When the nebula disappeared, the protoplanets would retain some of these atmospheres and thereby acquire noble gases from the solar nebula.

Genda and Abe[1] use a ruthlessly simplified model to describe how giant impacts interact with atmospheres[3]. They accept as a matter of course that much of the stricken hemisphere is lost, driven off by hydrodynamic jetting or the tangential momentum of a glancing blow. Their concern is with the hemisphere that is not hit directly.

Here the impact announces itself when the bow shock erupts through the surface. Indeed, the entire crust launches into space at high velocity, typically several kilometres per second. The crust drives a shock wave into the atmosphere that accelerates as it rises into thinner air. At some height the air reaches escape velocity, but escape is efficient only if the ground velocity approaches or exceeds the escape velocity[3,4]. Such high ground velocities are difficult to achieve if the planet itself survives; the highest ground motions achieved in successful Moon-forming impact simulations (a relatively gentle event) are typically less than half the escape velocity[5]. Genda and Abe therefore argue that most of a planet's atmosphere, including its primordial noble gases, is retained in giant impacts.

An ocean changes everything. When the crust hits the ocean, the ocean is driven outward at an even higher velocity and it is also vaporized. The resulting explosion of supercharged steam accelerates most of the overlying atmosphere to escape velocity and beyond (Fig. 2 in the supplementary information[1]). Genda and Abe therefore argue that, with an ocean, most of the atmosphere (and most of the noble gas) is lost in giant impacts. Because they were there, the noble gases provide the best test of their hypothesis.

The authors take the minority view that bound water was common to all the building blocks of Earth and Venus, so that from the start the protoplanets each had their own oceans and atmospheres, and independent lives as infant Earths. A more popular view is that Earth and Venus became wet while still accreting, but only because they were struck by cold, wet protoplanets ejected from what is now the asteroid belt[6]; with modest revision, however, Genda and Abe's hypothesis could apply in this context as well.

To distinguish between Earth and Venus, Genda and Abe invoke the runaway greenhouse effect[7]. On worlds nearer the Sun, water evaporates into a thick atmosphere, whereas on more distant worlds it condenses as oceans and ice sheets. With oceans, the building blocks of Earth lost much more of their primary atmospheres than did the building blocks of Venus. In this way, Genda and Abe's model can account for Venus having 70 times more argon than Earth.

Of course there are caveats. Genda and Abe stress low-velocity collisions that merge the two protoplanets. A broader assessment of impact geometries and velocities suggests that most giant impacts are bounces, rather than mergers, in which both bodies emerge slightly smaller (and much hotter) amidst a spray of silicates[5]. In a high-speed bouncing impact between unequal planets, the smaller one could easily lose both its crust and its atmosphere.

But the big problem with gravitational capture of nebular noble gases is the abundance of neon. The neon:argon ratio on Venus, Earth, Mars and meteorites is invariably about 1% of what it is in the Sun[8]. Explaining this requires both a heroic theory of selective neon escape[9] and some luck to make the neon:argon ratio always come out the same. It may work better to start from some other source of noble gases that discriminates against neon — say, extremely low-temperature condensates that quantitatively trap argon[10] (neon freezes only if hydrogen freezes), or noble gas implantation by the solar wind into unaccreted grains and boulders[11–13]. If you merely wish to bury the argon, there is no limit to how much.

The new work offers a fresh look at planetary accretion. The argument that oceans speed the loss of atmospheres is more broadly applicable than the authors imply. It need not be restricted to atmospheres of solar composition acquired gravitationally; and it need not be restricted to water oceans or even liquid oceans. It applies generally during or before the giant-impact stage of accretion, and it could apply to satellites of the outer Solar System as easily as to Earth. ■

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Human immunodeficiency virus

# Refolding the envelope

Peter D. Kwong

HIV has evolved to avoid neutralization by human antibodies. New atomic-level details reveal that such evasion involves substantial refolding of its exterior glycoprotein.

