Published in final edited form as:
Microbiol Spectr. ; 2(4): 1–17.

Functions of Antibodies

Donald N. Forthal, MD [Professor]
Chief, Infectious Diseases, University of California, Irvine, 3044 Hewitt Hall, Irvine, CA 92617, 949-824-3366

Donald N. Forthal: dnfortha@uci.edu

Introduction

In the setting of infectious diseases, antibody function refers to the biological effect that antibody has on a pathogen or its toxin. Thus, assays that measure antibody function are differentiated from those that strictly measure the ability of an antibody to bind to its cognate antigen. Examples of antibody functions include neutralization of infectivity, phagocytosis, antibody-dependent cellular cytotoxicity (ADCC), and complement-mediated lysis of pathogens or of infected cells.

Antibodies can impact pathogens in the presence or in the absence of effector cells or effector molecules such as complement, and experiments can often sort out with precision the mechanisms by which an antibody inhibits a pathogen*in vitro*. In addition, *in vivo* models, particularly those engineered to knock in or knock out effector cells or effector molecules are excellent tools for understanding antibody functions. However, it is highly likely that multiple antibody functions occur simultaneously or sequentially in the presence of an infecting organism *in vivo*.

The most critical incentive for measuring antibody functions is to provide a basis for vaccine development and for the development of therapeutic antibodies. In this respect, some functions, such as virus neutralization, serve to inhibit the acquisition of a pathogen or limit its pathogenesis. However, antibody can also enhance replication or contribute to pathogenesis. This chapter will emphasize those functions of antibody that are potentially beneficial to the host; a separate chapter is devoted to a discussion of antibody-dependent enhancement of infection. In addition, this chapter will focus on the effects of antibodies on organisms themselves, rather than on the toxins the organisms may produce. Finally, the role of antibody in modulating T cell immunity is not discussed in detail.

Antibody functions independent of effector cells or effector molecules

Antibodies are capable of having an impact on organisms in the absence of effector cells or effector molecules such as complement. For the most part, the impact of antibodies by themselves can be measured *in vitro* as neutralization of organism infectivity. Neutralization is herein referred to as the ability of antibody by itself to inhibit infection of susceptible cells or, in the case of some extracellular organisms, to inhibit an initial pathogenic step. Importantly, as described below, neutralization involves many potential mechanisms. Furthermore, it should be emphasized that other antibody functions in addition to

neutralization may ultimately be involved in prevention or clearance of infection, even by antibodies that neutralize the relevant organism *in vitro* (1).

Neutralization of infectivity—*In vitro*, antibodies are capable of blocking the infectivity or pathogenesis of viruses, bacteria, parasites, and fungi. Neutralization generally occurs as a result of interfering with an organism's attachment to host tissues. However, it is now clear that several mechanisms account for neutralization and that a single antibody or antibodies with different specificities can neutralize a given organism, at least *in vitro*, through multiple mechanisms.

Pre-attachment neutralization

Some antibodies have been shown to inhibit infectivity by binding to organisms and causing them to aggregate. Aggregation or agglutination by IgA may allow more efficient entrapment of bacteria in mucous and subsequent clearance by peristalsis (2,3). Although aggregation is more likely to occur with polymeric IgA and IgM, some neutralizing IgG antibodies can aggregate polio virus; the aggregation results in less infectivity, probably by reducing the number of encounters between virus and host cells (4,5).

Antibodies have also been shown to immobilize or “paralyze” organisms, such as the channel catfish pathogen *Ichtyophthirius multifiliis* (6). The IgA mAb Sal4 can render *Salmonella enterica* immobile, independently of agglutination, although Sal4 also specifically interferes with uptake into epithelial cells. Antibodies directed against *Pseudomonas aeruginosa* flagella inhibit motility of that organism (7). Polyclonal antibodies, induced by immunizing mice with *Vibrio cholerae* outer membrane vesicles, protect suckling mice from oral *V. cholerae* challenge, likely by inhibiting the motility of the organism (8). Antibody may slow the random movement of HIV-1 in vaginal mucous, presumably reducing the number of times the virus can make contact with the epithelial surface; this antibody function appears to rely in part on Fc interactions with components of the mucous (9).

Some antibodies appear to destabilize organisms, rendering them non-infectious. For example, the anti-foot-and-mouth-disease virus mAb 4C9 disrupts virion capsids, possibly by mimicking the virus' cell receptor (10). A neutralizing antibody against the E1 glycoprotein of Sinbis virus also induces conformational changes (11). Binding of HIV-1 gp120 can result in the shedding of gp120, leaving the transmembrane glycoprotein on the surface. However, the overall effect of such shedding on neutralization sensitivity is unclear (12).

mAbs binding to a surface protein of *Borrelia* can kill the organism by inducing pores in the outer membrane (13). AmAb directed against fungal heat-shock protein 90, a component of yeast cell walls, directly inhibits the growth of *Candida* (14,15) and works in synergy with anti-fungal drugs to inhibit *C. neoformans* (16). IgG1 and IgM mAbs that bind to the *C. neoformans* capsule affect gene expression, lipid biosynthesis, cellular metabolism and protein phosphorylation or susceptibility to amphotericin B (17). Other mechanisms by

which antibody inhibits bacterial and fungal infections directly and prior to attachment have been described (18-20).

Interference with pathogen attachment

Antibodies that bind to pathogen ligands essential for attachment of the pathogen to its host receptor have been described for many pathogens. In the case of viruses, such antibodies generally inhibit infectivity without altering their cognate antigen, thus strictly inhibiting by virtue of steric interference. This mechanism of virus inhibition has been described for many enveloped and non-enveloped antibodies. Well-studied example are antibodies against HIV-1 gp120 that interfere with binding of gp120 to CD4 (21). In addition, antibodies that neutralize, among others, flaviviruses (22), Newcastle disease virus (23), papillomavirus (24), and rotavirus (25) may do so by interfering with attachment. Some antibodies that block virus attachment do not bind directly to the virus attachment site. For example, an antibody against human rhinovirus type 14 binds to surrounding viral structures but nonetheless sterically hinders interactions between the virus and its ICAM-1 host receptor (26).

The stoichiometry of antibody-antigen interactions required for neutralization has been studied for many viruses, and evidence supports a “multiple hit” phenomenon in which neutralization requires the engagement of more than one antibody on the virion (27). Both antibody affinity and the accessibility of epitopes on the organism are the critical factors in determining whether antibody binding will exceed the threshold required for neutralization. Thus, for example, one cannot necessarily predict neutralizing potency by measuring antibody affinity alone or on the basis of epitope specificity. Antibody Fab or F (ab') 2 fragments are often capable of providing sufficient blockade of attachment to inhibit neutralization. These and other details regarding virus neutralization, including kinetics and requirements for steric hindrance can be found elsewhere (12,28,29).

Adhesion of bacteria to the surface of host cells or tissue allows targeting of the organism to a specific cell type and allows the bacteria to resist physical removal by hydrodynamic shear forces (30). Thus, adhesion is a first step in bacterial pathogenesis. The molecules responsible for bacterial adhesion are known as adhesins and are generally incorporated into pili or fimbriae (30,31). These adhesins are targets for antibodies that, in a manner somewhat analogous to virus neutralization, can inhibit attachment (32-34). Thus, vaccines have been developed in order to elicit antibodies directed against adhesions. In most cases, this strategy has failed because of sequence variation in the structural proteins of fimbriae. Nonetheless, vaccination with FimH was able to reduce bladder infection of mice and monkeys with uropathogenic *E. coli* (35-37). The use of this vaccination strategy in humans is made difficult by a shared epitope between FimH and human LAMP-2 and thus a fear of autoimmunity (38). Another example of adherence inhibition was described by Manjarrez-Hernanadez, *et al.*, who found that secretory IgA (sIgA) in breast milk was able to inhibit the adherence of enteropathogenic *E. coli* to cells (39). A mAb against lipoarabinomannan, a surface lipoglycan of *M. tuberculosis*, is able to prevent adherence of *M. tuberculosis* to human monocyte-derived macrophages (40). Antibodies can also inhibit attachment of bacteria to abiotic surfaces (41).

Antibodies to merozoite surface protein 1 (MSP1) on *Plasmodium* spp. can protect rodents against infection (42). One mechanism that might account for this is inhibition of attachment of the parasite to red blood cells (43,44). Plasmodium-infected red cells express *P. falciparum* erythrocyte membrane protein 1 (PfEMP1), which mediates binding to host endothelia and placenta. Antibodies have been elicited that can inhibit the interaction between infected erythrocytes and chondroitin sulfate proteoglycan, their ligand on placenta (45). Inhibition of binding in this manner would not impact infection *per se*, but might influence pathogenesis.

As with other organisms, binding of fungi to host-cell surfaces is a first step in infection. mAb 2G8, directed against β1,3-glucan, can inhibit binding of *Candida albicans* to human epithelial cells (49). It should be noted that mAb 2G8 also directly inhibits fungal growth and facilitates antifungal activity of human polymorphonuclear neutrophils (49,50). Other antibodies can also inhibit adhesion of *C. albicans* to HEC cells (51) and of *Cryptococcus neoformans* to a human lung epithelial cell line (52). As with bacteria, antibodies can inhibit *C. albicans* adherence to abiotic surfaces (53).

In the case of several parasites that infect the gastrointestinal tract, the mechanisms by which Ig, and in particular, IgA, may function are unclear, but it is likely that inhibition of attachment plays a role (46). For example, mucosal anti-*Giardia* IgA antibodies may prevent infection by inhibiting attachment of the organism to the intestinal epithelium (47). Intestinal IgE antibodies might contribute to the elimination of *T. spiralis* in rats, possibly by blockade of attachment to intestinal epithelium (48), and immune serum can block the attachment of *Cryptosporidium parvum* to epithelial cells (49).

Finally, antibodies generated against the host receptors themselves can also block infection of a number of different organisms (50-57).

Post-attachment neutralization

Inhibition of fusion/entry—Intracellular pathogens can be neutralized by antibodies at post-attachment steps in their lifecycle. In the case of viruses, several studies have identified antibodies that inhibit fusion of viral and host membranes or entry into susceptible target cells. For enveloped viruses, antibodies can block an interaction between a viral protein necessary for fusion and its cellular receptor (58). mAb 2F5, an HIV-1 neutralizing antibody, may block fusion of HIV-1 by obstructing the juxtaposition of viral and cellular membranes (29,59). 4E10, another HIV-1 neutralizing mAb, may interfere with the formation of fusion-competent complexes of gp41 (60). In the case of West Nile virus, a neutralizing monoclonal antibody likely sterically constrains low-pH-mediated rearrangements of E proteins (61,62). Similarly, anti-influenza virus HA antibodies can hinder the low pH-induced structural changes necessary for fusion of viral and endosomal membranes (63,64). It is possible that anti-influenza HA antibodies can inhibit both attachment and post-attachment steps (65).

An interesting twist on fusion inhibition was described for a mAb against influenza virus HA. The mAb becomes internalized at acid pH through the Fc neonatal receptor (FcRn) and reduces viral replication following apical exposure of Madin-Darby canine kidney cells to

influenza virus. As virus, mAb, and FcRn colocalize within endosomes, it is possible that inhibition of infectivity occurs by interfering with fusion of viral envelope and endosomal membranes (66).

Non-enveloped viruses generally enter cells by endocytosis, and escape from the endocytic vesicle is mediated by capsid protein. Antibodies against polio virus may stabilize the capsid and prevent the structural rearrangements necessary for vesicle escape (29,67,68).

Inhibition of other steps in organism lifecycles—A number of studies have revealed the ability of antibodies to inhibit organisms once they have successfully entered cells. In order for intracellular neutralization to be accomplished, antibodies must be internalized by host cells. Internalization of antibodies can occur as a result of coating of the organism, in which case, the coated organism must be capable of cell entry, or through Fc receptors. In addition, cells have been engineered to express intracellular antibodies (intrabodies) for potential therapeutic purposes (69). Intracellular neutralization can potentially interrupt an organism's lifecycle by interfering with the release, replication or expression of genomic material. As an example, adenovirus type 5 antihexon mAb (9C12) allows viral attachment, cell entry and intracellular transport of the virus to the nuclear periphery (70). Nonetheless, 9C12 neutralizes virus infectivity, likely by interfering with capsid uncoating and the release of viral genome (70). A rabbit anti-HPV16 L2 serum was able to neutralize HPV16 pseudoviruses through a mechanism that appeared to involve, at least in part, blocking the transport of viral genome to the nucleus (71).

IgA directed against surface proteins or glycoproteins can mediate neutralization of Sendai virus, influenza virus, and measles virus within susceptible target cells (72-74). In addition, IgA directed against measles virus M and N proteins, which are internal to the membrane, can inhibit measles virus replication within Vero cells (73,75). Polymeric IgA or sIgM can intracellulary block the transcytosis of HIV-1 through epithelial cells. Although the epithelial cells are not thought to be a target of HIV-1 infection and replication, such blocking of transcytosis could block access *in vivo* to sub-epithelial CD4+ cells (76). Similarly, IgA inhibits transcytosis of rotavirus through polarized Caco-2 cells (77). IgA can also introduce a conformational change in the rotavirus VP6 trimer, which is exposed after internalization of virus. The structural change results in transcriptionally incompetent particles (78,79).

A novel mechanism of intracellular virus inhibition was described by Mallery, *et al.*, wherein antibody bound to adenovirus interacted with cytosolic TRIM21; this interaction resulted in the antibody-bound virus being targeted to the proteasome for degradation (80). This mechanism of inhibition would not be expected to work with enveloped virus, since the antibody would be shed along with the envelope prior to internalization within the cytoplasm.

