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Antibody-Dependent Cellular Cytotoxicity (ADCC) in HIV Infection

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Introduction

Much of the antiviral activity of antibody is mediated by interactions between the Fc segment of immunoglobulin and Fc receptors (FcRs) present on many different cell types. Such interactions could have a beneficial impact on viral infection through, for example, antibody-dependent cellular cytotoxicity (ADCC), phagocytosis, or trogocytosis (wherein plasma membranes are sheared off of one cell by another cell). However, Fc-FcR interactions may also result in antibody-dependent enhancement of infection, a phenomenon best described with respect to dengue virus infections. In this review, we will focus primarily on ADCC in the setting of HIV-1 and related lentiviral infections and also touch briefly on other potentially beneficial functions. For a discussion of antibody-dependent enhancement, the interested reader is directed elsewhere [1,2]. In addition, detailed treatments of FcR biology can be found in recent reviews [3,4].

ADCC occurs when antibody forms a bridge between a target cell bearing foreign antigens on its surface and an effector cell, typically a natural killer (NK) cell expressing FcRs. The cross-linking of the FcRs initiates a cascade of signals leading to the release of lytic compounds from the effector cell that ultimately result in the lysis of the target cell. Thus, as is the case with cytotoxic T cell activity, ADCC has the potential to remove cells producing virus. ADCC is best described for IgG interacting with Fc receptors for IgG (FcγRs). However, IgA-FcαR and IgE-FcεR interactions leading to ADCC also occur [5,6]. Of the IgG subclasses, IgG1 and IgG3 are best at engaging Fc receptors [3,7]. Fc glycosylation can also have a major impact on Fc-FcγR interactions [8]. Finally, polymorphisms in the FcγRs themselves, particularly those in FcγRIIIa and FcγRIIa, can influence the affinity for IgG and the ADCC activity in a subclass-specific manner [7,9].

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Antibody-dependent phagocytosis (ADP) occurs when antibody opsonizing a cell or a cell-free pathogen cross-links FcRs on phagocytic cells such as monocytes, macrophages, dendritic cells, or neutrophils. The opsonized cell or pathogen is then internalized and, for the most part, degraded in phagolysosomes. However, FcR-mediated internalization of virus also represents a means of virus entry into susceptible target cells that could potentially result in enhanced infection [10,11]. Using GFP-expressing HIV-1, it has been shown that virions are poor targets for ADP by Env-specific IgG, likely because of the paucity of Env spikes on the virion surface and because of the inability of IgG antibodies to aggregate virus [12]. However, cells decorated with virus on their surface, a state imitating target cells in the process of being infected, may undergo ADP or trogocytosis [12–15]. Whether or not phagocytosis or trogocytosis of such cells, or of infected cells, contributes to virus clearance is unknown.

Apart from functions that result in target cell death, triggering of FcRs by opsonizing antibodies can result in the secretion of various chemokines and cytokines with direct and indirect antiviral and inflammation-modulating effects [16,17]. Finally, the sum total of FcR-triggered effects on virus replication can be measured using the antibody-dependent cell-mediated virus inhibition (ADCVI) assay, in which viral yield is measured after incubating infected lymphocytes with effector cells and antibody [16,18].

Measuring ADCC: concepts and controversies

Env-coated vs. infected target cells.

One of the earliest and most widely used techniques to measure anti-HIV ADCC activity relies on the coating of CD4+ T cells—either cell lines such as CEM-NKr or primary CD4+ T cells—with recombinant Env proteins gp120 or gp140 or with inactivated viral particles [19–32]. Killing of Env-coated target cells is then measured by the release of ^{51}Chromium (chromium release assay) [26,33,34] or by calculating the emergence of pre-labeled coated cells that lose a viability dye (rapid and fluorometric ADCC [RFADCC] assay) [25,32,35]. ADCC activity has also been evaluated by quantifying the cleavage of a fluorogenic peptide substrate that generates a fluorescent signal when cleaved by granzyme B (ADCC GranToxiLux assay) [27,28,36,37], by detecting intracellular IFN-γ or cell-surface expression of CD107a or by measuring the loss of intracellular granzyme B [38,39]. Note that these latter assays do not directly measure ADCC but more precisely measure activities that requires NK effector cell responses similar to those occurring during ADCC.

