IgE, mast cells, basophils, and eosinophils

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IgE, mast cells, basophils, and eosinophils are essential components of allergic inflammation. Antigen-specific IgE production, with subsequent fixation of IgE to FcεRI receptors on mast cells and basophils, is central to the initiation and propagation of immediate hypersensitivity reactions. Mast cells, basophils, and eosinophils are central effector cells in allergic inflammation, as well as in innate and adaptive immunity. This review highlights what is known about these components and their roles in disease pathogenesis.
Mechanisms of IgE Inflammation.

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Source

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Abstract

The prevalence of diseases such as allergic asthma and rhinitis continues to increase in the United States, affecting millions of people. It is well-established that allergy contributes to the pathogenesis of most asthma, especially in children and young adults. Despite current therapy (e.g., inhaled corticosteroids, anti-leukotrienes, and bronchodilators), patients with moderate to severe asthma remain symptomatic and experience frequent exacerbations of disease requiring oral corticosteroids, emergency department treatments, and hospitalizations. Allergic diseases are traditionally referred to as immediate or type 1 hypersensitivity reactions, with IgE as a critical factor. IgE is involved in allergic inflammation, especially in early-phase response, but it may also be involved in the late-phase allergic response. A direct correlation between serum IgE levels and asthma exists. As logarithm IgE values increase, asthma prevalence increases linearly, even in patients who are categorized as having nonallergic asthma. In addition, there is a significant, although low association in allergic rhinitis with IgE levels and positive skin test reactivity to pollens. Recent advances in our understanding of the role of IgE in allergic inflammation have led to the development of a monoclonal antibody to IgE that reduces IgE levels, thereby reducing allergic inflammation. This review aims to provide an overview of the basic science of the IgE molecule and the clinical efficacy of anti-IgE therapy in allergic and asthmatic diseases.
IgE An overlooked regulator of allergic disease

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Abstract

Given the importance of immunoglobulin (Ig) E in mediating type I hypersensitivity, inhibiting IgE production would be a general way of controlling allergic disease. The low-affinity IgE receptor (FcεRII or CD23) has long been proposed to be a natural regulator of IgE synthesis. In vivo research supporting this concept includes the observation that mice lacking CD23 have increased IgE production whereas mice overexpressing CD23 show strongly suppressed IgE responses. In addition, the finding that mice injected with monoclonal antibody directed against the coiled-coil stalk of CD23 have enhanced soluble CD23 release and increased IgE production demonstrates that full-length, trimeric CD23 is responsible for initiating an IgE inhibitory signal. The recent identification of ADAM10 (a disintegrin and metalloprotease) as the CD23 metalloprotease provides an alternative approach for designing therapies to combat allergic disease. Current data suggest that stabilizing cell-surface CD23 would be a natural means to decrease IgE synthesis and thus control type I hypersensitivity.

Anti-IgE monoclonal antibody (omalizumab) in the treatment of atopic asthma and allergic respiratory diseases.
Abstract
Since the discovery of immunoglobulin E (IgE) antibodies thirty-six years ago, our understanding of the mechanisms of allergy has improved to such an extent that we can now better differentiate allergy from non-allergic hypersensitivity, and allergic/atopic from intrinsic/non-atopic bronchial asthma. IgE antibodies are crucial immune mediators of airway inflammation in allergic atopic asthma and IgE-mediated hypersensitivity reactions are the likely mechanisms of allergen-induced airway obstruction. In addition, IgE may cause chronic airway inflammation in asthma through effector cells activated via high-affinity (Fcepsilon RI) or low-affinity (Fcepsilon RII) IgE receptors. Therapeutic anti-IgE antibodies able to reduce free IgE levels and to block the binding of IgE to Fcepsilon RI without cross-linking IgE and triggering degranulation of IgE-sensitised cells have been developed. This non-anaphylactogenic anti-IgE monoclonal antibody (rhuMAb-E25; omalizumab) binds IgE at the same site as these antibodies bind Fcepsilon RI and Fcepsilon RII. As a consequence, omalizumab inhibits IgE effector functions by blocking IgE binding to high-affinity receptors on IgE effector cells and does not cause mast cell or basophil activation because it cannot bind to IgE on cell surfaces where the Fcepsilon R1 receptor already masks the anti-IgE epitope. Studies in patients with atopic asthma demonstrated that omalizumab decreases serum IgE levels and allergen-induced bronchoconstriction during both the early and late-phase responses to inhaled allergen. In several clinical controlled trials omalizumab resulted to be able to reduce asthma-related symptoms, to decrease corticosteroid use and to improve quality of life of asthmatic patients. The anti-IgE approach to asthma treatment has several advantages, including concomitant treatment of other IgE-mediated diseases (allergic rhinitis, allergic conjunctivitis, atopic dermatitis and food allergies), a favourable side-effect profile and a twice-monthly dosing frequency.
Categories of inflammation mediated by the immune system

