

The History of IgE: From Discovery to 2010

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Abstract The discovery of IgE and the role of IgE-mediated inflammation gave clinical allergy a scientific backbone, and as a result, the reputation of the specialty allergy has increased considerably over the years. Allergy diagnosis was improved by assays for in vitro determination of the presence and concentration of IgE antibodies, and clinical knowledge also broadened, allowing better service for the increasing number of allergic individuals. Access to immune assays for allergens finally allowed characterization and standardization of allergen preparations used for diagnosis and allergen-specific immunotherapy. Improved basic molecular technologies have further increased our knowledge about the complex component composition of an allergen extract, introduced IgE-specific immunotherapy, and allowed the allergist to better handle even severe allergic reactions such as anaphylaxis.

Keywords IgE antibody · ASIT · ESIT · CD-sens

Introduction

The presence in serum of a factor causing allergy was proposed in 1919. However, it would take half a century before IgE could be identified and officially recognized by the World Health Organization. After this crucial event, our understanding of allergy and immunology increased drastically, and the possibilities for managing allergic patients have improved immensely.

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The first case of hay fever induced by pollen was reported in 1819 by the patient himself, Dr. John Bostock [1]. It took another 100 years before the connection to a serum factor was made. In 1919, a case of asthma caused by allergy passively transferred by blood transfusion was reported by Ramirez [2]. Then, in 1921, Prausnitz and Küstner [3] performed their famous passive transfer of a positive skin test, the PK test. In 1923, Coca and Cooke [4] first used the term *atopy* and linked this hereditary trait to the presence of “bodies” that they chose to call *reagins*.

Then nothing much happened for several decades. Finally, in the 1960s, new sensitive techniques for the separation and identification of proteins enabled new approaches to serology and finally made the discovery of IgE possible.

The Discovery

The discovery of IgE was made independently by two research teams: Kimishige and Teruko Ishizaka in Denver in the United States, and Hans Bennich and S.G.O. Johansson in Uppsala, Sweden. The two groups approached the issue from different points of departure and used different methodologies but arrived at the same conclusion and were able to corroborate each other's findings.

The Denver group was specifically looking for the causes of the reagin-mediated histamine release reaction by structured laboratory work. In 1964, they reported that they had found that the reagin was an antibody belonging to the IgA class, at the time called γA [5]. That this was a mistake was soon pointed out by many authorities in the field.

However, they continued their search, using methods for protein separation combined with immunization of experimental animals. In 1966–1967, they found an antiserum that could precipitate a serum fraction, resulting in a decrease in

PK activity [6]. They postulated that this represented a new immunoglobulin class and provisionally called it γ E-globulin. However, as γ E was never purified, it was not possible to prove that it was a homogeneous immunoglobulin, or rather a complex of known inflammatory factors.

The Uppsala group approached the problem from another direction. The starting point was the discovery in the summer of 1965 of a serum with an atypical myeloma protein. The M component could not be identified as belonging to any of the then-established immunoglobulin classes (IgG, IgM, or IgA). It also was not IgD, which had recently been discovered [7]. Investigations confirmed that it had unique antigens and unique biochemical/physiochemical properties that distinguished it from the four known immunoglobulins, and it was provisionally called IgX. A radioimmunoassay based on antibodies to antigens on the Fc fragment of IgX was developed, and the sera of blood donors inhibited the assay in a dose-response manner. Thus, IgX had all the properties needed for the definition of a new immunoglobulin class; it was a unique biochemical structure carrying unique antigens generally present in the population. In addition, it was shown that the new immunoglobulin, and later its Fc fragment, blocked the PK test [8]. The new immunoglobulin was provisionally named IgND, using the initials of the patient from whom the original blood sample came, as was the tradition at the time.

Further studies revealed that the serum IgND concentration was increased in about 60% of the cases with allergic asthma [9]. A radioimmunoassay for IgND antibodies to common allergens was developed, the radioallergosorbent test (RAST), the results of which correlated well with clinical allergy diagnoses [10].

In early-1967, reagents were exchanged between the Denver and Uppsala groups. It was found that antiserum to γ E-globulin reacted with isolated IgND, and that purified IgND could block the reaction of anti- γ E in a biological test system for reaginic activity. Apparently, γ E and IgND shared antigenic determinants and biological activity. The official declaration of a new immunoglobulin class, IgE, was then made in 1968 by the World Health Organization Immunoglobulin Reference Centre in Lausanne [11].