It is important to consider that Env coating of CD4+ T cells is achieved through the interaction of gp120 with the CD4 receptor. Thus, these assays cannot detect activity mediated by antibodies that target the gp120 CD4 binding site (CD4BS) [40–44]. Moreover, gp120-coated cells do not expose quaternary epitopes present in the untriggered Env trimer and therefore are not useful to measure ADCC activity mediated by antibodies recognizing such quaternary epitopes (e.g., PG9, PG16, etc.) [45–48]. These considerations and others have led to several approaches to measure ADCC against infected target cells. Such target cells can be made by infecting CD4+ T cells, mostly CEM-NKr cells or primary CD4+ T cells, with infectious HIV-1 molecular clones (IMCs). However, an overlooked problem of this approach is the intrinsic ability of gp120 to shed from the surface of infected cells. Shed

gp120 binds to uninfected, bystander T cells through a CD4 interaction, thus providing another susceptible target cell population in addition to the infected cells (figure 1). This natural phenomenon greatly complicates ADCC measurements. While infected cells express trimeric Env at their surface, uninfected bystander cells are coated with monomeric gp120. It is therefore paramount to discern ADCC responses against infected versus uninfected cells, since anti-Env Abs have different specificities [40]. Indeed, while some preferentially recognize monomeric gp120, others only bind the untriggered “closed” trimer (discussed below).

Though NK cell activation and GranToxiLux assays fail to differentiate responses against infected versus uninfected cells, other approaches do. Infected cells can easily be identified by performing intracellular p24+ staining; ADCC activity is then determined by calculating the loss of the percentage of infected (p24+) cells by flow cytometry [36,49–55]. Similar flow cytometry approaches use modified IMCs coding for reporter genes such as green fluorescent protein (GFP) [52,53,56–60]. Another method to measure ADCC activity against the infected cell population is the use of IMCs coding for the luciferase reporter gene (LucR). This approach is amenable to high-throughput assays and has been widely used in the field [37,61–74]. However, great caution should be exerted in selecting these reporter IMCs in order to ensure that insertion of the reporter gene does not affect expression of viral proteins, particularly Nef, that play a critical role in protecting infected cells from ADCC responses (detailed below; figure 1) [75]. Finally, another luciferase-based method uses a T-cell line encoding a Tat-driven luciferase gene, which allows Luciferase to be expressed only upon productive HIV-1 or SIV infection [76]. Since the cell line codes for the reporter gene, unmutated IMCs can be used, and elimination of infected cells is determined by simply calculating the loss of luciferase activity [76]. It is worth noting that this assay, using an unmutated CRF01_AE IMC, was used to identify ADCC as a correlate of protection in the RV144 trial [77].

The role of Env conformation and accessory proteins in ADCC.

The functional Env trimer is highly flexible and transits from its unliganded “closed” conformation (state 1) to its “open” CD4-bound (state 3) (figure 2). Interaction with CD4 induces changes in Env resulting in some CD4-inducible epitopes (CD4i) exposed by the intermediate “partially open” conformation (state 2). The rest of the CD4i epitopes are unveiled in the open conformation (state 3) [78–80]. Env flexibility and controlled conformational transitions represent a formidable barrier against antibody attack. Envs from primary HIV-1 isolates are relatively resistant to easy-to-elicit CD4i Abs, which are predominant in the sera of HIV-1-infected individuals [58,81,82]. This is mostly due to the “closed” nature of primary Envs which primarily sample state 1 [79], thus effectively occluding epitopes recognized by CD4i Abs. CD4 engagement drives Env into states 2/3 and renders it susceptible to CD4i Ab binding [58,59,78,83–85]. In order to avoid exposure of these vulnerable epitopes, Env tightly controls its transition from state 1 to states 2/3. The V1/V2 and V3 loops play a critical role in preventing spontaneous transitions to downstream conformations [86,87]. A conserved ~150-Å3 pocket where phenylalanine 43 of CD4 engages with the gp120 can predispose Env to spontaneously assume conformations closer to states 2/3 when it is filled with large hydrophobic residues, [84] [88] which in turn

sensitizes infected cells to ADCC mediated by CD4i Abs [84] (figure 2). While residue S375 is well-conserved in the majority of group M HIV-1 isolates, CRF01_AE strains have a naturally occurring histidine at this position (H375); such strains predominate in Thailand. A recent report suggests that the presence of H375 in Thai strains might have contributed to the observed vaccine efficacy of RV144 [84]. Other HIV-1 Env strains have a small residue at position 375 (serine or threonine) and therefore predominantly sample closed state 1 conformations [79].