An interesting example of intracellular antibody function in a bacterial infection was described by Wang, *et al.*, who showed that a mAb against *Anaplasma phagocytophilum* inhibits morulae formation within HL-60 cells (a human promyelocytic leukemia cell line) (81). A mAb against listeriolysin O, the pore-forming toxin of *Listeria monocytogenes*,

blocks *L. monocytogenes* infection within macrophages. Inhibition likely occurs as a result of intracellular neutralization of a secreted *Listeria* virulence factor (82).

With respect to parasites, IgA is reported to inhibit the replication of *Toxoplasma gondii* in enterocytes (83). In addition, a mouse monoclonal IgG2b antibody, which enters host fibroblasts upon invasion of the antibody-treated organism, inhibits the intracellular growth of *T. gondii* (84).

Inhibition of later steps—Antibodies are capable of binding to nascent virus and inhibiting their liberation from infected cells. This function has been described for antibodies directed against the neuraminidase of influenza A virus (85). It has also been suggested that antibody directed against influenza A virus M2 protein influences the efficiency of virus budding (86). An mAb against rubella virus E1 glycoprotein was reported to delay the release of virus, perhaps by affecting virion assembly (87)

Antibody functions dependent on complement

Activation of the complement cascade by antibody can result in the lysis of organisms or of infected cells (88). In addition, organisms bound by complement can be internalized by phagocytic cells, with resultant clearance of the organism. Internalization through complement receptors on antigen-presenting cells can also result in the processing of antigen for presentation to T lymphocytes. The details of complement activation have been reviewed elsewhere (88). It is important to note that antibodies that bind and activate complement may also directly inhibit pathogens in the absence of complement. Complement activation may also have an indirect effect on pathogens by recruiting and activating leukocytes to sites of infection (89,90). Similarly, complement-activating antibodies may engage Fc receptors (see below). The Ig subtype and IgG subclass of antibody are major determinants of complement activation (91). For the most part in this review, we limit the discussion to antibodies that affect pathogens in the presence of complement but that in the absence of complement either have no or reduced anti-microbial activity.

A role for IgM and complement in limiting West Nile virus infection in mice has been suggested (92). More recently, Vogt, et al. determined that a non-neutralizing mouse IgG1 mAb decreased West Nile virus load in mice in a manner that required C1q as well as phagocytic cells and FcγRIII (93). C1q, as well as FcγRs, contributed to the enhancement of CD4+ T cell responses mediated by non-neutralizing anti-respiratory syncytial virus (RSV) antibody during RSV infection (94).

Antibodies that both neutralize and mediate complement-dependent lysis of influenza virus-infected cells may provide broader strain cross-reactivity than antibodies that only neutralize (95). Furthermore, the addition of complement has long been known to increase the infectivity-inhibiting activity of neutralizing antibodies against several viruses, including influenza viruses (96), Newcastle disease virus (97), herpes simplex virus (98), and Japanese encephalitis virus (99). Paramyxoviruses represent an interesting case in terms of the role of complement, since one study has shown that antibody can neutralize human parainfluenza

virus type 2 with little contribution by complement, whereas neutralization of mumps virus and simian virus 5 was dependent on complement (100).

In a mouse model of respiratory syncytial virus, passive immunization of a non-neutralizing mAb was shown to protect animals from intranasal challenge. The mAb lost protective activity as a Fab, and de-complementation of mice reduced the degree of protection (101). Similarly, protective mAbs against Semliki Forest virus lose some effect in complement-depleted mice (102).

HIV-1 Env-specific antibodies are capable of lysing HIV-1-infected cells or virus in the presence of complement. However, such complement-mediated effects are inhibited by the presence of regulators of complement activation found on infected cells or on the virus itself (103,104). Recently, complement-mediated phagocytosis of apoptotic, HIV-1 infected T cells by polyreactive antibodies has been reported (105). Another study has found that antibody from HIV-2-infected subjects is more potent than that from HIV-1-infected subjects in complement-mediated inactivation of the respective virus. Given the multiple potential consequences of complement, either directly or indirectly, its role in HIV infection *in vivo* remains unsettled (106-108).

Natural antibodies, generally of the IgM subtype, activate complement and can neutralize influenza virus (109). Moreover, natural IgM recognizing influenza virus or a surface protein of *Leishmania* may be involved in regulating CD4+ or CD8+ T cells through complement (110,111).

A unique function of antibody is to initiate the clearance of pathogens via complement activation and binding to erythrocyte complement receptor 1 (CR1); the result of such binding sequesters the pathogen from invading susceptible tissue and may facilitate the destruction of the organisms by tissue macrophages (112). This phenomenon was first noted for bacteria by Nelson in 1953 (113).

Bacterial pathogens have developed strategies to evade the effects of complement. However, in the presence of specific antibody, effective activation of complement can result in the death or clearance of organisms such as *N. meningitidis*, *N. gonorrhoeae* and *H. influenzae* (114). Individuals with complement deficiencies are at higher risk of infection with these organisms, and, in the case of *N. meningitides* and *H. influenza*, vaccine-induced antibody may protect through complement-mediated bacterial killing (115,116). However, even with late complement component deficiencies, C3b deposition allows antibodies to kill the organisms by complement-mediated phagocytosis (115-119).

Antibody-mediated complement lysis of *Legionella pneumophila* is ineffective; however, organisms opsonized with both antibody and complement are phagocytosed by PMNs, although killing of ingested bacteria is limited (120). Vaccination of humans with an oral typhoid vaccine, M01ZH09, results in antibodies that are bactericidal to *S. typhi* in the presence of complement; the antibodies also promote phagocytosis of *S. typhi* by macrophages in a complement-independent manner (121).

Antibody and complement augment proinflammatory cytokine production of human PBMCs stimulated with *C. albicans*, which could be a factor in host defense against *C. albicans* infection (122). Han, *et al.* found that protective IgM or IgG3 mAbs more efficiently bind C3 to the yeast cell than does a non-protective mAb and that protection is likely associated with enhanced phagocytosis and killing (123). In *C. neoformans*, immune serum or an IgG1 mAb localize C3 at the edge of the organism's capsule, allowing phagocytosis through complement receptors (124). IgM also promotes complement deposition and PMN phagocytosis of *C. neoformans* (125). Interestingly, IgM, IgA and IgG1 can promote the phagocytosis of *C. neoformans* through complement receptors in the absence of complement; this occurs because of an antibody-mediated change in the organism's capsule that allows an interaction with complement receptors (126).

Non-specific autologous antibodies can opsonize *P. falciparum*-parasitized erythrocytes, activate complement, and clear the infected cells through phagocytosis (127). Interestingly, antibody and complement deposition and phagocytosis are increased in erythrocytes from individuals with G6PD deficiency, sickle trait, and β-thalassemia; it has been proposed that this antibody-mediated phenomenon underlies the protection against falciparum malaria in individuals with certain genetic disorders of red blood cells (127-130). Antibody and complement can promote the killing of P. falciparum blood forms by THP-1 cells (a myelomonocytic cell line) and neutrophils (131,132). In addition, antibody-dependent complement-mediated lysis of schizonts results in growth inhibition of *P. falciparum* (133). Antibodies to *P. falciparum* gametes can abolish infectivity of the gametes to mosquitoes; the gametes are lysed in the presence of complement and antibody, and antibody that binds to gametes but doesn't lyse them does not abolish mosquito infectivity (134-137). Antibody has also been shown to clear experimental *Trypanosoma brucei* infection in a manner dependent on C3 and associated with uptake of organisms in the liver (138). Moreover, clearance of African trypanosomes by IgM, which is a major factor in controlling parasitemia, is mediated by complement and CR3 (139). Complement may also be involved in the pathogenesis of severe malaria(140,141).

Finally, it is important to note that antibodies that neutralize *in vitro* only in the presence of complement may protect *in vivo* through other means (142).

Antibody functions dependent on Fc-Fc receptor interactions

Much of the biological activity of antibody is mediated through interactions between Fc and Fc receptors found on a number of cells important for host defense. The engagement of Fc receptors by immune complexes (ICs) results in several downstream effects, depending on the Fc receptor-bearing cell, the form of the IC, the cytokine milieu, and the presence of complement. Fc receptor-mediated antibody activity can impact virus, bacteria, fungi and parasites and can have beneficial or adverse consequences to the host.

Fc receptors have been identified for IgG (FcγR), IgE (FcεR), and IgA (FcαR) and for both IgA and IgM (FcRα/μ). Five FcγRs have been identified in humans: FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa, and FcγRIIIb that differ from one another in their cellular distribution, function, and binding to IgG Fc (143,144). There are two known forms of FcεR and one

expressed form each of FcRα and FcRα/μ(144). FcγRIIa, FcγRIIIa, and FcγRIIIb are each encoded by polymorphic genes that result in phenotypically different receptors with respect to binding to different IgG subclasses (145-149). As a rule, IgG1 and IgG3 bind best to FcγRs, whereas IgG2 and IgG4 bind less well (150). Despite the similar magnitude of IgG1 and IgG3 binding to FcγRs, it has been reported that IgG3 mAbs are less able to mediate phagocytosis of antibody-coated red blood cells than are IgG1 mAbs, whereas ADCC activity of IgG3 is greater than that of IgG1 (151). In addition, glycosylation of the Fc segment of antibody can impact binding to FcRs (152-155).

Interactions between Fc and FcRs can result in the death of pathogens or of cells infected with pathogens by a process known as antibody-dependent cellular cytotoxicity (ADCC) (156-158). Fc-FcR interactions are also important for phagocytosis of pathogens or of infected cells, although phagocytosis can occur in the absence of antibody or in the presence of antibody through other receptors (including complement receptors)(144). Engagement of FcRs can also inhibit intracellular pathogens without apparently killing the host cell (159). Modulation of inflammation is another FcR-mediated antibody function that can impact several pathogens (160-164). Finally, studies have documented the impact of FcR engagement on assays used to measure the neutralizing activity of antibodies (165-168).

Antibody-Dependent Cellular Cytotoxicity (ADCC)

ADCC occurs when antibody forms a bridge between an infected target cell (or directly with some pathogens) and an FcR-bearing effector cell. The result of this three-way interaction is the death of the target cell, either by lysis or apoptosis. ADCC is likely to play an important role in the clinical effects of anti-tumor mAbs, such as rituximab and herceptin, but its role in infections is less clear and complicated by the multiple functions of antibody (169-171).

ADCC, first described against virus-infected cells by Shore, *et al.* for HSV-1 (172), becomes most interesting with regard to antibodies that protect animals but that poorly neutralize thepathogen *in vitro*. Non-neutralizing mAbs directed against HSV-2 glycoproteins can protect mice after a footpad injection of a lethal dose of HSV-2. The mAbs are equally efficient in protection in complement-sufficient and complement-deficient mice (173). More recently, Gorander, *et al.* found that vaccination of mice with glycoprotein G of HSV-2 plus CpG could protect animals from vaginal challenge with HSV-2. The protective vaccine was associated with CD4+ T cell IFN-γ responses. In addition, the vaccine resulted in non-neutralizing antibodies that mediated ADCC and might have been involved in protection (174). Chu, *et al.* found that passive infusion of IgG antibodies decreased symptoms and mortality and decreased vaginal viral quantity in normal mice infected with HSV-2; although the antibody had neutralizing activity, protection was significantly diminished in mice lacking FcγR expression (175). Influenza A virus M2 vaccination results in partial protection of mice from influenza A infection that is mediated by non-neutralizing antibodies; ADCC is likely involved, since protection is not dependent on complement, whereas NK cells depletion reduces the protective effect (176).

The role of ADCC in HIV-1 and other lentivirus infections has been reviewed recently (156,177). A great deal of correlative evidence in monkeys, as well as in humans, suggests a role for ADCC or other FcγR-mediated antibody activities in preventing or modulating

lentivirus infections. A more definitive study has demonstrated that mutations in the Fc segment of antibody that abrogate FcγR binding render a neutralizing mAb (IgG1b12) less protective *in vivo* against vaginal SHIV challenge than the unmutated mAb (1). However, whether the decreased protection is due to a lack of ADCC or to some other FcγR-mediated activity remains unknown.

There is scant literature on the role of ADCC in bacterial infections. However, complement-independent killing of bacteria *in vitro* in the presence of "killer" lymphocytes has been described for *N. meningitidis* and *Shigella flexneri* (178,179). IgA, as well as IgG, in combination with lymphocytes from murine gut-associated lymphoid tissue, is reported to mediate ADCC against *S. flexneri* and *Salmonella* spp. (180,181). Similarly, the same group found antibacterial activity against *Streptococcus pneumoniae* by mouse lung lymphocytes in conjunction with IgA (182). ADCC has also been described for *Ehrlichia risticii* and *Coxiella burnetii*-infected cells and for *Brucella abortus*, though, as with other bacteria, the role, if any, of ADCC in these infection *in vivo* is unknown (183-185). In the case of *C. burnetii*, passive antibody treatment can protect mice from *C. burnetii* infection in common γ-chain knockout mice, suggesting that Fc-FcγR interactions were not required for protection (186).

ADCC has been documented *in vitro* for a number of parasites. IgG opsonized *Trichinella spiralis* larvae are susceptible to ADCC by eosinophils, neutrophils, and monocytes (187,188). Schistosomula are killed by eosinophils, macrophages or platelets in the presence of specific antibody, including IgE and IgG (189-192). *In vivo* protection of rats from *S. mansoni* infection is likely the result of such IgE-mediated ADCC (193). Antibodies that bind poorly to FcRs, such as IgM, IgG2 and IgG4, can inhibit ADCC against schistosomula and have been epidemiogically linked to increased susceptibility of infection in humans (194-196). ADCC mediated by IgG or IgE and by macrophages, eosinophils or neutrophil effectors cells has also been shown *in vitro* to kill larval or adult filarial (197-202). *In vivo*, clearance of *Brugia malayi* microfilaria is very likely mediated through ADCC (203). ADCC activity against trypanosomes and other parasites has also been documented (204-210).