The ability to initiate an allergic reaction by passive sensitization via a blood transfusion had been reported by Ramirez [2] in 1919. Interestingly, a few years ago, we studied this and finally, after close to 100 years, confirmed the observation. It was found that if plasma used for transfusion contained at least 5 to 10 kilounits per liter of an IgE antibody, the receiving patient became IgE sensitized, and the sensitization disappeared rather slowly; a half-life of 5 to 10 days was observed [12]. Thus, plasma donors with IgE antibodies should be avoided.

The Function of IgE

The IgE molecule is a single four-chain unit with a molecular weight close to 190,000 D and a carbohydrate content of about 12%. It shares the general characteristics of all immunoglobulins, but two features stand out: the extremely low concentration in normal serum and its unique function to activate basophils and mast cells. IgE-mediated inflammation is the triggering mechanism in, for example, allergic asthma and rhinitis, anaphylaxis, and the atopic subgroup of eczema.

Although the pathological role of IgE in allergy and asthma is now well-established, the normal beneficial function remains unclear. It has been speculated that the primary purpose of IgE could be in the defense against parasitic infections. It does not seem likely, however, that an immunoglobulin with the salient feature of being able to detect extremely minute amounts of proteins (eg, the annual dose of ragweed pollen allergen being in the order of 1 μ g [13]) should primarily defend against organisms secreting large amounts of proteins. It might be engaged, however. The finding of IgE antibodies to the infecting helminth and a high serum IgE concentration could be an indication of a failure of the immune system to protect the individual. Actually, the high level of nonparasitic IgE may be the result of the defense of the parasite; non-antibody active IgE seems capable of blocking the mast cells and basophils from being triggered by allergen cross-binding antibody [14].

Given the ability of IgE to detect minute amounts of foreign proteins in combination with its ability to activate other parts of the immune system, it appears much more probable that it may have a “gatekeeper” function—to be the first to raise the alarm when a foreign protein enters the body, activating and recruiting other antibodies and cells that can attack and defeat the intruder.

There also has been much speculation about a possible connection between IgE and cancer. Different hypotheses have been proposed that are quite contradictory. On the one hand, it has been suggested that IgE could have a protective effect against cancer by enhancing immune surveillance. On the other hand, it has been proposed that allergy could be associated with an increased risk of cancer due to chronic immune stimulation. A survey of the literature [15] seems to leave open the possibility for a small increase of a few types of cancer, but an epidemiologic study did not support either hypothesis [16].

Diagnostic Tests

The discovery of IgE and the development of tests for IgE and IgE antibodies meant that clinical diagnostics and scientific investigations of allergy could be performed in

vitro. In vivo skin tests had long been used, but they suffered—and still do today—from severe drawbacks in terms of accuracy and safety. They also can be difficult to perform and interpret [17–19].

The method used when in vitro tests for IgE were first developed more than 30 years ago was to measure the total amount of circulating IgE in the blood “total IgE” [9]. The first commercial IgE test was introduced in 1972.

However, allergen specific IgE antibodies “specific IgE” are responsible for the allergic symptoms and are clinically relevant. The first test enabling the measurement of such IgE antibodies was the RAST test [10], made generally available in 1974.

Continued developmental work over the past few decades has resulted in increasingly sensitive and accurate test systems, enabling measurements of IgE antibodies to many hundreds of allergens. As the vast majority of allergic patients are handled in primary care, a need also exists for simple tools that can help the primary care physician diagnose allergy, appropriately manage the less severe cases, and identify the patients who should be referred to specialists. Today there are reliable near-patient tests for IgE antibodies that give yes/no answers in a couple of minutes.

However, quantitative measurements of IgE antibodies are essential in many cases in which a better understanding of the allergic disease is needed (eg, before starting allergen-specific immunotherapy [ASIT] or IgE-specific immunotherapy [ESIT], or when evaluating the prognosis of the disease). A clear relationship has been demonstrated among the concentration of IgE antibodies in the individual patient, the likelihood of him/her developing allergic symptoms, and the severity of the symptoms [20, 21].

