modes of imbalance in the ice sheet. Some will have their origin in contemporary climate change, but others will not. Furthermore, the future development of each mode of change may be quite different; the fact that one contribution is greater than another at the moment does not mean that it will continue to be so. For example, if snowfall rates were to revert to their 1991 level, thickening in East Antarctica might cease immediately; on the other hand, if the observed thinning in West Antarctica is accelerating, as one study has suggested (*12*), then that could dominate. Evaluating and understanding each mode of change is the first step toward producing defensible predictions for the whole of Antarctica.

The current thickening in East Antarctica is not sufficient to completely stop sea level rise. It might, in the short term, counteract one of the other contributions, such as the melting of the Greenland ice sheet. But the remaining contributors—melting of nonpolar glaciers, thermal expansion of the oceans, and groundwater changes—will be sufficient to produce sea level rise over the coming decades and centuries, regardless of any thickening that might occur in East Antarctica.

To respond appropriately to the threat of sea level rise, policy-makers urgently need accurate predictions of sea level rise as the sum of all its contributions. Davis *et al*. (*1*) provide the first observation-based estimate of one important contribution, that of the East Antarctic ice sheet. This is a huge step forward, but to reduce our uncertainty, much work is required to determine the underlying cause and likely future of each and every contribution, both positive and negative, in Antarctica and elsewhere.

References

1. C. H. Davis, Y. Li, J. R. McConnell, M. M. Frey, E. Hanna, *Science* **308**, 1898 (2005); published online 19 May 2005 (10.1126/science.1110662).
2. D. J. Wingham, A. J. Ridout, R. Scharroo, R. J. Arthern, C. K. Schum, *Science* **282**, 456 (1998).
3. A. Shepherd, D. J. Wingham, J. A. D. Mansley, H. F. J. Corr, *Science* **291**, 862 (2001).
4. J. A. Church *et al.*, in *Climate Change 2001: The Scientific Basis*, J. T. Houghton *et al.*, Eds. (Cambridge Univ. Press, Cambridge, 2001), pp. 583–638.
5. A. Shepherd, D. J. Wingham, J. A. D. Mansley, *Geophys. Res. Lett.* **29**, 1364 (2002).
6. E. J. Rignot, D. G. Vaughan, M. Schmeltz, T. Dupont, D. R. MacAyeal, *Ann. Glaciol.* **34**, 189 (2002).
7. A. J. Payne, A. Vieli, A. Shepherd, D. J. Wingham, E. Rignot, *Geophys. Res. Lett.* **31**, L23401 (2004).
8. J. O. Stone *et al.*, *Science* **299**, 99 (2003).
9. A. M. Smith, D. G. Vaughan, C. S. M. Doake, A. C. Johnson, *Ann. Glaciol.* **27**, 113 (1998).
10. H. De Angelis, P. Skvarca, *Science* **299**, 1560 (2003).
11. I. Joughin, S. Tulaczyk, *Science* **295**, 476 (2002).
12. R. Thomas *et al.*, *Science* **306**, 255 (2004).