The immune processes are probably ongoing and, in most cases, lead to the elimination of antigens without producing clinically detectable inflammation. The development of clinically apparent inflammation indicates that the immune system has encountered either an unusually large amount of antigen, antigen in an unusual location, or antigen that is difficult to digest. In some diseases, such as rheumatoid arthritis, the initiating agent is unknown or may be normal host tissue components. In others (e.g. systemic lupus erythematosus), inherent or acquired immunoregulatory abnormalities may contribute to the sustained nature of the inflammatory process. Coombs and Gell divided inflammatory responses mediated by the immune system into four categories, called I, II, III, and IV, which represent four distinct immune mechanisms that result in tissue injury. These same four processes represent mechanisms of immune protection from infectious agents:

I. **Immediate hypersensitivity** (allergic, or reaginic acute inflammation).

II. **Cytotoxic** (inflammation mediated by cytotoxic antibodies).

III. **Immune complex** (inflammation mediated by immune complex).

IV. **Delayed hypersensitivity** (chronic inflammation mediated by lymphocytes and macrophages).
Allergic (reaginic) acute inflammation

Type I hypersensitivity is characterized by an allergic reaction that occurs immediately following contact with antigen, which is referred to as the allergen. The term allergy means "changed reactivity" of the host when meeting an "agent" on a second or subsequent occasion. In some individuals certain allergens have a propensity to stimulate production of IgE antibodies. IgE antibodies bind nonspecifically, via their high affinity Fc receptors, to mast cells and basophils. Subsequent attachment of antigen to the Fab portion of cell-bound IgE antibodies results in release of contents of cytoplasmic granules from mast cells and basophils (e.g. histamine), as well as in synthesis and secretion of biologically active products of arachidonic acid (e.g. leukotrienes). Mast cell products increase vascular permeability and constrict bronchial smooth muscle. A wheal and flare reaction occurs within seconds to minutes. Neutrophils and eosinophils characteristically predominate and mononuclear cells can also be seen.

Reaginic reactions are responsible for such allergic phenomena as urticaria, seasonal rhinitis, asthma, and in settings where large amounts of antigens (allergens) enter the host circulation, systemic anaphylaxis. These occur when an IgE response is directed against innocuous environmental antigens, such as pollen, house-dust mites or animal dander. The resulting release of pharmacological mediators by IgE-sensitized mast cell produces an acute inflammatory reaction with symptoms such as asthma or rhinitis. The importance of type I reactions in protection from infectious organisms is uncertain, although the increased vascular permeability mediated by these reactions probably facilitates the
capacity of antibody and inflammatory cells to arrive at the infected site. In addition, homocytotropic IgE antibodies and cells containing inflammatory mediators probably participate in the defence against large, non-phagocytatable organisms, most notably the multicellular helminthic parasites.

There is an important question why one individual express atopic diseases and another does not. At least two reasons exist -- environmental exposure and genetics. A third reason -- an external event that alters IgE regulation -- may be important in certain clinical situation but may represent a rare cause of atopic diseases.

The atopic diseases, allergic rhinitis, asthma, and atopic dermatitis have a genetic component. Some or all of these clinical syndromes can be present in a single member or in several member of the same family. The natural history of atopic diseases is not known, but it appears that atopic individuals appear to have a relatively high frequency of food allergy before the age of two years; food allergy then becomes rarer but the patients develop IgE antibodies to inhalant allergens and manifest allergic rhinitis and/or asthma.

