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Commentary

The Yin and Yang of ADCC-Mediating Antibodies

Marjorie Robert-Guroff

Vaccine Branch, National Cancer Institute, 41 Medlars Drive, Building 41, Room D804, Bethesda, MD 20892-5065, United States

Antibodies mediating antibody-dependent cellular cytotoxicity (ADCC) have been of increasing interest since their identification as a protective immune correlate in the RV144 clinical vaccine efficacy trial (Haynes et al., 2012). Earlier studies associated these non-neutralizing antibodies with protection against HIV infection and disease progression in both humans and non-human primates (for review see Vargas-Inchaustegui and Robert-Guroff, 2013). Therefore it is somewhat surprising to find them now linked to HIV pathogenesis. HIV disease progression is marked by a gradual loss of $CD4^+$ T cells during which a small proportion of HIV-infected $CD4^+$ T cells and a much larger proportion of uninfected "bystander" $CD4^+$ T cells are killed. While numerous mechanisms have been described for infected cell killing, the mechanism of bystander killing has remained controversial. In this issue, Richard et al. (2016) attribute bystander killing largely to antibodies mediating ADCC. They further suggest that a small CD4 mimetic developed by the Sodroski group might be used to alter this pathogenic mechanism for therapeutic benefit. How can the conflicting findings regarding ADCC antibodies be explained? And what caveats should be considered in using CD4 mimetics?

As reported by Richard et al. in this issue of *EBioMedicine*, the external envelope of HIV is labile and continually sheds the gp120 component which then binds the primary viral receptor, CD4, on bystander uninfected T cells. A subsequent conformational change opens the co-receptor binding site exposing an epitope recognized by cluster A antibodies, including the prototypic ADCC-mediating monoclonal antibody, A32. Killing of the bystander $CD4^+$ T cells follows. Concurrently, the virus subverts killing of infected cells by down-regulating CD4, inhibiting tetherin, and internalizing Env (as cited in von Bredow et al., 2015). Consequently, less Env is expressed on the infected-cell surface, less CD4 is available to complex with gp120, and less expression of Env in the open conformation occurs. Thus ADCC killing of the infected cell is diminished in favor of bystander killing.

CD4 mimetics were previously shown to interact with the viral envelope, inducing conformational changes, exposing the co-receptor binding site, and rendering the virus susceptible to neutralization by CD4-induced antibodies (Madani et al., 2008; Madani et al., 2014). The Finzi laboratory also previously reported that gp120/CD4 binding within the same infected cell led to exposure of ADCC epitopes (Veillette et al., 2014) and that the CD4 mimetic sensitized infected cells to ADCC killing (Richard et al., 2015). In the current paper they show that the mimetic decreases binding of shed gp120 to bystander CD4 cells, inferring that less ADCC-mediated killing of these uninfected cells will result. They also suggest that binding of the mimetic to envelope remaining on the infected cell surface should "redirect" ADCC-mediating antibodies to the infected cell away from bystanders, as stated above. Recent support of this hypothesis showed ADCC killing of primary HIV-infected T cells was enhanced *in vitro* by co-culturing with the CD4 mimetic (Lee et al., 2015).

The current study was conducted primarily with the A32 antibody, together with a small number of sera from HIV-infected individuals. ADCC antibodies are among the first elicited following infection, as the gp120–CD4 interaction leads to exposure of cluster A epitopes. Not all such CD4-induced epitopes elicit equivalent ADCC activities, due to subtle differences in antibody-epitope recognition and/or Fc differences (Gohain et al., 2015). Moreover, antibodies targeting other Env sites, including some with neutralizing activity such as 2G12 and b12, also mediate ADCC. The relative abundance of all these antibodies in the human sera tested was not determined. Further, the degree of gp120 shedding and levels of CD4 and Env present on the cells tested *in vitro* compared to uncultured, primary HIV-infected cells was not reported. It will be critical to confirm the observations made with *in vivo* studies using the SHIV model. Similarly, the *in vivo* effects of CD4 mimetic administration must be determined. It is an obvious therapeutic candidate, however, the possibility that it might facilitate greater CD4-independent infection must be considered.

Vaccine-elicited ADCC antibodies recognizing cluster A epitopes might well be protective, as they target an early epitope uncovered during virus transmission. Use of the CD4 mimetic in vaccine design might also stimulate development of such ADCC-mediating antibodies. However, if incomplete protection and break-through infection occurred following administration of such a vaccine, accelerated CD4 T cell loss and disease progression might occur by the mechanism reported by Richard et al.. To circumvent this possibility, vaccine design should include several immune targets to achieve balanced protection against HIV infection.

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