Overall, cells infected with primary viruses and coding for functional Nef and Vpu proteins (see below) are largely resistant to ADCC mediated by CD4i Abs [49,53,56,59,81,89]. Despite the different elements precluding a premature opening of Env, interaction with membrane-bound CD4 results in exposure of vulnerable CD4i epitopes [59]. Consequently, ADCC susceptibility to CD4i Abs is dramatically enhanced when infected cells express Env in its open state 2/3 conformation [58,83,84]. Since CD4i Abs are easily-elicited and achieve high titers during HIV-1 infection [90], the virus evolved to minimize exposure of this vulnerable Env conformation. HIV-1 limits Env-CD4 interaction by downregulating CD4 and preventing accumulation of Env [58,59,91–93]. Nef and Vpu accessory proteins reduce accumulation of CD4 at the cell surface [58,59] in a two-step mechanism. First, during the early phases of the HIV-1 replication cycle, Nef downregulates CD4 from the plasma membrane. Second, Vpu, expressed from a bicistronic mRNA also coding for Env, induces CD4 degradation through an endoplasmic reticulum (ER)-associated protein degradation mechanism [94]. The action of Vpu liberates Env from CD4-dependent retention in the ER [95]. Env is then free to traffic to the plasma membrane in a “closed” conformation effectively occluding CD4i epitopes. Hence, several reports have shown that cells infected with viruses defective for Nef and/or Vpu expression are more susceptible to ADCC responses mediated by HIV+ sera or CD4i antibodies [49,57–59,75,92,93,96–100]. Besides its role in CD4-downregulation, Nef also protects infected cells from ADCC responses by downregulating the expression of NKG2D ligands (MICA, ULBP1, and ULBP2) [97,101,102], which otherwise activate NK cells by interacting with the NKG2D receptor [96,97]. Therefore, Nef and Vpu accessory proteins protect infected cells from ADCC.

Effector cells.

Besides antigen recognition, antibodies through their Fc segment must engage with specific receptors located at the surface of certain immune effector cells. Receptor engagement is required in order to activate effector cells and trigger the release of perforin and granzyme required to kill the target cell. Most assays have relied on peripheral blood mononuclear cells (PBMC) [40,41,50,51,58,59,65,83,84], NK cells isolated from PBMCs [76,81,89,91,96,103,104], or NK cell lines [76,81,103,105,106]. NK cell effector functions have been extensively analyzed and are controlled by an equilibrium established between signals delivered through inhibitory (e.g. KIR, CD94/NKG2A), activating (e.g. FcγRIIIa, NKG2D, DNAM-1, NKp46) or co-activating (e.g. NTB-A, 2B4) receptors [107]. The HIV-1 Nef accessory protein decreases NKG2D ligand expression [49,75,97,101,102] and therefore modulates the activation status of NK cells.

Monocytes, macrophages, neutrophils and NK cells are also reported to mediate ADCC against HIV-1-infected or Env-coated cells [41,108–110] through the FcγRs expressed on those cells [3]. However, it should be noted that monocytes, macrophages and neutrophils function as phagocytes, presenting a problem in interpreting some assays [14]. Discerning ADCC from antibody-mediated phagocytosis *in vivo* may be particularly difficult [111].

Role of ADCC and other Fc receptor-mediated functions in preventing infection

It is clear from numerous studies using animal models that antibodies capable of neutralizing a lentivirus challenge strain can prevent infection [112–125]. Thus, developing vaccines that elicit neutralizing antibodies against a broad array of virus strains is a major goal of HIV vaccine development. Although some progress has been made, eliciting broadly neutralizing antibodies by vaccination has largely been unsuccessful. An alternative approach would be to depend on non-neutralizing antibodies that nonetheless are potentially antiviral, such as those mediating ADCC or phagocytosis.

Early studies in monkeys hinted at a role for non-neutralizing antibodies in preventing infection. For example, passive infusion of polyclonal IgG derived from sera of vaccinated and infected monkeys was shown to prevent infection in newborn macaques following oral challenge with SIVmac251 [126]. The IgG was considered to be poorly neutralizing but had substantial ADCVI activity [127]. However, a subsequent similar study found no protection [128]. Moreover, several studies employing poorly neutralizing polyclonal or monoclonal antibodies with ADCVI and/or ADCC activity failed to prevent infection after intravenous, vaginal or rectal SIV or SHIV challenge [129–135]. One of these studies did, however, offer a glimmer of hope in that fewer transmitted/founder (T/F) strains established infection in monkeys challenged rectally with high-dose SHIVBaL after infusion of a non-neutralizing, ADCC-mediating antibody. Another study found two of five animals that received vaginally delivered F240 did not become infected after SHIV162P4 vaginal challenge, but there was no significant difference between the F240-treated and control animals [129]. Moreover, that same study demonstrated an increase in T/F strains after passive parenteral infusion or local application of the non-neutralizing antibody b6 [129]. From a mechanistic standpoint, it is unknown how passively infused antibody could reduce or increase the number of T/F strains without impacting the overall risk of infection; however, it is possible that larger sample sizes could reveal differences in infection risk A study by Hessell, et al. compared infusion of IgG1 and IgG3 versions of a non-neutralizing anti-v2i-specific monoclonal antibody in preventing infection after repeated rectal SHIVBal.P4 challenge. There were no significant differences between the IgG1, IgG3 and control antibodies, but the IgG1 version resulted in reduced plasma and PBMC virus levels and decreased viral DNA in lymphoid tissues compared to control antibody [133]. Finally, in a mouse model, a non-neutralizing antibody directed against influenza hemagglutinin (HA) cleared cells infected with HIV-1 modified to express HA and protected mice against infection; protection was likely mediated through FcγRs [136]. The relevance of this model organism to lentiviral infections in humans and non-human primates is unclear.

