Effects of Complement Activation on Development of Humoral Responses
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Very few real "paradigm shifts" occur in immunology. One such major shift in thinking came with the concept that innate immunity is essential to induction of an adaptive response first proposed by Charles Janeway as an explanation for the necessity of adjuvants to induce an adaptive response. The concept that complement C3 acts as a natural adjuvant in humoral immunity put forward by Fearon and Locksley a few years later also represents a major shift in the thinking of the field. Activation products of complement C3- namely C3d- work to enhance B cell immunity by at least three different pathways and they will be discussed as outlined below.
i) Uptake of antigens coupled to C3d via the Cr2 receptor lowers the threshold for B cell activation
ii) Formation of germinal centers and differentiation of B memory and B effector cells is dependent on follicular dendritic cell retention of C3d-antigen via CR2 receptor.
iii) Naïve B cells transport C3d-immune complexes into LNs via CR2 where they are off-loaded to FDC.

HIV Env Immunogens Are Deficient in Activating Complement
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As discussed by Dr. Carroll, complement facilitates the immune response to a variety of microbial pathogens and in addition contributes importantly to the antimicrobial activity of antibody toward a wide variety of pathogens. The initial reports suggested that gp120 as well as gp41 activated complement spontaneously even in the absence of antibody. Since antibody and complement often kill enveloped viruses, these reports were surprising. More detailed studies have suggested that these initial studies were incorrect. Neither gp120 nor gp140 activate and bind significant amounts of complement. Presumably the glycan shield prevents complement binding. Mannose binding lectin (MBL) does bind to these envelope proteins, but the concentration of MBL is plasma is low and may well be insignificant is some people. Even when C3 is activated by and binds to the MBL-Env complex, one can show that the C3 is bound to the MBL and not Env. In striking contrast gp41 does bind complement spontaneously, however this only occurs when the gp120 is shed from the Env spike exposing gp41. Once the gp120 is shed the Env spike can no longer support infection. Interestingly, the first antibody detected in patients is to the gp41 fragment. Gp41 coated with C3 degradation fragments binds to CD21, the C3d receptor present on FDC and B cells, providing a cell membrane reservoir for the virus.
1. Complement binding to a variety of microorganisms contributes to an early immune response.

2. In both humans and animals, failure to bind complement leads to poor germinal center formation, low antibody titers and a short lived immune response.
3. These abnormalities are similar to those seen in HIV infection.
4. Although early reports of complement binding by HIV Env suggested that gp120 spontaneously binds complement, we find that it is not the case. Gp120 and gp140 bind complement poorly or not at all. Thus patients infected with HIV are similar to complement deficient patients and complement cannot contribute to the early immune response.
5. Similarly the virus resists complement mediated damage protecting it from destruction.

Enhanced complement fixation is associated with durable and spontaneous control of HIV

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While the development of an HIV vaccine able to induce neutralizing antibodies able to block HIV acquisition is the ultimate goal, vaccines to date have had limited success in inducing these types of immune responses. Conversely, a small fraction of HIV-infected patients are able to spontaneously control HIV infection in the absence of antiretroviral therapy, Controllers, offering a unique vaccine goal, the induction of immunity able to rapidly contain viral replication, also known as a functional cure. Previous reports have noted an enrichment of functional antibodies in slow progressors including antibodies able to elicit cytotoxicity and antibody-dependent cellular viral inhibition. However, because antibody functionality is greatly influenced by gender and age, we aimed to comprehensively define the specific antibody functions associated with long term spontaneous control of HIV infection. Two hundred HIV infected subjects were selected, split into 100 controllers, 50 subjects with progressive infection on therapy and 50 subjects with progressive infection on therapy. All groups were balanced for gender and age. Contrary to previous reports, no differences were observed in ADCC and phagocytic activity. Unexpectedly, a significant difference was associated with the ability of spontaneous controllers to fix complement resulting in neutrophil phagocytosis. These data point to a critical, previously unknown role, of complement mediated neutrophil activation in long-term antiviral control. Moreover, because complement is abundant at mucosal sites where transmission occurs, and neutrophils patrol these sites, it is plausible that vaccination could potentially lead to both long-term functional cure as well as potentially induce protection from infection.