It is important to note that many of the effector cells mediating ADCC against parasites are capable of antibody-mediated phagocytosis as well. In both ADCC and phagocytosis, organisms are killed and radioisotopes or dyes are released, and distinguishing between these two antibody functions requires careful consideration (204,205).

Finally, antibodies may also inhibit infections in a manner that requires the components of ADCC (*i.e.*, infected target cells, antibody, and FcR-bearing effector cells) but does not necessarily rely on target cell lysis. Thus, antibody-dependent cell-mediated inhibition of *P. falciparum* has been described, where the development of intracellular parasites is blocked in a manner dependent on blood monocytes and antibody; triggering of both FcγRIIa and FcγRIIIa may be required but erythrocyte target cells do not appear to be killed (159,211,212). Forthal, *et al.* have described antibody-dependent cell-mediated virus inhibition (ADCVI) with measles virus HIV, SIV and SHIV (1,160,213,214). ADCVI is a

measure of virus inhibition occurring as a result of antibody-FcR interactions and is likely dependent on combinations of ADCC, phagocytosis, and chemokine/cytokine production.

Phagocytosis

The internalization and degradation of antibody-coated pathogens by phagocytes via FcRs has been well-described for a number of organisms and is likely a critical antibody function for clearance of pathogens *in vivo*. Since phagocytosis and ADCC often require the same components (antibody and effector cells), it is often difficult to definitively and specifically demonstrate a role for phagocytosis in preventing or modulating infections in animals or humans.

With respect to viruses, passive infusion of antibodies results in the rapid elimination of cell-free organism from the blood of animals (215,216). This is consistent with information indicating that the rate of clearance of antigen by the reticuloendothelial system is greatly increased in the presence of specific antibody (217,218).

A recent example comes close to demonstrating a key role for phagocytosis in preventing a viral infection (93). In that study a poorly neutralizing antibody against West Nile virus envelope could reduce viremia in mice via an FcγRIII- and C1q-dependent mechanism that required phagocytic cells. Since NK cells did not seem to be involved, it is less likely that ADCC played a significant role in protection. However, it remains possible that lysis of infected cells mediated by the phagocytes, in addition to or instead of phagocytosis of antibody-coated virus, was involved in protection. A possible role for phagocytosis in clearing influenza virus from the lungs of mice was suggested by Fujisawa (219). In that study, both PMNs and passive infusion of neutralizing antibody were required for maximum viral clearance and survival. A particularly interesting point about this study was the need for PMNs despite the high neutralizing titer of the infused immune serum; this finding is consistent with that of Hessell, et al., where maximal protection against SHIV was afforded by a neutralizing antibody that engaged Fc receptors (1). Huber, et al., using passive antibody transfer in $FcR\gamma^{-/-}$ mice, also concluded that phagocytosis is important in clearance of influenza virus (220). In all of these studies, however, it is not possible to precisely define the antibody function responsible for protection, as phagocytosis, ADCC, or soluble factors could have contributed.

An interesting phenomenon related to phagocytosis was described by Chan et al. (221) who showed that inhibition of dengue virus phagocytosis, by aggregating virus and cross-linking of FcγRIIb, resulted in neutralization of virus infectivity.

Phagocytosis of antibody-coated infected cells, in addition to phagocytosis of immune complexed cell-free virus, could be a contributor to protection, although virus-infected cells can be phagocytosed in the absence of antibody (222,223). Surprisingly, two studies indicated that neither human monocytes nor human neutrophils were able to phagocytose IgA or IgG immune complexes formed with influenza virus *in vitro* (224,225).

FcγR-mediated phagocytosis and clearance of Bordetella pertussis has been demonstrated *in vitro* and in a mouse model (226). Similarly, natural and vaccine-induced antibodies mediate

phagocytosis of S. pneumoniae, and such FcγR-mediated phagocytosis may play a role in protection (227). In FcγRIIb-deficient mice, phagocytosis and survival after *S. pneumoniae* challenge are both improved relative to control mice, although the survival advantage is reversed after immunization followed by challenge with a high dose of bacteria (227). In the later case, it is likely that inflammatory cytokines triggered by interactions between anti-pneumococcal antibody and activating FcγRs—in the absence of the inhibitory FcγRIIb—were responsible for the higher mortality. Other studies in mice have found that antibody-mediated protection from *S. pneumoniae* does not depend on FcγRs (228). In humans, IgG2, a relatively inefficient activator of complement, is thought to be important in protection against *S. pneumoniae*. Although IgG2 is also relatively poor at engaging FcγRs, it binds best to the H isoform of FcγRIIa and to the V isoform of FcγRIIIa (150). Consistent with a role for FcγR-mediated phagocytosis, there appears to be an association between homozygosity for the R isoform of FcγRIIa and severe or invasive pneumococcal disease (229,230). Moreover, PMNs from FcγRIIa HH homozygous donors have higher phagocytic activity against antibody-opsonized *S. pneumoniae* (231). In the case of *N. meningitidis*, complement-mediated clearance or bactericidal activity appears to be more important than FcγR-mediated phagocytosis (see above). However, FcγR-mediated phagocytosis can be demonstrated *in vitro* (232,233). Furthermore, some studies, but not all, have found associations between FcγRIIa genotypes and susceptibility to or severity of meningococcal infection (233-238). Finally, γδT cells capable of phagocytosing antibody-opsonized *E. coli* via FcγRIIIa have been described (239).

Opsonization and phagocytosis by IgG subclass-switched mouse mAbs has been described for *C. neoformans* (240). Passive infusion of the mAbs had some effect on clearing yeast from mice, however the phagocytic activity *in vitro* did not correlate well with clearing of organisms *in vivo* (241). A study of *C. neoformans* phagocytosis has suggested a specific receptor for IgG3 in mice different from the known FcγRs (242). A recent study using X-linked immunodeficient mice indicated that IgM promotes containment of *C. neoformans* in the lungs by augmenting phagocytosis (243).

In many cases, parasites may be too large for phagocytosis: lysosomal and parasitic membranes fuse after Fc-FcR (γ, α, or ε) interactions, resulting in lysis of parasites extracellularly (244). However, IgG from individuals living in malaria-endemic areas can mediated the phagocytosis of *P. falciparum*-infected erythrocytes by monocytes (245). In addition, the *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) is the major target of antibodies that mediate phagocytosis, and anti-PfEMP1 antibodies are associated with a reduced risk of developing symptomatic malaria (246).

Other antibody functions

Apart from specific effects on organisms, antibodies may modulate inflammation and thereby indirectly affect pathogenesis. Such immune modulation is well-described for FcγR triggering by immune complexes, which results in the generation, secretion or repression of various pro- or anti-inflammatory substances (247-256). In addition to modulation of cytokines by FcRs themselves, internalization of immune complexes via FcRs can result in

the engagement of toll-like receptors, adding a further layer of complexity and control over inflammation (255,257-260).

An example of the role of FcγRs in inflammation was the demonstration that soluble FcγRII, by competing with IC binding to cellular FcγRs, can limit the inflammation due to the IC (*i.e.*, the Arthus reaction) (261). Soon thereafter, it was established that the Arthus reaction was markedly attenuated in FcRγ-chain knockout mice (262). These types of studies have important implications for autoimmune diseases (263).

Engagement of FcγRIIbby IgG immune complexes serve to regulate B-cell activity and survival and may serve as a means of maintaining peripheral tolerance for B cells (264-266). Immune complex binding and internalization via FcγRs also result in dendritic cell maturation and in efficient MHC class I-restricted presentation of the exogenous peptides making up the immune-complexed antigen (267).

Another important mechanism of immune modulation by antibodies is through the activation of complement components, which can then serve as chemotactic agents (268). Moreover, C5a anaphylatoxin is involved in immune complex-mediated injury in part because it results in a shifting of the balance between activating and inhibitory FcγRs toward a more inflammatory phenotype (269). Activation of C3bi on immune complexes can result in blunting of the inflammatory response by diverting interactions of the IC away from FcγRs and toward CR3 (270).

Conclusions

The inhibitory effects of antibodies on pathogenic organisms have been documented since the late 1800's (271). Since that time, much has been learned regarding the mechanisms that underlie the anti-microbial activity of antibodies. However, antibodies often have multiple functions *in vitro* and *in vivo*, either directly or through interactions with FcRs or complement. Modern tools, such as knockout mice or antibodies engineered to abrogate or enhance functions have proven useful for more precise explorations of antibody function. Nonetheless, major questions regarding the way in which an antibody functions *in vivo* remain, and multiple activities are likely to contribute to the anti-microbial effect.

Acknowledgments

The author receives financial support from the US Public Health Service (grants AI084136, AI0797775, and AI102715). He wishes to acknowledge the editorial assistance of Gabriel J. A. Forthal.

References

1. Hessell AJ, Hangartner L, Hunter M, Havenith CE, Beurskens FJ, Bakker JM, Lanigan CM, Landucci G, Forthal DN, Parren PW, Marx PA, Burton DR. Fc receptor but not complement binding is important in antibody protection against HIV. Nature. 2007; 449:101–104. [PubMed: 17805298]
2. Brandtzaeg P. Induction of secretory immunity and memory at mucosal surfaces. Vaccine. 2007; 25:5467–5484. [PubMed: 17227687]

3. Phalipon A, Cardona A, Kraehenbuhl JP, Edelman L, Sansonetti PJ, Corthesy B. Secretory component: a new role in secretory IgA-mediated immune exclusion in vivo. Immunity. 2002; 17:107–115. [PubMed: 12150896]
4. Brioen P, Dekegel D, Boeye A. Neutralization of poliovirus by antibody-mediated polymerization. Virology. 1983; 127:463–468. [PubMed: 6306919]
5. Thomas AA, Vrijsen R, Boeye A. Relationship between poliovirus neutralization and aggregation. J Virol. 1986; 59:479–485. [PubMed: 3016307]
6. Lin TL, Clark TG, Dickerson H. Passive immunization of channel catfish (Ictalurus punctatus) against the ciliated protozoan parasite Ichthyophthirius multifiliis by use of murine monoclonal antibodies. Infect Immun. 1996; 64:4085–4090. [PubMed: 8926073]
7. Campodonico VL, Llosa NJ, Grout M, Doring G, Maira-Litran T, Pier GB. Evaluation of flagella and flagellin of Pseudomonas aeruginosa as vaccines. Infect Immun. 2010; 78:746–755. [PubMed: 19995892]
8. Bishop AL, Schild S, Patimalla B, Klein B, Camilli A. Mucosal immunization with Vibrio cholerae outer membrane vesicles provides maternal protection mediated by antilipopolysaccharide antibodies that inhibit bacterial motility. Infect Immun. 2010; 78:4402–4420. [PubMed: 20679439]
9. Hope, T. AIDS Vaccine Conference. Atlanta, GA: 2010. Defining the interaction of HIV with the mucosal barriers to gain insights into the mechanisms of sexual transmission. Abstract
10. McCullough KC, Smale CJ, Carpenter WC, Crowther JR, Brocchi E, De Simone F. Conformational alteration in foot-and-mouth disease virus virion capsid structure after complexing with monospecific antibody. Immunology. 1987; 60:75–82. [PubMed: 3028937]
11. Hernandez R, Paredes A, Brown DT. Sindbis virus conformational changes induced by a neutralizing anti-E1 monoclonal antibody. J Virol. 2008; 82:5750–5760. [PubMed: 18417595]
12. Klasse PJ, Sattentau QJ. Occupancy and mechanism in antibody-mediated neutralization of animal viruses. J Gen Virol. 2002; 83:2091–2108. [PubMed: 12185262]
13. LaRocca TJ, Holthausen DJ, Hsieh C, Renken C, Mannella CA, Benach JL. The bactericidal effect of a complement-independent antibody is osmolytic and specific to Borrelia. Proc Natl Acad Sci U S A. 2009; 106:10752–10757. [PubMed: 19549817]
14. Matthews RC, Rigg G, Hodgetts S, Carter T, Chapman C, Gregory C, Illidge C, Burnie J. Preclinical assessment of the efficacy of mycograb, a human recombinant antibody against fungal HSP90. Antimicrob Agents Chemother. 2003; 47:2208–2216. [PubMed: 12821470]
15. Pachl J, Svoboda P, Jacobs F, Vandewoude K, van der Hoven B, Spronk P, Masterson G, Malbrain M, Aoun M, Garbino J, Takala J, Drgona L, Burnie J, Matthews R. A randomized, blinded, multicenter trial of lipid-associated amphotericin B alone versus in combination with an antibody-based inhibitor of heat shock protein 90 in patients with invasive candidiasis. Clin Infect Dis. 2006; 42:1404–1413. [PubMed: 16619152]
16. Nooney L, Matthews RC, Burnie JP. Evaluation of Mycograb, amphotericin B, caspofungin, and fluconazole in combination against Cryptococcus neoformans by checkerboard and time-kill methodologies. Diagn Microbiol Infect Dis. 2005; 51:19–29. [PubMed: 15629225]
17. McClelland EE, Nicola AM, Prados-Rosales R, Casadevall A. Ab binding alters gene expression in Cryptococcus neoformans and directly modulates fungal metabolism. J Clin Invest. 2010; 120:1355–1361. [PubMed: 20335660]
18. Watanabe M, Blobel G. Site-specific antibodies against the PrlA (secY) protein of Escherichia coli inhibit protein export by interfering with plasma membrane binding of preproteins. Proc Natl Acad Sci U S A. 1989; 86:1895–1899. [PubMed: 2538820]
19. Gregory RL, Michalek SM, Shechmeister IL, McGhee JR. Function of anti-Streptococcus mutans antibodies: anti-ribosomal antibodies inhibit acid production, growth, and glucose phosphotransferase activity. Infect Immun. 1984; 45:286–289. [PubMed: 6203840]
20. Casadevall A, Pirofski LA. Immunoglobulins in defense, pathogenesis, and therapy of fungal diseases. Cell Host Microbe. 2012; 11:447–456. [PubMed: 22607798]
21. Klasse PJ, Sanders RW, Cerutti A, Moore JP. How can HIV-type-1-Env immunogenicity be improved to facilitate antibody-based vaccine development? AIDS Res Hum Retroviruses. 2012; 28:1–15. [PubMed: 21495876]