Studies of the role of ADCC or other FcR-mediated antibody functions in preventing HIV infection in humans also reveal uncertainty but point toward little, if any benefit. ADCVI antibody activity was demonstrated not to be associated with the risk of HIV-1 superinfection [137]. However, ADCC activity of IgG in breast milk (measured by RF-ADCC assay using gp120-coated CEM.NKr cells) correlated inversely with infant infection risk; however, maternal plasma ADCC activity was not associated with transmission risk [138]. The same group found that ADCC activity in infant plasma was higher in uninfected than in infected infants, although the difference was not significant [74]; infant plasma ADCC activity did, however, correlate with reduced mortality. In a larger study, neither breast milk nor maternal plasma ADCC activity (measured by both gp120-coated and HIV-1 infected CEM.NKr-CCR5 cells) were associated with maternal-to-child transmission [74]. A trial comparing passive immunotherapy with polyclonal IgG (HIVIGLOB) plus nevirapine to nevirapine alone in preventing mother-to-child transmission demonstrated no benefit attributable to HIVIGLOB [139]. Moreover, there was a suggestion, though controversial, that the HIVIGLOB might have increased the rate of infection. HIVIGLOB was able to neutralize some strains of HIV-1, but neither ADCC nor other FcγR-mediated antibody activities in HIVIGLOB were reported [140].

Although studies employing passive infusion do not support the notion that non-neutralizing antibodies, in and of themselves, can prevent infection, vaccine trials in monkeys and humans provide some, albeit non-definitive, evidence to the contrary. For example, adenovirus-based regimens, particularly when boosted with Env glycoprotein, offered protection against intra-rectal challenge with SIVmac251 [141]. Protection correlated with binding antibody titers as well as with a composite measure of FcγR- and complement-mediated antibody functions; ADCC as well as ADP individually correlated with protection, although the magnitude of the correlation was not reported [141]. It should be noted that ADP was measured using 1μM beads coated with recombinant gp140 and ADCC was measured by the RF-ADCC assay using CEM-NKr cells also coated with recombinant gp140; as discussed above, there are questions regarding the relevance of these assays. In another vaccine study using adenovirus- and MVA-based vaccines without Env boosting, protection against acquisition after rectal challenge correlated with V2-specific binding antibodies; there was a trend for ADCC activity that did not meet statistical significance after adjusting for multiple comparisons [142]. Vaccine regimens using DNA and/or MVA expressing SIVmac239 sequences provided about 60% per-challenge protection after intrarectal exposure to SIVsme660 [143]. The vaccines elicited serum ADCC activity, which did not correlate with protection [143]. ADCC, measured using cells that express luciferase upon infection, was associated with complete protection following intravenous SIVmac251NE challenge in animals that had been previously immunized with live-attenuated versions of SIVmac239Δnef [103]. Partial protection from vaginal challenge with a different SIVmac251 variant was also associated with serum ADCC activity [103]. gp120-CD4 chimeric subunit protein vaccines gave protection against low-dose repeated rectal challenges with heterologous SHIV162P3 or SIVmac251, and protection was shown to correlate with ADCC measured using gp120-coated target cells [144]. A recent study using a pentavalent vaccine otherwise similar to the RV144 immunogen resulted in 55% protection from low-dose repeated rectal SHIV challenge; several antibody assays, including a bead-

based phagocytosis assay and ADCC using gp120-coated target cells or cells infected with Nef-defective IMCs correlated with protection [65,145]. Finally, immunization with truncated, trimeric HIV-1 gp41 and the P1 peptide (amino acids 649–683 of gp41) inserted into the lipid membrane of virosomes (a virus-like particle derived from influenza virus) resulted in a high degree of protection from low-dose, repeated vaginal challenge of Chinese macaques with SHIVSF162P3. Cervicovaginal-secretion ADCC activity, as well as transcytosis-inhibition activity, correlated with protection. Notably, the vaccine regimen did not elicit any circulating ADCC activity [146].

