

ACTIVATION OF HUMAN BASOPHILS AND MAST CELLS BY SUPERALLERGENS

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Superantigens have the unique ability to interact specifically with most lymphocytes expressing antigen receptors from a particular variable region gene family. Classical superantigens are T-cell superantigens. However, some naturally occurring proteins have the properties of superantigens for B-lymphocytes. These proteins are endowed with unconventional immunoglobulin-binding capacities. Human basophils and mast cells are the only cells expressing the high affinity receptor for IgE and they play a prime role in the pathophysiology of allergic disorders through the elaboration and release of numerous proinflammatory and immunoregulatory molecules. We conducted experiments to determine whether immunoglobulin superantigens activate human basophils and mast cells to release pro-inflammatory mediators and cytokines. Protein Fv is released in the biological fluids of patients affected by viral hepatitis. Protein Fv preparations from viral hepatitis patients stimulated histamine and cytokine release from purified basophils. IL-4 and IL-13 mRNA, constitutively present in basophils, were increased after stimulation by protein Fv. Basophils from which IgE have been removed no longer released IL-4 in response to protein Fv and anti-IgE. Human monoclonal IgM V_H3^+ , but not V_H6^+ , concentration-dependently inhibited protein Fv-induced secretion of IL-4 and histamine from basophils and lung mast cells. HIV-1 gp120 is a superantigen, which might explain the activation of B-lymphocytes in patients with AIDS. We found that recombinant gp120 from divergent HIV-1 isolates increased IL-4 and IL-13 mRNA expression parallel to histamine secretion from basophils and lung mast cells. Gp120 activates $Fc\epsilon RI^+$ cells through interaction with IgE, since removal of IgE completely blocked the glycoprotein's effects on secretion. Preincubation of gp120 with monoclonal IgM V_H3^+ also inhibited its effect on secretion from $Fc\epsilon RI^+$ cells. *Peptostreptococcus magnus* is a bacterium expressing a cell wall protein L that binds human immunoglobulin through high-affinity interaction with immunoglobulin light chains. Increasing concentrations of *Peptostreptococcus magnus* and protein L induced histamine release from basophils and mast cells. Protein L and a recombinantly expressed fragment covering the immunoglobulin-binding domains B1-B4 also induced IL-4 and IL-13 release from basophils. Preincubation of protein L with IgE from myelomas expressing λ chains did not affect the activating property of protein L, whereas IgE from myeloma with κ chains completely blocked the activity of protein L. These results indicate that protein L interacts with the κ light chains of IgE on human $Fc\epsilon RI^+$ cells to induce the release of mediators. Thus, a novel mechanism may be envisaged by which endogenous, viral and bacterial proteins specifically activate human $Fc\epsilon RI^+$ cells thereby acting as immunoglobulin superantigens. The *in vivo* implications of IgE-mediated activation of human basophils and mast cells by these immunoglobulin superantigens are yet to be defined.