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Immunoglobulin E

Clyde Schultz[1,2*]

[1]Department of Biology, The University of Calgary, Alberta, Canada

[2]BioGram Inc., Ponte Vedra, USA

Abstract

IgE represents the least abundant of all immunoglobulin classes, but as with the other classes, it has unique influences in the human and mammalian immune response. It is primarily a defense against pathogens but as has been determined by evolutionary pressure, this has evolved into the critical area of allergic reactions. Whether in response to a helminth or to a food allergen the basic role of IgE in the response is largely the same.

Introduction

Immunoglobulin E (IgE) is synthesized by plasma cells and is the least circulating of the five antibody classes, comprising about 0.05% of the total immunoglobulin concentration in humans. One of the main functions of IgE are in response to infections by helminths such as Schistosoma and protozoans such as Plasmodium. The other major function is in Type I hypersensitivity reactions. These are primarily reactions such as asthma and other various allergies. IgE does this by interaction with cells such as basophils and mast cells.

IgE was discovered in the mid-1960's more or less simultaneously by two different groups working independently of one another [1]. IgE has been found only in mammals to date. It has the same basic structure as the other antibody classes, indicating that the immune system in all animals has had at one point the same origin.

Structure

IgE is comprised of two heavy, and two light chains which are identical. IgE concentration in the blood is about 0.05% of all immunoglobulin types. They are held together by disulfide bonds and have two distinct regions, the FAB and the Fc regions. The Fc or constant region (C-epsilon) binds to the low and high affinity IgE cell receptor. These are called Fc€RI, the high affinity IgE receptor and Fc€RII, the low affinity receptor-also referred to as CD23. IgE has the capacity to activate (up-regulate) both. The Fc€RI receptor is found on mast cells, basophils and dendritic cells [2]. This will ultimately lead to the release of cytokines such as IL-3 and stem cell factor. Also released are IL-4, IL-5 and IL-13, which activate lymphoid cells. Inflammatory mediators that are released by mast cells and basophils include histamine tumor, necrosis factor, leukotrienes, and prostaglandins. IL-4, 5 and 13 release will feedback and cause the release of more IgE thus prolonging what is a late phase allergic reaction. The low affinity Fc€RII (CD23) receptor is found on B cells has a role in antigen presentation and in IgE synthesis. Both receptors appear to be involved in feedback loops which prolong the presence of IgE, thus in some cases prolonging the disease response.

Clinical implications

One of the most important aspects of IgE is its apparent co-evolution with immune cells such as mast cells and basophils both in terms of allergic responses but also in defense against parasites such as Schistosoma. In allergic responses IgE is elevated in autoimmune diseases such as psoriasis and Rheumatoid arthritis. Fc€RI is involved as the high affinity receptor. The understanding of the structure and function of this receptor has been useful in anti-allergen drug development.

Chronic disease related to IgE include such old and famous syndromes as asthma and Chronic Urticaria (CU). Asthma has historically been viewed as a Th2 mediated process linked to the recruitment of eosinophils, with the early onset for the of the disease the most widely studied. Irritants such as allergens have the ability to activate dendritic cells in the airway passages in humans (and other animals). This activation regardless of the means leads directly to Th2 activation, with the accompanying IgE accumulation. Cytokines are also produced, with the addition of recruitment of mast cells, basophils and eosinophils. These then produce other cytokines in a feedback loop, with the additional factors such as histamine and prostaglandins. Mucous production increases and well as bronchoconstriction, with the end result of breathing difficulty. Allergy is a hypersensitivity reaction to environmental antigens. The caveat is that individuals must be susceptible. IgE that is allergen specific produced by B-cells, binds to IgE receptors present of other effector cells such as mast cells and basophils [3]. Once bound, the subsequent effector cells are programed and activated upon re-exposure to that given (usually environmental or food) allergen, and release soluble effector proteins such as histamine, cytokines, and prostaglandin's which are pre-formed and located in cellular granules. De-granulation releases these molecules, thus leading to wider activation of the cytokine cascade including cell migration by cells such as eosinophils to an exposure site or location. Allergens initially captured by dendritic cells are presented to CD4(+) T cells in lymphatic tissue. There is downstream activation of the cytokine system, with the resulting feedback loops which prolong the response often to the detriment of the allergen sufferer [4,5]. There are numerous

Correspondence to: Clyde Schultz, Department of Biology, The University of Calgary, Alberta, Canada, Tel: 4032205278; E-mail: schultzc@ucalgary.ca

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over the counter treatments for allergic conditions. The resulting industry grosses profits in the billions (US) of dollars worldwide, with patient use increasing.

CU manifests clinically as pruritic wheals that develop in the areas around the erythema [6]. Wheal size and duration is variable. CU may be either an acute form which may be allergic and can last up to six weeks, but often of a shorter duration. A chronic form also exists which last at least 6 weeks. This form occurs in less than 0.8% of the population. The chronic form occurs as a result of mast and basophil release of mediators, the most prominent of which is histamine. Histamine which acts on H1 and H2 receptors in the skin. Binding of H1 receptors causes edema and vasodilation [7]. Treatments for the condition fall mainly into the realm of H1-antihistamines [8]. These include standard dosed and up-dosed (4 times) non-sedating H1-antihistamines. However, some patients do not have a resolution of symptoms. In these cases, a third line therapy, omalizumab is given [9].

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