

REVIEW

IgE immune complexes in food allergy: significance, pathogenicity and clinical considerations

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Introduction

The existence of lesions associated with the localization of immune complexes in tissues has been recognized for a long time. However, the data collected in the last few years revealed the high incidence of circulating immune complexes (CIC) in various clinical conditions in the absence of a classic CIC-associated pathological situation (e.g. atopic diseases, AIDS or others). Therefore, it may be appropriate to wonder about the significance of the formation of CIC and about the relative pathogenicity of those CIC particularly in atopic diseases. It is currently accepted that high levels of CIC may be considered pathological. However, in most human diseases the relationship of immune complexes to the type of lesions is not yet cleared, since raised levels of complexes have been found in several conditions. However, many types of complexes can be formed even in response to the same antigen and in the course of the same disease, so that different tests based on physicochemical or biological characteristics may detect only a limited portion of them.

Intestinal barrier: control and pathological states

Absorption of macromolecules from the gastrointestinal tract

Experimental and clinical evidence suggest that macromolecules may be transported under physiological conditions across the intestinal epithelium, not in sufficient quantities to be of nutritional value but in quantities that are both antigenic and biologically active and a possible cause of hypersensitivity reactions in susceptible individuals [1]. Previous work by Walker *et al.* [2] showed, in experimental models, after oral immunization, a significant decrease in the subsequent passage of the antigen through the gastrointestinal wall. In order to elucidate further the mechanisms for the decrease in absorption, these authors were able to demonstrate that gut sacs from immunized rats bound more antigen to the epithelium than did gut sacs from

unimmunized animals [3]. From these experiments, it has been suggested that antibodies present on mucosal surfaces may protect against absorption of ingested antigens that have escaped digestion in the intestinal lumen. Further evidence in support of this hypothesis comes from two separate lines of approach.

Stokes *et al.* [4] reported that animals with local IgA antibody (IgG anti-DNP) absorbed ten-fold less antigens than those without such antibody. Conversely, subjects who were IgA deficient showed enhanced antigen absorption [5]. However, the particular type of response to food antigens is regulated by the repeated exposure of minute quantities and the peculiarity of the mucosal immune system. Antigen feeding may lead, in experimental models, to development of systemic tolerance on subsequent parenteral immunizations [6], a secretory antibody response [7] and the formation of isotype-restricted suppressor cells and suppressor factors [8], a decrease of on-going specific-IgE response [9], and a reduced incidence of immune complex diseases [10].

Most reports appear in favour of the idea that hyporesponsiveness follows antigen entry through the gut. Thus, this event seems to protect from pathological damage caused by food antigens. In this respect we regard food allergy as a breakdown in orally induced tolerance.

Factors modulating antigen uptake

Non-immunological control. A number of non-immunological factors, present either within the intestinal lumen or on the intestinal mucosal surface, exist and are of importance as an adjunct to more classical adaptive control mechanisms of the gut. These factors include peristaltic movement, goblet-cell release of mucus, pancreatic enzymes and hepatic reticuloendothelial filtration.

Walker *et al.* [11] have reported that pancreatic enzymes absorbed onto the surface of the small intestine facilitate the breakdown of antigen-antibody complexes at that site. More recently, Walker *et al.* [12] have shown that antigen-antibody complex formation within the intestinal lumen may trigger the release of goblet-cell mucus, which in turn can interfere with further antigen penetration across the mucosal barrier.

It is clear that these non-specific defences may work synergistically with immunological defences in the control of antigen entry in the gastrointestinal tract. Thus, decreased adherence of organisms to the gut surface may have a secondary effect in reducing the level of endotoxin, which itself may increase gut permeability [13].

Immunological control. An important, if not the most important, component of host defence at the intestinal epithelial surface is the presence of intestinal antibodies. There is now substantial evidence that the main function of intestinal antibodies is the process of immune exclusion at the mucosal surface [4,14]. Williams and Gibbons [15] examined the adherence properties of some oral pathogens, such as *Streptococcus viridans*, to epithelial cell surfaces, before and after exposure to specific secretory IgA antibodies. They observed a decrease in adhesion of the pathogens to the cell membrane of epithelial cells after the exposure to IgA antibodies and concluded that secretory IgA blocks sites on the bacterial cell wall and thereby interferes with bacterial adherence to epithelial surfaces. A defect in adherence results in decreased colonization, as well as enhanced clearance of the bacteria by oral secretions. These phenomena have also been shown to hold for *Vibrio cholerae* [16]. Table 1 represents a more comprehensive list of intestinal factors modulating excessive uptake of intestinal antigens.

