Back to primary school

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ATTACK by the human immunodeficiency virus on T cells involves binding of the viral envelope gp (for glycoprotein) 120 subunit to the cells' CD4 receptor. Binding is followed by fusion of virus and cell, the first step in the viral replication cycle. Because gp120 is central to this process, using gp120 subunit vaccines to generate neutralizing antibodies against HIV-1 has been at the forefront of vaccine strategies for many years. Yet there has been vigorous debate about whether such an approach will work.

That debate now takes on a new dimension with the appearance of a paper by Sullivan *et al.* in *Journal of Virology*¹. In general, the findings bear on the issue of the relative resistance of primary strains of HIV-1, as opposed to strains highly passaged *in vitro*, to neutralizing antibodies, and whether such variable resistance is real or an assay-dependent artefact. In particular, the new results may help explain why antibodies raised to current monomeric gp120 vaccines do not neutralize primary viruses^{2,3}.

Neutralization

Sullivan *et al.* have measured the interactions of monoclonal antibodies (mAbs) with the native, oligomeric forms of the HIV-1 envelope glycoproteins, found on virions and virus-infected cells, and compared the results with levels of virus neutralization. They draw various conclusions. First, they confirm that mAb interactions with monomeric gp120 do not predict the extent of virus neutralization⁴. Second, they take things further and show that mAb reactivity with oligomeric glycoprotein is a good correlate of neutralization, which is consistent with observations on HIV-1 LAI from Sattentau and myself⁵.

The third conclusion is that mAbs don't bind nearly as well to oligomers from primary viruses as to oligomers from strains whose envelope glycoproteins have been altered by passage in T-cell lines *in vitro*^{1,6,7}. The relative inaccessibility of neutralization sites on primary viruses, including the V3 loop, combined with Sullivan and colleagues' observation that such viruses have a greater density of surface glycoproteins, may account for much of the mechanism behind neutralization resistance. HIV-1 has presumably evolved these defences to counter the abundant antibodies raised against it in infected humans, perhaps at the expense of some loss of replication efficiency^{1,4}. As disease progresses and the immune system collapses, the more virulent strains that can emerge may need less protection.

Resistance of primary virus to neutralization

was first documented from studies on soluble CD4 (sCD4)⁸, and is known to be a function of the oligomeric structure of the envelope glycoproteins⁹. But it has not been widely appreciated that resistance to neutralization by antibodies probably has the same basis, in that sCD4 resistance is an indirect consequence of a more natural phenomenon. Soluble CD4 strongly neutralizes strains of HIV-1 adapted to T-cell lines; yet it increases the infectivity of certain strains of simian immunodeficiency virus and HIV-2¹⁰, which led to the proposal that SIV's capacity for fusing with a cell ('fusogenicity') is activated by binding of CD4¹¹.

It now seems clear that HIV shares this property. Sullivan *et al.* show that sCD4 has a biphasic effect on the fusogenicity of two strains of primary HIV-1, increasing it at low concentrations, but inhibiting it at higher concentrations as gp120-sCD4 complexes are stripped from the virus. Schutten *et al.*¹² have also observed sCD4-enhanced fusogenicity of primary HIV-1 clones. Previous studies with sCD4 helped create the perception that the envelope glycoproteins of HIV-1 were in some critical way different to those of other primate lentiviruses. But it now seems clear that the anomalous viruses are the highly adapted strains of HIV-1 such as LAI and MN, not HIV-1 *per se* — a lesson we are learning, once again, the hard way.

Yet perhaps even more striking are results stemming from Sullivan and colleagues' experiments with a human mAb (F105) to a complex gp120 epitope near the CD4-receptor binding site. F105, they find, not only fails to neutralize a primary strain of HIV-1, but actually increases its infectivity. It does, however, effectively neutralize strains that are adapted to T-cell lines.

These observations are akin to those with sCD4 — by binding to an epitope overlapping the CD4-binding site, an antibody seems to be able to trigger some of the fusion-activating conformational rearrangements in the viral envelope. As different mAbs to this epitope cluster induce different conformational changes in gp120 monomers, whether an antibody mediates activation of fusion^{1,12}, or neutralization^{1,4}, might be a subtle function of the geometry of its epitope in relation to the CD4-binding site. Schutten *et al.*¹² have also shown that two other human mAbs to CD4-binding-site epitopes, and one to the V3 loop, increase the fusogenicity of a primary HIV-1 clone; the latter finding is in itself notable, for there is a growing understanding that the V3 loop is not the principal neutralizing determinant for primary viruses.

What are the implications of all this for vaccine development? Several high-quality, monomeric gp120 vaccines have been tested in humans. One advantage of the correctly folded forms of these proteins has been their ability to induce antibodies to the complex epitopes surrounding the CD4 binding site; indeed rodent mAbs have been raised against gp120 that are indistinguishable from antibodies made in infected humans¹³. Yet although sera from gp120-immunized animals and humans neutralize viruses adapted to T-cell lines, they are inactive against primary strains of HIV-1^{2,3}.

Infectivity

There is, as yet, no evidence that the increase in infectivity mediated by F105-like antibodies contributes to such lack of activity, but the possibility should now be considered. We have found that many sera from HIV-1 infected humans, selected for high titres of anti-gp120 antibodies, weakly increase the infectivity of primary HIV-1 strains; other sera merely lack net neutralizing activity (Y. Cao *et al.*, unpublished data). Perhaps F105-like antibodies contribute to this effect by counteracting, wholly or in part, any neutralizing antibodies present (although the involvement of antibodies that increase infectivity in more conventional ways¹⁴ should not be discounted).

The present generation of monomeric gp120 immunogens seems unable to breach HIV-1's defences, and Sullivan *et al.* show just how formidable is the wall that lies across the path to an antibody-mediated, anti-HIV vaccine. We now must decide whether to blast a way through this barrier, subtly undermine it or even choose another route entirely. But brute force is rarely the answer, so the need for a large and costly infrastructure to evaluate the available gp120 vaccines should be reconsidered. □

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