In general, atopy is a hereditary feature manifested by abnormal immediate type hypersensitivity to a certain allergen or a group of allergens.

Anaphylaxis denotes an acute systemic immediate reaction to allergen, typically mediated by IgE antibodies. The mildest form of anaphylaxis, involving only the skin, is termed urticaria or "hives". More severe reactions involve the mucous membranes and the gastrointestinal, pulmonary, and cardiovascular organs. Anaphylaxis may be life-threatening. The manifestations range from urticaria to angioedema (swelling of mucous membranes, for example, of the lips, tongue, palate, and larynx), nausea and vomiting (edema and smooth muscle contraction of gastrointestinal tract), asthma (bronchial smooth muscle contraction), and
hypotension (increased vascular permeability resulting in a loss of blood volume into tissue and thus a fall in blood pressure; reducing contractility of the heart also contributes to hypotension). Life-threatening reactions involve laryngeal edema, severe asthma, or severe hypotension and circulatory collapse. Agents that induce IgE-mediated anaphylaxis include penicillin, insect venoms, foods, and occasionally immunotherapy (i.e. injection of allergen to which a person is allergic, in order to treat allergic diseases).

Identical symptoms, which are not immune mediated, are sometimes termed *anaphylactoid*. Anaphylactoid reactions may be caused by radiocontrast dye (used for x-ray studies) and exercise.

Although antigen-IgE antibody interaction is the major cause of anaphylaxis, other immune mechanisms may occasionally induce the syndrome. Thus immune complexes may mediate anaphylaxis in some patients who are IgA-deficient and receive infusions of IgA, which interacts with preformed anti-IgA antibody. Anaphylactoid reactions may also occur after repeated intravenous administration of normal human immunoglobulin preparation that contain more than 5% of IgG aggregates in agammaglobulinaemic or hypogammaglobulinaemic patients. These aggregates activate complement to produce C5a and C3a anaphylatoxins which stimulate mediator release from basophils and perhaps some Type II, or *antibody-dependent cytotoxic hypersensitivity* occurs when antibody binds to either self antigen or foreign antigen on cells, and leads to phagocytosis, killer cell activity or complement-mediated lysis.

Both type II and type III hypersensitivity are caused by IgG and IgM antibodies. The main distinction is that type II reactions involved antibodies directed to antigens on the surface of specific cells or tissues, whereas type III reactions involve antibodies against widely distributed soluble antigens in the serum. Thus, damage caused by type II reactions is localized to a particular
tissue or cell type, whereas damage caused by type III reactions affects those organs where antigen-antibody complexes are deposited.

These hypersensitivity reactions are related to normal immune responses seen against microorganisms and larger multicellular parasites. Indeed, in mounting a reaction to a pathogen, exaggerated immune reactions may sometimes be as damaging to the host as the effects of the pathogen itself. In such cases the borderline between a normal, useful immune response and hypersensitivity is blurred. Hypersensitivity reactions may also occur in many other conditions involving immune reactions, particularly autoimmunity and transplantation.

In type II hypersensitivity, antibody directed against cell surface or tissue antigens forms immune complex which interacts with complement and a variety of effector cells to bring about damage to the target cells. Antibodies can link the target cells to effector cells, such as macrophages, neutrophils, eosinophils and generally, K cells, by means of Fc receptors on these effector cells. This is so-called *antibody-dependent cell-mediated cytotoxicity (ADCC)*. Alternatively, the antibodies after binding to tissue antigens can interact with complement by activating C1 of the classical pathway. This results in the deposition of the C5b678(9)n membrane attack complex and following lysis of antibody-sensitized cells.

Both the complement fragments and IgG can act as opsonins bound to host tissues or to microorganisms, and phagocytes take up the opsonized particles. By enhancing the lysosomal activity of phagocytes, and potentiating their capacity to produce reactive oxygen intermediates, the opsonins increase the phagocytes' capacity to destroy pathogen, but also increase their ability to produce immunopathological damage in hypersensitivity reactions. For example, neutrophils from the synovial fluid of patients with
rheumatoid arthritis produce more superoxide when stimulated than neutrophils from the blood. This is thought to be related to their activation, in the rheumatoid joint, by mediators which include immune complexes and complement fragments.