However, whatever mechanisms are involved, absorption does play an important

Table 1. Factors controlling macromolecular transport in the gut

Factors
Local immunological defences
Secretory IgA
Cell-mediated immunity
Other immunoglobulins (IgG, IgM, IgE)
Non-immunological factors
Indigenous intestinal flora
Secretions
Gastric barrier
Peristaltic movement
Liver filtration
Miscellaneous
Pancreatic enzymes
Goblet cell mucus

role in the pathogenesis of a number of immunologically mediated gastrointestinal diseases. A break in the mucosal barrier might, therefore, be expected to have pathogenetic consequences [17]. Moreover, since the vast majority of mammals show no ill effects from a limited intestinal permeability to large molecules, it seems likely that some additional alteration must take place in the intraluminal digestive process controlling the permeability of macromolecules, before the process results in clinical disease. In attempts to clarify the factors controlling the effect of oral immunization on the antigen absorption, model systems have been examined in animals [6,18]. In these experimental models, oral immunization may elicit a local immune response involving secretory IgA antibody, as well as a state of systemic hyporesponsiveness or 'tolerance' in which the animal is incapable of mounting an appropriate serum antibody response when the same antigen is administered parentally [19,20].

Factors contributing to the pathological uptake of macromolecules

Although macromolecules, as previously mentioned, can traverse the intestinal mucosa of man in small quantities, this passage induces no ill effects in the majority of adults. However, excessive uptake could disrupt and cause direct toxic or immunological reactions resulting in local intestinal or systemic disease [21].

Several conditions are now thought to lead to abnormal or deranged transport of macromolecules (Table 2). The factors listed are meant to be representative but not comprehensive.

A few years ago an association was discovered between atopy and certain primary immunodeficiency states such as the Wiskott-Aldrich Syndrome [22] and selective IgA deficiency [23]. The relationship between atopy and IgA deficiency has aroused particular interest. Indeed, Kaufman and Hobbs [24] initially demonstrated that IgA deficiency could be found with increased frequency in an atopic population and it was subsequently shown that transient IgA deficiency was relatively common in those infants of atopic parents, who subsequently developed positive prick test and atopic eczema [25,26]. There now is evidence that IgE may play an important role in antigen exclusion at mucosal surfaces [4] and enhanced gastrointestinal absorption of antigen

Table 2. Conditions contributing to pathological transport of macromolecules

Conditions
Local antibody deficiency
Alterations in the mucosal barrier
Change in surface membrane charge
Inflammation
Ulceration
Lysosomal dysfunction
Intraluminal factors
Decreased gastric acidity
Pancreatic insufficiency

has been demonstrated in IgA-deficient patients [5,27,28]. These patients frequently develop high levels of circulating precipitating antibodies to milk antigens [29], presumably as a response to increased absorption of such antigens. Such antibodies are probably of IgG class and are likely to be important in the clearance of antigens from the circulation. It is, therefore, possible that the increased serum levels of IgE antibodies also found in these patients are similarly a response to enhanced antigenic stimulation.

Since transient IgA deficiency is a relatively common immunodeficiency it might underlie much atopic disease, inducing immunological imbalance, which persists after the spontaneous resolution of the original IgA deficiency. It is tempting to speculate that the frequent resolution of much atopic disease reflects successful self-correction of immunological imbalance induced in this way. However, it has not yet been proven that increased antigen absorption is the actual cause by which atopy arises in the IgA-deficient individual.

Jarrett [30] has argued that this is impossible, if one can extrapolate from her experimental data in laboratory animals to man. The gut mucosa is normally permeable to antigens even in the absence of IgA deficiency and her experiments in rats have suggested that absorption is important in suppressing the IgE response [31]. Furthermore, the more antigen that is provided, the greater appears to be the degree of suppression.

An alternative explanation for the association of IgA deficiency with atopy arises from the evidence that synthesis of these two immunoglobulin classes (IgA and IgE) has particular dependence on the influence of T lymphocytes. Thus, if abnormalities of lymphocyte function were responsible for the development of enhanced IgE responsiveness, in some individuals such abnormalities might at the same time have the effect of suppressing IgA responsiveness [32]. Clearly, the problem is unsolved but it is still likely that immunological defects are associated with, and may precede, atopy.

Sensitization

Antigen that penetrates the intestinal mucosa reaches antibody-producing cells in the lamina propria, in the lymphatic follicles (Peyer's patches), in the spleen and lymph glands, and in the circulation. A heterogeneous response of specific antibodies in all classes of immunoglobulins may be stimulated by each food antigen. The presence of IgE antibodies constitutes sensitization of the person and creates the potential for

various types of immunological reactions upon re-exposure to the specific antigen. In addition to sensitization by humoral antibodies, there is the possibility of antigen induction of specific cell-mediated immunity [33–35]. It must be emphasized that the presence of specific antibodies or sensitized cells is evidence of immunological memory and does not necessarily imply that clinical symptoms will occur after ingestion of the relevant food antigen.

