Published in final edited form as:
Curr Opin HIV AIDS. 2009 September ; 4(5): 388–393. doi:10.1097/COH.0b013e32832f0a89.

Fc receptor-mediated antiviral antibodies

Donald N. Forthal and
Department of Medicine, Division of Infectious Diseases, University of California, Irvine School of Medicine, 3044 Hewitt Hall, Irvine, CA 92697, Tel: 949-824-3366

Christiane Moog
U778 INSERM/UDS, Faculté de Strasbourg, Institut de Virologie, Strasbourg, France

Donald N. Forthal: dnfortha@uci.edu

Abstract

Purpose of review—We summarize current information on Fc receptor-mediated anti-viral activities of antibodies. These activites include FcγR-mediated inhibtion and neutralization of HIV on antigen presenting cells (APCs), antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cell-mediated virus inhibition (ADCVI).

Recent findings—An FcγR-mediated mechanism that results in augmented neutralization and may render non-neutralizing antibodies inhibitory has been demonstrated in APC. ADCC antibody activity correlates inversely with HIV disease progression in humans, and higher vaccine-induced ADCC antibody responses are associated with lower acute SIV viremia levels in macaques. Following vaccination with rgp120, ADCVI antibody levels are higher among those with a lower rate of sexually acquired HIV infection. Non-neutralizing SIV immune serum that prevents infection of newborn macaques after oral challenge has potent ADCVI antibody activity. Abrogating the ability of the Fc segment of the broadly neutralizing monoclonal antibody IgG1b12 to bind to FcγRs and to mediate ADCVI substantially reduces IgG1b12's protective effect in a SHIV vaginal challenge model.

Summary—Fc-FcγR interactions play a critical role in the biological function of antibody and are likely to be instrumental in preventing or modulating lentiviral infection. Exploiting antibody responses that depend on Fc-FcγR interactions may help widen the breadth and increase the potency of vaccine-induced antibody. Although the importance of generating optimal Fab-antigen interactions cannot be overestimated, improving Fc-FcγR interactions through adjuvants or other strategies provides another option for improving HIV vaccines and immunotherapies.

Keywords

Antibody-dependent cellular cytotoxicity (ADCC); antibody-dependent cell-mediated virus inhibition (ADCVI); neutralization; Fcγ receptor (FcγR); HIV

Introduction

Antibodies recognize and bind to antigen through their Fab segment. However, much of the biological activity of antibody is mediated through its Fc portion and, in particular, through interactions between Fc and Fc receptors found on a number of cells important for host defense. Some of these biological activities, such as virus neutralization, antibody-dependent cellular

Correspondence to: Donald N. Forthal, dnfortha@uci.edu.

cytotoxicity (ADCC), antibody-dependent cell-mediated virus inhibition (ADCVI), and phagocytosis are likely to play a role in preventing or modulating HIV infection.

Receptors for the Fc segment of IgG (Fcy receptors; FcγRs) are expressed on the surface of a number of cells involved or potentially involved in HIV infection, including natural killer cells (NKs), monocytes, macrophages, dendritic cells, and neutrophils [1]. With the exception of γδ T cells, FcγRs are normally not found on T lymphocytes. In addition to the neonatal Fc receptor (not discussed in this review), five major FcγRs have been identified in humans: FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa, and FcγRIIIb [1]. FcγRI and FcγRIIIa generally serve to activate cells and require an interaction with a separate immune tyrosine activating motif (ITAM)-containing protein, such as the Fc receptor common γ-chain or the CD3 ζ-chain. FcγRIIa is also an activating receptor but contains an ITAM in its cytoplasmic tail [2]. FcγRIIIb is linked to the plasma membrane by a glycosyl phosphatidylinositol anchor and is only found on neutrophils and eosinophils [1,2]. FcγRIIb is exceptional in that it contains an immune tyrosine inhibitory receptor (ITIM) in its cytoplasmic tail and results in inhibition of activation [3].

