



Preface

Complement consists of over 30 different proteins in the plasma and on cell surfaces. Its name comes from the first activity or capacity it was found to be active in the immune system. Initial discovery of complement occurred when a Dr. Bordat in 1896, heated serum and found that resulted in a minimized immune response once injected back into an animal compared to non-heated serum. This led to the discovery that some heat sensitive part of the antibody-antigen complex was “complementing” the immune system. It was then discovered that complement proteins bind to antibodies such as IgM and IgG and complement the immune system’s response to bacteria.

Understanding to complement further developed as we continued to research its role in infectious disease. We learned that when complement was present it dictated a level of immune response in the presence of antibodies such as IgG and IgM. For example, some of the research team that worked on the polio vaccine discovered that it was not the titer to polio, or IgG, that correlated with the greatest immune response. A patient could have a higher IgG titer, but less immune activation and vice versa. When they began to track the level of complement and IgG, the correlation with disease progression became more linear. That is to say, when IgG and complement were both present, there was more debilitation in terms of an inflammatory symptoms. This demonstrates that the antibody and complement illicit a larger response when together.

Complement is a part of the innate immune system. It is a part of the innate immune system that is clearly correlate with disease progression in the literature, and its importance becomes more and more defined each day. Just like everything in the immune system, we need a balance. An absence of complement creates dysfunction, as is the case in Lupus. Too much complement can create more inflammation especially when it is being made in response to foods, a classic case of immune confusion.

Small amounts of complement present, in the form of C1q are a good thing. They keep the immune system ready to respond to non-specific signals from infection such as a bacteria or virus. This is often described as how the immune system is kept in idle, foot on the gas, ready to go if necessary. C1 binds partially to IgG, keeping it ready to respond to antigen with any first exposure to an invader. If this binding to antigen occurs, the binding of complement becomes tighter, triggering different epitopes or binding sites to be exposed, and results in cleavage of C1. This triggers the complement cascade, and as C3 is cleaved downstream, it creates an inflammatory response.

When there are lower levels of IgG, there is less binding of complement, but if more IgG is formed and complexed with antigen, it can begin to elicit enough complement binding and activity that a complement cascade is ignited and more inflammation occurs in the body. Lower levels of immune complexes and this partial binding of C1q actually stimulate the liver and spleen to uptake antibodies and prevent them from being deposited in the tissue. This is part of the pathophysiology of Lupus, an absence of C1q. The lack of complement causes antibodies to be deposited in the tissue and cause damage. However, if there are high amounts of complement triggered by IgG immune complexes, it will trigger the classical complement cascade and create high levels of inflammation. The greatest inflammation and food sensitivity reaction occurs when complement is present and bound to IgG. Complement without IgG can largely be from another source besides food reactions and would not necessarily amplify a food reaction. It is when you see both together that there is the greatest clinical concern because that will be the most inflammatory immune response to food. When testing the immune complexes of IgG and complement, complement, or C3d remains bound to IgG, and the complement measured is specific to that antibody.

When IgG is present without antigen, C1 lightly binds, and regulates the body's ability to clear immunoglobulins. When IgG is bound to an antigen, in this case a food, C1 has an increased affinity for a receptor site, which can begin the cleavage of complement and the inflammatory cascade. This is part of why food removal will improve symptoms even before IgG titers go down. Less of the offending food, will mean less activation of complement bound to IgG. This decreases the inflammatory potential of the IgG titer, even before the titer has decreased in amount. Removing the offending food is the first step to calm down this immune reaction.

Complement was designed to help us have a quick and effective response to an infectious assault. However, in the case of food allergies and sensitivities, the immune system has become confused and is now recognizing a food as an infection. This results in an inflammatory response to foods based on the patient's own immune individuality, or personal immune confusion. Mounting an effective complement response is useful in the case of infection, but in the case of food immune confusion, the body is now fighting a food instead of a bug. Creating complement to "kill" it is misguided, and only serves to damage tissue, and increase inflammation in the patient.