Genetic predisposition

The importance of genetic factors in predisposing the patient to food-allergic diseases has been emphasized repeatedly. A number of observations link food-allergic disease with genetic predisposition; for example, links between gluten sensitivity and HLA-B8 and DW-3 [36] and also between atopic eczema and HLA haplotype A-1 B-8 [37,38]. Genetic factors alone do not seem to determine predisposition to this disorder since environmental factors also play an important role. However, genetic factors probably determine the fate of allergens after absorption and the pattern of immune responses these provoke.

Environmental factors

Although it is clear that heredity is of great importance in terms of liability to allergy, environmental factors appear to be of considerable importance in determining whether such liability becomes manifest as disease. Several studies have now shown that asthma is more common in the relatively 'westernized' cities of developing countries than among genetically similar populations in rural areas [39,40]. Asthma and eczema are much less common in children born in tropical countries than in children of similar race, or indeed the same families, born in England [41]. Month of birth appears to have some influence on the subsequent development of hay fever [42–44] and it is presumed that this reflects the effect during early life of the changing patterns of antigen exposure during various seasons of the year. That antigen exposure, during early life, is an important factor in the development of atopic disease is supported by the finding that eczema develops more commonly in bottle-fed than in wholly breast-fed infants [45–48]. The protective effect of breast feeding appears to be prolonged, in the study of Matthew *et al.* [46] the prevalence of eczema remained significantly lower at 1 year in the breast-fed group even though breast feeding had been exclusive for the first 3 months only. The data of Saarinen *et al.* [47] confirm this prolonged benefit. There is now also some evidence that the incidence of atopic respiratory allergy may also be reduced by exclusive breast feeding [48]. Conversely, the beneficial effect of breast milk in this respect may not be solely due to its reduced antigen content. Pittard and Bill [49] have shown that breast-milk lymphocytes may play an important role in active stimulation of IgA synthesis by the neonate. Furthermore, Jarrett and Hall [32] have found that breast milk in rats appears to contain a factor that can specifically suppress the synthesis of IgE antibodies by offspring against antigens to which the mother has been immunized prior to conception. It has now been shown in rats, by Jarrett and Hall [50], that this factor contained in the mother's milk is a maternal IgG antibody, which suppresses IgE antibody responsiveness and might play a physiological regulatory process with a role in inhibiting the development of infantile allergies. It is now important to find out if IgE suppression by maternal IgG also occurs in the human and whether this may represent a physiological regulatory process. Evidence suggesting that it may occur in human babies is discussed in the work of Dannaeus *et al.* [51,52],

who found that IgG antibodies to milk and egg proteins in the serum of newborn babies reflected the corresponding maternal concentration, and that high levels in cord sera appeared to protect against the onset of atopic symptoms during the first 2 years of life.

In conclusion, exclusive breast feeding certainly does not entirely protect the infant from antigen experience, neither does it protect completely against the development of atopy. On the contrary, there is some evidence that non-exclusive breast feeding, i.e. small supplements of cows' milk, may be more likely to provoke atopy than whole cows' milk feeding [53,54]. If this is true, a possible clue to the mechanism is to be found in the work of Jarrett *et al.* [31], demonstrating the more ready elicitation of an IgE response by oral administration of small rather than large quantities of antigen.

Food antigen absorption and immune complex formation

The absorption of food antigens across the enteric mucosa into the circulation triggers their combination with antibodies. The type and amount of complexes formed differ according to both gut permeability and antibody class present. In infants exclusively fed with cows' milk, the antibody belongs mostly to the IgG class [55]. It has been reported that formation of CIC containing specific antigen (ovalbumin or Betalactoglobulin), occurs in normal subjects 1 or 3 hr after oral challenge [56]. The complexes were predominantly of the IgA and IgG type and their clearance was rapid [57]. the formation of such complexes can be considered as a physiological mechanism for the elimination of foreign and noxious material from the circulation [56,57]. Indeed, they have been shown in the sera of healthy subjects under physiological conditions [58] and in people after eating food [57,59,60]. Clearly the formation of such complexes does not usually have pathological consequences [61]. Indeed, circulating IgG immune complexes containing milk proteins can be found transiently in normals after drinking milk [59,62], and these may reflect a physiological way of metabolizing the absorbed antigen from the circulation [56,58,63]. Conversely, defective clearance of soluble CIC (e.g. malfunction of the reticuloendothelial system—RES) may lead to their prolonged circulation and the elicitation of a serum sickness reaction. Their persistence in high concentration for abnormally long periods of time can also cause inflammation and cell destruction due to the consequent deposition of the skin or other organs [64]. It has been suggested that immune complexes formed between dietary antigens and circulating antibodies in atopic subjects are qualitatively and quantitatively different from those formed in normal subjects [65–67]. Food-allergic individuals form immune complexes containing allergens and specific IgG, IgA and IgE in concentrations far exceeding those detectable in the blood of normal subjects [56,57,60]. It has been shown that IgE immune complexes, in particular, may play an important role on the pathogenetic mechanism of food allergy [68].