22. He RT, Innis BL, Nisalak A, Usawattanakul W, Wang S, Kalayanarooj S, Anderson R. Antibodies that block virus attachment to Vero cells are a major component of the human neutralizing antibody response against dengue virus type 2. J Med Virol. 1995; 45:451–461. [PubMed: 7666046]

23. Iorio RM, Glickman RL, Riel AM, Sheehan JP, Bratt MA. Functional and neutralization profile of seven overlapping antigenic sites on the HN glycoprotein of Newcastle disease virus: monoclonal antibodies to some sites prevent viral attachment. Virus Res. 1989; 13:245–261. [PubMed: 2475989]

24. Booy FP, Roden RB, Greenstone HL, Schiller JT, Trus BL. Two antibodies that neutralize papillomavirus by different mechanisms show distinct binding patterns at 13 A resolution. J Mol Biol. 1998; 281:95–106. [PubMed: 9680478]

25. Ruggeri FM, Greenberg HB. Antibodies to the trypsin cleavage peptide VP8 neutralize rotavirus by inhibiting binding of virions to target cells in culture. J Virol. 1991; 65:2211–2219. [PubMed: 1850007]

26. Smith TJ, Olson NH, Cheng RH, Liu H, Chase ES, Lee WM, Leippe DM, Mosser AG, Rueckert RR, Baker TS. Structure of human rhinovirus complexed with Fab fragments from a neutralizing antibody. J Virol. 1993; 67:1148–1158. [PubMed: 7679742]

27. Della-Porta AJ, Westaway EG. A multi-hit model for the neutralization of animal viruses. J Gen Virol. 1978; 38:1–19. [PubMed: 74400]

28. Platt EJ, Gomes MM, Kabat D. Kinetic mechanism for HIV-1 neutralization by antibody 2G12 entails reversible glycan binding that slows cell entry. Proc Natl Acad Sci U S A. 2012; 109:7829–7834. [PubMed: 22547820]

29. Reading SA, Dimmock NJ. Neutralization of animal virus infectivity by antibody. Arch Virol. 2007; 152:1047–1059. [PubMed: 17516034]

30. Klemm P, Vejborg RM, Hancock V. Prevention of bacterial adhesion. Appl Microbiol Biotechnol. 2010; 88:451–459. [PubMed: 20694794]

31. Cegelski L, Marshall GR, Eldridge GR, Hultgren SJ. The biology and future prospects of antivirulence therapies. Nat Rev Microbiol. 2008; 6:17–27. [PubMed: 18079741]

32. Smani Y, McConnell MJ, Pachon J. Role of fibronectin in the adhesion of Acinetobacter baumannii to host cells. PLoS One. 2012; 7:e33073. [PubMed: 22514602]

33. Tsang TM, Annis DS, Kronshage M, Fenno JT, Usselman LD, Mosher DF, Krukonis ES. Ail protein binds ninth type III fibronectin repeat (9FNIII) within central 120-kDa region of fibronectin to facilitate cell binding by Yersinia pestis. J Biol Chem. 2012; 287:16759–16767. [PubMed: 22447929]

34. Khan MN, Pichichero ME. Vaccine candidates PhtD and PhtE of Streptococcus pneumoniae are adhesins that elicit functional antibodies in humans. Vaccine. 2012; 30:2900–2907. [PubMed: 22349524]

35. Langermann S, Ballou WR. Development of a recombinant FimCH vaccine for urinary tract infections. Adv Exp Med Biol. 2003; 539:635–648. [PubMed: 15176317]

36. Langermann S, Palaszynski S, Barnhart M, Auguste G, Pinkner JS, Burlein J, Barren P, Koenig S, Leath S, Jones CH, Hultgren SJ. Prevention of mucosal Escherichia coli infection by FimH-adhesin-based systemic vaccination. Science. 1997; 276:607–611. [PubMed: 9110982]

37. Langermann S, Mollby R, Burlein JE, Palaszynski SR, Auguste CG, DeFusco A, Strouse R, Schenerman MA, Hultgren SJ, Pinkner JS, Winberg J, Guldevall L, Soderhall M, Ishikawa K, Normark S, Koenig S. Vaccination with FimH adhesin protects cynomolgus monkeys from colonization and infection by uropathogenic Escherichia coli. J Infect Dis. 2000; 181:774–778. [PubMed: 10669375]

38. Kain R, Exner M, Brandes R, Ziebermayr R, Cunningham D, Alderson CA, Davidovits A, Raab I, Jahn R, Ashour O, Spitzauer S, Sunder-Plassmann G, Fukuda M, Klemm P, Rees AJ, Kerjaschki D. Molecular mimicry in pauci-immune focal necrotizing glomerulonephritis. Nat Med. 2008; 14:1088–1096. [PubMed: 18836458]

39. Manjarrez-Hernandez HA, Gavilanes-Parra S, Chavez-Berrocal E, Navarro-Ocana A, Cravioto A. Antigen detection in enteropathogenic Escherichia coli using secretory immunoglobulin A

antibodies isolated from human breast milk. Infect Immun. 2000; 68:5030–5036. [PubMed: 10948121]

40. Schlesinger LS, Hull SR, Kaufman TM. Binding of the terminal mannosyl units of lipoarabinomannan from a virulent strain of Mycobacterium tuberculosis to human macrophages. J Immunol. 1994; 152:4070–4079. [PubMed: 8144972]
41. Kornspan JD, Tarshis M, Rottem S. Adhesion and biofilm formation of Mycoplasma pneumoniae on an abiotic surface. Arch Microbiol. 2011; 193:833–836. [PubMed: 21879294]
42. Holder AA, Freeman RR. Immunization against blood-stage rodent malaria using purified parasite antigens. Nature. 1981; 294:361–364. [PubMed: 7312033]
43. Perkins ME, Rocco LJ. Sialic acid-dependent binding of Plasmodium falciparum merozoite surface antigen, Pf200, to human erythrocytes. J Immunol. 1988; 141:3190–3196. [PubMed: 2459245]
44. Bolad A, Berzins K. Antigenic diversity of Plasmodium falciparum and antibody-mediated parasite neutralization. Scand J Immunol. 2000; 52:233–239. [PubMed: 10972898]
45. Clausen TM, Christoffersen S, Dahlback M, Langkilde AE, Jensen KE, Resende M, Agerbaek MO, Andersen D, Berisha B, Ditlev SB, Pinto VV, Nielsen MA, Theander TG, Larsen S, Salanti A. Structural and functional insight into how the Plasmodium falciparum VAR2CSA protein mediates binding to chondroitin sulfate A in placental malaria. J Biol Chem. 2012; 287:23332–23345. [PubMed: 22570492]
46. Yun CH, Lillehoj HS, Lillehoj EP. Intestinal immune responses to coccidiosis. Dev Comp Immunol. 2000; 24:303–324. [PubMed: 10717295]
47. Eckmann L. Mucosal defences against Giardia. Parasite Immunol. 2003; 25:259–270. [PubMed: 12969444]
48. Negrao-Correa D. Importance of immunoglobulin E (IgE) in the protective mechanism against gastrointestinal nematode infection: looking at the intestinal mucosae. Rev Inst Med Trop Sao Paulo. 2001; 43:291–299. [PubMed: 11696854]
49. Cevallos AM, Zhang X, Waldor MK, Jaison S, Zhou X, Tzipori S, Neutra MR, Ward HD. Molecular cloning and expression of a gene encoding Cryptosporidium parvum glycoproteins gp40 and gp15. Infect Immun. 2000; 68:4108–4116. [PubMed: 10858228]
50. Lopalco L, Barassi C, Pastori C, Longhi R, Burastero SE, Tambussi G, Mazzotta F, Lazzarin A, Clerici M, Siccardi AG. CCR5-reactive antibodies in seronegative partners of HIV-seropositive individuals down-modulate surface CCR5 in vivo and neutralize the infectivity of R5 strains of HIV-1 In vitro. J Immunol. 2000; 164:3426–3433. [PubMed: 10706739]
51. Barassi C, Soprana E, Pastori C, Longhi R, Buratti E, Lillo F, Marenzi C, Lazzarin A, Siccardi AG, Lopalco L. Induction of murine mucosal CCR5-reactive antibodies as an anti-human immunodeficiency virus strategy. J Virol. 2005; 79:6848–6858. [PubMed: 15890924]
52. Wintachai P, Wikan N, Kuadkitkan A, Jaimipuk T, Ubol S, Pulmanausahakul R, Auewarakul P, Kasinrerk W, Weng WY, Panyasrivanit M, Paemanee A, Kittisenachai S, Roytrakul S, Smith DR. Identification of prohibitin as a Chikungunya virus receptor protein. J Med Virol. 2012; 84:1757–1770. [PubMed: 22997079]
53. Kondratowicz AS, Lennemann NJ, Sinn PL, Davey RA, Hunt CL, Moller-Tank S, Meyerholz DK, Rennert P, Mullins RF, Brindley M, Sandersfeld LM, Quinn K, Weller M, McCray PB Jr, Chiorini J, Maury W. T-cell immunoglobulin and mucin domain 1 (TIM-1) is a receptor for Zaire Ebolavirus and Lake Victoria Marburgvirus. Proc Natl Acad Sci U S A. 2011; 108:8426–8431. [PubMed: 21536871]
54. Bruno CJ, Jacobson JM. Ibalizumab: an anti-CD4 monoclonal antibody for the treatment of HIV-1 infection. J Antimicrob Chemother. 2010; 65:1839–1841. [PubMed: 20639524]
55. Meuleman P, Hesselgesser J, Paulson M, Vanwolleghem T, Desombere I, Reiser H, Leroux-Roels G. Anti-CD81 antibodies can prevent a hepatitis C virus infection in vivo. Hepatology. 2008; 48:1761–1768. [PubMed: 19030166]
56. Silvie O, Rubinstein E, Franetich JF, Prenant M, Belnoue E, Renia L, Hannoun L, Eling W, Levy S, Boucheix C, Mazier D. Hepatocyte CD81 is required for Plasmodium falciparum and Plasmodium yoelii sporozoite infectivity. Nat Med. 2003; 9:93–96. [PubMed: 12483205]

57. Schubert A, Zakikhany K, Pietrocola G, Meinke A, Speziale P, Eikmanns BJ, Reinscheid DJ. The fibrinogen receptor FbsA promotes adherence of Streptococcus agalactiae to human epithelial cells. Infect Immun. 2004; 72:6197–6205. [PubMed: 15501744]
58. Edwards MJ, Dimmock NJ. Hemagglutinin 1-specific immunoglobulin G and Fab molecules mediate postattachment neutralization of influenza A virus by inhibition of an early fusion event. J Virol. 2001; 75:10208–10218. [PubMed: 11581389]
59. de Rosny E, Vassell R, Jiang S, Kunert R, Weiss CD. Binding of the 2F5 monoclonal antibody to native and fusion-intermediate forms of human immunodeficiency virus type 1 gp41: implications for fusion-inducing conformational changes. J Virol. 2004; 78:2627–2631. [PubMed: 14963170]
60. Lorizate M, Cruz A, Huarte N, Kunert R, Perez-Gil J, Nieva JL. Recognition and blocking of HIV-1 gp41 pre-transmembrane sequence by monoclonal 4E10 antibody in a Raft-like membrane environment. J Biol Chem. 2006; 281:39598–39606. [PubMed: 17050535]
61. Kaufmann B, Nybakken GE, Chipman PR, Zhang W, Diamond MS, Fremont DH, Kuhn RJ, Rossmann MG. West Nile virus in complex with the Fab fragment of a neutralizing monoclonal antibody. Proc Natl Acad Sci U S A. 2006; 103:12400–12404. [PubMed: 16895988]
62. Pierson TC, Diamond MS. Molecular mechanisms of antibody-mediated neutralisation of flavivirus infection. Expert Rev Mol Med. 2008; 10:e12. [PubMed: 18471342]
63. Barbey-Martin C, Gigant B, Bizebard T, Calder LJ, Wharton SA, Skehel JJ, Knossow M. An antibody that prevents the hemagglutinin low pH fusogenic transition. Virology. 2002; 294:70–74. [PubMed: 11886266]
64. Ekiert DC, Bhabha G, Elsliger MA, Friesen RH, Jongeneelen M, Throsby M, Goudsmit J, Wilson IA. Antibody recognition of a highly conserved influenza virus epitope. Science. 2009; 324:246–251. [PubMed: 19251591]
65. Cao Z, Meng J, Li X, Wu R, Huang Y, He Y. The epitope and neutralization mechanism of AVFluIgG01, a broad-reactive human monoclonal antibody against H5N1 influenza virus. PLoS One. 2012; 7:e38126. [PubMed: 22662275]
66. Bai Y, Ye L, Tesar DB, Song H, Zhao D, Bjorkman PJ, Roopenian DC, Zhu X. Intracellular neutralization of viral infection in polarized epithelial cells by neonatal Fc receptor (FcRn)-mediated IgG transport. Proc Natl Acad Sci U S A. 2011; 108:18406–18411. [PubMed: 22042859]
67. Stewart PL, Nemerow GR. Recent structural solutions for antibody neutralization of viruses. Trends Microbiol. 1997; 5:229–233. [PubMed: 9211643]
68. Wien MW, Filman DJ, Stura EA, Guillot S, Delpeyroux F, Crainic R, Hogle JM. Structure of the complex between the Fab fragment of a neutralizing antibody for type 1 poliovirus and its viral epitope. Nat Struct Biol. 1995; 2:232–243. [PubMed: 7539711]
69. Maciejewski JP, Weichold FF, Young NS, Cara A, Zella D, Reitz MS Jr, Gallo RC. Intracellular expression of antibody fragments directed against HIV reverse transcriptase prevents HIV infection in vitro. Nat Med. 1995; 1:667–673. [PubMed: 7585149]
70. Varghese R, Mikyas Y, Stewart PL, Ralston R. Postentry neutralization of adenovirus type 5 by an antihexon antibody. J Virol. 2004; 78:12320–12332. [PubMed: 15507619]
71. Ishii Y, Tanaka K, Kondo K, Takeuchi T, Mori S, Kanda T. Inhibition of nuclear entry of HPV16 pseudovirus-packaged DNA by an anti-HPV16 L2 neutralizing antibody. Virology. 2010; 406:181–188. [PubMed: 20684966]
72. Mazanec MB, Kaetzel CS, Lamm ME, Fletcher D, Nedrud JG. Intracellular neutralization of virus by immunoglobulin A antibodies. Proc Natl Acad Sci U S A. 1992; 89:6901–6905. [PubMed: 1323121]
73. Yan H, Lamm ME, Bjorling E, Huang YT. Multiple functions of immunoglobulin A in mucosal defense against viruses: an in vitro measles virus model. J Virol. 2002; 76:10972–10979. [PubMed: 12368340]
74. Mazanec MB, Coudret CL, Fletcher DR. Intracellular neutralization of influenza virus by immunoglobulin A anti-hemagglutinin monoclonal antibodies. J Virol. 1995; 69:1339–1343. [PubMed: 7815518]
75. Zhou D, Zhang Y, Li Q, Chen Y, He B, Yang J, Tu H, Lei L, Yan H. Matrix protein-specific IgA antibody inhibits measles virus replication by intracellular neutralization. J Virol. 2011; 85:11090–11097. [PubMed: 21865386]