Other factors that help to determine how damaging complement is are the intensity of an IgE titer, IgG titer as well as hsCRP. C-reactive protein is triggered by complement and has a circular effect. When it is present, it increases activity and response of complement. Higher titers make complement more active. Another factor dictating the inflammatory potential of complement is your ability to metabolize it. This is determined by level of complement receptors. Complement receptors are defined by type, CR1, CR2 and CR3. Those with more CR1 receptor type are more likely to metabolize complement more quickly and will be less effected by it.

C3 and C3d

C3 plays a central role in the activation of the complement system. Its activation is required for both classical and alternative complement activation pathways. People with C3 deficiency are susceptible to bacterial infection as it increases inflammation in the body, which is good in the case of infection, but harmful in response to a food.

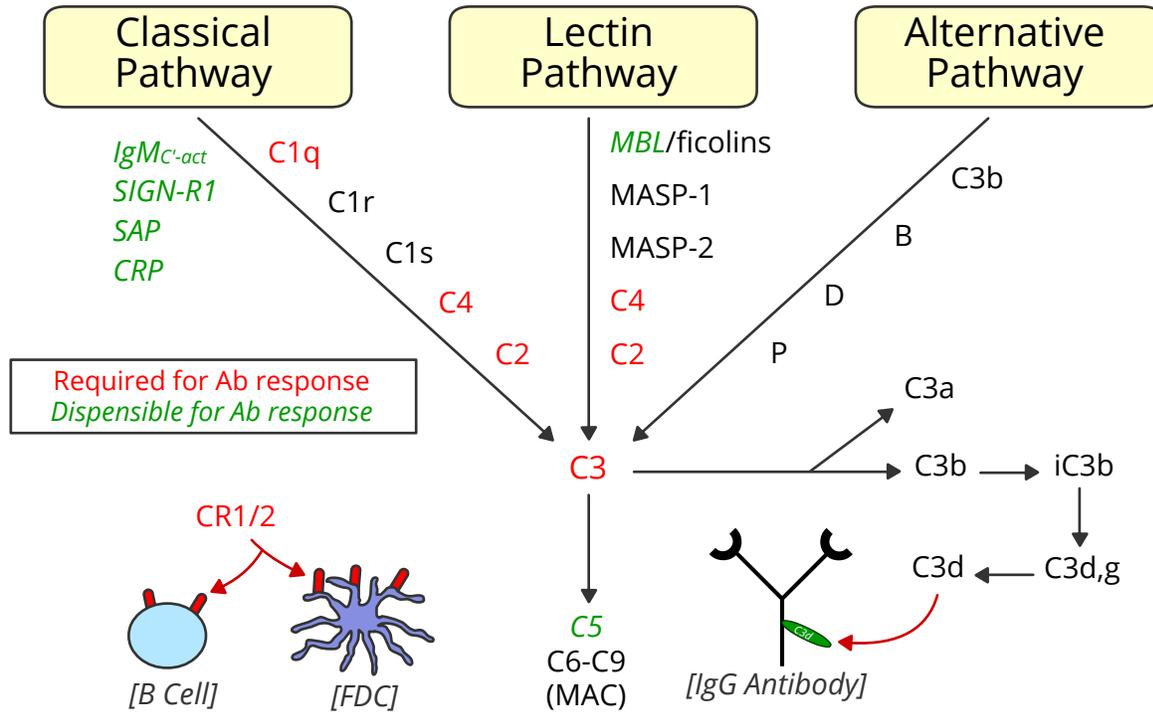
One form of C3-convertase, also known as C4b2a, is formed by a heterodimer of activated forms of C4 and C2. It catalyzes the proteolytic cleavage of C3 into C3a and C3b, generated during activation through the classical pathway as well as the lectin pathway. C3a is an anaphylotoxin and the precursor of some cytokines such as ASP, and C3b serves as an opsonizing agent. Factor I can cleave C3b into C3c and C3d, the latter of which plays a role in enhancing B cell responses. C3d remains bound to IgG.

