIIb. FcγRIIb contains an immunoreceptor tyrosine-based inhibition motif (ITIM), which generates an inhibitory signal that suppresses the activation of mast cells, basophils or both^{1,3,5,6}.

airways^{2,9,11,12}. Several lines of evidence indicate that multiple types of effector cells in addition to mast cells and basophils may drive the pathology of chronic asthma, including T cells, eosinophils, monocytes, macrophages and neutrophils^{2,9,11,12}. Indeed, even in animal models, the extent to which antibody-dependent mast cell or basophil activation can contribute to the chronic changes associated with asthma remains to be determined¹².

If much of the pathology of chronic asthma can be attributed to effector cells other than mast cells and basophils, then even the most effective ‘targeting’ of IgE, FcεRI or downstream elements of FcεRI-dependent signaling pathways will not be fully effective in this disorder.

It is encouraging, then, that the Fcγ-allergen fusion protein also appears to be able to serve as a novel ‘allergen vaccine’ for the long-term immunomodulation of cat allergy, at least in the mouse model tested by Zhu

*et al.*⁷ It will be of great interest to define in detail the nature of the long-term ‘protective immune response’ induced by this agent. Unlike conventional allergens used for immunotherapy, the new fusion protein apparently does not carry the potential for inadvertently inducing an acute allergic response—although it will be important to rule out the possibility that it could do so in humans. In the worst case, the protein could induce an IgE response. Finally, from a practical standpoint, this type of therapy will be applicable to subjects with severe allergies to one allergen or a few. Unfortunately, many individuals suffer from multiple allergic sensitivities.

The work of Zhu *et al.* points the way to a new class of agents for the treatment of patients with severe allergic diseases. Will this approach be effective in the long term for such patients, and, especially, for those with chronic atopic asthma provoked by Fel d1 or other allergens? At this time, one can hope

so, but in the near future the best advice for people with cat allergies might be to call ahead before visiting.

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