Both FcγRIIa and FcγRIIIa are encoded by polymorphic genes that result in phenotypically different receptors. In the case of FcγRIIa, a single nucleotide polymorphism results in either a histidine (H) or an arginine (R) at amino acid position 131 [4,5]. Both the H and R isoforms of the receptor bind all four IgG subclasses, but IgG2 binding to the R isoform is weak [6]. The HH and RR genotypes are each found in about 25% of individuals with European or African ancestry [7–10]. This distribution is markedly skewed among Asians, where homozygosity for the H allele is found in about 50–60% and the homozygous R genotype is found in less than 10% [11,12]. A polymorphism in the FcγRIIIa gene encodes either a phenylalanine (F) or a valine (V) at amino acid 158 [13]. The V isoform binds with all subclasses but IgG2 binding is weak; the F isoform binds IgG1 with lower affinity than does the V isoform, and the F isoform does not bind either IgG2 or IgG4 [6]. Worldwide, the VV genotype has been found in about 10–20% of the population, and the FV and FF genotypes account for about 40–50% each [7,8,10,11]. Importantly, the polymorphisms in both FcγRIIa and FcγRIIIa have been noted to influence susceptibility to or severity of a number of infectious and autoimmune diseases [14]. In this review, we will outline the current state of knowledge about the role of Fc-FcγR interactions in HIV infection, with particular attention paid to neutralization, ADCC, and ADCVI.

FcγR-mediated inhibtion and neutralization of HIV

Neutralization has often been defined by the ability of the antibody Fab fragment to bind to epitopes on functional spikes of cell-free virions and to inhibit entry into susceptible cells. However, an FcγR-dependent mechanism of HIV inhibition involving the concomitant binding of Fab to the virus and Fc to FcγRs was detected in antigen presenting cells (APCs) [15–17]. Involvement of Fc-FcγR interactions in this manner resulted in a marked augmentation of antibody neutralizing activity on macrophages (about 1000-fold) and dendritic cells (about 100-fold) compared to lymphocytes lacking FcγRs. For macrophages, FcγRI was mainly involved [15], whereas FcγRII was mostly implicated with monocyte-derived dendritic cells [17] and Langerhans or interstitial dendritic cells (Peressin M, personnal communication). The specific pathway of virus degradation is under evaluation but it is hypothesized that the binding of HIV-IgG immune complexes to FcγRs at the surface of APCs leads to viral endocytosis and degradation in acidic lysosomes.

The FcγR-mediated inhibitory activity was detected for the five well-known neutralizing mAbs (2F5, 4E10, 2G12, b12 and 447-D) and, remarkably, for some non-neutralizing antibodies (referred to as non-neutralizing inhibitory antibodies [NNIAbs]). It is noteworthy that only a

small proportion of antibodies able to bind HIV-1 native particles, including some antibodies directed against the principal immunodominant domain of gp41, exhibit FcγR-mediated inhibitory activity. This strongly suggests that, as for classical neutralizing antibodies, special features were associated with the FcγR-mediated functional activity. The parameters associated with the NNIAbs remain to be defined, but preliminary experiments indicate that this inhibitory activity was not simply related to binding affinity of the antibodies to virus particles. NNIAbs were detected in sera form numerous, but not all HIV-infected individuals, indicating that such antibodies are frequently induced after infection and may thus also be induced by vaccination [16,18]. Since these antibodies were present in sera of numerous infected individuals, NNIAb may be of limited benefits once the infection has occured. Indeed, these antibodies do not inhibit infection of CD4+ lymphocytes, the principal HIV targets. However, as NNIAbs are powerful inhibitors of APC infection, their presence directly on or near mucosal surfaces could prevent infection of macrophages or dendritic cells, which are thought to be very early targets during sexual transmission of HIV.

Finally, in the case of antibodies directed against the membrane proximal external region (MPER) of gp41, neutralization may be augmented through a mechanism whereby FcγR (especially FcγRI) engagement provides a more favorable interaction between antibody and a pre-hairpin intermediate conformation of gp41 [19]. This suggestion has been made on the basis of enhanced neutralization by anti-MPER antibodies on TZMbl cells that were transfected to express FcγRs [19]; the biological relevance of such a mechanism is not known.

Antibody-dependent cellular cytotoxicity (ADCC)

ADCC occurs when antibody forms a bridge between a target cell expressing foreign antigens and an effector cell bearing Fc receptors. With respect to HIV, target cells have usually consisted of cell lines coated with gp120, engineered to express HIV antigens or infected with HIV-1, and PBMCs, NKs, monocytes or neutrophils have been used as effector cells. In any case, the result of the three-way interaction between target cell, antibody and effector cell is target cell death, usually measured by the release of ^{51} Cr, dye, or enzymes [20–22]. Importantly, ADCC and neutralizing antibodies differ from each other in that ADCC antibody is directed against infected cells, rather than against cell-free virus, and cell death, rather than virus inhibition, is measured in ADCC assays. Indeed, some monoclonal antibodies (mAbs) are discordant with respect to these two antibody functions [23].