Vaccine trials in humans also provide correlative evidence of a role for FcγR-mediated antibody functions in preventing HIV-1 infection. The first human phase III HIV-1 vaccine trial (VAX004) utilized bivalent recombinant gp120 [147]. Although no protection was demonstrated, higher serum ADCVI activity against a clinical R5 strain of HIV-1 correlated inversely with infection rate [148]. The only human vaccine trial to register vaccine efficacy was the RV144 trial conducted in Thailand [148]. The approximately 30% efficacy allowed an examination of immune correlates, which revealed an associated between higher V1/V2 binding antibodies and protection [77]. In addition, higher anti-Env IgA antibodies were associated with a higher rate of infection. In a secondary analysis, higher ADCC activity (using HIV-$1_{92TH023}$-infected CEM.NKr-CCR5 target cells) was associated with protection, but only after controlling for IgA levels. It should be noted, however, that neutralizing activity against tier 1 HIV-1 was similarly associated with protection after controlling for IgA levels [77]. A subsequent analysis of antibody responses in the RV144 trial revealed that v1-v2 IgG3 antibodies that correlate with lower infection risk also correlate with ADCC activity using gp120-coated or HIV-$1_{92TH023}$-infected target cells[149].

Whereas animal models have not demonstrated preventative efficacy of non-neutralizing antibodies, there is direct evidence that engagement of FcγRs by IgG is essential for optimal prevention of SHIV infection by neutralizing antibodies. Thus, Hessell, et al., found that mutations in the neutralizing antibody b12 that abrogated FcγR binding resulted in less protection than wild-type b12 following passive infusion and vaginal SHIV challenge of macaques [150,151]. Similar conclusions were reached by Bournazos, et al. using mouse models and HIV-1 [152]. However, a non-fucosylated version of b12, which allowed increased FcγRIIIa binding and greater ADCC (using an NK cell line as effectors) and ADCVI (with human PBMCs as effectors) activities *in vitro*, did not improve protection over wild-type b12 after a repeated low-dose vaginal challenge with SHIVSF162P3 [153]. ADCVI activity using human monocytes was equivalent between the wild-type and non-fucosylated versions of b12. The lack of improved protection may have been due to already maximum *in vivo* FcγR-mediated activity of the wild-type antibody. Alternatively, an FcγR-mediated antibody function other than one involving ADCC due to FcγRIIIa on NK cells may be important in the optimal effect of neutralizing antibodies. Finally, a more recent study suggests that FcγR engagement is not always necessary for optimal prevention by a neutralizing antibody: a version of the human mAb PGT121 with the same Fc mutation used in the Hessell study of b12 was equally effective as wild-type PGT121 in preventing intravenous SHIV challenge. Moreover, both versions of the antibody similarly lowered viral loads when used in already infected animals (Stephen Kent, unpublished).

In summary, there is little direct evidence in support of non-neutralizing antibodies with anti-viral activities such as ADCC having a substantial protective effect (table). The correlative evidence is interesting but the intercorrelations between immune functions and the inability to directly pinpoint a given function or functions in prevention makes it difficult to draw conclusions. Fc-FcγR interactions do appear to augment the protective effect of neutralizing antibodies, although the augmented protection may not apply to all antibodies.

The role of ADCC in modulating infection

There are several studies in both animals and humans suggesting that ADCC plays a role in controlling viremia with HIV, SIV or SHIV. However, most of the studies depend on correlations rather than direct evidence. For example, Banks, et al. demonstrated a correlation between plasma ADCC activity and progression to AIDS in SIV17E-Br-infected macaques [154]. In a vaccine trial using adenovirus type 5 (Ad5)-expressing SIV recombinants followed by gp120 boosting, serum ADCC activity correlated with low viral burden during the acute phase of infection following intrarectal challenge with SIVmac251 [155]. ADCC in this study was measured using the RFADCC assay and chronically SIVmac251-infected H9 target cells. An Ad5-based regimen given intranasally and orally or with the addition of an intratracheal prime, followed by intramuscular Env boosting, resulted in reduced acute viremia following intrarectal challenge with SIVmac251. Reductions in acute viremia correlated with serum ADCC (using gp120-coated CEM-NKr cells) and ADCVI activity (using SIVmac251-infected rhesus PBMCs) [156,157]. Similar findings of reduced viremia following vaccination that correlated with ADCC and ADCVI activity were reported after intravenous challenge with SHIV89.6P [158].