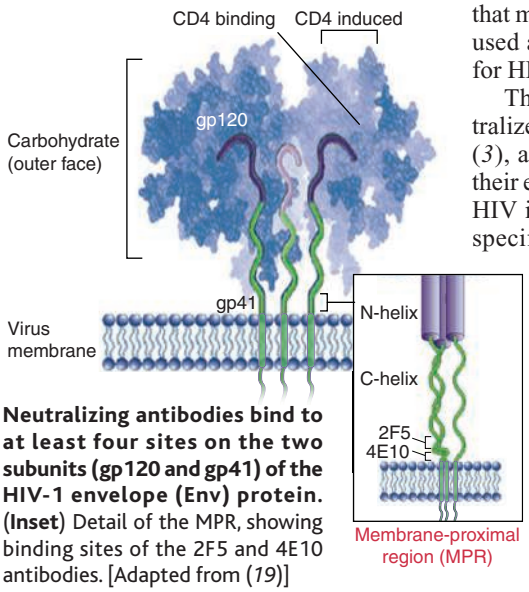
10.1126/science.1114670

IMMUNOLOGY

Close to the Edge: Neutralizing the HIV-1 Envelope

Gary J. Nabel

Human immunodeficiency virus–1 (HIV-1) has infected more than 60 million people worldwide. Nonetheless, there have been few, if any, instances of infected individuals naturally developing protective immunity to the virus. Although cellular immunity (in which HIV-specific immune cells attack and destroy the virus) can help to control HIV infection, the development of a completely effective AIDS vaccine will likely require neutralizing antibodies that react with the diverse strains of this virus. The HIV-1 envelope (Env) glycoprotein contains at least four sites for such antibodies: The first is the binding site for CD4, the T cell protein through which HIV infects these immune cells; the second is a region on Env formed after it binds to CD4, which then interacts with a chemokine receptor in the next step of HIV infection; the third are carbohydrates on the outer face of Env; and the fourth is the region of Env adjacent to the viral membrane, the so-called membrane-proximal region (MPR) (see the first figure). The MPR is particularly attractive as an antibody target because it facilitates viral entry into T cells and is highly conserved among viral strains. Two recent papers provide insights into this antiviral target, at the same time raising several concerns. On page 1906 in this issue, Haynes *et al*. (*1*) report the unexpected result that two well-described antibodies directed against MPR, 2F5 and 4E10, react with self-antigens, including cardiolipin, a phospholipid to which antibodies are formed in lupus and other autoimmune diseases. These antibodies react with their SP41 epitopes 10 to 100 times better than with cardiolipin. A second study, by Trkola *et al*. in *Nature Medicine* (*2*), evaluated the antiviral responses of HIV-infected individuals treated with antibodies 2F5 and 4E10 plus the 2G12 antibody, which targets an unrelated carbohydrate structure. Their data showing lack of response to these antibodies suggest that the MPR region may not be very accessible to 2F5 or 4E10 neutralization in vivo. Together, these studies suggest challenges that must be overcome if the MPR region is used as a target of neutralizing antibodies for HIV vaccines.

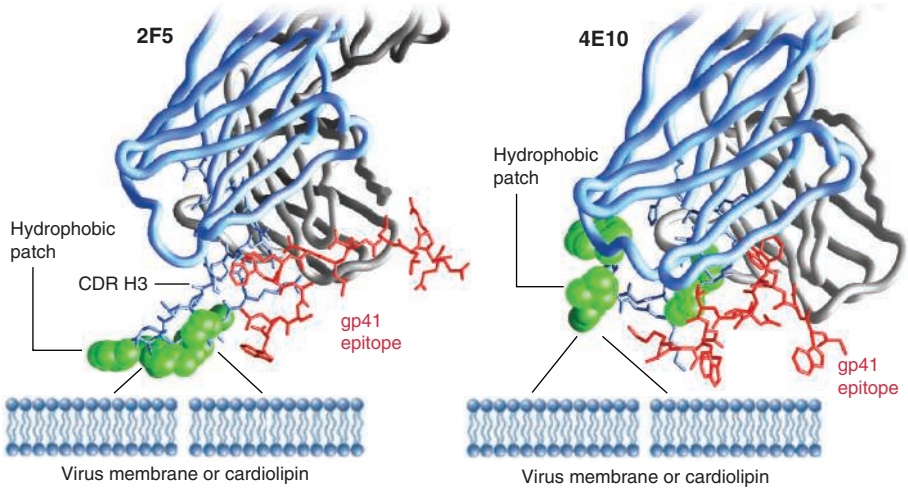


Neutralizing antibodies bind to at least four sites on the two subunits (gp120 and gp41) of the HIV-1 envelope (Env) protein. (Inset) Detail of the MPR, showing binding sites of the 2F5 and 4E10 antibodies. [Adapted from (*19*)]

