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Opinion

An Immune Response to Dietary Antigens; the Sum May Be Greater Than the Parts

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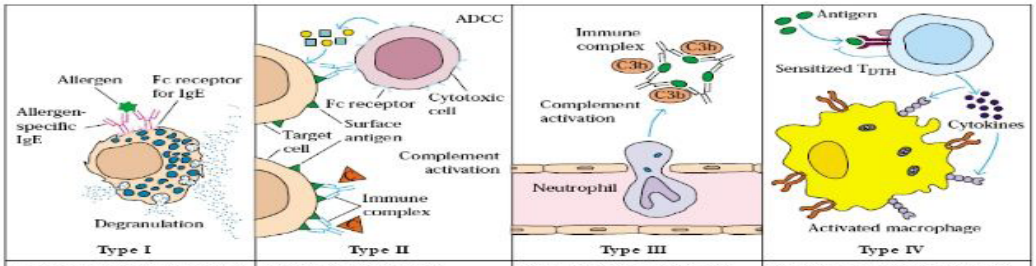
Opinion

Classically, as we define reactions to antigens, either environmental or foods, we have broken the immune reaction down and divided them based on specific activity. This definition allows us to describe the difference between Type I IgE Medicated Hypersensitivity and Type II IgG mediated activity, and Type III driven by complement activation as well as Type IV Cell-Mediated Hypersensitivity. While these descriptions are not wrong, they are not the whole picture. While it is true IgE and IgG maintain distinct activity, it is also true that IgG, particularly type 1-3 will increase the activity of IgE [1]. Patterns of immune response can be seen for other reasons as well. For example, someone who is in general, more up regulated in terms of IgE reactions, may be low in sIgA. A decrease in sIgA creates a deficiency in a first line of defense, the 85% of the immune system that lines the mucosa. Because of this low level of defense or sIgA, the immune system works to compensate. One way the immune system will compensate is by up regulating IgE activity, relying on a higher level of response in that pathway to overcome short comings created by low sIgA [2]. When we look at various immunoglobulin's responses together, rather than in isolation, we will get a deeper understanding into what is truly happening with immune function (Figure 1).



IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
Ag induces crosslinking of IgE bound to mast cells and basophils with release of vasoactive mediators	Ab directed against cell surface antigens meditates cell destruction via complement activation or ADCC	Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils	Sensitized T_H1 cells release cytokines that activate macrophages or T_C cells which mediate direct cellular damage
Typical manifestations include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema	Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia	Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulnephritis, rheumatoid arthritis, and systemic lupus erythematosus	Typical manifestations include contact dermatitis, tubercular lesions and graft rejection

Figure 1: Types of Hypersensitivity.

While IgE and complement are shown as distinct in the above figure, this is not always physiologically the case. Many studies show that complement is involved in IgE driven anaphylaxis and that IgG1 and IgG4 may also play a role. IgG is not limited to the action of delayed sensitivities, but can directly amplify IgE becoming a player in anaphylaxis [3]. Other pathways of anaphylaxis involve complement alone, with no IgE. The Journal of Allergy and Clinical Immunology published in 2009 that complement is involved in the anaphylactic activation of the immune system to peanut, and other studies have shown the same to be true for allergic pathology in general [4]. Further studies have demonstrated IgE-independent anaphylaxis. These pathways involved IgG4, complement, and total IgG [5,6]. When these antibodies are measured contiguously, observation of amplification across immunoglobulin class, points to a result that is likely associated with more aggressive symptoms, increasing clinical value. Complement amplifies IgG reactions, which in turn, may increase the activity of IgE.

Complement and the complement system continue to demonstrate particular importance in allergies and human disease. Complement has 31 proteins and is involved not only in the lysis of bacteria and protecting humans from infectious microorganisms but also in its ability to drive anaphylatoxin which is produced in and responsible for allergies. C3d is a fragment of C3a anaphylatoxin which creates allergies. By measuring C3d you can measure whether C3a anaphylatoxin is being activated in response to various foods (Figure.2).

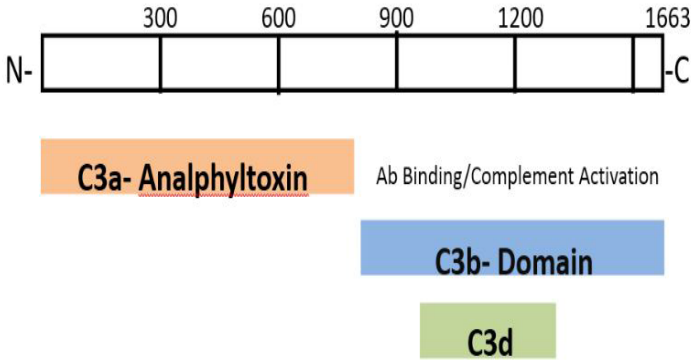


Figure 2: This figure shows that C3d is a byproduct of activation of C3a, an analphyltoxin involved in increasing risk of anaphylactic symptoms.