In this connection, it is interesting to note that the size of the IgE antibody fraction in relation to the total amount of IgE plays a role: the higher the percentage of IgE antibodies out of the IgE, the less allergen needed to trigger the basophils [14]. Also, if a patient is sensitized to several allergens to which

he or she is exposed simultaneously (eg, cat dander, house dust mites, and molds), the IgE antibodies seem to “work together” in the triggering process. Their concentration thus should be added together when the size of the clinically relevant antibody fraction is calculated [22]. However, this does not apply to IgE antibodies to cross-reacting allergens (eg, different mites) [23]. Adding up their concentrations would mean counting the same IgE antibody several times.

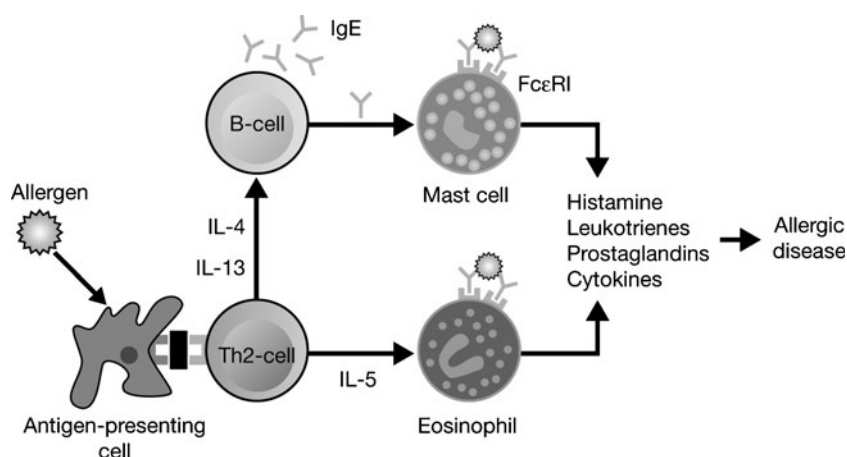
In recent years, interesting data have been published showing that what was previously regarded as one specific allergen actually consists of many non-cross-reacting allergenic components [24]. Because some of these are allergens cross-reacting with rather innocent allergens such as pollens, while others seem to carry the major allergenic property of the allergen source in question, knowledge about the IgE sensitization to the allergen component profile is of clinical importance.

Treatment

Knowledge about IgE and IgE antibodies in patients has a great impact on the treatment of individuals with allergy and asthma (Fig. 1).

The first step in the management of allergic patients should be avoidance/elimination of the allergen source triggering the symptoms. A prerequisite for this is, of course, the identification of this source, and here the ability to test for IgE antibodies in the patient’s blood makes a fundamental difference. A most remarkable example of this is the “pholcodine story” [25]. In some countries (eg, Norway, France, the United Kingdom, and Australia), there is a high prevalence of anaphylaxis to neuromuscular blocking agents during anesthesia, while in others (eg, Sweden), reactions are very rare. In Norway, such anaphylactic reactions were 10 to 20 times more common than in Sweden. It was found that the most likely reason was that many individuals in Norway became IgE sensitized to a cough

Fig. 1 Possible targets for interfering in the inflammatory cascade. IL—interleukin; Th2—T-helper type 2. (Image courtesy of Novartis, Basel, Switzerland)



syrup that was not available in Sweden and contained pholcodine, which shared allergenic determinants with the neuromuscular blocking agents. In 2007, the cough syrup was withdrawn from the market, and the annual number of cases of anaphylaxis has now decreased from about 20 to 1 or 2 cases per year (Florvaag et al. Allergy, 2011, in press).

The ability to measure IgE antibodies also made possible the characterization of allergen extracts used for immunotherapy, ASIT, in terms of both content and potency, making this form of treatment safer and more effective. However, because immunotherapy in some countries is often initiated based exclusively on intradermal skin tests, which have been shown not to indicate the presence of clinically significant sensitivity [18], it seems that ASIT could actually be an efficient placebo. The recently suggested use in ASIT of chemically modified allergens incapable of triggering mast cells or basophils is a most interesting approach that may broaden the basis for immunotherapy [26••].

A new approach to the treatment of IgE-mediated allergic asthma is the use of anti-IgE monoclonal antibodies, ESIT (eg, omalizumab [Xolair; Novartis, Basel, Switzerland] (Fig. 2) [27]. This treatment is currently prescribed based on the serum level of IgE “total IgE”, and no recommendations are provided concerning anti-IgE dosage in relation to the concentration of IgE antibodies.