76. Bomsel M, Heyman M, Hocini H, Lagaye S, Belec L, Dupont C, Desgranges C. Intracellular neutralization of HIV transcytosis across tight epithelial barriers by anti-HIV envelope protein dIgA or IgM. Immunity. 1998; 9:277–287. [PubMed: 9729048]
77. Corthesy B, Benureau Y, Perrier C, Fourgeux C, Parez N, Greenberg H, Schwartz-Cornil I. Rotavirus anti-VP6 secretory immunoglobulin A contributes to protection via intracellular neutralization but not via immune exclusion. J Virol. 2006; 80:10692–10699. [PubMed: 16956954]
78. Feng N, Lawton JA, Gilbert J, Kuklin N, Vo P, Prasad BV, Greenberg HB. Inhibition of rotavirus replication by a non-neutralizing, rotavirus VP6-specific IgA mAb. J Clin Invest. 2002; 109:1203–1213. [PubMed: 11994409]
79. Thouvenin E, Schoehn G, Rey F, Petitpas I, Mathieu M, Vaney MC, Cohen J, Kohli E, Pothier P, Hewat E. Antibody inhibition of the transcriptase activity of the rotavirus DLP: a structural view. J Mol Biol. 2001; 307:161–172. [PubMed: 11243811]
80. Mallery DL, McEwan WA, Bidgood SR, Towers GJ, Johnson CM, James LC. Antibodies mediate intracellular immunity through tripartite motif-containing 21 (TRIM21). Proc Natl Acad Sci U S A. 2010; 107:19985–19990. [PubMed: 21045130]
81. Wang X, Kikuchi T, Rikihisa Y. Two monoclonal antibodies with defined epitopes of P44 major surface proteins neutralize Anaplasma phagocytophilum by distinct mechanisms. Infect Immun. 2006; 74:1873–1882. [PubMed: 16495562]
82. Edelson BT, Unanue ER. Intracellular antibody neutralizes Listeria growth. Immunity. 2001; 14:503–512. [PubMed: 11371353]
83. Bout D, Moretto M, Dimier-Poisson I, Gatel DB. Interaction between Toxoplasma gondii and enterocyte. Immunobiology. 1999; 201:225–228. [PubMed: 10631571]
84. Mineo JR, Khan IA, Kasper LH. Toxoplasma gondii: a monoclonal antibody that inhibits intracellular replication. Exp Parasitol. 1994; 79:351–361. [PubMed: 7525337]
85. Webster RG, Laver WG. Preparation and properties of antibody directed specifically against the neuraminidase of influenza virus. J Immunol. 1967; 99:49–55. [PubMed: 6029282]
86. Hughey PG, Roberts PC, Holsinger LJ, Zebedee SL, Lamb RA, Compans RW. Effects of antibody to the influenza A virus M2 protein on M2 surface expression and virus assembly. Virology. 1995; 212:411–421. [PubMed: 7571410]
87. Corboba P, Grutadauria S, Cuffini C, Zapata M. Neutralizing monoclonal antibody to the E1 glycoprotein epitope of rubella virus mediates virus arrest in VERO cells. Viral Immunol. 2000; 13:83–92. [PubMed: 10733171]
88. Murphy, K.; Travers, P.; Walport, M. Janeway's Immunobiology. 7th. Garland Science; New York and London: 2008. The complement system and innate immunity; p. 61-80.
89. DiScipio RG, Schraufstatter IU. The role of the complement anaphylatoxins in the recruitment of eosinophils. Int Immunopharmacol. 2007; 7:1909–1923. [PubMed: 18039528]
90. Walport MJ. Complement. First of two parts. N Engl J Med. 2001; 344:1058–1066. [PubMed: 11287977]
91. Prodinger, WM.; Wurzner, R.; Stoiber, H.; Dierich, MP. Complement. In: Paul, W., editor. Fundamental Immunology. 5th. Lippincott Williams and Wilkins; Philadelphia: 2003. p. 1077-1103.
92. Diamond MS, Shrestha B, Mehlhop E, Sitati E, Engle M. Innate and adaptive immune responses determine protection against disseminated infection by West Nile encephalitis virus. Viral Immunol. 2003; 16:259–278. [PubMed: 14583143]
93. Vogt MR, Dowd KA, Engle M, Tesh RB, Johnson S, Pierson TC, Diamond MS. Poorly neutralizing cross-reactive antibodies against the fusion loop of West Nile virus envelope protein protect in vivo via Fcgamma receptor and complement-dependent effector mechanisms. J Virol. 2011; 85:11567–11580. [PubMed: 21917960]
94. Kruijsen D, Bakkers MJ, van Uden NO, Viveen MC, van der Sluis TC, Kimpen JL, Leusen JH, Coenjaerts FE, van Bleek GM. Serum antibodies critically affect virus-specific CD4+/CD8+ T cell balance during respiratory syncytial virus infections. J Immunol. 2010; 185:6489–6498. [PubMed: 20971927]

95. Terajima M, Cruz J, Co MD, Lee JH, Kaur K, Wrammert J, Wilson PC, Ennis FA. Complement-dependent lysis of influenza a virus-infected cells by broadly cross-reactive human monoclonal antibodies. J Virol. 2011; 85:13463–13467. [PubMed: 21994454]

96. Frank AL, Puck J, Hughes BJ, Cate TR. Microneutralization test for influenza A and B and parainfluenza 1 and 2 viruses that uses continuous cell lines and fresh serum enhancement. J Clin Microbiol. 1980; 12:426–432. [PubMed: 6260835]

97. Linscott WD, Levinson WE. Complement components required for virus neutralization by early immunoglobulin antibody. Proc Natl Acad Sci U S A. 1969; 64:520–527. [PubMed: 4982356]

98. Yoshino K, Taniguchi S. Studies on the Neutralization of Herpes Simplex Virus. I. Appearance of Neutralizing Antibodies Having Different Grades of Complement Requirement. Virology. 1965; 26:44–53. [PubMed: 14295231]

99. Ozaki Y, Tabeyi K. Studies on the neutralization of Japanese encephalitis virus. I. Application of kinetic neutralization to the measurement of the neutralizing potency of antiserum. J Immunol. 1967; 98:1218–1223. [PubMed: 6026747]

100. Johnson JB, Capraro GA, Parks GD. Differential mechanisms of complement-mediated neutralization of the closely related paramyxoviruses simian virus 5 and mumps virus. Virology. 2008; 376:112–123. [PubMed: 18440578]

101. Corbeil S, Seguin C, Trudel M. Involvement of the complement system in the protection of mice from challenge with respiratory syncytial virus Long strain following passive immunization with monoclonal antibody 18A2B2. Vaccine. 1996; 14:521–525. [PubMed: 8782350]

102. Boere WA, Benaissa-Trouw BJ, Harmsen T, Erich T, Kraaijeveld CA, Snippe H. The role of complement in monoclonal antibody-mediated protection against virulent Semliki Forest virus. Immunology. 1986; 58:553–559. [PubMed: 3015781]

103. Saifuddin M, Parker CJ, Peeples ME, Gorny MK, Zolla-Pazner S, Ghassemi M, Rooney IA, Atkinson JP, Spear GT. Role of virion-associated glycosylphosphatidylinositol-linked proteins CD55 and CD59 in complement resistance of cell line-derived and primary isolates of HIV-1. J Exp Med. 1995; 182:501–509. [PubMed: 7543140]

104. Schmitz J, Zimmer JP, Kluxen B, Aries S, Bogel M, Gigli I, Schmitz H. Antibody-dependent complement-mediated cytotoxicity in sera from patients with HIV-1 infection is controlled by CD55 and CD59. J Clin Invest. 1995; 96:1520–1526. [PubMed: 7544808]

105. Zhou ZH, Wild T, Xiong Y, Sylvers P, Zhang Y, Zhang L, Wahl L, Wahl SM, Kozlowski S, Notkins AL. Polyreactive Antibodies Plus Complement Enhance the Phagocytosis of Cells Made Apoptotic by UV-Light or HIV. Sci Rep. 2013; 3:2271. [PubMed: 23881356]

106. Willey S, Aasa-Chapman MM, O'Farrell S, Pellegrino P, Williams I, Weiss RA, Neil SJ. Extensive complement-dependent enhancement of HIV-1 by autologous non-neutralising antibodies at early stages of infection. Retrovirology. 2011; 8:16. [PubMed: 21401915]

107. Stoiber H, Banki Z, Wilflingseder D, Dierich MP. Complement-HIV interactions during all steps of viral pathogenesis. Vaccine. 2008; 26:3046–3054. [PubMed: 18191309]

108. Huber G, Banki Z, Lengauer S, Stoiber H. Emerging role for complement in HIV infection. Curr Opin HIV AIDS. 2011; 6:419–426. [PubMed: 21825871]

109. Jayasekera JP, Moseman EA, Carroll MC. Natural antibody and complement mediate neutralization of influenza virus in the absence of prior immunity. J Virol. 2007; 81:3487–3494. [PubMed: 17202212]

110. Carroll MC. The complement system in regulation of adaptive immunity. Nat Immunol. 2004; 5:981–986. [PubMed: 15454921]

111. Stager S, Alexander J, Kirby AC, Botto M, Rooijen NV, Smith DF, Brombacher F, Kaye PM. Natural antibodies and complement are endogenous adjuvants for vaccine-induced CD8+ T-cell responses. Nat Med. 2003; 9:1287–1292. [PubMed: 14502281]

112. Lindorfer MA, Hahn CS, Foley PL, Taylor RP. Heteropolymer-mediated clearance of immune complexes via erythrocyte CR1: mechanisms and applications. Immunol Rev. 2001; 183:10–24. [PubMed: 11782244]

113. Nelson RA Jr. The immune-adherence phenomenon; an immunologically specific reaction between microorganisms and erythrocytes leading to enhanced phagocytosis. Science. 1953; 118:733–737. [PubMed: 13122009]

114. Ram S, Lewis LA, Rice PA. Infections of people with complement deficiencies and patients who have undergone splenectomy. Clin Microbiol Rev. 2010; 23:740–780. [PubMed: 20930072]

115. Amir J, Scott MG, Nahm MH, Granoff DM. Bactericidal and opsonic activity of IgG1 and IgG2 anticapsular antibodies to Haemophilus influenzae type b. J Infect Dis. 1990; 162:163–171. [PubMed: 2355193]

116. Frasch CE, Borrow R, Donnelly J. Bactericidal antibody is the immunologic surrogate of protection against meningococcal disease. Vaccine. 2009; 27(Suppl 2):B112–116. [PubMed: 19464093]

117. Welsch JA, Moe GR, Rossi R, Adu-Bobie J, Rappuoli R, Granoff DM. Antibody to genome-derived neisserial antigen 2132, a Neisseria meningitidis candidate vaccine, confers protection against bacteremia in the absence of complement-mediated bactericidal activity. J Infect Dis. 2003; 188:1730–1740. [PubMed: 14639545]

118. Plested JS, Welsch JA, Granoff DM. Ex vivo model of meningococcal bacteremia using human blood for measuring vaccine-induced serum passive protective activity. Clin Vaccine Immunol. 2009; 16:785–791. [PubMed: 19339487]

119. Granoff DM. Relative importance of complement-mediated bactericidal and opsonic activity for protection against meningococcal disease. Vaccine. 2009; 27(Suppl 2):B117–125. [PubMed: 19477054]

120. Horwitz MA, Silverstein SC. Interaction of the Legionnaires' disease bacterium (Legionella pneumophila) with human phagocytes. I. L. pneumophila resists killing by polymorphonuclear leukocytes, antibody, and complement. J Exp Med. 1981; 153:386–397. [PubMed: 7017062]

121. Lindow JC, Fimlaid KA, Bunn JY, Kirkpatrick BD. Antibodies in action: role of human opsonins in killing Salmonella enterica serovar Typhi. Infect Immun. 2011; 79:3188–3194. [PubMed: 21628517]