Particularly interesting were the reports of Paganelli *et al.* [59,60], which showed the presence of food antigens as constituents of immune complexes, using an immune complex splitting method; however, the amount of complexed antigen was not significantly different from that measured in healthy subjects. Major differences were observed when these authors analysed the immunoglobulin isotype involved in the formation of immune complexes after challenging patients allergic to food. In these patients, IgG and IgE isotypes have been reported to be prevalent [68–70]. Up to 20% or more of total IgE was present in complexed form. The heterogeneity of these complexes was analysed and confirmed by ultracentrifugation technique [66,70]. These

complexes were also able to activate the complement pathway, as demonstrated by their C1q binding activity and the reduction of complement-mediated lysis [67]. It now seems clear that there is a relationship between the presence of such complexes and the appearance of symptoms even seen at distant sites (skin and bronchi etc.), at either short or long intervals after challenge with the specific allergen [71].

The profound differences of the structure of such complexes found after oral challenge may reflect the various types of isotype responses to food antigens detected in serological studies. Although most complexes are considered to be composed of specific IgE and corresponding antigens or mixed complexes (i.e. IgG-allergen-IgE) [70]. However, we cannot completely exclude the possibility that the IgE peak of the large molecular weight, detected by ultracentrifugation technique, may be composed by an antiglobulin (i.e. IgG anti-IgE) and it is clear, from further studies, that the anti-IgE autoantibody corresponding to the large molecular weight of IgE peak in the immune complex ultracentrifugation profile is also present and might play a certain role in the IgE regulation system [72–78].

We now have preliminary evidence that at least some of the IgG anti-IgE antiglobulins detected in patients with asthma and atopic eczema do belong markedly to the subclasses IgG1 and IgG4 [79]. It is also relevant to mention the study of Cunningham-Rundles [80], where the detection of anti-idiotypic antibodies have shown in patients with selective IgA deficiency with serum IgG antibodies to cows' milk protein.

Indeed, the IgA isotype is the most represented in the formation of immune complexes in normal individuals, certainly they could represent a safer response with regard to immunopathological consequences. The entero-hepatic recirculation of IgA and its elimination into bile further supports its role into antigenic clearance [81], which may also play a homeostatic purpose [56]. The potential inflammatory effect of complexes with other isotypes makes them the best candidates for the role of immunobiological mediators of some late and delayed reactions. It has been recently reported that deposition in tissue or antigen released from such complexes may be involved in a local damage by the production of, *in situ*, molecules mediating inflammatory reactions [59]. This is supported further by the data of Brostoff *et al.* [69,70], who showed that pre-treatment of patients allergic to food with sodium cromoglycate could block symptom appearance and immune complex formation, indicating that antigen absorption may play a crucial role in the appearance of food-allergic manifestations.

Role of immune complexes

There are many reports concerning the presence of CIC in sera from patients with atopic disease [66,82–90]. The occurrence and formation of immune complexes has been extensively investigated in human allergic conditions but the occurrence of CIC at the intestinal levels (e.g. food allergy) might result in a local inflammation with increased permeability to food antigens [91–97]. Thus, the presence of CIC, after challenge, may rather represent a way of metabolizing the antigen without any clinical relevance. This is probably the case of CIC formation in normal subjects [60,66,68]. Conversely, these complexes containing IgE have the potential for triggering mediator release from various cell types [98–100]. In this respect, type I and type II reactions would co-exist since immune complexes containing antigen-specific IgE, as well as other classes of immunoglobulins and autoantibodies, could contribute to the

inflammation mechanism and the expression of the clinical symptomatology. The knowledge of complexed IgE in atopic diseases [68,82–102], suggests that their continuous presence (e.g. caused by interaction with anti-IgE) could favour the chronic course of certain diseases. Among these, atopic eczema, hyper-IgE syndrome [76] and food-allergic diseases are prominent, although IgG and IgE complexes have also been found in perennial rhinitis and asthma [87]. When antigen is continuously present, as in food allergy, chronic stimulation of the immune system may more easily lead to autoantibody formation [97].