Basophil allergen threshold sensitivity [28], referred to by us as CD-sens, has been shown to be a most useful approach to evaluate a patient’s allergen sensitivity (ie, the link in the allergy chain that anti-IgE treatment is supposed to eliminate) [14]. In a recent study using CD-sens, we evaluated the importance of the relative size of the IgE antibody fraction in patients undergoing anti-IgE treatment and found that if the percentage of IgE antibodies was higher than 3.8%, none of the patients responded with a

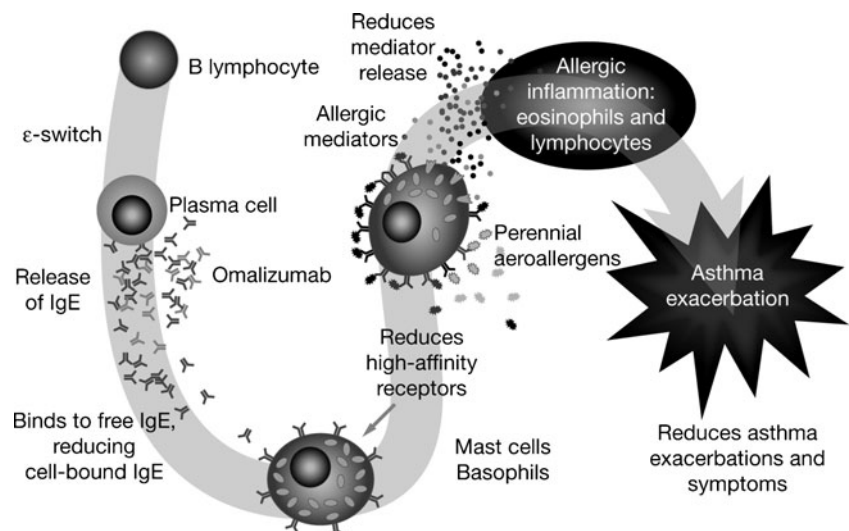
“turning off” of the IgE triggering [29••]. A recent study of patients with allergic rhinitis confirmed these findings [30]. An increase in the anti-IgE dosage given to such patients therefore should be considered, and when calculating the patient’s antibody fraction, the concentration of IgE antibodies with different relevant specificities must be added together. Obviously, to obtain a good response by ESIT, the presence and concentration of clinically relevant IgE antibodies must be duly taken into consideration, and this may be of special importance in the “real atopsics” with low IgE concentrations but large IgE antibody fractions [31].

Into the Future

As our scientific knowledge and technological abilities continue to develop, new approaches to the management of the pathological conditions triggered by IgE are emerging. The increasing global communication between allergists and other physicians—and also nonclinical scientists, journalists, and patients—created a demand for an updated allergy nomenclature. If we interpret the allergy terms differently, we cannot understand each other. Both the European Academy of Allergy and Clinical Immunology [32] and the World Allergy Organization [33••] created committees that published official updates of the nomenclature to great benefit for the field.

Much interest has been devoted recently to the single components (proteins) of what we usually call allergens. Allergenic proteins can now be produced in large quantities by recombinant DNA technology. This opens up new possibilities to study the exact sensitization profile of a patient; to investigate allergic reactions in more detail to determine if they are caused by “true” sensitization to the substance, or by IgE antibodies cross-reacting to different

Fig. 2 The allergy chain starting at allergen exposure and ending up with clinical allergy. Omalizumab will eliminate or markedly reduce the IgE link, thus interrupting the chain reaction. (Adapted from Ledford DK, Expert Opin Biol Ther. 2009 Jul;9(7):933-43 with permission of Informa Healthcare)



allergens; and to optimize the selection of patients for immunotherapy [26••].

The development of such more detailed knowledge, assisted by the emergence of high-throughput array test technologies, undoubtedly will help us expand our insights into IgE and its role in allergy and asthma. However, it should be noted that the daily work of the practicing physician is hardly made easier by “component resolved diagnostics.” The vastly increased number of factors to take into consideration unavoidably complicates matters, so there is a great need for practical tools to help interpret the huge amount of information.

Conclusions

The discovery of IgE in 1967 ended the search for the elusive “reagin” and made possible several new developments in allergology and immunology. Today we have more knowledge upon which to base our work and many new technological tools at our disposal. As we have seen, many aspects of IgE, allergy, and asthma remain to be explored and clarified. We can rest assured that the coming decades will yield some answers that in turn will lead to new questions.

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