proposal has also been followed by other authors (*11*, *12*).

However, Mirica *et al.* demonstrate that upon phenol binding, a mode II species is converted to a mode III species (*1*). The latter subsequently performs the hydroxylation. Their advanced low-temperature experiments, supported by high-level density functional theory calculations, provide the first experimental proof for this species, contrary to earlier assumptions.

The finding of O–O bond breakage upon binding of the substrate (*1*) points to a potentially important mechanism through which enzymes can deal with small molecules. It remains to be shown whether such a reaction occurs in natural enzymes.

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OCEANS

How Does the Antarctic Ice Sheet Affect Sea Level Rise?

David G. Vaughan

The greatest uncertainty in predictions of future sea level rise lies in the contribution of the Antarctic ice sheet. To the first order, the annual snowfall on the ice sheet is balanced by loss to melting and iceberg calving. However, the equivalent of more than 5 mm of global sea level passes in and out of the ice sheet every year; therefore, even small imbalances between input and output will have a substantial impact on global sea level. Changes in surface elevation are currently the best indication of imbalance in the ice sheet. On page 1898 of this issue, Davis *et al.* (*1*) use altimeter measurements from the European remote sensing (ERS) satellites to compile the longest (11-year) record to date of surface elevation change over Antarctica.

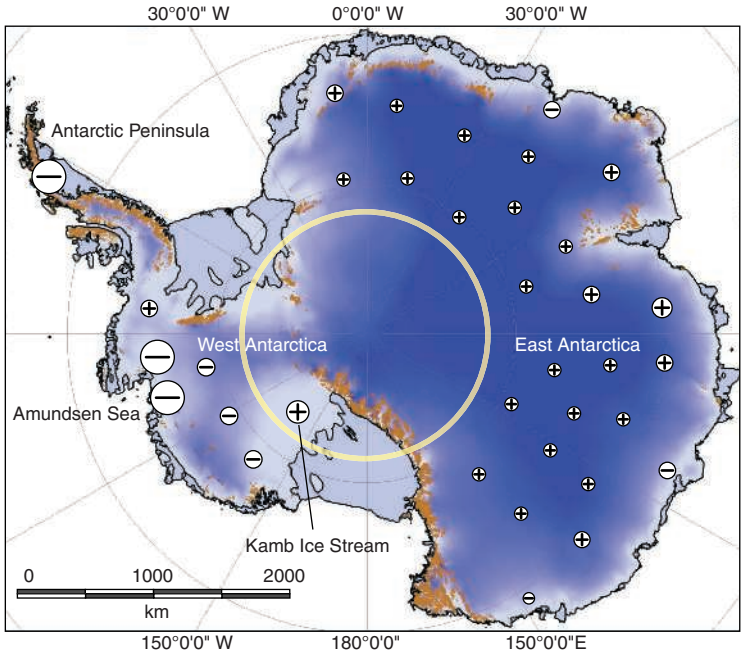
Before the launch of the ERS-1 satellite in 1992, imbalances in the Antarctic ice sheet were hypothesized, but could not be measured over wide areas with the existing technology. A series of studies using data from the ERS satellites (*2*, *3*) is revealing changes over wide areas with ever-increasing precision, demonstrating the value of an infrastructure for measurements of long-term change. Davis *et al.* now demonstrate imbalance in several areas of the ice sheet, but focus on the finding that the East Antarctic ice sheet is thickening (see the figure) (*1*). The thickening is small (1.8 ± 0.3 cm per year) but the area is vast, and its effect is to slow sea level rise by 0.12 ± 0.02 mm per year.

Using output from meteorological forecast models for the same period, Davis *et al.* show that the thickening is probably a result of increased snowfall. It may be premature to predict that the East Antarctic ice sheet will continue to thicken, but the measured change is roughly that expected as a mean response to 20th-century climate change (*4*). If this part of the ice sheet continues to grow—as general circulation model predictions suggest it should (*4*)—then this thickening may become a large negative term in the sea level change equation.

Thickening due to increasing snowfall appears to be the dominant effect in East Antarctica at the present time, but it is not the only change going on in the Antarctic ice sheet (see the figure). A substantial part of West Antarctica is thinning (*5*) in response to acceleration and widening of the glaciers that drain it (*6*). The changes in the glaciers were probably caused by changes in circulation or temperature of the surrounding ocean (*7*). The new maps presented by Davis *et al.* (*1*) show this thinning clearly. They also show that in another part of West Antarctica, the current rates of thinning match those measured by dating the exposure ages of mountains that protrude through the ice sheet [~4 cm per year for the past 10,000 years (*8*)]. This part of the ice sheet may not yet have ended the retreat begun at the end of the last glacial period.

The ERS satellites do not successfully track steep ice surfaces. Therefore, the new maps do not show the thinning of the ice sheet observed in coastal areas of the Antarctic Peninsula as a result of recent regional climate warming (*9*) and glacier acceleration (*10*). Furthermore, the satellite data do not extend south of 81.6°S, precluding measurements of the thickening upstream of the Kamb Ice Stream. This ice stream slowed down around 130 years ago; today, almost all new snowfall remains in its basin, piling up year by year (*11*).

We may aspire to determine the overall contribution of the Antarctic ice sheet to changing sea level as a single number with a single estimate of uncertainty. But this number will necessarily arise from many different



Modes of imbalance. In some parts of Antarctica, such as East Antarctica, the ice sheet is thickening (+ symbols), whereas in others, it is thinning (– symbols). The reasons for these changes differ, making it difficult to predict the future contribution of the Antarctic ice sheet to sea level change.

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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.

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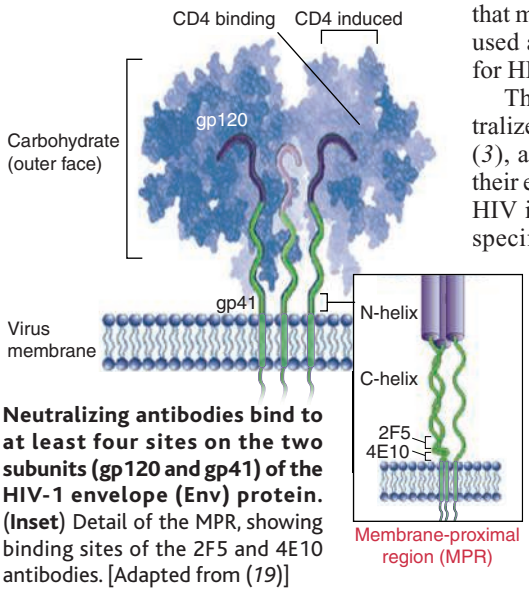
IMMUNOLOGY

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

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