The IgE immune complexes certainly deserve more attention than the other isotypes in the CIC formation for what regards the atopic diseases. Indeed, much has been speculated about the IgE immune complexes' composition. However, a few possibilities are now taken into account: (i) antigen (parasitic or allergen) and antibody; (ii) mixed complexes, i.e., IgG-allergen-IgE (the latter has been postulated and later proven by Brostoff *et al.* [67]: these authors also pointed out that these complexes through IgG can activate the complement pathway); (iii) anti-idiotypic antibody and IgE; (iv) IgE rheumatoid factor (i.e. IgG anti-IgE).

Previous studies using different techniques have suggested that between 20% and 100% of IgE in the sera from patients with atopic diseases exist as complexes [67]. Low affinity for Fc receptors for IgE have been found on human macrophages and monocytes [103–105], and the number of peripheral blood monocytes with this type of Fc receptor (Fc_ε) is increased in patients with severe atopic diseases [104]. It has been speculated that the material ligand for these receptors is IgE-containing immune complexes (IgE CIC) [65,66,104] and that IgE CIC may play a significant pathogenetic role in atopic diseases [103,104]. There are indeed several reasons for studying the possible role of IgE CIC in atopic diseases such as asthma and rhinitis. Firstly, it is impossible to explain the symptomatology of allergic asthma, only via IgE-mediated type I reactions. Even with the recent studies on the role of leukotrienes and the platelet activating factor [99–100], additional pathophysiological mechanisms are not excluded. Secondly, early and late responses occur after bronchial allergen-provocation and here too it might be worthwhile to look for a possible role of CIC. Thirdly, it is known that some aggregated IgE can activate complement [106]. IgE CIC could, thus, play a role in the pathogenesis of atopic diseases. The presence of IgE CIC have been reported in many other diseases than atopic diseases (e.g. rheumatoid arthritis, AIDS infected people) [107–110], endemic Kaposi sarcoma [111], and again very high levels of IgE CIC in human T leukaemia virus I and III [112] and, of course, many parasitic diseases [113–114].

Significance of IgE immune complex formation and persistence

The generation and persistence of CIC in the blood or in any given tissue depends on the concomitance of antigen and of corresponding antibodies. The generation of immune complexes now appears to be an important feature in certain types of immunological status (e.g. autoimmune diseases and atopic diseases), although it probably occurs frequently in normal subjects too. Indeed, the presence and percentage of high levels of CIC may either represent an inefficient immune response against infectious and exogenous antigens or reflect polyclonal B cell activation (PBA). The triggering of B cell proliferation and the differentiation by antigen non-specific mechanisms results in the expression of a large portion of the B-cell repertoire (e.g. AIDS, mononucleosis, Kala-azar etc.). It has been reported that all situations

associated with PBA showed a generation of CIC, in which antibody–anti-antibody interactions appear to play an important role [115]. It is well known that antibodies produced against the constant portion of IgG (RFs), frequently occur during the PBA. In atopic diseases, for instance, anti-IgE antibodies occur and there is a close correlation between the production of these autoantibodies and the appearance of CIC [70,76,89].

Immune complexes as a tool in food allergy diagnosis

It would be tempting to speculate that antigen–antibody complexes are of significant importance in atopic diseases and particularly in food allergy. IgE immune complexes might play a pathogenetic role, however we should avoid the risk of general assumptions. There are many reasons for this: (i) antigen–antibody do combine to form complexes in different combinations and their amount and clearance will dictate whether they can be detected by an assay; (ii) it is questionable whether the different IgG concentrations to food [116] have any biological meaning. As for the IgE antibodies, they also combine with allergens and IgE complexes have been found in many atopic diseases [67,87,89]. Specific IgE can certainly contribute to the presence of mixed IgG–IgE complexes [70], but non-specific factor may affect this process. It is now established that around 50% of all circulating IgE may be in complexed form in atopic individuals [70,77,87], most of them bind to IgG autoantibodies against serum IgE, simulate the presence of specific IgG, enhance or prevent IgE binding to allergen or cell receptors and cause the formation of IgG–IgE mixed complexes even in the absence of antigens [77,89]. We should be very careful before assigning a role to IgE complexes in any atopic conditions [70,102]. Despite these limitations, there is evidence for the presence of antigen-specific complexes after food challenge, and changes in amount and composition of complexes after oral provocation [60,68,69,71].

In conclusion, the biological and immunopathological role played by these IgE immune complexes is not yet clearly understood.

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