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Challenges of antibody-mediated protection against HIV-1

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Enthusiasm for a role of antibodies in protection against HIV-1 has waxed and waned over the 25-year search for an AIDS vaccine. However, it is now clear that antibodies not only contribute to the control of infection once it is established [1,2], as a series of seminal passive immunization studies in nonhuman primates (NHPs) going back almost 20 years show unequivocally that antibodies can prevent infection with model AIDS viruses [3–14]. These latter observations are currently driving an intense effort to identify epitopes recognized by broadly neutralizing monoclonal antibodies (mAbs) to serve as templates for AIDS vaccine design. To this end, a handful of broadly neutralizing mAbs have been successfully vetted in passive immunization studies in NHPs using SHIVs that are model simian immuno-deficiency viruses (SIV) in which the SIV envelope glycoprotein (Env) is replaced by a HIV-1 Env glycoprotein. The Env glycoprotein is the only HIV-1 protein known to be recognized by neutralizing antibodies. These studies show that SHIV infection can be blocked by individual mAbs specific for epitopes associated with distinct regions of the HIV-1 Env protein. These include the CD4-binding site [9,15] and high-mannose oligosaccharides [7,16] of gp120, as well as the membrane proximal region of gp41 [17]. It should be noted that while individual mAbs can be effective, mAb mixtures [7,18] or neutralizing sera [19,20] might be more potent. Collectively, these studies strongly argue that the correct antibodies can mediate sterilizing (i.e., transmission-blocking) immunity to HIV-1 and that an AIDS vaccine must elicit such antibodies to be effective. There are three key challenges to the development of an ‘antibody-based’ vaccine that are potentially solvable with the experimental tools currently in hand.

Identification of epitopes recognized by broadly neutralizing antibodies

Extreme genetic diversity is a hallmark of retroviral infections, including HIV-1, which surfaces as a significant and long-recognized antigenic diversity problem in AIDS vaccine development [21–25]. For example, there are 12 distinct clades (genetic subtypes) of HIV-1

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[26,27] whose Env proteins are only approximately 70% homologous, showing only slightly less variation within a clade. While clade diversity is not congruent with epitope diversity, no single broadly neutralizing mAb or broadly neutralizing antiserum blocks infectivity of all isolates (reviewed in [24]). Fortunately, recent technological developments in the isolation of human mAbs from circulating B cells in HIV-infected individuals [28–32] are starting to yield new mAbs of significant neutralization breadth. Most recently, two mAbs, PG9 and PG16, were isolated from the memory B cells of a HIV-1-infected individual that neutralize over 70% of a diverse cross-clade reference panel of HIV-1 isolates [31]. These mAbs recognize a new epitope (or epitopes) that is (are) dependent upon the V2 and V3 regions of gp120 in addition to its glycan structures. It is important to note that these two mAbs hold the current record for neutralization breadth. The ability to isolate such mAbs using new high-throughput methods augurs well for the prospect of identifying new epitopes associated with neutralization breadth to serve as templates for vaccine design. However, there is a caveat of this approach that is not widely recognized outside the field.

Owing to the high-throughput requirement of screening, standardized cell line-based neutralization assays must be employed that might not faithfully recapitulate the neutralization potencies of mAbs (or immune sera) when they are evaluated on assays using peripheral blood mononuclear cells as targets [33–35]. Thus, potentially important neutralizing antibodies might be missed when focusing only on cell line-based assays. This is not an indictment of cell line-based assays as it is clear that no single assay format detects all activities [36] and there are insufficient data correlating protection *in vivo* with neutralization measured in the different assay formats to decide which is superior. Indeed, several NHP vaccination studies have demonstrated correlations between protection and antibody responses that do not score well in conventional neutralization assays [37–39]. This issue is subject to intense study across many laboratories and the boundary conditions for the interpretation of neutralization assays should emerge over the next few years. This information will be essential in the refinement of immunogens to elicit broadly neutralizing antibodies.