A number of early studies documented the presence of ADCC antibodies during HIV-1 infection [24–27]. As expected, these antibodies have been largely directed against HIV Env, since there is a requirement for antigen expression on the surface of target cells [28,29]. More recent studies indicate that Nef-specific ADCC antibodies arise during infection [30]. An assay that measures intracellular cytokines produced by NK cells in the presence of HIV antibody and exogenous antigen suggests that Vpu and Pol may also serve as a target for ADCC antibodies [31]; this finding will need to be verified by documenting ADCC activity of anti-Vpu and anti-Pol antibodies using infected or transfected target cells.

A potential role for ADCC in modulating the course of HIV infection was first proposed on the basis of studies showing an inverse association between ADCC antibody levels and clinical stage of disease. The strongest evidence of a role for ADCC antibody in disease progression comes from a study by Baum, et al. of the Multicenter AIDS Cohort Study (MACS) [20]. In that study, rapid progressors had significantly lower ADCC antibody titers against CEM.NKR cells coated with gp120 than did non-rapid progressors at corresponding visits or non-progressors at any visit. More recently, HIV-infected individuals with spontaneously undetectable viremia were shown to have higher ADCC antibody levels than viremic subjects, whereas neutralizing antibodies were either lower or similar, depending on the assay or virus

strain used [18]. Direct evidence that ADCC antibodies might play a role in disease progression comes from a study of rhesus macaques with rapidly progressive disease [32]. The authors observed that passive infusion of SIV IgG from SIVmac251-infected animals with a normal course of disease resulted in a transient decrease in viremia in the rapidly progressing animals; the kinetics of the anti-viral effect suggested that ADCC activity of the infused antibody was killing virus-infected cells [32].

In another study using subjects from the MACS, those with the FcγRIIa RR genotype had a faster rate of progression to a CD4+ cell count less than 200/mm^3 than did subjects with either the RH or HH genotypes; ADCC antibody activity was not measured [33]. Interestingly, rituximab, whose anti-tumor activity is largely due to ADCC, may be less effective in treating lymphoma in patients with the lower affinity RR genotype [34]. Thus, the results of the MACS genotype study are consistent with a role for antibody-FcγR interactions in modulating the course of HIV infection. However, if the FcγRIIa polymorphism impacted progression of HIV infection because of its influence on ADCC, one might expect individuals with the RR genotype to have lower viral loads. In fact, there was no significant relationship between set point viral load and FcγRIIa genotype [33]. Since anti-HIV ADCC antibody was not measured in the FcγR genotype study, it is possible that simultaneous consideration of ADCC antibody level and FcγR genotype might have predicted both viral load and disease progression.

The role of vaccine-induced ADCC antibody in preventing lentivirus infection has recently been evaluated. Using a replicating Ad5-SIV recombinant prime and gp120 boost that resulted in control of acute SIVmac251 viremia upon intrarectal challenge, the vaccine-induced ADCC antibody response (measured against target cells infected with a laboratory passaged SIVmac251) was associated with lower acute viremia [21]. In a study comparing oral/oral versus intranasal/oral priming with similar Ad5-SIV constructs followed, in both cases, by intramuscular gp120 boosting, the intranasal/oral regimen resulted in a small advantage in acute viremia control and in transiently higher ADCC antibody responses; differences between the two vaccine regimens were more apparent and sustained for ADCVI antibody responses [35].

There have been no studies correlating vaccine-induced ADCC responses with protection from HIV infection in humans. Of note, however, vaccination with rgp120 results in ADCC antibody against gp120-coated target cells in most patients [36,37]. On the other hand, DNA- or ALVAC-based HIV vaccines, without protein boosting, elicit little or no ADCC antibody [37,38].

Antibody-dependent cell-mediated virus inhibition (ADCVI)

Like ADCC, ADCVI results from an interaction between a target cell, antibody, and an Fc receptor-bearing effector cell. However, rather than being a measure of target cell death, as is the case with ADCC, ADCVI is a measure of the impact of antibody and effector cells on virus output from infected target cells [39,40]. Thus, the readout in ADCVI assays is the percentage of virus inhibition due to a test antibody and effector cells relative to a negative control antibody and effector cells. This biologically relevant endpoint allows the use of any lentiviral strain capable of infecting the target cell. Much of the anti-viral effect of ADCVI is due to target cell killing, and ADCVI and ADCC activities likely overlap considerably. However, non-cytolytic mechanisms, such as FcγR-triggered production of β-chemokines, can also play a role in the virus inhibition measured in ADCVI assays [40].