One study did directly show some effect of non-neutralizing antibody on control of viremia, although the effect was weak and transitory. In that study, IgG from SIVmac251-infected animals was infused into other SIVmac251-infected animals deemed to be rapid progressors. The rapid progressors had negligible anti-SIV antibody titers prior to the infusion, but the infusion resulted in a two- to three-fold reduction in viremia that began rising after 12 hours. The kinetics of the viral load reduction suggested that an effector mechanism, such as ADCC, was responsible [159].

In humans, Baum, et al. demonstrated an inverse correlation with serum ADCC antibody responses and disease progression (using a chromium-release assay and HIV-1_{MN} gp120-coated cells) [26]. Another study focused on the function of NK cells to mediate ADCC against cytomegalovirus-infected cells and found an association between higher activity and improved survival [160]. ADCC antibody activities among HIV-infected subjects who control viremia in the absence of anti-retroviral therapy (elite controllers) have been reported to be higher when compared to those with poorer control [161,162]. However, one of these studies found higher ADCC activity in elite controllers only with an assay relying on granzyme B entry into target cells and found no difference when the RF-ADCC assay was used [161]. Although these studies are consistent with a role for FcγR-mediated antibody functions in modulating infection in humans, their correlative nature makes it equally likely that better functions are the result of better viremia control through other mechanisms (table).

Finally, with respect to modulating existing infection, direct evidence in humans indicates that passive infusion of potent bNabs leads to rapid but transient lowering of viral load [163,164]. The fact that clearance of infected cells through an FcγR-mediated process likely contributes to the reduced viremia suggests that neutralizing antibodies with effector functions might be a useful component of strategies aimed to reduce virus reservoirs [165].

Conclusions

The results of the RV144 vaccine trial in Thailand and subsequent evaluations of immune correlates of protection in that trial have generated renewed interest in eliciting antibodies with FcγR-mediated functions to prevent HIV-1 infection. However, studies aimed at directly testing the role for such functions—in the presence of weak neutralizing activity—have been disappointing. HIV-1 appears to have evolved different mechanisms, including Nef and Vpu downregulation of CD4 expression on infected cells and Vpu antagonism of BST/tetherin to evade ADCC. Moreover, many antibodies elicited during infection or vaccination that mediate ADCC are directed against CD4i epitopes, which, related to CD4 downregulation, are generally not expressed on infected cells. Although analyses have revealed correlations between ADCC and protection in human and animal vaccine trials (table), it is difficult to ascertain with any degree of certainty whether or not ADCC is actually a key factor in preventing infection. Stronger evidence indicates that FcγR-mediated antibody functions augment the protective effect of neutralizing antibodies, though the exact function(s) playing such a role is unknown. Finally, the impact of FcγR-mediated activities in augmenting the effect of neutralizing antibodies could be a key factor in immunotherapies designed to reduce viral reservoirs.