The accumulation of inflammatory cells (neutrophils), with release of neutrophil lysosomal enzymes and generation of toxic oxygen intermediates, together with complement-mediated tissue lysis, leads to destruction of tissues as in the glomerular and pulmonary basement membrane damage in Goodpasture's syndrome or in the autoimmune haemolytic anemia and immune-mediated thrombocytopenia of systemic lupus erythematosus.

There are three main subtypes of cytotoxic hypersensitivity:

Type II reactions between members of the same species. They are caused by isoinmunization and include transfusion reactions after transfusion of blood incompatible in the AB0 system, haemolytic disease of the newborn due to rhesus incompatibility and/or transplantation reaction provoked by antibodies in the recipient directed against surface transplantation antigens on the graft.

Autoimmune type II hypersensitivity reactions are evoked by antibodies in the host directed against his own cell or tissue antigens (autoantibodies). As an example may serve autoimmune haemolytic anaemia caused by autoantibodies to the patient's own red cells; Hashimoto's thyroiditis with autoantibodies against thyroid peroxidase surface antigen; idiopathic thrombocytopenic purpura manifest by platelet destruction evoked by anti-platelet antibodies; Goodpasture's syndrome in which complement-mediated damage to basement membrane due to specific autoantibodies is observed. Many diseases are caused by autoantibodies against hormone receptors. Recently, they are also known as type V
**Hypersensitivity reactions.** Autoantibodies directed against receptors can have the function of agonist resulting in *stimulatory hypersensitivity* and/or of antagonist leading to the *blockade of signal* transmited through the receptor occupied by such an autoantibody. The example of stimulatory hypersensitivity is *thyrotoxicosis* where pathological stimulation of TSH receptor occurs, whereas to the *blocking hypersensitivity* belong *primary myxoedema* (blockade of TSH receptor) or *myasthenia gravis* (blockade of acetylcholine receptor).

subsets of mast cells.

**Chronic inflammation (delayed-type of hypersensitivity reaction)**

Type IV or **delayed type hypersensitivity (DTH)**, is most seriously manifested when antigens (for example those of tubercle bacilli) are trapped in a macrophage and cannot be cleared. T cells are then stimulated to elaborate lymphokines which mediate a range of inflammatory responses. Other aspects of DTH reactions are seen in graft rejection and allergic contact dermatitis. DTH is used as a general category to describe all those hypersensitivity reactions which take more than 12 hours to develop, and which involve cell-mediated immune reactions rather than humoral immune reactions. Whereas allergic reactions occur within seconds and minutes and immune complex reactions occur within several hours to one day, DTH reactions peak at 2 to 3 days.

Unlike other forms of hypersensitivity, type IV hypersensitivity cannot be transferred from one animal to another by serum, but can be transferred by T cells (T<sub>H</sub>1 cells in mice). In humans, transfer from a sensitized to a non-sensitized individual can be also achieved only by T lymphocytes and, interestingly, by a low
molecular weight material extracted from them (transfer factor). Delayed type hypersensitivity is obviously associated with T cell protective immunity but does not necessarily run parallel with it -- there is not always a complete correlation between delayed hypersensitivity and protective immunity. The T cells necessary for producing the delayed response are cells which have become specifically sensitized to the particular antigen by a previous encounter, and they act by recruiting other cell types to the site of the reaction.

Three types of delayed hypersensitivity reaction are recognized: Contact hypersensitivity and tuberculin-type hypersensitivity both occur within 72 hours of antigen challenge, whereas granulomatous reactions develop over a period of weeks. The granulomas are formed by the aggregation and proliferation of macrophages, and may persist for weeks. This reaction is, in terms of its clinical consequences, by far the most serious type of delayed type hypersensitivity response. The position is complicated because these different types of reaction may overlap, or occur sequentially following a single antigenic challenge.