In the alternative complement pathway, C3 is cleaved by C3bBb, another form of C3-convertase composed of activated forms of C3 (C3b) and factor B (Bb). The alternative pathway is triggered by things such as LPS and mycotoxins. Once C3 is activated to C3b, it exposes a reactive thioester that allows the peptide to covalently attach to any surface that can provide a nucleophile such as a primary amine or a hydroxyl group.

C3bBb is deactivated in steps. First, the proteolytic component of the convertase, Bb, is removed by complement regulatory proteins having decay-accelerating factor (DAF) activity. Next, C3b is broken down progressively to first iC3b, then C3c + C3dg, and then finally C3d. C3d is the final step in the pathway and is bound to IgG. By measuring C3d, you know that you are measuring a fully activated complement cascade as well as measuring something that is specific to the IgG food reaction. Not all complement antigens bind to IgG as C3d does. This makes it the most specific and important in terms of degerming complement response related to a particular IgG food specific antibody. It is common to measure C3 fragments such as C3d clinically and experimentally as biomarkers of immune activation. For example, renal biopsies from patients with glomerulonephritis are routinely measured for these fragments to serve as a robust indicator of disease activity. C3 fragment deposition is recognized in many inflammatory and age-related conditions.

Understanding Complement

Why It Matters, The Innate and Adaptive Immune Response



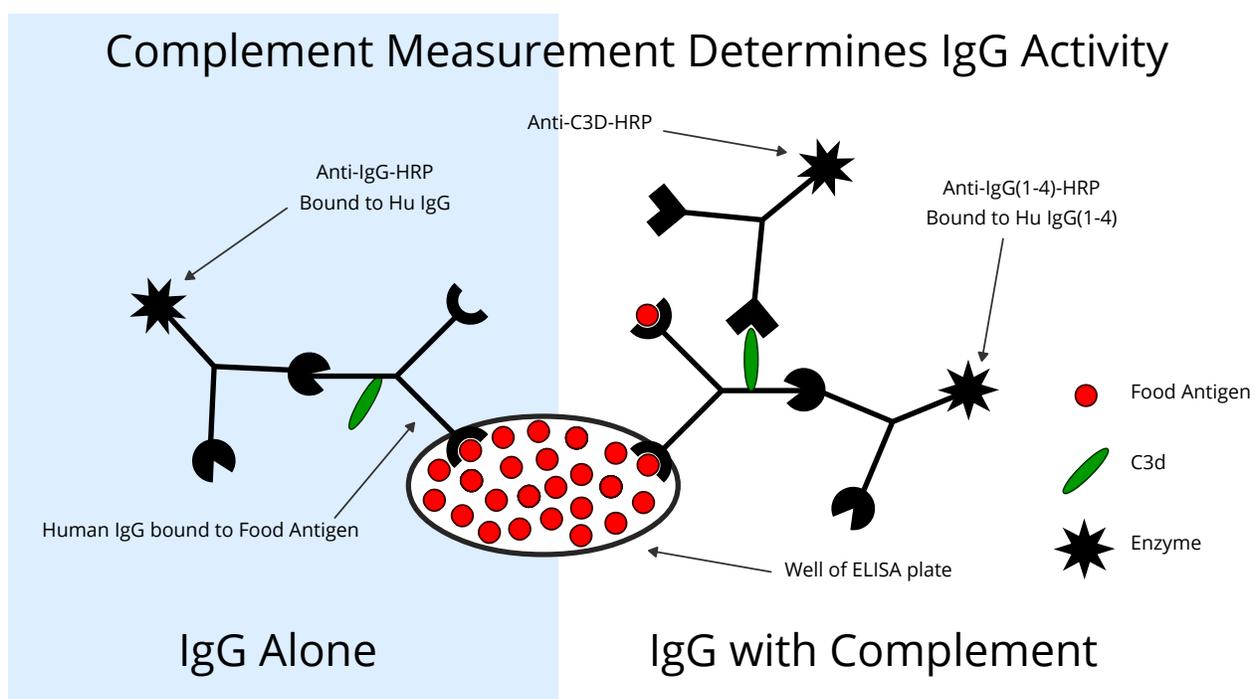
Different IgG antibodies bind with different affinity to complement. As you can see from below, IgG4 has an exceptionally low binding affinity which explains why it is less inflammatory.