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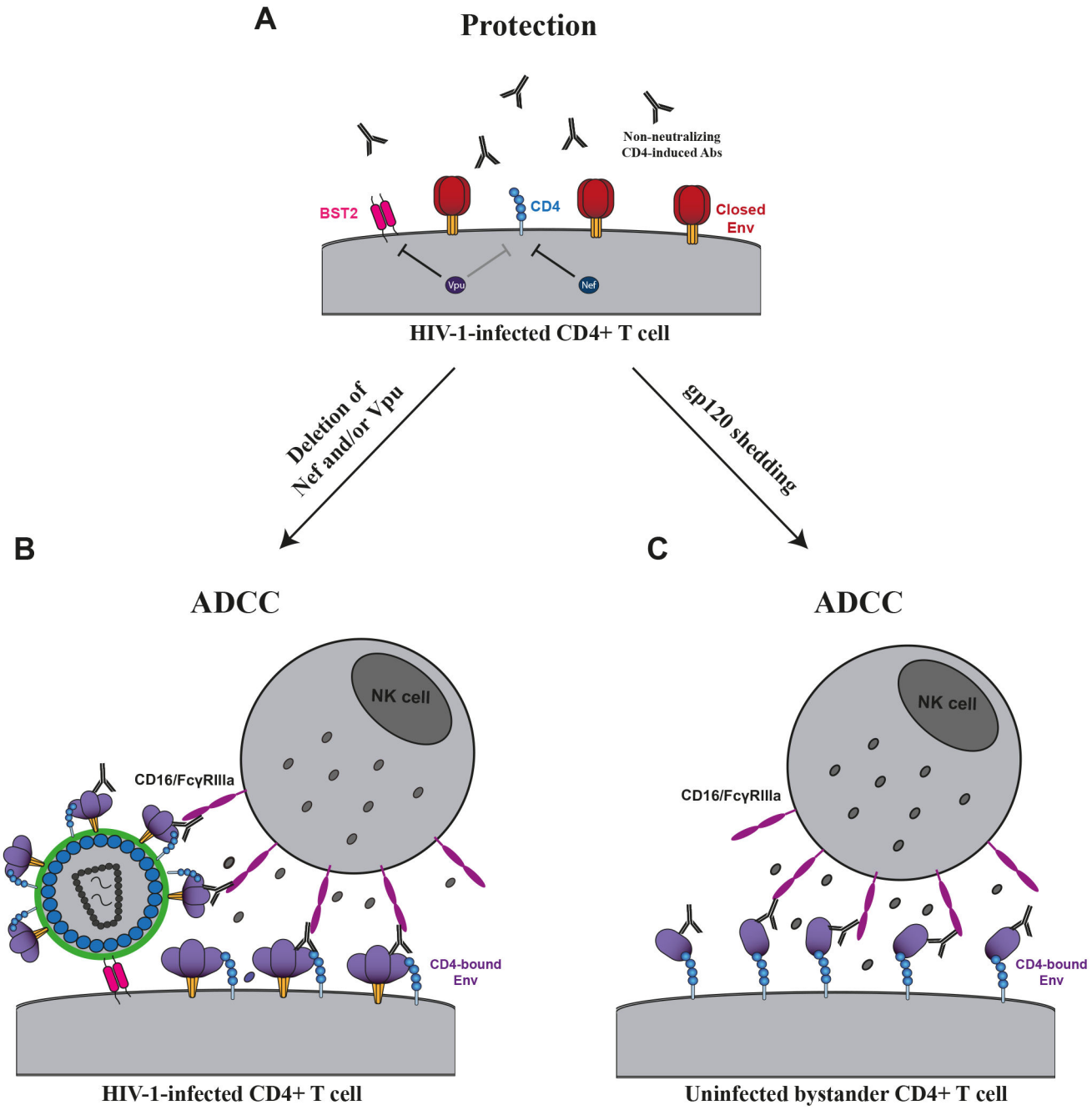

Figure 1. HIV-1-infected cells are protected from ADCC responses.

To avoid exposing vulnerable CD4-induced epitopes, HIV-1 controls the level of cell surface CD4 through the action of Nef and Vpu and limits Env accumulation through Vpu-mediated BST-2/Tethering downmodulation (**A**). In the absence of Nef and/or Vpu, Env and CD4 can interact at the cell surface, thus sensitizing infected cells to ADCC mediated by CD4i Abs (**B**). An intrinsic property of HIV-1 Env is that its gp120 subunits sheds. This is due to the noncovalent association between gp41 and gp120. Shed gp120 interacts with the CD4 receptor present at the surface of uninfected bystander cells, thus resulting in the exposure of

vulnerable epitopes leading to the sensitization of these cells to ADCC responses mediated by CD4i Abs (**C**).