In a study of subjects with acute HIV infection, we found that ADCVI antibodies developed as early as the first week after symptom onset or the first month after exposure [40]. The ADCVI antibody response occurred with similar timing as the cytotoxic T-cell (CTL) response but much earlier than has been reported for the neutralizing antibody response [41,42].

Furthermore, the ADCVI antibody response became more potent as viremia fell (in the absence of anti-retroviral therapy), resulting in an inverse relationship between ADCVI antibody and plasma viremia [40]. ADCVI antibodies also appear to be more broadly reactive with different HIV strains than are antibodies measured in neutralizing assays [40]. Thus, it is possible that ADCVI contributes to the fall in viremia, in a manner similar to that proposed for CTLs. It should be noted, however, in a separate study, we were unable to detect ADCVI antibodies in the first 40 days after exposure [41].

The role of ADCVI antibodies in preventing lentivirus infection has been studied in the SIV, SHIV, and HIV models. Passive infusion of SIV immune serum that prevented newborn macaques from an oral challenge with SIV_{mac251} was found to have no neutralizing activity against the challenge strain [43]. However, in an ADCVI assay, the infused serum had potent activity with a 50% inhibitory titer of 1:12,800 [23]. Moreover, the ADCVI activity resided in the IgG fraction, and IgG mediated anti-viral activity when target cells and effector cells from the same animals were used [23]. In a direct evaluation of the role of Fc-FcγR interactions in preventing lentivirus infection, Hessell, et al. were able to protect eight of nine macaques from vaginal $SHIV_{163p3}$ challenge with native IgG1b12 infusion prior to challenge [44]. Similarly, eight of nine macaques were protected by infusion of an IgG1b12 variant that was equivalent to native IgG1b12 with respect to FcγR binding and ADCVI and neutralizing activities but bound poorly to complement. However, using a second variant of IgG1b12 that bound poorly to both complement and to FcγR and did not mediate ADCVI—but retained neutralizing activity equivalent to native IgG1b12—only five of eight animals were protected. Thus, maximum protection after passive antibody infusion requires ADCVI and/or other Fc-FcγR-mediated activity.

An evaluation of the ADCVI response in humans following recombinant gp120 (rgp120) vaccination in the Vax004 trial revealed an inverse correlation between HIV infection rate and ADCVI antibody activity measured against a clinical R5 isolate of HIV-1 [45]. Thus, for every 10% increase in ADCVI activity, there was a 6.3% decrease in the hazard rate of infection ($p = 0.019$). Moreover, the rate of infection was about 2-fold less among subjects in the highest quartile of ADCVI antibody responses compared with those in the lowest quartile (hazard ratio = 0.54, $p = 0.035$). Thus, although, there was no overall efficacy in the Vax004 trial [46], it is possible that individuals with the most potent vaccine-induced antibody responses had some degree of protection.

Conclusions

Antibody inhibitory activities related to Fc-FcγR interactions include blocking of virus infectivity via degradation of immune complexes in APCs, impairing virus replication by lysis of infected cells, and FcγR-triggering of β-chemokine production. In addition to increasing the potency of the antiviral antibodies, Fc-FcγR interactions also increase their breadth. Although this has not been studied systematically, it is possible that the increased potency and breadth is a consequence of the ability of Fc-FcγR interactions to occur when the Fab portion of antibody binds to any exposed Env component, even with relatively low affinity or avidity. This is unlike the situation with classical neutralizing antibodies, which may need to bind with epitopes in such a way that there is interference with virus-receptor or virus-co-receptor interactions.

Fc-FcγR interactions play a critical role in the biological function of antibody and are likely to be instrumental in preventing or modulating lentiviral infection. Exploiting antibody responses that depend on Fc-FcγR interactions may help overcome some of the difficulties associated with vaccine development by widening the breadth and increasing the potency of the antibody response. Although the importance of generating optimal Fab-antigen interactions

cannot be overestimated, improving Fc-FcγR interactions through adjuvants, by directly altering the Fc segment of mAbs or by other strategies provides another option for improving HIV vaccines and immunotherapies [47–49].

Acknowledgments

Donald Forthal is funded by the NIH (AI078477, AI079775, AI073147) and the Center for HIV/AIDS Vaccine Immunology (U19AI67854). Christiane Moog is funded by the ANRS, Europrise (LSHPCT-2006-037611), EuroNeut41 (FP7-2007-201038) and Fondation Dormeur.

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