

The discovery of immunoglobulin E

S.G.O. Johansson, M.D., Ph.D. (Sweden)

ABSTRACT

As early as 1919, from a case of transient asthma caused by blood transfusion, the presence in serum of a factor causing allergy was proposed. Despite intense search, this factor was not identified until 1968, when immunoglobulin E (IgE) was officially recognized by the World Health Organization. The knowledge about IgE mediating allergy has greatly improved our understanding of allergic inflammation and diagnoses and treatment of allergic diseases. (Allergy Asthma Proc 27:S3–S6, 2006)

Although the exact causes for the development of an allergic disease still needs to be explained, our knowledge about allergy and the immunologic mechanisms involved has improved immensely during the last decades. The crucial event was the discovery of immunoglobulin E (IgE) in the late 1960s.

Despite excellent work at many centers around the world, allergology was, in those days, still a clinical specialty with a questionable reputation. In the absence of solid facts about mechanisms, the field was open for speculations. Allergy diagnosis still relied on intradermal skin tests that were painful to the patients and of limited reliability, because the allergen extracts were far from standardized and varied widely in content and activity. The discovery of IgE and the identification of its role in allergic inflammation would change this situation significantly.

HISTORIC BACKGROUND

The nature of allergic activity had long remained a riddle. The first case of pollen-induced hay fever was reported to the Royal Medical and Chirurgical Society in London in the 1819 by the patient himself, Dr. John Bostock.¹ Although the clinical significance of pollen counts and allergen provocation challenge tests was well understood in the late 19th century, it took another 100 years from Bostock's report before the connection to a serum factor was first made. In 1919 a case of asthma caused by allergy to horse dander passively transferred by blood transfusion was reported.² Interestingly, the immunologic and inflammatory reactions behind this clinical observation recently have been studied in detail.³ In 1921 Prausnitz and Küstner performed their famous passive transfer of a positive skin test,⁴ later called the PK test. When Coca and Cooke

introduced the term "atopy" in 1923⁵ they linked this hereditary trait to the presence of "bodies" that they called "reagins," because these were believed to display the same type of heat sensitivity as the heat-labile reagents (complement) of the Wassermann reaction. However, they recommended that the term "antibodies" should be avoided because there is "no evidence that these bodies appear as the result of immunologic stimulation."⁶

During the next 40 years not much progress was made toward the isolation and characterization of the reagins, despite serious efforts by many. Today, it is easy to understand why. The extremely low concentration in serum and the lability of the cell-interacting, biologic activity of the illusive immunoglobulin obscured most experimental data obtained with the techniques available at the time. In the 1960s scientific progress in the fields of immunochemistry/immunology and the development of new sensitive techniques for protein separation and identification enabled new approaches to the study of blood serology, opening the way for the discovery of IgE.

PIONEERING WORK BY TWO GROUPS

The breakthrough discovery was made simultaneously by two independent research teams on opposite sides of the Atlantic, one in Denver, CO (Kimishige and Teruko Ishizaka) and the other in Uppsala, Sweden (Hans Bennich and myself). The two groups had different points of departure and used different methodologies, but when they eventually arrived at the same discovery, they were able to corroborate each other's findings.

The Uppsala Group

In Uppsala, we initially focused on characterizing anti-Rh blood group antibodies into the then known immunoglobulin classes, but also we focused on exploring the structure and function of immunoglobulins in general. It was known that in multiple myeloma, a rather uncommon disease affecting the immunoglobulin-producing plasma cells, a very high and homogeneous increase in the cell product could be secreted. In

From the Department of Medicine, Clinical Immunology and Allergy Unit, Karolinska Institute, Stockholm, Sweden and Department of Clinical Immunology and Transfusion Medicine, Karolinska University Hospital, Stockholm, Sweden

E-mail address: s.g.o.johansson@ki.se

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electrophoresis this product was seen as a narrow, usually strongly stained, band referred to as an M component. I was responsible for running the immunoelectrophoresis to identify each M component detected in the routine screening of sera.

In the early summer of 1965, I found a serum with an atypical myeloma protein. The M component could not be identified as belonging to any of the established immunoglobulin classes IgG, IgM, or IgA, and it was not the newly found IgD, which recently had been discovered by D.S. Rowe, at that time at Johns Hopkins in Baltimore. Therefore, it was internally referred to as IgX, "the unknown immunoglobulin." Biochemical investigations confirmed that IgX had unique antigens and biochemical/physicochemical properties compared with the four known immunoglobulins.

