

CLINICAL IMPLICATIONS OF BASIC RESEARCH

A New Strategy to Counter Allergy

Jean-Pierre Kinet, M.D.

Many features of cellular programs are tightly controlled by the balancing actions of activation and inhibitory signals. This principle applies in particular to the cells of the immune system, which are regulated by activating and inhibitory cell-surface receptors. Zhu and colleagues¹ have recently described a clever strategy to repress specific allergic reactions by muting the activity of activation receptors.

The first step of the allergic response is the immunization phase, in which innocuous allergens trigger B cells to produce IgE and IgG that react specifically to these allergens. These IgE molecules then bind to high-affinity receptors for IgE (FcεRI) on circulating basophils and mast cells in many tissues (Fig. 1). The binding of IgE to FcεRI does not itself induce allergic reactions. A second step is required. Allergens are multivalent: they express multiple epitopes that are recognized by specific IgEs and IgGs. Simultaneous multivalent binding of allergens to several membrane-bound IgEs induces receptor aggregation, which triggers a signaling cascade that leads to the production and release of allergic and inflammatory mediators (histamine, leukotrienes, chemokines, and cytokines) responsible for the symptoms of allergic diseases. This chain of events is central to many allergic diseases, including allergic rhinitis, allergic asthma, urticaria, and systemic anaphylaxis.

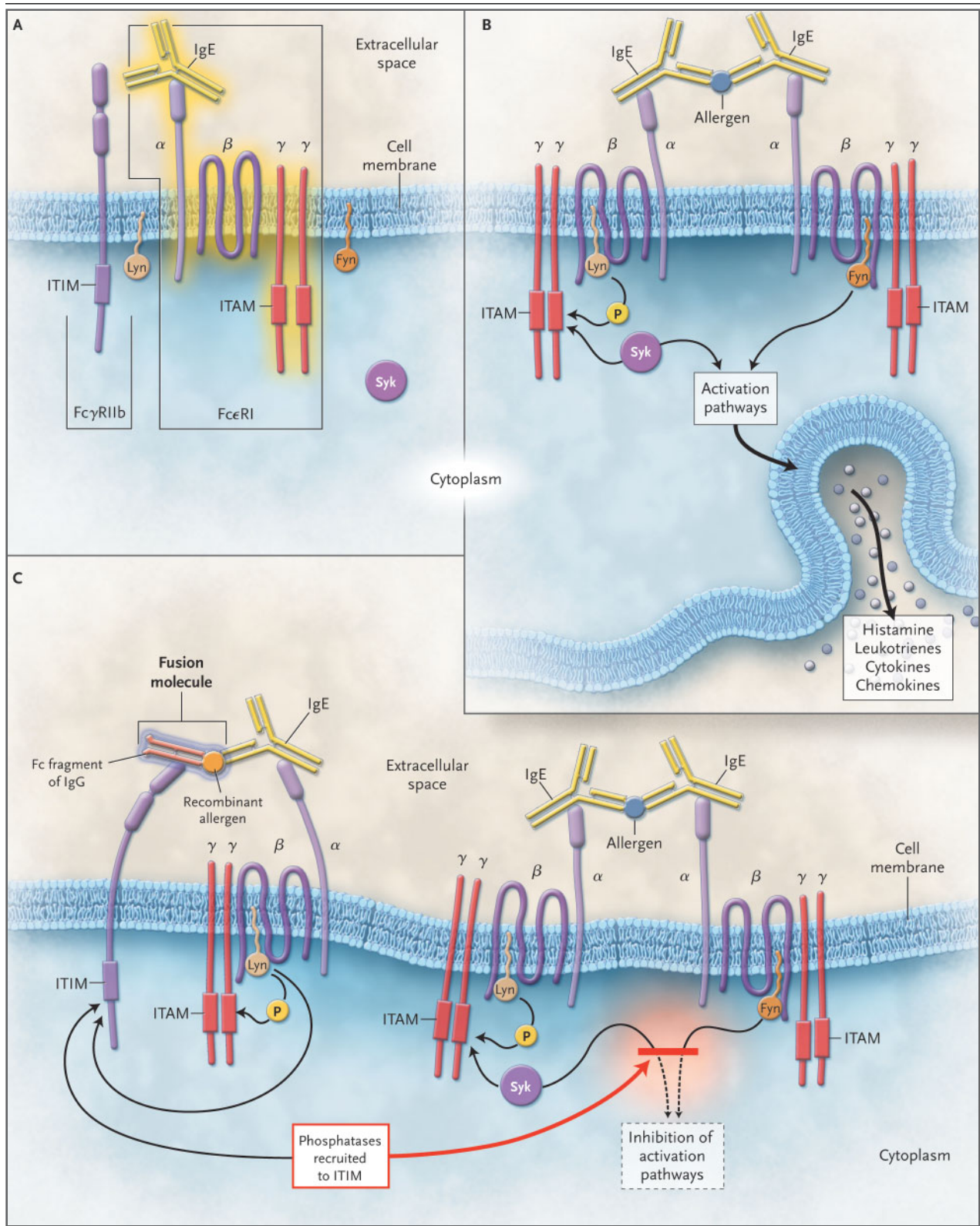
How does the aggregation of FcεRI generate this signaling cascade? FcεRI is composed of an IgE-binding unit (the α chain) and a signaling unit (one β and two γ chains) (Fig. 1). The aggregation of FcεRI induces the activation of a tyrosine kinase bound to the β chain; the tyrosine kinase then phosphorylates two tyrosine residues in the γ chains. These tyrosine residues are a central feature of the immunoreceptor tyrosine-based activation motif (ITAM), the canonical activation motif present on numerous receptors in the immune system. After phosphorylation, the ITAMs of the γ chains activate Syk tyrosine kinase, which, through the activation of downstream pathways, induces the release of allergic mediators (Fig. 1).^{2,3}