Understanding the mechanisms of antibody-mediated protection

It has long been accepted that an antibody that neutralizes HIV-1 potently in an *in vitro* assay will also protect against a neutralization-sensitive virus *in vivo*. Indeed, several studies have demonstrated a good correlation between neutralization potency *in vitro* and the degree of sterilizing protection *in vivo* using passive immunization models [3,40–44]. This picture was rendered more complex by a seminal study demonstrating the importance of Fc-mediated effector function in the ability of the CD4-binding site mAb, b12, to mediate sterilizing protection against a pathogenic SHIV challenge [45]. In that study, the Fc region of mAb b12 was mutagenized to abrogate Fc-mediated effector functions such as antibody-dependent cell-mediated cytotoxicity [46] and antibody-dependent cell-mediated viral inhibition (ADCVI; reviewed in [47]) while preserving neutralization potency *in vitro*. Abrogation of Fc-mediated effector function in this mAb compromised its ability to mediate sterilizing protection against SHIV *in vivo*, although some protective potency was retained [45]. This seminal study and a follow-up study using a more clinically relevant virus challenge model [15] provide the most direct evidence to date that biological mechanisms in

addition to neutralization are important in antibody-mediated protection against the transmission of SHIV *in vivo*.

As already mentioned, several studies have demonstrated correlations between non-neutralizing antibodies (as measured in conventional neutralization assays) and protection against SIV/SHIV transmission in NHPs [37–39,48]. Most interestingly, a similar correlation in the Vax-004 trial using ADCVI as the readout was reported for a subset of HIV-1-resistant subjects defined by Fc-receptor polymorphisms [49], although global efficacy was not found in that study. Taken together, these observations have renewed interest in defining the mechanisms of antibody-mediated protection. In addition to the Fc-mediated effector functions listed earlier, there are data suggesting that protective antibodies might act by aggregating virus in mucosal fluids, blocking transcytosis across epithelial barriers [50] and complement-mediated virolysis [51], although the latter mechanism was not supported by b12 mutagenesis [45].

Solving the ‘persistence’ problem

The poor persistence of ongoing anti-Env antibody responses (serological memory) in the absence of continuous antigenic stimulation is a sleeping giant that confronts the development of an antibody-based AIDS vaccine ([28,52] and reviewed in [24]). Passive immunization studies show that there is approximately a 24-h window for an antibody to mediate protection against virus exposure [53,54]. This suggests that antibody responses elicited by a vaccine must persist at protective levels as long as the recipient is engaging in behavior associated with exposure to HIV-1. Poor serological memory is potentially a major problem in the deployment of antibody-based vaccines. Poor persistence of anti-Env antibody responses was observed in the early days of antibody-based diagnostics development [55] and it has repeatedly surfaced in clinical trials of Env-based subunit vaccines [24]. The poor persistence of anti-Env antibody responses in the absence of continuous antigenic stimulation contrasts with protective antibody responses to common vaccine antigens such as diphtheria and tetanus toxoids (among others) where serological memory can persist for years after immunization [56]. The nature of this problem has not been studied systematically but it is almost certainly an outcome of the unusual structural aspects of the HIV-1 Env glycoprotein that is heavily glycosylated (reviewed in [57]) and conformationally plastic [58,59]. The poor persistence of anti-Env responses without continuous boosting is probably due to the poor ability of Env to elicit antibody responses characterized by the long-lived plasma cells in the bone marrow (reviewed in [60]) that are characteristic of persistent serological memory. Whether this is due to unusual helper T-cell responses to Env, the B-cell subset addressed by Env, or both of these variables remains to be determined, as do the relationships among these variables and Env structure. It is interesting to note that the persistence problem appears to have surfaced recently in the RV144 study where modest efficacy was demonstrated for the first time in an AIDS vaccine trial [61].

That study employed a combination immunization strategy using gp120 expressed by a poxvirus vector in conjunction with a subunit gp120 matched to locally circulating clades of HIV-1 [61]. Modest but significant protection against transmission was observed that waned

over time [61], much in the same way as anti-Env antibody responses do to these types of immunogens [24]. While it is currently conjecture that this protection is antibody-based and that it wanes in lock step with anti-Env antibody responses, its temporal dependence is strongly suggestive of the poorly persistent antibody responses typically elicited by Env immunogens. In order to determine whether this is so, further study is required.

Conclusion

Currently, an antibody-based strategy is the only track to a preventative AIDS vaccine that is supported by direct experimental evidence from passive immunization studies. As such, the pace of this strategy is impacted by the three aforementioned developmental challenges and it is difficult to know when (or even if) these problems can be solved. Despite these uncertainties, there is renewed optimism that an effective AIDS vaccine can be developed. This optimism is due to success in the RV144 vaccine trial [61], along with a confluence of new information on the specificity and mechanisms of antibody-mediated protection against HIV-1, the development of new tools to study antibody responses, and the strong ability to translate new findings into clinical trials. It will be interesting to take stock of these three challenges over the next few years as there now appears to be light at the end of the long tunnel to an AIDS vaccine.

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