122. Cheng SC, Sprong T, Joosten LA, van der Meer JW, Kullberg BJ, Hube B, Schejbel L, Garred P, van Deuren M, Netea MG. Complement plays a central role in Candida albicans-induced cytokine production by human PBMCs. Eur J Immunol. 2012; 42:993–1004. [PubMed: 22531923]

123. Han Y, Kozel TR, Zhang MX, MacGill RS, Carroll MC, Cutler JE. Complement is essential for protection by an IgM and an IgG3 monoclonal antibody against experimental, hematogenously disseminated candidiasis. J Immunol. 2001; 167:1550–1557. [PubMed: 11466376]

124. Zaragoza O, Casadevall A. Monoclonal antibodies can affect complement deposition on the capsule of the pathogenic fungus Cryptococcus neoformans by both classical pathway activation and steric hindrance. Cell Microbiol. 2006; 8:1862–1876. [PubMed: 16824038]

125. Zhong Z, Pirofski LA. Antifungal activity of a human antiglucuronoxylomannan antibody. Clin Diagn Lab Immunol. 1998; 5:58–64. [PubMed: 9455881]

126. Taborda CP, Casadevall A. CR3 (CD11b/CD18) and CR4 (CD11c/CD18) are involved in complement-independent antibody-mediated phagocytosis of Cryptococcus neoformans. Immunity. 2002; 16:791–802. [PubMed: 12121661]

127. Ayi K, Turrini F, Piga A, Arese P. Enhanced phagocytosis of ring-parasitized mutant erythrocytes: a common mechanism that may explain protection against falciparum malaria in sickle trait and beta-thalassemia trait. Blood. 2004; 104:3364–3371. [PubMed: 15280204]

128. Luzzi GA, Merry AH, Newbold CI, Marsh K, Pasvol G. Protection by alpha-thalassaemia against Plasmodium falciparum malaria: modified surface antigen expression rather than impaired growth or cytoadherence. Immunol Lett. 1991; 30:233–240. [PubMed: 1757109]

129. Yuthavong Y, Bunyaratvej A, Kamchonwongpaisan S. Increased susceptibility of malaria-infected variant erythrocytes to the mononuclear phagocyte system. Blood Cells. 1990; 16:591–597. [PubMed: 2098019]

130. Cappadoro M, Giribaldi G, O'Brien E, Turrini F, Mannu F, Ulliers D, Simula G, Luzzatto L, Arese P. Early phagocytosis of glucose-6-phosphate dehydrogenase (G6PD)-deficient erythrocytes parasitized by Plasmodium falciparum may explain malaria protection in G6PD deficiency. Blood. 1998; 92:2527–2534. [PubMed: 9746794]

131. Kumaratilake LM, Ferrante A, Jaeger T, Morris-Jones SD. The role of complement, antibody, and tumor necrosis factor alpha in the killing of Plasmodium falciparum by the monocytic cell line THP-1. Infect Immun. 1997; 65:5342–5345. [PubMed: 9393837]

132. Salmon D, Vilde JL, Andrieu B, Simonovic R, Lebras J. Role of immune serum and complement in stimulation of the metabolic burst of human neutrophils by Plasmodium falciparum. Infect Immun. 1986; 51:801–806. [PubMed: 3512435]

133. Pang XL, Horii T. Complement-mediated killing of Plasmodium falciparum erythrocytic schizont with antibodies to the recombinant serine repeat antigen (SERA). Vaccine. 1998; 16:1299–1305. [PubMed: 9682394]

134. Healer J, McGuinness D, Hopcroft P, Haley S, Carter R, Riley E. Complement-mediated lysis of Plasmodium falciparum gametes by malaria-immune human sera is associated with antibodies to the gamete surface antigen Pfs230. Infect Immun. 1997; 65:3017–3023. [PubMed: 9234748]

135. Read D, Lensen AH, Begarnie S, Haley S, Raza A, Carter R. Transmission-blocking antibodies against multiple, non-variant target epitopes of the Plasmodium falciparum gamete surface antigen Pfs230 are all complement-fixing. Parasite Immunol. 1994; 16:511–519. [PubMed: 7532850]

136. Rener J, Graves PM, Carter R, Williams JL, Burkot TR. Target antigens of transmission-blocking immunity on gametes of plasmodium falciparum. J Exp Med. 1983; 158:976–981. [PubMed: 6350527]

137. Roeffen W, Geeraedts F, Eling W, Beckers P, Wizel B, Kumar N, Lensen T, Sauerwein R. Transmission blockade of Plasmodium falciparum malaria by anti-Pfs230-specific antibodies is isotype dependent. Infect Immun. 1995; 63:467–471. [PubMed: 7822011]

138. Macaskill JA, Holmes PH, Whitelaw DD, McConnell I, Jennings FW, Urquhart GM. Immunological clearance of 75Se-labelled Trypanosoma brucei in mice. II. Mechanisms in immune animals. Immunology. 1980; 40:629–635. [PubMed: 7429544]

139. Pan W, Ogunremi O, Wei G, Shi M, Tabel H. CR3 (CD11b/CD18) is the major macrophage receptor for IgM antibody-mediated phagocytosis of African trypanosomes: diverse effect on subsequent synthesis of tumor necrosis factor alpha and nitric oxide. Microbes Infect. 2006; 8:1209–1218. [PubMed: 16616573]

140. Owuor BO, Odhiambo CO, Otieno WO, Adhiambo C, Makawiti DW, Stoute JA. Reduced immune complex binding capacity and increased complement susceptibility of red cells from children with severe malaria-associated anemia. Mol Med. 2008; 14:89–97. [PubMed: 18317566]

141. Patel SN, Berghout J, Lovegrove FE, Ayi K, Conroy A, Serghides L, Min-oo G, Gowda DC, Sarma JV, Rittirsch D, Ward PA, Liles WC, Gros P, Kain KC. C5 deficiency and C5a or C5aR blockade protects against cerebral malaria. J Exp Med. 2008; 205:1133–1143. [PubMed: 18426986]

142. Farrell HE, Shellam GR. Protection against murine cytomegalovirus infection by passive transfer of neutralizing and non-neutralizing monoclonal antibodies. J Gen Virol. 1991; 72(Pt 1):149–156. [PubMed: 1846643]

143. Horton RE, Vidarsson G. Antibodies and their receptors: different potential roles in mucosal defense. Front Immunol. 2013; 4:200. [PubMed: 23882268]

144. Takai T. Roles of Fc receptors in autoimmunity. Nat Rev Immunol. 2002; 2:580–592. [PubMed: 12154377]

145. Clark MR, Clarkson SB, Ory PA, Stollman N, Goldstein IM. Molecular basis for a polymorphism involving Fc receptor II on human monocytes. J Immunol. 1989; 143:1731–1734. [PubMed: 2527271]

146. Warmerdam PA, van de Winkel JG, Vlug A, Westerdaal NA, Capel PJ. A single amino acid in the second Ig-like domain of the human Fc gamma receptor II is critical for human IgG2 binding. J Immunol. 1991; 147:1338–1343. [PubMed: 1831223]

147. Ravetch JV, Perussia B. Alternative membrane forms of Fc gamma RIII (CD16) on human natural killer cells and neutrophils. Cell type-specific expression of two genes that differ in single nucleotide substitutions. J Exp Med. 1989; 170:481–497. [PubMed: 2526846]

148. Ory PA, Goldstein IM, Kwoh EE, Clarkson SB. Characterization of polymorphic forms of Fc receptor III on human neutrophils. J Clin Invest. 1989; 83:1676–1681. [PubMed: 2523415]

149. Ory PA, Clark MR, Kwoh EE, Clarkson SB, Goldstein IM. Sequences of complementary DNAs that encode the NA1 and NA2 forms of Fc receptor III on human neutrophils. J Clin Invest. 1989; 84:1688–1691. [PubMed: 2478590]

150. Bruhns P, Iannascoli B, England P, Mancardi DA, Fernandez N, Jorieux S, Daeron M. Specificity and affinity of human Fcgamma receptors and their polymorphic variants for human IgG subclasses. Blood. 2009; 113:3716–3725. [PubMed: 19018092]

151. Wiener E, Jolliffe VM, Scott HC, Kumpel BM, Thompson KM, Melamed MD, Hughes-Jones NC. Differences between the activities of human monoclonal IgG1 and IgG3 anti-D antibodies of the Rh blood group system in their abilities to mediate effector functions of monocytes. Immunology. 1988; 65:159–163. [PubMed: 3192267]

152. Shields RL, Lai J, Keck R, O'Connell LY, Hong K, Meng YG, Weikert SH, Presta LG. Lack of fucose on human IgG1 N-linked oligosaccharide improves binding to human Fcgamma RIII and antibody-dependent cellular toxicity. J Biol Chem. 2002; 277:26733–26740. [PubMed: 11986321]

153. Forthal DN, Gach JS, Landucci G, Jez J, Strasser R, Kunert R, Steinkellner H. Fc-glycosylation influences Fcgamma receptor binding and cell-mediated anti-HIV activity of monoclonal antibody 2G12. J Immunol. 2010; 185:6876–6882. [PubMed: 21041724]

154. Lux A, Nimmerjahn F. Impact of differential glycosylation on IgG activity. Adv Exp Med Biol. 2011; 780:113–124. [PubMed: 21842369]

155. Moldt B, Shibata-Koyama M, Rakasz EG, Schultz N, Kanda Y, Dunlop DC, Finstad SL, Jin C, Landucci G, Alpert MD, Dugast AS, Parren PW, Nimmerjahn F, Evans DT, Alter G, Forthal DN, Schmitz JE, Iida S, Poignard P, Watkins DI, Hessell AJ, Burton DR. A nonfucosylated variant of the anti-HIV-1 monoclonal antibody b12 has enhanced FcgammaRIIIa-mediated antiviral activity in vitro but does not improve protection against mucosal SHIV challenge in macaques. J Virol. 2012; 86:6189–6196. [PubMed: 22457527]

156. Forthal DN, Moog C. Fc receptor-mediated antiviral antibodies. Curr Opin HIV AIDS. 2009; 4:388–393. [PubMed: 20048702]

157. Lyerly HK, Reed DL, Matthews TJ, Langlois AJ, Ahearne PA, Petteway SR Jr, Weinhold KJ. Anti-GP 120 antibodies from HIV seropositive individuals mediate broadly reactive anti-HIV ADCC. AIDS Res Hum Retroviruses. 1987; 3:409–422. [PubMed: 2833917]

158. Torben W, Ahmad G, Zhang W, Nash S, Le L, Karmakar S, Siddiqui AA. Role of antibody dependent cell mediated cytotoxicity (ADCC) in Sm-p80-mediated protection against Schistosoma mansoni. Vaccine. 2012; 30:6753–6758. [PubMed: 23000221]

159. Bouharoun-Tayoun H, Oeuvray C, Lunel F, Druilhe P. Mechanisms underlying the monocyte-mediated antibody-dependent killing of Plasmodium falciparum asexual blood stages. J Exp Med. 1995; 182:409–418. [PubMed: 7629503]

160. Forthal DN, Landucci G, Daar ES. Antibody from patients with acute human immunodeficiency virus (HIV) infection inhibits primary strains of HIV type 1 in the presence of natural-killer effector cells. J Virol. 2001; 75:6953–6961. [PubMed: 11435575]

161. Weber S, Tian H, van Rooijen N, Pirofski LA. A serotype 3 pneumococcal capsular polysaccharide-specific monoclonal antibody requires Fcgamma receptor III and macrophages to mediate protection against pneumococcal pneumonia in mice. Infect Immun. 2012; 80:1314–1322. [PubMed: 22290146]

162. Sun D, Raisley B, Langer M, Iyer JK, Vedham V, Ballard JL, James JA, Metcalf J, Coggeshall KM. Anti-peptidoglycan antibodies and Fcgamma receptors are the key mediators of inflammation in Gram-positive sepsis. J Immunol. 2012; 189:2423–2431. [PubMed: 22815288]

163. Song X, Tanaka S, Cox D, Lee SC. Fcgamma receptor signaling in primary human microglia: differential roles of PI-3K and Ras/ERK MAPK pathways in phagocytosis and chemokine induction. J Leukoc Biol. 2004; 75:1147–1155. [PubMed: 14982949]

164. Porcherie A, Mathieu C, Peronet R, Schneider E, Claver J, Commere PH, Kiefer-Biasizzo H, Karasuyama H, Milon G, Dy M, Kinet JP, Louis J, Blank U, Mecheri S. Critical role of the neutrophil-associated high-affinity receptor for IgE in the pathogenesis of experimental cerebral malaria. J Exp Med. 2011; 208:2225–2236. [PubMed: 21967768]

165. Forthal DN, Landucci G, Phan TB, Becerra J. Interactions between natural killer cells and antibody Fc result in enhanced antibody neutralization of human immunodeficiency virus type 1. J Virol. 2005; 79:2042–2049. [PubMed: 15681406]

166. Brown BK, Wieczorek L, Kijak G, Lombardi K, Currier J, Wesberry M, Kappes JC, Ngauy V, Marovich M, Michael N, Ochsenbauer C, Montefiori DC, Polonis VR. The role of natural killer (NK) cells and NK cell receptor polymorphisms in the assessment of HIV-1 neutralization. PLoS One. 2012; 7:e29454. [PubMed: 22509241]

167. Holl V, Peressin M, Decoville T, Schmidt S, Zolla-Pazner S, Aubertin AM, Moog C. Nonneutralizing antibodies are able to inhibit human immunodeficiency virus type 1 replication in macrophages and immature dendritic cells. J Virol. 2006; 80:6177–6181. [PubMed: 16731957]

168. Holl V, Hemmerter S, Burrer R, Schmidt S, Bohbot A, Aubertin AM, Moog C. Involvement of Fc gamma RI (CD64) in the mechanism of HIV-1 inhibition by polyclonal IgG purified from infected patients in cultured monocyte-derived macrophages. J Immunol. 2004; 173:6274–6283. [PubMed: 15528366]