A defining feature of HIV is the ability to thrive for a decade or more despite sustained and vigorous immune attack. How does the virus remain able to infect host cells at the same time as evading immune surveillance? The solution resides largely in the molecular trickery of a single viral protein, gp120 — the component of the 'spikes' on the viral surface that binds to receptors on host cells.

Tantalizing new details of this trickery are revealed on page 834 of this issue[1], where Chen and colleagues report the structure of the unliganded (receptor-free) form of gp120. Comparison with the previously determined structure[2] of gp120 in complex with one of its cell-surface receptors reveals that receptor binding induces roughly half of the protein to refold. Like a trick jigsaw puzzle that can form two entirely different pictures, the refolding preserves pieces of gp120's secondary structure, but reshuffles their location and relative orientation. In the viral spike, this reshuffling moves pieces of protein by more than 40 Å, rivalling the largest changes ever observed for a single protein domain.

Soon after HIV was identified as the aetiological agent of AIDS, it became clear that although infection prompts the human body to produce a large number of HIV-reactive antibodies, they are mostly ineffective at neutralizing the virus[3]. The machinery behind HIV's remarkable evasion involves a protective membrane around the virus and an ordered, two-receptor mechanism of entry into cells. The membrane is derived from a previous host cell and forms the outer surface of HIV — its envelope. The only viral proteins that protrude through this membrane are the envelope glycoproteins, gp120 and gp41: three copies of each make up a viral spike.

The two-receptor mechanism involves the virus first binding to the CD4 glycoprotein on the surface of a potential host cell. This binding induces changes in gp120 that permit it to interact with a second cell-surface receptor, or co-receptor[4,5]. This mechanism is not essential for viral propagation,

as variants that do not require CD4 for entry (CD4-independent isolates) can be obtained *in vitro*[6]. Rather, the mechanism appears to be necessary for immune evasion, as alterations in gp120 that lead to CD4 independence are invariably linked to increased sensitivity to neutralization by antibody.

The upshot of all this is that, in HIV isolates that resist neutralization, gp120 can exist in two quite different states. Before it interacts with the cell surface, it is highly resistant to antibody binding — hidden by the overlapping defences of steric occlusion, conformational masking and glycan (sugar) shielding[7–9]. After binding to CD4, gp120 is primed for interaction with other proteins, including the co-receptor. In this 'CD4-induced' state, it would in theory be sensitive to antibody binding. But the sensitizing trigger occurs at the interface between the virus and the host cell, and the close proximity to the cell membrane sterically inhibits antibody binding[10].

The structure of gp120 before CD4 binding has been sought for almost 20 years, but the machinery that prevents antibody binding also inhibits the lattice interactions necessary for X-ray analysis. In a technical *tour de force*, however, Chen and colleagues[1] have now been able to grow crystals of an unliganded gp120 core, build an atomic-level structure, model the expected orientation of the unliganded gp120 in the viral spike, and outline a pathway for how CD4 binding triggers large conformational rearrangements.

The results show that the unliganded gp120 attaches to the rest of the viral spike through a highly hydrated inner domain, suggesting that it would retain considerable flexibility in the assembled spike. Sequence-variable regions from neighbouring gp120s point towards each other; by interlocking to restrict gp120 movements, they provide a means for the variable regions to control conformational masking[8].

N-linked glycans cover much of the surface of gp120 that would be expected to form the spike's outer face, and one can envisage them forming a shield to prevent antibody binding[9]. Much of the glycan has an ordered structure, implying that glycans at high density may display a limited range of conformations. Structural elements needed to bind the gp120 co-receptor — elements that, when assembled together, would in theory be sensitive to antibodies — are spatially separated in the unliganded structure, and only assemble upon CD4 binding (Fig. 1). All of these details lay the groundwork for understanding how gp120 in the viral spike can evade antibodies.

Several issues remain. First, the relationship between the monomeric form of gp120 studied by Chen and colleagues and the oligomeric form in the viral spike is unclear. Does oligomeric gp120 fold into a different conformation? Possibly so: secondary-structure analysis[11] strongly predicts that portions of gp120 that are involved in co-receptor binding should have α-helical structure, but they adopt mostly β-strand configurations in the unliganded[1] and CD4-bound[2] structures. Second, the unliganded structure does not contain regions of the protein that govern protein–protein interactions in the spike.