The delayed type hypersensitivity reactions are probably important for host defence against intracellular parasites such as tuberculosis and certain viruses and are prevalent in certain disease such as sarcoidosis, Wegener's granulomatosis, and polymyositis. In some diseases, such as chronic granulomatous disease of childhood, granuloma formation can lead to obstruction of vital structures such as the esophagus or ureters. The contact dermatitis is caused by sensitization to certain simple chemicals.

Perhaps the best known example of cell-mediated hypersensitivity is the Mantoux reaction obtained by injection of tuberculin into the skin of an individual in whom previous infection with the mycobacterium had induced a state of cell-mediated immunity. The reaction is characterized by erythema and induration which
appears only after several hours and reach a maximum at 24-48 hours, thereafter subsiding. Histologically the earliest phase of the reaction is seen as a perivascular cuffing with mononuclear cells followed by a more extensive exudation of mononuclear and polymorphonuclear cells. The latter soon migrate out of the lesion leaving behind a predominantly mononuclear cell infiltrate consisting of lymphocytes and cells of the monocyte - macrophage series. This contrasts with the essentially "polymorph" character of the Arthus reaction.
IgE network - regulation of allergy and inflammation.

With Hannah Gould and Brian Sutton (King's College London).

Antibodies of the immunoglobulin E isotype (IgE) play a key role in the immune response to host defense against parasitic infection and in the development of allergic and inflammatory responses. IgE elicits a range of cellular responses to antigens which are designed to exclude parasites from the body. These include inflammation, itching, coughing, lacrimation, bronchoconstriction, mucus secretion, vomiting and diarrhoea; all common symptoms in allergic disorders. In industrialized countries, where parasitic infections are rare, the prevalence of allergic disorders are increasing at an alarming rate; the marked increases in its prevalence, morbidity and mortality has led to the designation of allergy as the "number one environmental disease" (1). A recent study found that asthma now accounts for approximately one-third
of all paediatric emergency room hospital visits. Allergy, in one form or another, currently afflicts more than 20 per cent of the population, with profound estimated socio-economic effects.

The effector functions of all antibodies depend on their ability to sensitize cells for antigen-induced activation by binding to cell surface receptors through their Fc region. IgE mediates its biological effects through interactions with its cellular receptors FcεRI and FcεRII. The ability to regulate these interactions offers the potential to control the harmful effects of IgE.

In this research program we aim to determine the three-dimensional structure of the portion of IgE responsible for binding to its cellular receptors. We will characterize the molecular topology of the interaction site and elucidate the physical basis of IgE's interactions with its receptors. This information will then be used to develop specific inhibitors of IgE/receptor interactions.
IgM

Clinical significance

IgM antibodies appear early in the course of an infection and usually reappear, to a lesser extent, after further exposure. IgM antibodies do not pass across the human placenta (only isotype IgG).

These two biological properties of IgM make it useful in the diagnosis of infectious diseases. Demonstrating IgM antibodies in a patient's serum indicates recent infection, or in a neonate's serum indicates intrauterine infection (e.g. congenital rubella).

The development of anti-donor IgM after organ transplantation is not associated with graft rejection but it may have a protective effect.[6]

Other points

IgM in normal serum is often found to bind to specific antigens, even in the absence of prior immunization. For this reason IgM has sometimes been called a "natural antibody". This phenomenon is probably due to the high avidity of IgM that allow it to bind detectably even to weakly cross-reacting antigens that are naturally occurring. For example the IgM antibodies that bind to the red blood cell A and B antigens might be formed in early life as a result of exposure to A- and B-like substances that are present on bacteria or perhaps also on plant materials.

IgM antibodies are mainly responsible for the clumping (agglutination) of red blood cells if the recipient of a blood transfusion receives blood that is not compatible with their blood type.