169. Anderson DR, Grillo-Lopez A, Varns C, Chambers KS, Hanna N. Targeted anti-cancer therapy using rituximab, a chimaeric anti-CD20 antibody (IDEC-C2B8) in the treatment of non-Hodgkin's B-cell lymphoma. Biochem Soc Trans. 1997; 25:705–708. [PubMed: 9191187]

170. Sliwkowski MX, Lofgren JA, Lewis GD, Hotaling TE, Fendly BM, Fox JA. Nonclinical studies addressing the mechanism of action of trastuzumab (Herceptin). Semin Oncol. 1999; 26:60–70. [PubMed: 10482195]

171. Clynes RA, Towers TL, Presta LG, Ravetch JV. Inhibitory Fc receptors modulate in vivo cytotoxicity against tumor targets. Nat Med. 2000; 6:443–446. [PubMed: 10742152]

172. Shore SL, Nahmias AJ, Starr SE, Wood PA, McFarlin DE. Detection of cell-dependent cytotoxic antibody to cells infected with herpes simplex virus. Nature. 1974; 251:350–352. [PubMed: 4372535]

173. Balachandran N, Bacchetti S, Rawls WE. Protection against lethal challenge of BALB/c mice by passive transfer of monoclonal antibodies to five glycoproteins of herpes simplex virus type 2. Infect Immun. 1982; 37:1132–1137. [PubMed: 6290390]

174. Gorander S, Harandi AM, Lindqvist M, Bergstrom T, Liljeqvist JA. Glycoprotein G of herpes simplex virus 2 as a novel vaccine antigen for immunity to genital and neurological disease. J Virol. 2012; 86:7544–7553. [PubMed: 22553328]

175. Chu CF, Meador MG, Young CG, Strasser JE, Bourne N, Milligan GN. Antibody-mediated protection against genital herpes simplex virus type 2 disease in mice by Fc gamma receptor-dependent and -independent mechanisms. J Reprod Immunol. 2008; 78:58–67. [PubMed: 17950908]

176. Jegerlehner A, Schmitz N, Storni T, Bachmann MF. Influenza A vaccine based on the extracellular domain of M2: weak protection mediated via antibody-dependent NK cell activity. J Immunol. 2004; 172:5598–5605. [PubMed: 15100303]

177. Forthal D, Hope TJ, Alter G. New paradigms for functional HIV-specific nonneutralizing antibodies. Curr Opin HIV AIDS. 2013; 8:392–400.

178. Lowell GH, Smith LF, Artenstein MS, Nash GS, MacDermott RP Jr. Antibody-dependent cell-mediated antibacterial activity of human mononuclear cells. I. K lymphocytes and monocytes are effective against meningococci in cooperation with human imune sera. J Exp Med. 1979; 150:127–137. [PubMed: 109572]

179. Lowell GH, MacDermott RP, Summers PL, Reeder AA, Bertovich MJ, Formal SB. Antibody-dependent cell-mediated antibacterial activity: K lymphocytes, monocytes, and granulocytes are effective against shigella. J Immunol. 1980; 125:2778–2784. [PubMed: 7000906]

180. Tagliabue A, Nencioni L, Villa L, Keren DF, Lowell GH, Boraschi D. Antibody-dependent cell-mediated antibacterial activity of intestinal lymphocytes with secretory IgA. Nature. 1983; 306:184–186. [PubMed: 6646200]

181. Tagliabue A, Boraschi D, Villa L, Keren DF, Lowell GH, Rappuoli R, Nencioni L. IgA-dependent cell-mediated activity against enteropathogenic bacteria: distribution, specificity, and characterization of the effector cells. J Immunol. 1984; 133:988–992. [PubMed: 6376633]

182. Sestini P, Nencioni L, Villa L, Boraschi D, Tagliabue A. IgA-driven antibacterial activity against Streptococcus pneumoniae by mouse lung lymphocytes. Am Rev Respir Dis. 1988; 137:138–143. [PubMed: 3337454]

183. Messick JB, Rikihisa Y. Presence of parasite antigen on the surface of P388D1 cells infected with Ehrlichia risticii. Infect Immun. 1992; 60:3079–3086. [PubMed: 1639476]

184. Koster FT, Kirkpatrick TL, Rowatt JD, Baca OG. Antibody-dependent cellular cytotoxicity of Coxiella burnetii-infected J774 macrophage target cells. Infect Immun. 1984; 43:253–256. [PubMed: 6690402]

185. Galdiero F, Romano Carratelli C, Nuzzo I, Folgore A. Cytotoxic antibody dependent cells in mice experimentally infected with Brucella abortus. Microbiologica. 1985; 8:217–224. [PubMed: 3929026]

186. Shannon JG, Cockrell DC, Takahashi K, Stahl GL, Heinzen RA. Antibody-mediated immunity to the obligate intracellular bacterial pathogen Coxiella burnetii is Fc receptor- and complement-independent. BMC Immunol. 2009; 10:26. [PubMed: 19426498]

187. Kazura JW. Host defense mechanisms against nematode parasites: destruction of newborn Trichinella spiralis larvae by human antibodies and granulocytes. J Infect Dis. 1981; 143:712–718. [PubMed: 7017021]

188. Venturiello SM, Giambartolomei GH, Costantino SN. Immune killing of newborn Trichinella larvae by human leucocytes. Parasite Immunol. 1993; 15:559–564. [PubMed: 7877832]

189. Gounni AS, Lamkhioued B, Ochiai K, Tanaka Y, Delaporte E, Capron A, Kinet JP, Capron M. High-affinity IgE receptor on eosinophils is involved in defence against parasites. Nature. 1994; 367:183–186. [PubMed: 8114916]

190. Capron M, Capron A. Immunoglobulin E and effector cells in schistosomiasis. Science. 1994; 264:1876–1877. [PubMed: 8009216]

191. Zhou S, Liu S, Song G, Xu Y, Sun W. Protective immunity induced by the full-length cDNA encoding paramyosin of Chinese Schistosoma japonicum. Vaccine. 2000; 18:3196–3204. [PubMed: 10856799]

192. Capron A. Schistosomiasis: forty years' war on the worm. Parasitol Today. 1998; 14:379–384. [PubMed: 17040824]

193. Joseph M, Auriault C, Capron A, Vorng H, Viens P. A new function for platelets: IgE-dependent killing of schistosomes. Nature. 1983; 303:810–812. [PubMed: 6866081]

194. Khalife J, Capron M, Capron A, Grzych JM, Butterworth AE, Dunne DW, Ouma JH. Immunity in human schistosomiasis mansoni. Regulation of protective immune mechanisms by IgM blocking antibodies. J Exp Med. 1986; 164:1626–1640. [PubMed: 2430044]

195. Auriault C, Gras-Masse H, Pierce RJ, Butterworth AE, Wolowczuk I, Capron M, Ouma JH, Balloul JM, Khalife J, Neyrinck JL, et al. Antibody response of Schistosoma mansoni-infected human subjects to the recombinant P28 glutathione-S-transferase and to synthetic peptides. J Clin Microbiol. 1990; 28:1918–1924. [PubMed: 2121788]

196. Demeure CE, Rihet P, Abel L, Ouattara M, Bourgois A, Dessein AJ. Resistance to Schistosoma mansoni in humans: influence of the IgE/IgG4 balance and IgG2 in immunity to reinfection after chemotherapy. J Infect Dis. 1993; 168:1000–1008. [PubMed: 7690821]

197. Lawrence RA. Immunity to filarial nematodes. Vet Parasitol. 2001; 100:33–44. [PubMed: 11522404]

198. Haque A, Joseph M, Ouaissi MA, Capron M, Capron A. IgE antibody-mediated cytotoxicity of rat macrophages against microfilaria of Dipetalonema citeae in vitro. Clin Exp Immunol. 1980; 40:487–495. [PubMed: 7191359]

199. Weiss N, Tanner M. Studies on Dipetalonema viteae (Filarioidea) 3. Antibody-dependent cell-mediated destruction of microfilariae in vivo. Tropenmed Parasitol. 1979; 30:73–80. [PubMed: 375512]

200. Mehta K, Sindhu RK, Subrahmanyam D, Hopper K, Nelson DS, Rao CK. Antibody-dependent cell-mediated effects in bancroftian filariasis. Immunology. 1981; 43:117–123. [PubMed: 7019047]

201. Sim BK, Kwa BH, Mak JW. Immune responses in human Brugia malayi infections: serum dependent cell-mediated destruction of infective larvae in vitro. Trans R Soc Trop Med Hyg. 1982; 76:362–370. [PubMed: 7112659]

202. Parab PB, Rajasekariah GR, Chandrashekar R, Alkan SS, Braun DG, Subrahmanyam D. Characterization of a monoclonal antibody against infective larvae of Brugia malayi. Immunology. 1988; 64:169–174. [PubMed: 3384450]

203. Gray CA, Lawrence RA. A role for antibody and Fc receptor in the clearance of Brugia malayi microfilariae. Eur J Immunol. 2002; 32:1114–1120. [PubMed: 11920579]

204. Albright JW, Stewart MJ, Latham PS, Albright JF. Antibody-facilitated macrophage killing of Trypanosoma musculi is an extracellular process as studied in several variations of an in vitro analytical system. J Leukoc Biol. 1994; 56:636–643. [PubMed: 7964170]

205. Townsend J, Duffus WP. Trypanosoma theileri: antibody-dependent killing by purified populations of bovine leucocytes. Clin Exp Immunol. 1982; 48:289–299. [PubMed: 7105486]

206. Kierszenbaum F, Hayes MM. Mechanisms of resistance against experimental Trypanosoma cruzi infection. Requirements for cellular destruction of circulating forms of T. cruzi in human and murine in vitro systems. Immunology. 1980; 40:61–66. [PubMed: 6998860]

207. Piedrafita D, Parsons JC, Sandeman RM, Wood PR, Estuningsih SE, Partoutomo S, Spithill TW. Antibody-dependent cell-mediated cytotoxicity to newly excysted juvenile Fasciola hepatica in vitro is mediated by reactive nitrogen intermediates. Parasite Immunol. 2001; 23:473–482. [PubMed: 11589776]

208. Nolan TJ, Rotman HL, Bhopale VM, Schad GA, Abraham D. Immunity to a challenge infection of Strongyloides stercoralis third-stage larvae in the jird. Parasite Immunol. 1995; 17:599–604. [PubMed: 8817607]

209. Bekhti K, Kazanji M, Pery P. In vitro interactions between murine neutrophils and Eimeria falciformis sporozoites. Res Immunol. 1992; 143:909–917. [PubMed: 1337796]

210. Smith PD, Keister DB, Elson CO. Human host response to Giardia lamblia. II. Antibody-dependent killing in vitro. Cell Immunol. 1983; 82:308–315. [PubMed: 6652688]

211. Khusmith S, Druilhe P. Cooperation between antibodies and monocytes that inhibit in vitro proliferation of Plasmodium falciparum. Infect Immun. 1983; 41:219–223. [PubMed: 6345391]

212. Jafarshad A, Dziegiel MH, Lundquist R, Nielsen LK, Singh S, Druilhe PL. A novel antibody-dependent cellular cytotoxicity mechanism involved in defense against malaria requires costimulation of monocytes FcgammaRII and FcgammaRIII. J Immunol. 2007; 178:3099–3106. [PubMed: 17312157]

213. Forthal DN, Landucci G. In vitro reduction of virus infectivity by antibody-dependent cell-mediated immunity. J Immunol Methods. 1998; 220:129–138. [PubMed: 9839934]

214. Forthal DN, Landucci G, Cole KS, Marthas M, Becerra JC, Van Rompay K. Rhesus macaque polyclonal and monoclonal antibodies inhibit simian immunodeficiency virus in the presence of human or autologous rhesus effector cells. J Virol. 2006; 80:9217–9225. [PubMed: 16940533]

215. Brunner KT, Hurez D, Mc CR, Benacerraf B. Blood clearance of P32-labeled vesicular stomatitis and Newcastle disease viruses by the reticuloendothelial system in mice. J Immunol. 1960; 85:99–105. [PubMed: 13805345]

216. Igarashi T, Brown C, Azadegan A, Haigwood N, Dimitrov D, Martin MA, Shibata R. Human immunodeficiency virus type 1 neutralizing antibodies accelerate clearance of cell-free virions from blood plasma. Nat Med. 1999; 5:211–216. [PubMed: 9930870]

217. Kim YB, Bradley SG, Watson DW. Ontogeny of the immune response. IV. The role of antigen elimination in the true primary immune response in germfree, colostrum-deprived piglets. J Immunol. 1967; 99:320–326. [PubMed: 6031203]

218. Glenny AT, Hopkins BE. Duration of Passive Immunity. J Hyg (Lond). 1923; 22:208–221. [PubMed: 20474806]

219. Fujisawa H. Neutrophils play an essential role in cooperation with antibody in both protection against and recovery from pulmonary infection with influenza virus in mice. J Virol. 2008; 82:2772–2783. [PubMed: 18184718]

220. Huber VC, Lynch JM, Bucher DJ, Le J, Metzger DW. Fc receptor-mediated phagocytosis makes a significant contribution to clearance of influenza virus infections. J Immunol. 2001; 166:7381–7388. [PubMed: 11390489]

221. Chan KR, Zhang SL, Tan HC, Chan YK, Chow A, Lim AP, Vasudevan SG, Hanson BJ, Ooi EE. Ligation of Fc gamma receptor IIB inhibits antibody-dependent enhancement of dengue virus infection. Proc Natl Acad Sci U S A. 2011; 108:12479–12484. [PubMed: 21746897]

