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Invited Lecture

Superallergens: a new mechanism of immunologic activation of human basophils and mast cells

G. Marone, G. Spadaro, B. Liccardo, F.W. Rossi, C. D'Orio and A. Detoraki

Division of Clinical Immunology and Allergy, University of Naples Federico II, Via S. Pansini, 5, 80131 Naples, Italy, Fax: ++39 081 7462271, e-mail: marone@unina.it

A conventional antigen can usually stimulate less than 0.001 % of the naive lymphocyte pool. Superantigens are characterized by their ability to induce changes in the composition of a greater lymphocyte repertoire (>5 % of the naïve lymphocytes) [1]. This immunologic property derives from the unique ability of classical superantigens to interact with most T lymphocytes that express antigen receptors from a particular variable (V) region gene family.

Some naturally occurring proteins are superantigens for B-lymphocytes. B-cell superantigens are endowed with unconventional immunoglobulin-binding capacities that parallel the properties of T-cell superantigens to activate lymphocytes. The best characterized of these immunoglobulin (Ig) superantigens is *Staphylococcus aureus* protein A [2]. Other B-cell superantigens are the gp120 envelope glycoprotein of HIV-1 [3], a human gut-associated sialoprotein termed "protein Fv" [4], and protein L from *Peptostreptococcus magnus* [5].

The concept of Ig superantigens applied to the pathophysiology of allergic disorders could be translated as "superallergens" to indicate proteins of various origins able to activate FcεRI$^+$ cells (mast cells and basophils) through interaction with membrane-bound IgE.

It is generally thought that four canonical mechanisms (antigen, anti-IgE, anti-FcεRI and IgE-containing immune complexes) of IgE-mediated activation of human FcεRI$^+$ cells are responsible for the pathophysiologic involvement of these cells in the majority of allergic disorders [6]. However, there is evidence that a significant percentage of allergic diseases (e. g., certain cases of intrinsic asthma and chronic idiopathic urticaria) cannot be explained by the four classical mechanisms of FcεRI$^+$ cell activation. Therefore, we have investigated the hypothesis that Ig superantigens of various origins (endogenous, bacterial and viral) can activate FcεRI$^+$ cells to release proinflammatory mediators and cytokines.

Correspondence to: G. Marone

Urticarial reactions can occur in patients with acute and chronic viral hepatitis [7,8]. Protein Fv is a sialoprotein produced in the human liver and released in biological fluids during viral hepatitis A, B, C, and E [9]. Protein Fv binds to the variable domain of the heavy (H) chains of Ig, regardless of Ig class, subclass, and light (L) chain type (4). A single protein Fv molecule can bind six $F(ab')_2$ fragments of human IgM, IgG, and IgE [9]. Binding of protein Fv to the V_H3 region of Ig occurs in a domain external to the conventional antigen-binding pocket [10].

Protein Fv is the most potent IgE-mediated stimulus for the activation of human basophils and lung mast cells and acts as a complete secretagogue on FcεRI$^+$ cells by interacting with IgE V_H3^+ [11]. The V_H3 is the largest Ig family within the human repertoire (~50 %) [1]. Therefore, protein Fv can function as an endogenous Ig superantigen that interacts with a high frequency with IgE V_H3^+ bound to FcεRI$^+$ cells. Protein Fv also induces IL-4 secretion from basophils through interaction with IgE V_H3^+ [12]. IL-4 is a critical cytokine in the regulation of IgE synthesis by B lymphocytes. It is intriguing that some patients with viral hepatitis have high serum IgE levels [13].

The mechanism of FcεRI$^+$ cell activation by protein Fv represents a new pathogenetic cascade consisting of viral infection, endogenous Ig superantigen production, activation of FcεRI$^+$ cells and tissue injury. This sequence of events raises the possibility that additional endogenous Ig superantigens induced by viruses can cause tissue injury in allergic inflammation through this mechanism that involves FcεRI$^+$ cell activation.

HIV-1-infected children [14] and adults [15] have an increased serum IgE levels and prevalence of allergic reactions [16]. HIV-1 gp120 is a member of the Ig superantigen family and Ig V_H3^+ are a ligand for gp120 [17]. Recombinant gp120 derived from divergent HIV-1 isolates from different viral clades of various geographical origins stimulated the release of IL-4 and IL-13 parallel to the secretion of histamine from

basophils [18, 19]. By contrast, IFN-γ mRNA was not detected in any of the gp120-stimulated basophil preparations. Preincubation of gp120 with three preparations of human monoclonal IgM V_H3^+ inhibited the effects of gp120 on secretion from basophils. Therefore, the viral superantigen gp120 can rapidly activate FcεRI$^+$ cells through interaction with IgE V_H3^+. This raises the possibility that other viral Ig superantigens can cause allergic diseases through this novel mechanism.

Most clinical isolates of *Staphylococcus aureus* synthesize protein A, a cell wall protein that has unique Ig-binding properties. Protein A has a classical site that binds the Fcγ of IgG, and an alternative site that binds the Fab portion of 15–50% of human polyclonal IgG, IgM, IgA, and IgE [2]. *S. aureus* Cowan 1, which synthesizes protein A, and soluble protein A induce histamine release from basophils [20] and mast cells [21]. Protein A mediates the *Staphylococcus*-induced activation of FcεRI$^+$ cells through the interaction of the alternative binding site with IgE V_H3^+. This raises the possibility that exacerbations of atopic dermatitis [22] and certain forms of asthma [23] associated with *S. aureus* infection can be caused through this mechanism.

Protein L, a cell-wall protein synthesized by the bacterium *Peptostreptococcus magnus* [5], consists of up to five repeated Ig-binding domains (B1–B5) and appears to be a virulence determinant [24]. Each homologous domain binds to the variable domain of the Ig κ light chains, but does not bind to Ig H chains, λ chains, and the C_L domains of κ L chains [5, 24]. Protein L binds human Ig regardless of the H chain class, is mitogenic for B cells [25], and is an Ig superantigen [2]. We demonstrated that protein L induces the release of proinflammatory mediators and cytokines (IL-4 and IL-13) from basophils and lung mast cells by interacting with the IgE bound to FcεRI [21, 26, 27]. This is the first demonstration that a bacterial protein (protein L) activates human FcεRI$^+$ cells through the interaction with the κ light chains of IgE.

The association between certain viral infections and the induction and/or exacerbation of allergic reactions is well established [28]. Moreover, certain bacterial infections (e. g. *Staphylococcus aureus)* can also induce exacerbation of atopic dermatitis [22] and certain forms of asthma [23]. Our results provide a novel mechanism by which viral and bacterial infections can be involved in the induction and/or exacerbation of certain allergic reactions.

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