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Immunoglobulin E in health and disease

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The discovery of immunoglobulin E (IgE) was a breakthrough in the field of Allergy and Immunology. Our understanding of mechanisms of allergic reactions and the role of IgE in these disorders has paralleled to the discovery of treatment modalities for patients with allergy. Apart from allergic diseases, IgE is involved in pathogenesis of other disorders. Much controversy exists about the control of total IgE (tIgE) levels and allergen-specific IgE (sIgE) profiles in allergic individuals. This review aims at giving a comprehensive overview of IgE molecule and discussing the issues related to its importance in clinical setting.

Key words: Immunoglobulin E; Allergy

Basic characteristics of immunoglobulin E (IgE)

The discovery of IgE was made much later than the discovery of other immunoglobulin subclasses. The first clue to the existence of a substance responsible for hypersensitivity reactions was demonstrated in 1921 by Prausnitz and Kustner, and after only four decades (1967) it was identified as an immunoglobulin subclass by Ishizakas and co-workers [1]. In 1968, The WHO International Reference Centre for Immunoglobulins announced the presence of a fifth immunoglobulin isotype, IgE [2]. IgE is the antibody isotype that contains the ε heavy chain and it is a monomer with five domains in the immunoglobulin structure. It is normally present in plasma at a concentration of less than 1 μg/mL and has a half-life of about 2 days in serum [3]. A new unit (kU/L or IU/mL) was introduced to express the level of IgE in peripheral blood to alleviate the inconvenience in expressing the very low levels of serum IgE. One kU/L is equal to 2.4 ng/mL [4].

Once produced, IgE binds to its receptor FcεR, which are of two main types. High-affinity receptors (FcεRI) are found on wide variety of cells; mast cells, basophils, antigen presenting cells, monocytes and platelets [5-7] whereas low-affinity receptors (FcεRII) are found to be expressed on B-cells [7], monocytes [8] and dendritic cells [9]. The role of high affinity receptors in the pathogenesis of allergy is well understood [2, 7] but the biological role of low-affinity receptors is still unclear.

The role of IgE in health and disease

IgE was discovered for its involvement in allergic reactions (Type I hypersensitivities). People, who have a tendency to develop symptoms when exposed to allergens, produce IgE specific to that allergen, which evokes a cascade of reactions [10]. In terms of evolution, it is highly unlikely that IgE evolved to contribute to the pathology of allergy, hence people started

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investigating the exact role of IgE in human. It has been shown that the dominant role of IgE is to protect the host from parasitic infections, specially helminth infections [11]. Hence it is believed that IgE has evolved to protect the human from helminth infections, which once was the major threat for the survival of the human species [12, 13].

Role of IgE in helminth infections

IgE plays a vital role in the cross-talk between innate and adaptive immunity. Helminths are large parasites that can not be engulfed by phagocytes and could be best dealt by cytotoxic cells. Invasion of tissues by helminths stimulates an immune response which generates a cytokine milieu that shifts the TH_0 cells to mature along the TH_2 pathway. These TH_2 cells secrete interleukin (IL) 4 which induces the B cells to switch the immunoglobulin class to IgE. At the same time secreted IL 5 enhances the production and maturation of eosinophils [14].

IgE molecules coat the parasite which enables the tissue mast cells and circulating eosinophils to bind via their IgE receptors. This interaction of IgE with their receptors initiates a cascade of reactions in these cells which results in release of histamine and other toxic substances to the exterior [15]. Eosionophils that are recruited to the site of infection release granule proteins such as major basic protein, eosinophil cationic protein. These toxic substance released from the cells in the vicinity of the invading parasite are capable of killing the parasite [16, 17].

IgE in allergic reactions

Understanding the role of IgE in allergic reaction has been a major breakthrough in the field of allergy. It has paved the way for the discovery of effective drugs for these diseases. The sequence of events in the allergic reaction consists of the production of IgE antibodies in response to an allergen, binding of IgE to Fc receptors of mast cells, cross-linking of the bound IgE by the allergen upon re-exposure, and release of mast cell mediators such as histamine, lipid mediators and cytokines. Some mast cell mediators cause rapid increase in vascular permeability and smooth muscle contraction, resulting in many of the symptoms [18, 19].

The above reaction does not take place in every individual when exposed to environmental allergens. People with a genetic predisposition, called atopics, have a personal tendency to develop IgE when exposed to otherwise harmless environmental allergens. Such individuals have allergen-specific IgE (sIgE) in their serum reflecting their exposure to allergens in the past [10].

