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Commentary

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Blocking HIV-1 replication: are Fc–Fcγ receptor interactions required?

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Interactions between IgG Fc and its receptors (FcγRs) have been shown to augment broadly neutralizing Ab–mediated (BnAb-mediated) protection from simian-human immunodeficiency virus (SHIV) challenge. In the current issue of the *JCI*, Parsons and collaborators compared the BnAb PGT121 with a version engineered to have impaired FcγR binding for their ability to protect macaques from an intravenous challenge with SHIV-infected cells as well as to treat already infected animals. Unexpectedly, and in contrast to previous studies, both versions of the Ab were equally able to prevent infection and decrease viral loads in infected animals. Thus, FcγR engagement does not always improve the in vivo antiviral activity of BnAbs.

Need for non-neutralizing Abs with antiviral activity

Abs are highly effective at preventing viral infections. For most viruses, including the lentiviruses human immunodeficiency virus type 1 (HIV-1) and the simian–HIV-1 (SHIV) chimeric virus (1), protection can be attributed largely to the ability of Abs to neutralize virus infectivity. Neutralization occurs when the Fab segment of the Ab molecule binds to vulnerable areas on the virus, thus inhibiting critical interactions between the virus and the host. Unfortunately, immunization strategies have been unsuccessful at eliciting Abs capable of neutralizing the broad array of circulating HIV-1 strains. This lack of success has led to an interest in exploiting easier-to-elicit non-neutralizing Abs that nonetheless have antiviral activity.

The antiviral activity of non-neutralizing Abs is mediated through interactions between the Fc segment of Ab and either complement or Fc receptors found on a number of cells involved in host defense. Complement-mediated lysis of virus or infected cells, Ab-dependent cellular cytotoxicity (ADCC), Ab-dependent phagocytosis, and the production of antiviral chemokines or cytokines are all non-neutralizing Ab functions with the potential to prevent or control infection. Whereas there is correlative evidence suggesting a role for non-neutralizing Abs in protecting humans and nonhuman primates from lentivirus infections, passive infusion studies that directly address such a role have largely demonstrated minimal, if any, protective effect.

Nonetheless, direct evidence, first reported by Hessell et al. in 2007, implicates interactions between IgG Fc and its receptors (FcγRs) in the optimal in vivo protective effect of neutralizing Abs. Thus, while neutralizing Abs can prevent infection in the absence of FcγR engagement, they do so less efficiently than when such engagement is allowed to occur (2, 3).

Efficiency of the neutralizing Ab PGT121

In the current issue of the *JCI*, Parsons and collaborators (4) further explored the requirement for Fc-FcγR interactions in protecting nonhuman primates from SHIV acquisition by using a very potent BnAb, PGT121. They compared the protective capacity of PGT121 with that of a variant that has mutations in the Fc region that largely eliminated binding to FcγRs (PGT121 LALA). Surprisingly, and quite different from what was observed by Hessell et al., both versions of the Ab were able to prevent 100% of infections following a robust intravenous challenge with SHIV-infected cells. Thus, the ability of PGT121 to prevent infection was not improved by FcγR-mediated antiviral Ab activities. Consistent with this finding, the authors demonstrated that depleting NK cells, which are potent effectors of ADCC, had no effect on protection. At least for the doses of Ab given and the type of challenge utilized, it appears that the neutralizing activity of PGT121 alone is sufficient for maximal protection.

Perhaps an even more surprising result reported by Parsons et al. was that PGT121 and PGT121 LALA had the same transient effect on viremia in animals with established infection. Moreover, there was no difference between the two versions of PGT121 in the amount of viral DNA found within the cells of the infected animals. Other studies have suggested that, similar to preventing infection, Fc-mediated effector functions add to the in vivo potency of neutralizing Abs in controlling existing infection (2, 3, 5–8). Such an effect would likely be most apparent when measuring viral DNA in cells, since FcγR engagement of NK cells or macrophages, in contrast to virus neutralization alone, might be expected to take out infected cells. However, it should be noted that Parsons et al. did not find any reduction in viral DNA after treatment with either variant of PGT121. This is in marked contrast to what was reported by Barouch et al. (5), who demonstrated a substantial decrease in viral DNA after treatment with PGT121; the LALA version of PGT121 was not evaluated in that study.

Discrepancy in results explored

How can the results presented by Parsons and colleagues be reconciled with previous studies showing the importance of

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Fc-mediated effector functions for protection and therapeutic benefit? One possible explanation is that Parsons et al. chose to challenge animals with infected cells, rather than the more conventional challenge with cell-free virus used by Hessell et al. One could speculate that the potent neutralizing activity of PGT121, combined with some innate, Ab-independent immune response recognizing the foreign cells used for the challenge, was highly effective in preventing infection. However, it is unlikely that such an explanation underlies the lack of difference between PGT121 and its LALA variant in controlling existing infection, since the allogeneic infected cells would have been long gone. It is also plausible that the neutralization potency of a given Ab might dictate the requirement of Fc-mediated effector functions in antiviral activity in vivo. PGT121 is several-fold more potent than b12, the mAb used by Hessell et al. Therefore, it is possible that for a very potent BnAb, Fc-mediated effector functions might not be absolutely necessary to afford maximum protection, since its neutralizing activity alone is potent enough to prevent or control infection. However, a less potent Ab such as b12 might require the additional oomph provided by Fc-FcγR interactions. One might predict, then, that using a lower dose of PGT121 would yield differences between the Ab variants.

Parsons et al. certainly call into question the role of Fc-FcγR interactions in preventing and modulating lentivirus infections, at least in the particular setting of a very potent neutralizing Ab and an intravenous challenge with infected cells. Their results also underscore the importance of virus neutralization in developing HIV vaccines and immunotherapies.

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