Sensitive immunoassays for investigating the presence of IgX in sera of blood donors were developed in collaboration with Leif Wide at the Department of Clinical Chemistry, Uppsala University Hospital, Sweden. For a time, it proved difficult to find a counterpart in normal serum, but in January 1967 a radioimmunoassay based on antibodies to antigens on the 7S fragment was inhibited in a dose/response way by sera of blood donors. However, the concentration of the inhibiting factor was extremely low; $\sim 1/100,000$ of that of IgG. All of the evidence needed for the definition of a new immunoglobulin class thus was at hand: a unique biochemical structure carrying unique antigens generally present in the population. In addition, in collaboration with Dr. D.R. Stanworth in Birmingham, United Kingdom, it was shown that the new immunoglobulin, and later its Fc fragment, blocked the PK test. According to the convention of the time it was provisionally termed IgND, using the initials of the patient the original blood sample originated from. A detailed report on the discovery of IgND was published recently.⁷

Among the first blood donor sera tested, a remarkable outlier was found, with an IgND level about 30 times the mean of the group. The serum was found to originate from a person suffering from allergic asthma, which led us to investigate the presence of IgND in asthma patients. Serum IgND proved to be increased in about 60% of the cases with allergic asthma.⁸

Because IgND seemed to be linked to allergy, we, together with Leif Wide, developed a radioimmunoassay for IgND antibodies to common allergens. The assay was based on the antiglobulin principle used, e.g., to detect anti-Rh antibodies, but with several, innovative modifications. Thus, the allergen was covalently linked to the solid phase and the tracer anti-IgE was labeled with an isotope. This test (RAST), which became the legendary radioallergosorbent test, gave results that correlated well with the clinical allergy diagnosis.⁹ The study of serum IgND levels in asthma, the report on the radioallergosorbent test, and

findings of the dose/response blocking of the PK test with purified IgND¹⁰ were all published in *The Lancet* in the fall of 1967.

The Denver Group

The Ishizaka group in Denver, CO, was simultaneously approaching the problem from another angle. While the Uppsala group was exploring the properties of the previously unknown protein they had discovered, the Ishizakas were busy looking for the causes of the reagin-mediated histamine release reaction.

In 1964 they reported that the reagin was an antibody belonging to the IgA class, at the time called γA .¹¹ That this must be a mistake was, however, pointed out by many scientists in the field. Among other things, patients genetically deficient of IgA could have high titers of reagenic activity. Most likely, Ishizaka's Fc α preparation actually was contaminated with trace amounts of IgE sufficient to cause the biological reaction but not detectable by the protein assays available at the time.

The Denver group showed great tenacity and continued its search for the nature of the reagin, 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 activity¹², as well as binding to a mixture of reagenic serum and an allergen trace labeled with an isotope in autoradiography. This activity did not appear to belong to any of the four known immunoglobulin classes and therefore was postulated to represent a new immunoglobulin, provisionally called γE -globulin, because it was thought to mediate an erythema. Despite hard efforts, the Ishizaka group never succeeded in purifying the γE -globulin, which is not surprising, considering its extremely low concentration.

Comparing Notes

In early 1967, reagents were exchanged between the Uppsala and Denver groups and it was found that antiserum to γE -globulin reacted with isolated IgND, and that purified IgND could block the reaction of anti- γE -globulin in a biological test system for reagenic activity. It seemed γE and IgND shared antigenic determinants and biological activity.

At a workshop at the World Health Organization center in Lausanne in February, 1968, in which the main researchers from the two groups participated, it finally was agreed that, based on the unique biochemical and antigenic properties of IgND, supported by identical antigenic properties of γE -preparation, there were enough data available to allow the declaration of a new immunoglobulin. The very first report of the new immunoglobulin class, IgE, taking the fifth and, as it turned out, final alphabetical position, was pub-

Table 1 Some Physicochemical and Immunologic Properties of IgE Compared with the Other Immunoglobulins

	IgG	IgM	IgA	IgD	IgE
Heavy chain	γ	μ	α	δ	ϵ
Sedimentation constant (S)	7	19	7	7	8
Molecular weight ($\times 10^3$)	150	970	160	180	190
Half-life (d)	21	10	6	3	2
Carbohydrate (%)	2–3	12	7–11	9–14	12
Complement	++	+++	—	—	—
Placental transfer	+	—	—	—	—
Serum concentration (g/L)	10	1.5	2.5	0.03	0.000 05

lished.¹³ In addition, its relation to the reagenic activity was confirmed.