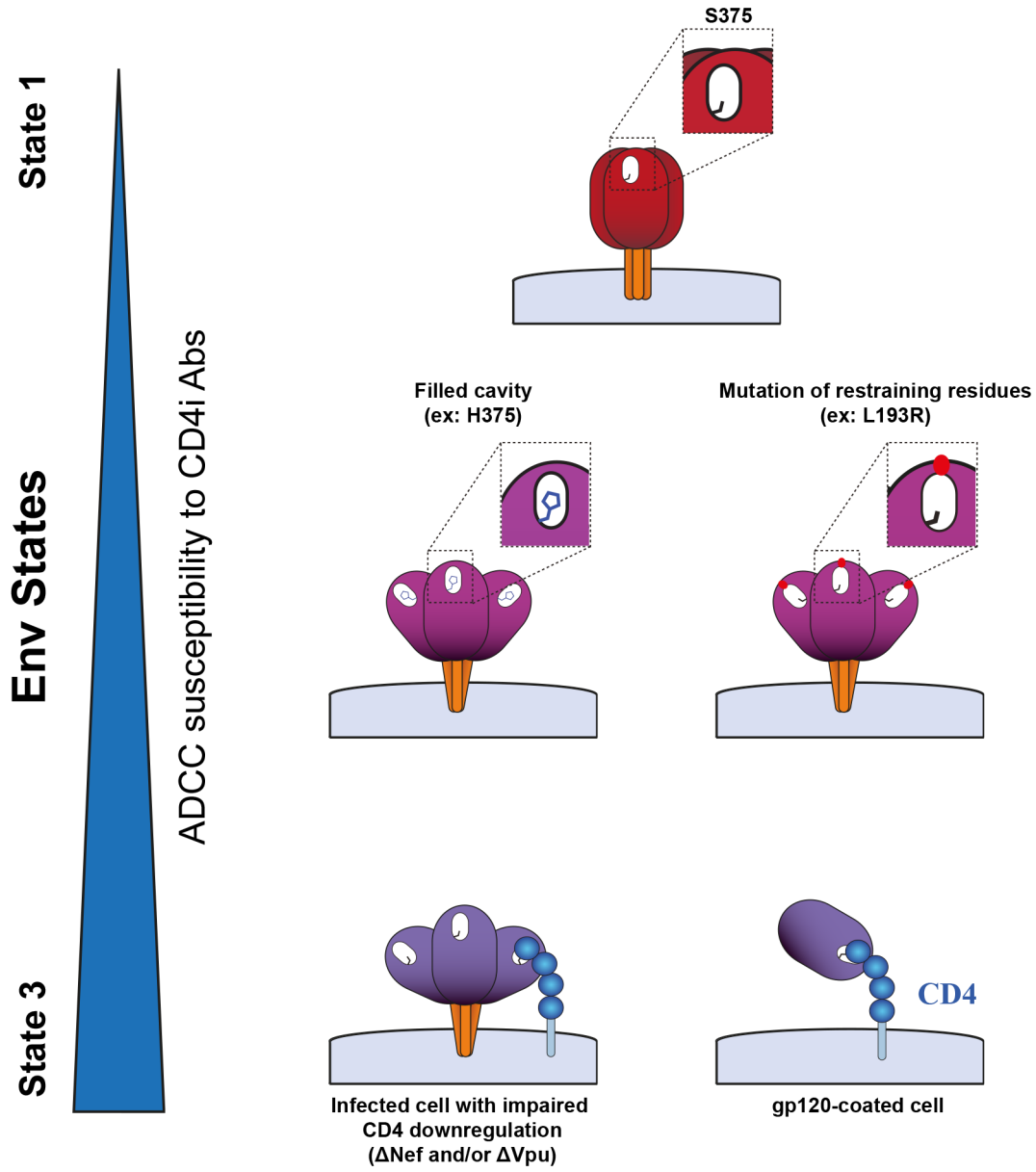

Figure 2. Impact of Env conformation on ADCC.

A small residue at position 375 in the Phe 43 cavity (shown in white) favors a closed (State 1) conformation. Larger hydrophobic residues at this position, such as histidine (H375), or mutations in restraining residues such as L193 shift Env to more open conformations. Env interactions with membrane-anchored CD4, due to Nef and/or Vpu deletion, stabilize State 3. This conformation is also sampled by monomeric gp120 bound to CD4, present at the surface of gp120-coated cells. Env conformational landscape modulates its opening and therefore the exposure of vulnerable epitopes recognized by ADCC-mediating CD4i Abs.

Table.

Summary of ADCC (or other Fc receptor-mediated antibody function) effects on infections with HIV-1 and related viruses.

Impact on Infection	Evidence	Results [refs.]
Protecting from acquisition	Passive infusion of non-neutralizing antibodies	Largely negative in preventing infection [126–135, 139]
		Possible impact on number of transmitted/founder variants [129, 132]
		Reduction of viral load in animals becoming infected [133]
	Correlations with vaccine-elicited antibody responses	ADCC associated with vaccine efficacy in some human and animal vaccine trials [77, 141, 103, 144–146, 148]
Modulating infection	Passive infusion of non-neutralizing antibodies	Infusion of polyclonal antibody can transiently decrease viremia [159]
	Correlations with vaccine-elicited antibody responses	ADCC activity shown to correlate with reduced viremia levels in some animals studies [155–158]
	Correlations with infection-induced responses	ADCC responses associated with disease progression in animals and humans [26, 154, 160–162]
Augmenting *in vivo* activity of neutralizing antibodies	Passive infusion of neutralizing antibodies	Fc-receptor engagement may improve protective effect of some antibodies and not others [150–152, unpublished]
		Fc-receptor engagement contributes to reduced viremia in infected animals and humans [165]