These FcεRI-mediated activation pathways are modulated by inhibitory receptors — the IgG receptor FcγRIIb in particular. The allergen-specific IgGs produced in response to immunization form complexes with allergens, which can, in turn, form a bridge between FcεRI and FcγRIIb. Both receptors are expressed on mast cells and basophils; the Fc fragment of IgG in the immune complex binds to FcγRIIb, whereas the allergen binds to IgE, which is already bound to adjacent FcεRI. The formation of this bridge induces the aggregation of activating FcεRI with inhibitory FcγRIIb, which inhibits the activation pathways activated by FcεRI. This capacity of IgG to counteract IgE is probably the central mechanism behind successful allergen desensitization, although this has yet to be established. However, desensitization does not always work, as illustrated by dramatic failures involving life-threatening anaphylactic shock.

How does FcγRIIb-mediated inhibition work?

Figure 1 (facing page). A New Strategy to Counter Allergy.

Allergens induce the aggregation of membrane-bound IgEs that react specifically to them. The IgEs are bound to the membrane of basophils and mast cells by IgE receptors called FcεRIs (Panel A). Thus, the aggregation of IgE induces the aggregation of FcεRI and, hence, the triggering of activation signals that eventually lead to the release of the mediators (such as histamine) of allergic reactions (Panel B). In persons without allergies, membrane-bound IgG also forms immune complexes with allergens. IgG is tethered to the membrane by binding the Fc fragment of FcγRIIb. When an allergen simultaneously binds IgE and IgG, the activating FcεRI is brought together with the inhibitory FcγRIIb, thereby silencing the FcεRI-mediated activation pathway. Zhu and colleagues¹ report a strategy that takes advantage of the natural capacity of FcγRIIb to inhibit the allergenic activity of FcεRI. They designed a chimeric molecule — a fusion of a cat allergen (Fel d1) and the Fc fragment of human IgG (Panel C) — that abolished allergic reactions to Fel d1 in vitro and in a mouse model. Similar fusion molecules could be designed to counter other types of allergy. Lyn, Fyn, and Syk are protein tyrosine kinases. P denotes phosphorylation.



FcγRIIb contains an immunoreceptor tyrosine-based inhibitory motif (ITIM), a modified version of the activating ITAM present in FcεRI. Like ITAM, ITIM must be phosphorylated by a tyrosine kinase to function. ITIM is phosphorylated when FcγRIIb is brought into proximity to FcεRI resulting in the aggregation of both receptors. Phosphorylated ITIM recruits phosphatases that inactivate key components in the activation pathway.^{4,5}

To circumvent the uncertainties of classic allergen desensitization, Zhu and colleagues engineered a chimeric molecule in which the Fc fragment of human IgG1 is fused to the recombinant major cat allergen Fel d1. The fusion molecule thus binds both FcγRIIb and the IgE specific for Fel d1. Because IgE is already bound to FcεRI, the authors predicted that the complex would form a bridge between FcγRIIb and FcεRI, thereby inhibiting allergic reactions. And this is exactly what happened. The fusion protein inhibited allergen-mediated activation of basophils and mast cells in vitro. It also inhibited allergic responses after long-term immunization with Fel d1 in a relevant mouse model.

The potential of this novel approach is not limited to treating allergies to cats. Zhu et al. have provided proof of principle that this strategy may be effective in treating any type of allergy. For example, replacing Fel d1 with the major peanut allergen should help prevent the devastating anaphylactic responses to peanuts seen in many children. The fusion protein could also displace allergens already bound to IgE, in which case it would help terminate ongoing anaphylactic reactions. A potential

problem, however, is that the fusion protein could actually induce or exacerbate an allergic reaction, because mast cells and basophils also express FcγRIIa, an ITAM-containing and activating IgG receptor. Classic desensitization may fail in a subgroup of patients because activating FcγRIIa prevails over inhibitory FcγRIIb. If so, it will be essential to identify this subgroup of patients before they receive therapy with fusion molecules, because the fusion molecules could aggregate with the two activating receptors FcεRI and FcγRIIa, thus inducing allergic reactions.

The study by Zhu et al. focuses on the second step of the allergic response, after allergen-specific immunoglobulins have been produced. However, the fusion molecule may have an even stronger effect on countering allergy if it is used to ablate IgE-producing B cells — the source of such immunoglobulins — which also express FcγRIIb. This approach would induce true desensitization.

From the Beth Israel Deaconess Medical Center, Harvard University, Boston.

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