Name	Percentage	Crosses Placenta Easily	Complement Activator	Binds to Fc Receptor on Phagocytic Cells	Half Life
IgG1	66%	yes (1.47)*	second highest	high affinity	21 days
IgG2	23%	no (0.8)*	third highest	extremely low affinity	21 days
IgG3	7%	yes (1.17)*	highest	high affinity	7 days
IgG4	4%	yes (1.15)*	no	intermediate affinity	21 days

This explains some of the objections people will have with IgG food sensitivity testing. There is a concern given that different levels of IgG create different levels of inflammation. IgG4 in fact will illicit an IL-10 response and decrease IgE reactions and has very minimal complement binding. This mechanism is well defined in immune desensitization research. As desensitization injections are given, IgG4 goes up, increasing IL-10, which lowers IgE and creates desensitization to an allergen/antigen. It is worth noting, that this effect is augmented in the presence of probiotics, underscoring the importance of the microbiome in decreasing reactions to foods in the body, and aiding in creation of immune tolerance to both foods and environmental triggers.

The binding of IgG to complement is well defined in Type III hypersensitivity, where as IgE is defined as a type I hypersensitivity. While an IgG-Complement reaction is not an allergy, it is still a well-defined immune reaction that will create inflammation in the system. These complexes are known to insert themselves into small blood vessels, joints, the glomeruli of the kidney, for example, and when complement is bound, they will create a greater degree of inflammation in that area. Complement also influences the release of histamine from mast cells, and the recruitment of more inflammatory cells to the area, increasing the inflammation and damage unless otherwise cleaned up. It appears that DHEA may also influence the complement proteins that are involved in cleaning up antigen-antibody complexes which may also explain part of the anti-inflammatory role of DHEA. It is the complex of IgG and complement that is most damaging, so when both are present this is when we have the most concern. Complement present without IgG may not be food specific

The graphic below shows the multiple binding sites of detection when both IgG and complement are measured. When both are present, the complex creates a more inflammatory response.



Any food antigen entering the bloodstream can produce symptoms associated with food sensitivities. Most food antigens enter the bloodstream through the intestinal epithelium and stimulate the production of IgG antibodies. IgG antibodies bind to food antigens that are free in the blood or that have deposited in tissues and form immune complexes (IC). The immune complex activates the activity of C3 which becomes covalently linked to the IgG forming IC-C3b. Ultimately, the C3b on the immune complex is cleaved forming IC-C3d. During this process, C3a (anaphylatoxin) is released which causes smooth muscle contraction and has a potent vascular effect. Under normal circumstances, circulating IC-C3b bind to the CR1 receptors on red blood cells and are cleared from the circulation in the liver and spleen. Continued production of antibody and formation of immune complexes may result in deposition of immune complexes in tissues which results in activation of the terminal complement pathway C5-9 on the surface of the tissue causing cell lysis and increased inflammation.

Complement dictates how inflammatory an IgG titer may be and plays a critical role as a functional bridge between innate and adaptive immune responses that allow for an integrated host defense to pathogenic challenge. However, if the immune response is confused and treating food as a pathogen, understanding which foods trigger a complement response is paramount for understanding which foods have the greatest inflammatory potential. It has been demonstrated that complement in the presence of IgG can increase the inflammatory potential 1000 to 10,000-fold underscoring its importance in an inflammatory food response. Measuring complement in the presence of IgG and measuring the type of IgG is critical for understanding inflammatory response of immune complexes made in response to food.

References

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