IgM is more sensitive to denaturation by 2-mercaptoethanol than IgG. This technique was historically used to distinguish between these isotypes before specific anti-IgG and anti-IgM secondary antibodies for immunoassays became commercially available. Serum samples would be tested for reactivity with an antigen before or after 2-mercaptoethanol treatment to determine whether the activity was due to IgM or IgG.[7]
Activities of IgG, IgM antibodies and the C3b inactivator-cleaved third component of complement in macrophage phagocytosis

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Abstract

Phagocytosis of SRBC by guinea-pig peritoneal macrophages is enhanced by opsonizing IgG antibody alone. IgM antibody requires the presence of bound C3. Treatment of C3b coated SRBC with purified C3b inactivator (yielding EA_{IgM} C1423d) does not reduce attachment to, and phagocytosis by, peritoneal macrophages. This finding suggests the existence of a C3d receptor on peritoneal macrophages. EC43b intermediates which have been produced by removing IgM antibody by mercaptoethanol treatment and by subsequent removal of C1 and C2, are phagocytosed despite the absence of IgM antibody. Furthermore, treatment of EC43b with C3b inactivator does not change phagocytosis. Thus, IgM antibody does not appear to be a necessary prerequisite for the stimulation of phagocytosis, C3b or C3d alone being sufficient.

Background

Selective immunoglobulin M (SIgM) deficiency is a rare form of dysgammaglobulinemia characterized by an isolated low level of serum immunoglobulin M (IgM). Reported IgM concentrations in SIgM deficiency vary from 40 mg/dL (though some sources say 20 mg/dL) to undetectable levels (reference range 45-150 mg/dL in adults).[1] Recent series report IgM levels of 29.7±8.7 mg/dL (mean±SD) for adults and 16.5±13.8 (mean±SD) in children.[2, 3] In this context, remember that 2.1% of "normal" individuals have values < 2 SD below the mean and that values in children must be compared with reference range values for age.[4] The levels of other immunoglobulin classes are within reference ranges.
SIgM deficiency may occur as a primary or secondary condition. Secondary SIgM deficiency is much more common than primary SIgM deficiency and may be seen in association with malignancy, autoimmune disease, gastrointestinal disease, and immunosuppressive treatment.

Some patients are asymptomatic, whereas others (often infants and small children) develop serious infections. Patients may develop prolonged or life-threatening infections caused by both encapsulated bacteria and viruses, especially in infancy. In older children and adults, SIgM deficiency is usually discovered during the investigation of other conditions, such as autoimmune disease or malignancy.

Serum immunoglobulin levels are controlled by intricate immunological regulatory mechanisms, and heterogeneity is believed to exist in the pathogenesis of SIgM deficiency. Little is known about the pathological features of SIgM deficiency at a cellular level, given that the condition is so uncommon. Processes that control the survival of IgM in the circulation and may otherwise regulate its concentration in serum have not been well described; alterations in clearance mechanisms, in addition to altered production of IgM by lymphocytes, may contribute to selective deficiency of this immunoglobulin isotype.

**Pathophysiology**

The cause of SIgM deficiency is unknown. Increased regulatory T-cell activity specific for IgM has been described. The absence of IgM in the presence of normal levels of immunoglobulin G (IgG) and immunoglobulin A (IgA) has yet to be explained, as this appears to contradict the theory of sequential immunoglobulin gene rearrangement. Normal mature B cells are expected to have IgM and immunoglobulin D (IgD) on their surfaces, and, with proper stimulation, rearrange their immunoglobulin genes to switch from expressing IgM to IgG, IgA, or immunoglobulin E (IgE).

Having normal levels of IgG and IgA in the face of low IgM is thus counterintuitive. One could speculate that failure to regenerate B-cell precursors could lead first to depletion of IgM, with gradual loss of IgG and other isotypes occurring later as class-switched memory B-cells and plasma cells fail to be replaced. This hypothesis has not been tested, and few studies are available to determine whether only the serum IgM level is low or whether the number of B cells with surface IgM is also decreased in patients with selective IgM deficiency. Gradually, current state-of-the-art laboratory technology is being applied in studying patients with SIgM...
deficiency, though much remains to be learned.

The currently available literature suggests a heterogeneous population of patients of SIgM deficiency. Some patients are capable of normal antibody responses of other immunoglobulin classes following specific immunization, whereas others respond poorly. Certain patients with decreased helper T-cell activity have been described.[6] Cell-mediated immunity appears to be intact, but an insufficient number of detailed studies are available to confirm this. Suggested etiologies include rapid isotype switching of B cells from production of IgM to production of other isotypes and hypercatabolism of IgM.