222. Chung KM, Thompson BS, Fremont DH, Diamond MS. Antibody recognition of cell surface-associated NS1 triggers Fc-gamma receptor-mediated phagocytosis and clearance of West Nile Virus-infected cells. J Virol. 2007; 81:9551–9555. [PubMed: 17582005]

223. Hashimoto Y, Moki T, Takizawa T, Shiratsuchi A, Nakanishi Y. Evidence for phagocytosis of influenza virus-infected, apoptotic cells by neutrophils and macrophages in mice. J Immunol. 2007; 178:2448–2457. [PubMed: 17277152]

224. Ratcliffe DR, Michl J, Cramer EB. Neutrophils do not bind to or phagocytize human immune complexes formed with influenza virus. Blood. 1993; 82:1639–1646. [PubMed: 8364212]

225. Scott CB, Ratcliffe DR, Cramer EB. Human monocytes are unable to bind to or phagocytize IgA and IgG immune complexes formed with influenza virus in vitro. J Immunol. 1996; 157:351–359. [PubMed: 8683137]

226. Hellwig SM, van Oirschot HF, Hazenbos WL, van Spriel AB, Mooi FR, van De Winkel JG. Targeting to Fcgamma receptors, but not CR3 (CD11b/CD18), increases clearance of Bordetella pertussis. J Infect Dis. 2001; 183:871–879. [PubMed: 11237803]

227. Clatworthy MR, Smith KG. FcgammaRIIb balances efficient pathogen clearance and the cytokine-mediated consequences of sepsis. J Exp Med. 2004; 199:717–723. [PubMed: 14981111]

228. Mold C, Rodic-Polic B, Du Clos TW. Protection from Streptococcus pneumoniae infection by C-reactive protein and natural antibody requires complement but not Fc gamma receptors. J Immunol. 2002; 168:6375–6381. [PubMed: 12055255]

229. Yee AM, Phan HM, Zuniga R, Salmon JE, Musher DM. Association between FcgammaRIIa-R131 allotype and bacteremic pneumococcal pneumonia. Clin Infect Dis. 2000; 30:25–28. [PubMed: 10619728]

230. Yuan FF, Wong M, Pererva N, Keating J, Davis AR, Bryant JA, Sullivan JS. FcgammaRIIA polymorphisms in Streptococcus pneumoniae infection. Immunol Cell Biol. 2003; 81:192–195. [PubMed: 12752683]

231. Rodriguez ME, van der Pol WL, Sanders LA, van de Winkel JG. Crucial role of FcgammaRIIa (CD32) in assessment of functional anti-Streptococcus pneumoniae antibody activity in human sera. J Infect Dis. 1999; 179:423–433. [PubMed: 9878027]

232. Bredius RG, Fijen CA, De Haas M, Kuijper EJ, Weening RS, Van de Winkel JG, Out TA. Role of neutrophil Fc gamma RIIa (CD32) and Fc gamma RIIIb (CD16) polymorphic forms in phagocytosis of human IgG1- and IgG3-opsonized bacteria and erythrocytes. Immunology. 1994; 83:624–630. [PubMed: 7875742]

233. Fijen CA, Bredius RG, Kuijper EJ, Out TA, De Haas M, De Wit AP, Daha MR, De Winkel JG. The role of Fcgamma receptor polymorphisms and C3 in the immune defence against Neisseria meningitidis in complement-deficient individuals. Clin Exp Immunol. 2000; 120:338–345. [PubMed: 10792385]

234. Bredius RG, Derkx BH, Fijen CA, de Wit TP, de Haas M, Weening RS, van de Winkel JG, Out TA. Fc gamma receptor IIa (CD32) polymorphism in fulminant meningococcal septic shock in children. J Infect Dis. 1994; 170:848–853. [PubMed: 7930726]

235. Platonov AE, Shipulin GA, Vershinina IV, Dankert J, van de Winkel JG, Kuijper EJ. Association of human Fc gamma RIIa (CD32) polymorphism with susceptibility to and severity of meningococcal disease. Clin Infect Dis. 1998; 27:746–750. [PubMed: 9798027]

236. Domingo P, Muniz-Diaz E, Baraldes MA, Arilla M, Barquet N, Pericas R, Juarez C, Madoz P, Vazquez G. Associations between Fc gamma receptor IIA polymorphisms and the risk and prognosis of meningococcal disease. Am J Med. 2002; 112:19–25. [PubMed: 11812402]

237. Domingo P, Muniz-Diaz E, Baraldes MA, Arilla M, Barquet N, Pericas R, Juarez C, Madoz P, Vazquez G. Relevance of genetically determined host factors to the prognosis of meningococcal disease. Eur J Clin Microbiol Infect Dis. 2004; 23:634–637. [PubMed: 15243816]

238. Smith I, Vedeler C, Halstensen A. FcgammaRIIa and FcgammaRIIIb polymorphisms were not associated with meningococcal disease in Western Norway. Epidemiol Infect. 2003; 130:193–199. [PubMed: 12729187]

239. Wu Y, Wu W, Wong WM, Ward E, Thrasher AJ, Goldblatt D, Osman M, Digard P, Canaday DH, Gustafsson K. Human gamma delta T cells: a lymphoid lineage cell capable of professional phagocytosis. J Immunol. 2009; 183:5622–5629. [PubMed: 19843947]

240. Schlageter AM, Kozel TR. Opsonization of Cryptococcus neoformans by a family of isotype-switch variant antibodies specific for the capsular polysaccharide. Infect Immun. 1990; 58:1914–1918. [PubMed: 2187813]

241. Sanford JE, Lupan DM, Schlageter AM, Kozel TR. Passive immunization against Cryptococcus neoformans with an isotype-switch family of monoclonal antibodies reactive with cryptococcal polysaccharide. Infect Immun. 1990; 58:1919–1923. [PubMed: 2341184]

242. Saylor CA, Dadachova E, Casadevall A. Murine IgG1 and IgG3 isotype switch variants promote phagocytosis of Cryptococcus neoformans through different receptors. J Immunol. 2010; 184:336–343. [PubMed: 19949107]

243. Szymczak WA, Davis MJ, Lundy SK, Dufaud C, Olszewski M, Pirofski LA. X-linked immunodeficient mice exhibit enhanced susceptibility to Cryptococcus neoformans Infection. MBio. 2013; 4

244. Murphy, K.; Travers, P.; Walport, M. Janeway's Immunobiology. 7th. Garland Science; New York and London: 2008. The destruction of antibody-coated pathogens via Fc receptors; p. 412

245. Celada A, Cruchaud A, Perrin LH. Opsonic activity of human immune serum on in vitro phagocytosis of Plasmodium falciparum infected red blood cells by monocytes. Clin Exp Immunol. 1982; 47:635–644. [PubMed: 7044626]

246. Chan JA, Howell KB, Reiling L, Ataide R, Mackintosh CL, Fowkes FJ, Petter M, Chesson JM, Langer C, Warimwe GM, Duffy MF, Rogerson SJ, Bull PC, Cowman AF, Marsh K, Beeson JG. Targets of antibodies against Plasmodium falciparum-infected erythrocytes in malaria immunity. J Clin Invest. 2012; 122:3227–3238. [PubMed: 22850879]

247. Tsuboi N, Asano K, Lauterbach M, Mayadas TN. Human neutrophil Fcgamma receptors initiate and play specialized nonredundant roles in antibody-mediated inflammatory diseases. Immunity. 2008; 28:833–846. [PubMed: 18538590]

248. Lendvai N, Qu XW, Hsueh W, Casadevall A. Mechanism for the isotype dependence of antibody-mediated toxicity in Cryptococcus neoformans-infected mice. J Immunol. 2000; 164:4367–4374. [PubMed: 10754337]

249. Alonso A, Bayon Y, Crespo MS. The expression of cytokine-induced neutrophil chemoattractants (CINC-1 and CINC-2) in rat peritoneal macrophages is triggered by Fc gamma receptor activation: study of the signaling mechanism. Eur J Immunol. 1996; 26:2165–2171. [PubMed: 8814263]

250. Fernandez N, Renedo M, Sanchez Crespo M. FcgammaR receptors activate MAP kinase and up-regulate the cyclooxygenase pathway without increasing arachidonic acid release in monocytic cells. Eur J Immunol. 2002; 32:383–392. [PubMed: 11813157]

251. Abrahams VM, Cambridge G, Lydyard PM, Edwards JC. Induction of tumor necrosis factor alpha production by adhered human monocytes: a key role for Fcgamma receptor type IIIa in rheumatoid arthritis. Arthritis Rheum. 2000; 43:608–616. [PubMed: 10728755]

252. Fernandez N, Renedo M, Garcia-Rodriguez C, Sanchez Crespo M. Activation of monocytic cells through Fc gamma receptors induces the expression of macrophage-inflammatory protein (MIP)-1 alpha, MIP-1 beta, and RANTES. J Immunol. 2002; 169:3321–3328. [PubMed: 12218153]

253. Zhang Y, Zhou Y, Yang Q, Mu C, Duan E, Chen J, Yang M, Xia P, Cui B. Ligation of Fc gamma receptor IIB enhances levels of antiviral cytokine in response to PRRSV infection in vitro. Vet Microbiol. 2012

254. Gallo P, Goncalves R, Mosser DM. The influence of IgG density and macrophage Fc (gamma) receptor cross-linking on phagocytosis and IL-10 production. Immunol Lett. 2010; 133:70–77. [PubMed: 20670655]

255. Parcina M, Wendt C, Goetz F, Zawatzky R, Zahringer U, Heeg K, Bekeredjian-Ding I. Staphylococcus aureus-induced plasmacytoid dendritic cell activation is based on an IgG-mediated memory response. J Immunol. 2008; 181:3823–3833. [PubMed: 18768836]

256. Jancar S, Sanchez Crespo M. Immune complex-mediated tissue injury: a multistep paradigm. Trends Immunol. 2005; 26:48–55. [PubMed: 15629409]

257. Bunk S, Sigel S, Metzdorf D, Sharif O, Triantafilou K, Triantafilou M, Hartung T, Knapp S, von Aulock S. Internalization and coreceptor expression are critical for TLR2-mediated recognition of lipoteichoic acid in human peripheral blood. J Immunol. 2010; 185:3708–3717. [PubMed: 20713893]

258. Lovgren T, Eloranta ML, Kastner B, Wahren-Herlenius M, Alm GV, Ronnblom L. Induction of interferon-alpha by immune complexes or liposomes containing systemic lupus erythematosus autoantigen- and Sjogren's syndrome autoantigen-associated RNA. Arthritis Rheum. 2006; 54:1917–1927. [PubMed: 16729300]

259. Boule MW, Broughton C, Mackay F, Akira S, Marshak-Rothstein A, Rifkin IR. Toll-like receptor 9-dependent and -independent dendritic cell activation by chromatin-immunoglobulin G complexes. J Exp Med. 2004; 199:1631–1640. [PubMed: 15197227]

260. Means TK, Latz E, Hayashi F, Murali MR, Golenbock DT, Luster AD. Human lupus autoantibody-DNA complexes activate DCs through cooperation of CD32 and TLR9. J Clin Invest. 2005; 115:407–417. [PubMed: 15668740]

261. Ierino FL, Powell MS, McKenzie IF, Hogarth PM. Recombinant soluble human Fc gamma RII: production, characterization, and inhibition of the Arthus reaction. J Exp Med. 1993; 178:1617–1628. [PubMed: 8228810]

262. Sylvestre DL, Ravetch JV. Fc receptors initiate the Arthus reaction: redefining the inflammatory cascade. Science. 1994; 265:1095–1098. [PubMed: 8066448]

263. Hogarth PM, Pietersz GA. Fc receptor-targeted therapies for the treatment of inflammation, cancer and beyond. Nat Rev Drug Discov. 2012; 11:311–331. [PubMed: 22460124]

264. Ravetch JV, Lanier LL. Immune inhibitory receptors. Science. 2000; 290:84–89. [PubMed: 11021804]

265. Pearse RN, Kawabe T, Bolland S, Guinamard R, Kurosaki T, Ravetch JV. SHIP recruitment attenuates Fc gamma RIIB-induced B cell apoptosis. Immunity. 1999; 10:753–760. [PubMed: 10403650]

266. Nimmerjahn F, Ravetch JV. Fcgamma receptors as regulators of immune responses. Nat Rev Immunol. 2008; 8:34–47. [PubMed: 18064051]

267. Regnault A, Lankar D, Lacabanne V, Rodriguez A, Thery C, Rescigno M, Saito T, Verbeek S, Bonnerot C, Ricciardi-Castagnoli P, Amigorena S. Fcgamma receptor-mediated induction of dendritic cell maturation and major histocompatibility complex class I-restricted antigen presentation after immune complex internalization. J Exp Med. 1999; 189:371–380. [PubMed: 9892619]

268. DiScipio RG, Daffern PJ, Jagels MA, Broide DH, Sriramarao P. A comparison of C3a and C5a-mediated stable adhesion of rolling eosinophils in postcapillary venules and transendothelial migration in vitro and in vivo. J Immunol. 1999; 162:1127–1136. [PubMed: 9916743]

269. Godau J, Heller T, Hawlisch H, Trappe M, Howells E, Best J, Zwirner J, Verbeek JS, Hogarth PM, Gerard C, Van Rooijen N, Klos A, Gessner JE, Kohl J. C5a initiates the inflammatory cascade in immune complex peritonitis. J Immunol. 2004; 173:3437–3445. [PubMed: 15322209]

270. Fernandez N, Renedo M, Alonso S, Crespo MS. Release of arachidonic acid by stimulation of opsonic receptors in human monocytes: the FcgammaR and the complement receptor 3 pathways. J Biol Chem. 2003; 278:52179–52187. [PubMed: 14532278]

271. Casadevall A, Scharff MD. Serum therapy revisited: animal models of infection and development of passive antibody therapy. Antimicrob Agents Chemother. 1994; 38:1695–1702. [PubMed: 7985997]