Aggregation geometry and signaling efficiency of the high affinity receptor for IgE (FcεRI) depend on IgE occupancy and antigen valency

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Abstract text

Text: **Introduction:** The immediate allergic response is initiated on the membrane of mast cells and basophils when allergen-specific IgE antibodies bound to the high-affinity receptor, FcεRI, are cross-linked by multivalent allergens, resulting in FcεRI aggregation, signal transduction, and rapid release of preformed inflammatory mediators.

Objectives: We investigated the impact of properties inherent to allergen molecules, such as IgE epitope number and distribution, on receptor aggregate formation at the cell surface and downstream events.

Methods: We used a monoclonal IgE antibody specific for a peptide derived from the major grass pollen allergen, Phl p 1, and recombinant IgE-reactive fusion proteins containing different copy numbers of the peptide at different positions within the protein, to study cell activation in rat basophil leukemia (RBL) cells. Intracellular calcium concentrations and mediator release from wildtype or Lyn^{KO}RBL cells were analyzed. Receptor aggregate formation was investigated by transmission electron microscopy and single particle tracking, complemented by computer simulations.

Results: MB4N containing 4 IgE epitopes in close vicinity elicited the highest degranulation response even at low IgE concentrations, accompanied by rapid and sustained intracellular calcium release. In contrast to lower valency molecules, it induced degranulation in the absence of Lyn tyrosine kinase. Computer simulations suggested that the recruitment of receptors into aggregates occurred faster and at higher numbers when cross-linked with high-valency antigen, resulting in highly branched, complex aggregates. Consistently, an increased receptor cluster size induced by MB4N compared to lower valency antigens was detected by transmission electron microscopy which translated into a marked slowdown of receptors on the cell surface upon cross-linking with MB4N, as determined by single particle tracking.

Conclusion: Our results demonstrate the impact of IgE epitope number and density on FcεRI aggregate formation and subsequent effector cell activation.

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Conflict of Interest statement

Do you have any conflict of interest to declare?: No

Affirmation

1. Consent to participate and present onsite: Yes

2. Consent to publication publication: Yes

3. Consent on treatment of contact details saved in this system: Yes