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Curr Opin Allergy Clin Immunol. 2004 Dec;4(6):563-8.

Genetically engineered negative signaling molecules in the immunomodulation of allergic diseases.

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Abstract

PURPOSE OF REVIEW: This review summarizes current knowledge regarding the control of human mast cell and basophil signaling and recent developments using a new therapeutic platform consisting of a human bifunctional gamma and epsilon heavy chain (Fc gamma-Fc epsilon) protein to inhibit allergic reactivity.

RECENT FINDINGS: Crosslinking of Fc gamma RIIb to Fc epsilon RI on human mast cells and basophils by a genetically engineered Fc gamma-Fc epsilon protein (GE2) leads to the inhibition of mediator release upon Fc epsilon RI challenge. GE2 protein was shown to inhibit cord blood-derived mast cell and peripheral blood basophil mediator release in vitro in a dose-dependent fashion, including inhibition of human IgE reactivity to cat. IgE-driven mediator release from lung tissue was also inhibited by GE2. The mechanism of inhibition in mast cells included alterations in IgE-mediated Ca mobilization, spleen tyrosine kinase phosphorylation and the formation of downstream of kinase-growth factor receptor-bound protein 2-SH2 domain-containing inositol 5-phosphatase (dok-grb2-SHIP) complexes. Proallergic effects of Langerhan's like dendritic cells and B-cell IgE switching were also inhibited by GE2. In vivo, GE2 was shown to block passive cutaneous anaphylaxis driven by human IgE in mice expressing the human Fc epsilon RI and inhibit skin test reactivity to dust mite antigen in a dose-dependent manner in rhesus monkeys.

SUMMARY: The balance between positive and negative signaling controls mast cell and basophil reactivity, which is critical in the expression of human allergic diseases. This approach using a human Fc gamma-Fc epsilon fusion protein to co-aggregate Fc epsilon RI with the Fc gamma RII holds promise as a new therapeutic platform for the immunomodulation of allergic diseases and potentially other mast cell/basophil-dependent disease states.

PMID:15640700[PubMed - indexed for MEDLINE]

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