Levels of total IgE (tIgE) and sIgE

The rising trend of allergic diseases in the affluent populations in developed countries was alarming [19]. Investigations were carried out to find markers of allergy in such populations. The observation of high levels of tIgE in allergic individuals compared to healthy controls lead to identifying a cut-off level of tIgE for a diagnosis of allergy. It was observed that the probability is very high in predicting allergy when the tIgE level is above 200 kU/L [20, 21]. Longitudinal studies have demonstrated that levels of IgE increases with age from birth, regardless of atopic status but the increment in atopic children is abrupt and continue to have high levels in adult hood [22, 23]. Since most somatic IgE is bound by its receptors, serum IgE may not necessarily reflect the systemic IgE levels. However, Dehlink and co-workers have been able to demonstrate that the level of serum IgE correlates well with cell-bound IgE [24]. Nevertheless, a high tIgE level alone is of limited value as a marker of allergy as it does not give any clue to sensitizing allergens in an individual. Hence, attention was paid more on sIgE as a biomarker.

The pool of IgE in an individual is the sum of IgE produced against different allergens - ie: specific IgE. Presence of sIgE in serum indicates that the individual has been exposed to the allergen earlier (sensitized). Presence of sIgE against a particular allergen above a level of 0.35 kU_A/L is deemed positive for that allergen [10]. A person is said to be atopic if laboratory data shows a positive test. It should be noted that a positive result does not always correlate well with the clinical feature of a person. People with positive test for a particular allergen may not necessarily get symptoms when exposed to that allergen [25, 26]. Although, a positive test (a level $\geq$ 0.35 kU_A/L) for aeroallergens generally correlates well with the clinical expression, much controversy exits for food allergens [27, 28, 29]. The difficulty in defining a single reference value for all the food allergens has made doctors uncomfortable in interpreting reports. Different reference values for different food allergens have been suggested based on clinical evidence, but this makes the clinicians life extremely complicated when managing patients. Thus, well conducted cross-sectional and longitudinal studies are needed to reach a consensus in this regard.

IgE levels in populations in tropics

Recently, there had been much interest on how the allergic response is modulated by helminths in people living in helminth endemic areas of the tropics. Serum levels of tIgE are very high in such people despite being non-atopic [13, 30]. Indeed, it is observed that the tIgE levels are several folds higher in them

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compared to atopic people in the developed western countries emphasizing the limited use of tIgE as a marker of allergy in tropics [13]. It is known that helminths are capable of inducing IgE synthesis markedly [30]. Analysis of IgE molecules in such people has revealed that most of these IgE are non-specific [31, 32]. It is postulated that polyclonal synthesis of IgE is a mechanism of the parasite to evade the host immune response against it [32]. The mechanism of immune evasion by helminths is not well elucidated to date. The observation of high tIgE and low sIgE levels in populations in tropics is interesting and needs to be explored since it reflects some of the facts related to the control of IgE synthesis.

Lynch et al have reported that helminths enhance the polyclonal synthesis of IgE resulting in high tIgE levels, while down-regulating the production of sIgE [32]. This suggests that control of tIgE and sIgE is independent from each other. Direct evidence for this comes from the study done by Sunyer and colleagues, which showed that tIgE levels are associated with asthma even in subjects negative for sIgE to common aeroallergens [33]. It should be noted that the population for the latter study comes from an area not endemic for helminth infections. Reinforcing this notion, genetic studies have revealed different genetic loci for tIgE levels and sIgE profiles [34-36]

Elevated tIgE in other diseases

The presence of high levels of tIgE in allergic diseases is well documented. Nevertheless, there are other situations where an increase in the level is observed. Hyper IgE syndrome, IgE myeloma, some disorders of vasculitis, though rare, should be considered in differential diagnosis for extremely high tIgE levels [37].

Therapeutic implications

The cornerstone of an allergic reaction is the cross-linking of IgE molecules bound to mast cell receptors. Neutralization of IgE antibodies is a conceptually new approach for the treatment of allergic diseases. Recombinant monoclonal humanized anti-IgE has demonstrated promising results as a treatment for asthma in adults [38]. Further studies are needed to evaluate long-term safety and efficacy in the treatment of allergic diseases with anti-IgE treatment in children [39].

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