CHARACTERISTICS AND FUNCTION OF IgE

IgE shares the same general features of all immunoglobulins. Like IgG, IgA, and IgD, the native IgE molecule consists of a single four-chain unit. Its molecular weight is close to 190,000 Da and its carbohydrate content is ~12%. Some physicochemical and immunologic properties are summarized in Table 1 and compared with those of the other serum immunoglobulins. Note the extremely low concentration of IgE in normal serum, the inability of IgE to activate complement, and its inability to pass through the placenta membranes.

IgE is unique in its function to activate mast cells and we know that IgE-mediated inflammation is the triggering mechanism in allergic asthma and rhinitis, anaphylaxis, and the atopic subgroup of eczema. This pathological role can not be the primary function of IgE in the body, and the normal beneficial function still has not been established. One opinion has been that the purpose of IgE could be to act in the defense against parasite infections. It does not seem very likely, however, that the prime function of an immunoglobulin uniquely able to detect minute amounts of proteins should play a key role in the recognition of parasites, in which its proteins appear in very large amounts in the exposed human. There also has been much speculation over a possible connection between IgE and cancer. Contradictory hypotheses have been proposed; allergy could have a protective effect against cancer by enhanced immune surveillance, or it could be associated with an increased risk of cancer due to chronic immune stimulation. An extensive survey¹⁴ of the literature seems to leave the possibility open for a small increase of a few types of cancer but a recent epidemiologic study does not support either of these hypotheses.¹⁵ The fact that IgE is the immunoglobulin most capable of detecting minute amounts of foreign proteins combined with its ability to activate other parts of the immune system gives much credence to the hypothesis

that it may have a “gatekeeper” function: to be the first one to detect a new antigen entering the body, opening the doors to flood it away, and activating and recruiting other antibodies and cells that can attack the intruder. However, this hypothesis needs confirmation and additional elucidation.

Another aspect of allergic disease that still is not well understood is the initial sensitization. What are the mechanisms allowing the establishment of an ongoing, significant IgE sensitization mediating an allergic inflammation? If the key cells and chemokines and their interactions were known, it might be possible to “turn off” completely a pathological IgE antibody production.

LASTING IMPACT

The discovery of IgE provided the solution to the old riddle of the nature of reagenic activity and was a solid piece of science that significantly improved the standard and reputation of allergology. With access to IgE and reliable tests for IgE and IgE antibodies, scientific experiments now could be performed *in vitro*. This led to an enormous increase in the research activity in the field, which during the past decades has greatly improved our knowledge of allergy and its mechanisms.

One basic, but most important, implication of the understanding of basic mechanisms of allergic inflammation was the possibility to define clearly allergy in contrast to nonallergic hypersensitivity. Two major allergy societies, the European Academy of Allergology and Clinical Immunology and the World Allergy Organization, have revised the confusing field of allergy nomenclature and published position papers on the updated nomenclature.^{16,17} This work will have a significant impact on our understanding of allergy.

The general availability of *in vitro* allergy tests to allergy specialists and doctors in general has greatly improved the quality of allergy diagnosis. The test methods also have continuously been developed and refined, today enabling accurate quantitative measurements of IgE antibodies to hundreds of allergens.

Another great benefit has been the possibility to analyze and characterize allergen preparations in terms of content as well as potency. However, in some countries there still is a limited number of standardized allergen extracts available for skin testing and allergen-specific immunotherapy. Recently, the next step in this development has been taken, as recombinant products of major allergenic components have become available for research, clinical testing, and allergen-specific immunotherapy.

Finding the key to allergic inflammation also has made it possible to develop new therapies aimed at this key substance. As other contributions to this special supplement attests, anti-IgE therapy has proved successful in many respects. However, many external factors, including bacteria,¹⁸ certain viruses,¹⁹ helminths,²⁰ air pollution, *e.g.*, tobacco smoke²¹ and alcohol,²² and certain drugs,²³ significantly stimulate IgE production in general, resulting in increased concentrations in the blood of mostly nonantibody active IgE. Therefore, the serum levels of IgE, sometimes called "total IgE," is not a suitable measure of IgE antibody activity and thus allergy, neither for determining the optimal individual dosage of anti-IgE nor for monitoring the effect of the therapy. A recent study points to the possibility of using evaluations based on basophil allergen threshold sensitivity for this purpose.²⁴

The discovery of IgE has proved a major contribution to our knowledge about allergy; however, allergy still remains a serious problem for hundreds of millions of patients, and not the least for society, as the increasing prevalence costs society great sums of money and puts pressure on the health care systems in all industrialized countries. Thus, we need to further intensify our efforts to understand why persons become sensitized and develop allergic symptoms and how to control IgE sensitization.

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