So it remains to be seen how spike interactions fix gp120 in such a way as to allow CD4-induced rearrangements while preventing antibody binding. A complete understanding of antibody resistance may require snapshots not only of each conformation of gp120, but of the entire spike.

The classic 'before' and 'after' images of the fusion peptide of influenza virus being thrown 100 Å towards the host-cell membrane shattered the staid notion of proteins having a single unique manner of folding[12]. Such extensive refolding seemed, however, to be a special facet of the process of fusing viral and host-cell membranes during viral entry — a process requiring large overall molecular movements. The newly revealed 'before' image of gp120 now shows that HIV deploys extensive refolding not only for fusion but also to evade neutralization by antibody.

Paradoxically, however, the refolding that protects HIV from antibodies may also be a source of vulnerability. One consequence of folding into more than one conformation is that dual packing restraints may leave empty pockets or cavities. Both the unliganded and the CD4-bound gp120 structures contain unusual pockets. One such pocket in the unliganded structure is, Chen and colleagues find, the binding site for a recently discovered class of viral-entry inhibitors[13]. Although the authors' unliganded gp120 crystals are not suitable for structure-based drug design, tinkering with lattice contacts and with this site of inhibitor binding may permit suitable complex crystals to form.

In terms of vaccine design, the structure of unliganded gp120 reveals the envelope at its potentially most vulnerable. This is the state before attachment — before occlusion at the cell interface — where HIV should be most accessible to antibody binding. But this is also the state in which the virus uses its full arsenal of tricks to evade antibody neutralization.

The details revealed by Chen and colleagues will enable each of these tricks to be probed by the increasingly sophisticated tools of protein design, to fix or expose otherwise transient or occluded sites of antibody binding. Will such modified envelopes — based on the unliganded structure — be capable of eliciting broadly neutralizing antibodies? In addition to altering the way we view receptor binding, this structure[1] opens the envelope on these and other experiments. ■

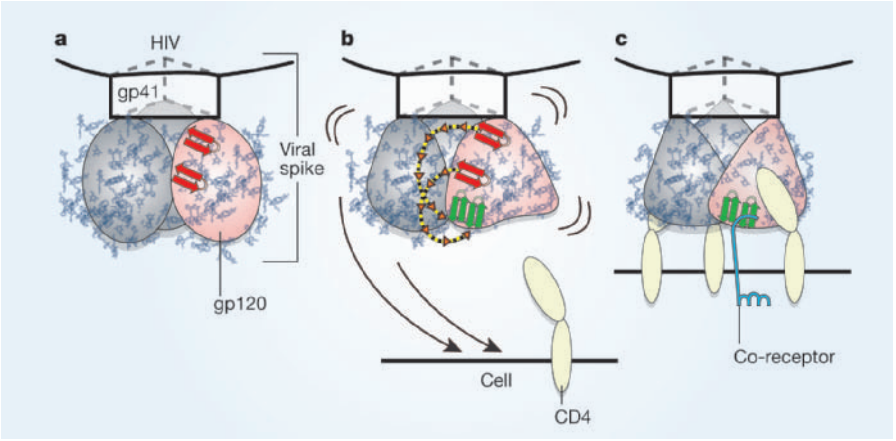


Figure 1 **Molecular tricks of HIV.** a, **Before HIV attaches to the surface of a host cell, its surface spikes (one of which is shown here) are accessible to antibodies, but protected by numerous viral defences. These include N-linked glycans (blue), which cloak the three gp120 glycoproteins (pink and grey ovals) and three gp41s (triangular plate) that make up a spike.** b, **Chen and colleagues[1] find that attachment to the cell's CD4 protein induces roughly half of the gp120 glycoprotein molecule to refold. This refolding is highlighted for two β-ribbons (red), which rearrange (green) to form part of a site that allows binding to a second receptor, the co-receptor.** c, **The crowded virus–cell interface protects the assembled co-receptor-binding site from antibodies.**

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