The 2F5 and 4E10 antibodies can neutralize viruses from multiple HIV-1 clades (*3*), and this characteristic has prompted their evaluation for both AIDS vaccines and HIV immunotherapy. Antibodies with this specificity appear infrequently in nature, however; in fact, 2F5 and 4E10 were identified through screening of recombinant antibody libraries. They have also been difficult to detect in serum samples from HIV-1–infected individuals. The results from Haynes *et al*. may explain why. 2F5 and 4E10 interact with autoantigens at affinities similar to those of antibodies associated with autoimmune disease. These findings may account for the low frequency of these antibodies in natural infection, because they would normally be deleted during development of the immune system. Their reactivity with self-antigens also suggests that such antibodies would not be easily elicited by vaccination.

Antibodies to self-antigens have been identified in a variety of diseases, but they do not always cause the underlying autoimmune disease. For example, autoreactive antibodies are causally implicated in myasthenia gravis, pernicious anemia, and Goodpasture's syndrome, where passive

The author is with the Vaccine Research Center (VRC), National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA. E-mail: gnabel@nih.gov



Model of antibody interaction with HIV Env. The proposed interaction of the hydrophobic patch on the CDR loop (green) of antibody 2F5 (**left**) or HE10 (**right**) with the viral membrane or cardiolipin is independent of the peptide binding domain of the gp41 subunit of Env (red). The structures of 2F5 and 4E10 bound to their cognate peptides are from (*4*) and (*6*).

transfer of specific antibodies can reproduce symptoms of the disease. In other autoimmune conditions, such as systemic lupus erythematosus, scleroderma, and rheumatoid arthritis, autoantibodies are a manifestation of an underlying immune response to unrelated antigens of unknown etiology. So it is conceivable that 4E10 and 2F5 may predispose to autoimmunity, although the animal data in favor of this possibility are not compelling. Further, Trkola *et al*. report no adverse events in their studies of humans treated with high, sustained concentrations of both antibodies for several weeks (*2*).

And what of the interaction of these antibodies with the highly lipophilic molecule cardiolipin? A structural study by Ofek and co-workers suggests a possible mechanistic explanation for this finding for 2F5 (*4*). They examined the structure of 2F5 bound to its peptide target and discovered a long complementarity-determining region (CDR) loop on the antibody. A hydrophobic patch of amino acids (Phe, Val, Ile, Leu) at the end of this loop interacts with both the target peptide and adjacent viral membrane (see the second figure, left panel). Mutation of the Phe residue decreases the neutralizing activity of 2F5, and membrane interaction enhances the antibody's reactivity with MPR (*5*). Whether this CDR loop also interacts with cardiolipin, itself a membrane-associated phospholipid, can be addressed by examining whether 2F5 with a mutation in the hydrophobic patch will bind to cardiolipin. Likewise, the crystal structure of 4E10 and its target peptide shows that this peptide adopts a helical conformation in the context of a hydrophobic surface of this immunoglobulin (*6*) (see the second figure, right panel). The 4E10 binding pocket itself is extremely hydrophobic, a property that might promote binding to other hydrophobic antigens.

One would expect strong negative selection against long or hydrophobic, autoreactive CDR regions that interact with lipid surfaces, possibly accounting for the rare occurrence of MPR-specific antibodies during immune cell selection (*7*–*15*). The few individuals with such autoimmune conditions may show relative protection from HIV infection, as suggested anecdotally for patients with systemic lupus (*16*–*18*). Another important consideration is whether specific immunization strategies will be needed to generate such potentially autoreactive antibodies.

If such antibodies can be generated, will they be able to access and neutralize the MPR? Maybe not. In the study by Trkola *et al.* (*2*), patients received passive infusion of monoclonal antibodies 2F5, 4E10, and 2G12, but there was no lasting effect on the virus. In the one instance where the virus was initially controlled but then escaped, mutations arose not to 2F5 or 4E10 epitopes but to the 2G12 epitope, which has more limited reactivity and is outside the MPR. The half-life of 2F5 in vivo was shorter than that of 2G12, but whether this resulted from 2F5 reactivity to self-antigens is not known. Alternatively, these antibodies may not have exerted an antiviral effect because the MPR is not accessible on the virus or is masked during cell-to-cell transfer of virus.