Complement is involved in producing a wheal-and-flare response in the skin, like immediate hypersensitivity responses found when induced by allergy extracts in the skin. Measuring complement helps to isolate allergic triggers that are not mediated by IgE. By measuring complement, the ability to isolate a distinct pathway by which a patient may have anaphylactic potential, is identified. This increases the sensitivity of IgE testing, and reduces false negatives. Complement, when bound to IgG, can increase its potential to increase histamine from 1000 to 10,000-fold [7]. Complement will activate basophils known to release histamine and drive allergic or atopic conditions such as urticaria, angioedema and asthma (Table1).

Lupus	Crohn's Disease	Rheumatoid Arthritis	Ulcerative Colitis
Psoriasis	Cystic Fibrosis	Epilepsy	Gout
Scleroderma	Thyroiditis	Reiter Syndrome	Dermatomyositis
Depression	Food Reactions	Increased CRP	Acute Rheumatic Fever
Typhoid Fever	Sarcoidosis	Traumatic Spinal Cord Injuries	Periarteritisnodosum
Dermatomyositis	Scleroderma	Acute Myocardial Infarction	Ankylosing Spondylitis

Table 1: Other conditions that complement is involved in, but not limited to.

Over the past 30 years, complement proteins have been cloned and sequenced. Complement-mediated tissue destruction occurs as part of the allergic process. By measuring complement we can detect underlying inflammatory mediators that augment the activity of IgG and IgE. Just as complement is measured to help diagnose many conditions, complement production specific to food can be looked at to know which dietary triggers are the most detrimental in relation to certain pathologies (Table 1). Identification of foods that trigger complement, allows for removal of foods, decreasing complement improving outcomes not only in allergies, but many other conditions as well.

In addition to certain IgG antibodies increasing reactivity, IgG4, when in the right ratio, can decrease risk of anaphylaxis. IgG4 increases as a way of developing tolerance to various allergies. Our body does not wish to remain anaphylactic to foods and so our immune system works to overcome the issue. IgG4 has a distinct mechanism of action, very different from subtype's I-III. IgG4 is smaller and has more thiol groups allowing it to easily slot into receptor sites where IgE binds. By doing this it blocks IgE from binding sites, keeping IgE from triggering de granulation or a mast cell or eosinophil resulting in release of histamine. Therapies designed to desensitize allergens, in the form of injections or sublingual drops are intended to increase IgG4, not in fact decrease IgE. The mechanism by which desensitization therapies work is to increase IgG4 over IgE, blocking its ability to cause anaphylaxis. By looking at IgG4 distinct from the rest of subtypes of IgG, you will be able to detect if tolerance has been achieved [8].

If IgG4 gets high enough, it can result in other issues. High levels of IgG4 precipitate out into tissue causing structural and histological problems. IgG4 antibodies are known to infiltrate into tissue such as the thyroid, resulting in thyroiditis, the esophagus resulting in eosinophilic esophagitis and the skin resulting in ec-

zema. The ovaries and prostate are also at risk of IgG4 damage as it likes to lodge in reproductive tissue decreasing fertility and hormonal balance [9] (Table 2).

IgG4 Conditions			
Autoimmune Pancreatitis	Salivary gland Disease	Orbital disease, often Complicated by Proptosis	Retroperitoneal Fibrosis
Increased number of Eosinophils / EosinoPhilic Esophagitis	Peripheral Eosinophilia	Atopy	Lymphadenopathy
Sclerosing Cholangitis	Mikulicz disease	Sclerosing-sialadenitis	IgG4-related Sub mandibular gland Disease
Lacrimal gland Enlargement	"Idiopathic" retroperitoneal fibrosis	IgG4-Related Thyroid disease	IgG4-Related thyroid disease
Lacrimal gland Enlargement	"Idiopathic" retroperitoneal fibrosis	IgG4-related thyroid disease	IgG4-related thyroid disease
IgG4-related kidney disease	Mimics sarcoidosis in the lung	Hypopituitarism Associated with IgG4-related Hypophysitis	Prostatitis
IgG4-related disease of the ovary	Constrictive pericarditis	Nasopharyngeal disease	Midline-destructive lesion

Table 2: IgG4 Conditions.

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