These studies have several implications. First, we knew that neutralizing antibodies to the MPR were detected rarely; now Haynes *et al*. suggest that these antigens may be a challenging target for immunization, both because of their association with the lipid membrane and because they resemble self-antigens and so will tend to be subject to tolerance. Specific vaccination protocols may be needed to elicit such antibodies.

Second, in future studies with therapeutic antibodies, patients will need to be monitored for the development of autoimmune diseases. Although no such diseases have been described in previous nonhuman primate studies or in the study by Trkola *et al*., screening for autoimmunity should be performed in future trials designed to elicit or transfer such autoreactive antibodies. Such theoretical concerns should not, however, preclude empirical research that directly addresses whether these antibodies succumb to tolerance mechanisms.

Finally, the role that 2F5, 4E10, and other MPR antibodies may play in preventive vaccines has not yet been assessed. These antibodies could possibly be effective in circumstances where there is a cell-free virus transmission. The task will not be easy: Passive-transfer studies in nonhuman primates suggest that neutralizing antibodies can protect against infection but that relatively high levels of immunoglobulin are required. Such levels will be difficult to attain with current immunization approaches.

The development of highly effective vaccines and immune therapies for HIV-1 infection remains a pressing need for this devastating infectious disease. Although the highly variable HIV Env protein has devised a myriad of mechanisms to evade the neutralizing antibody response, few such highly conserved structures are as accessible to neutralizing antibodies. It would be premature to abandon this promising therapeutic target for HIV neutralization on the basis of the evidence presented by the new work. Forearmed with the knowledge of both the possibilities and the challenges, investigators can better address these critical questions.

References and Notes

1. B. F. Haynes *et al.*, *Science* **308**, 1906 (2005); published online 28 April 2005 (10.1126/science.1111781).
2. A. Trkola *et al.*, *Nat. Med.* 10.1038/nm1244 (8 May 2005).
3. J. M. Binley *et al.*, *J. Virol.* **78**, 13232 (2004).
4. G. Ofek *et al.*, *J. Virol.* **78**, 10724 (2004).
5. M. B. Zwick *et al.*, *J. Virol.*, **79**, 1252, (2004).
6. R. M. Cardoso *et al.*, *Immunity* **22**, 163 (2005).
7. Y. Louzoun *et al.*, *Bull. Math. Biol.* **65**, 535 (2003).
8. D. Nemazee, *Immunol. Today* **17**, 25 (1996).
9. H. Wardemann *et al.*, *Science* **301**, 1374 (2003).
10. D. Gay *et al.*, *J. Exp. Med.* **177**, 999 (1993).
11. S. L. Tiegs, D. M. Russell, D. Nemazee, *J. Exp. Med.* **177**, 1009 (1993).
12. D. A. Nemazee, K. Burki, *Nature* **337**, 562 (1989).
13. E. Meffre *et al.*, *J. Clin. Invest.* **108**, 879 (2001).
14. F. M. Raaphorst, C. S. Raman, J. Tami, M. Fischbach, I. Sanz, *Int. Immunol.* **9**, 1503 (1997).
15. E. Meffre *et al.*, *Nat. Immunol.* **1**, 207 (2000).
16. R. A. Fox, D. A. Isenberg, *Arthritis Rheum.* **40**, 1168 (1997).
17. R. Palacios, J. Santos, *Int. J. STD AIDS* **15**, 277 (2004).
18. R. T. Canoso, L. I. Zon, J. E. Groopman, *Br. J. Haematol.* **65**, 495 (1987).
19. M. B. Zwick *et al.*, *Nat. Med.* **10**, 133 (2004).
20. I thank P. Kwong and R. Wyatt for discussions and for use of graphic representations of Env and 2F5 structures; J. Mascola, R. Koup, and other VRC scientists for comments; and A. Tislerics, T. Miller, and B. Hartman for preparation of the manuscript.

10.1126/science.1114854