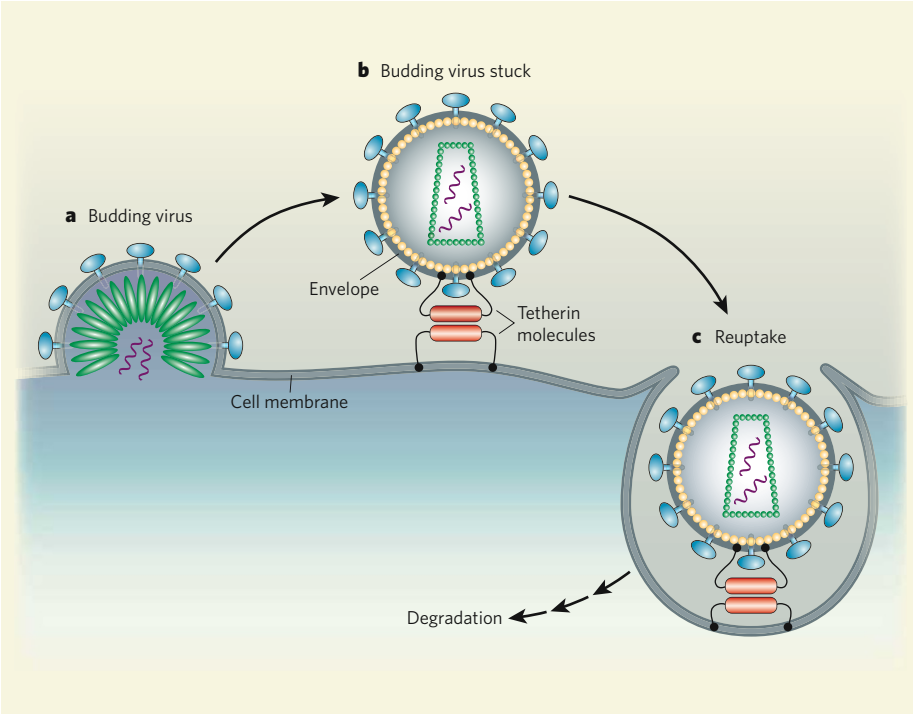

Figure 1 | Model for tetherin-mediated HIV-1 retention. **a**, HIV-1 virions assemble at the cell surface and leave infected cells by budding off from the cell membrane. Assembling virions thus become covered by a cell-membrane-derived envelope. **b**, Tetherin is localized on the outside of the cell surface, but is anchored in the cell membrane at both ends. Identifying tetherin as the cellular factor that prevents HIV-1 release, Neil *et al.*[1] speculate that this protein is also taken up by the budding virion and is firmly anchored in the viral envelope. Virion- and cell-associated tetherin could then interact, preventing the release of the mature virion from the cell surface. **c**, The authors also propose that, through one of its membrane anchors, tetherin might connect to the cell's endocytotic machinery, which engulfs extracellular material in cell-membrane invaginations and imports it into the cell. This could lead to the reuptake of mature virions by infected cells and their subsequent degradation by the cell's digestive system.

membrane through its unusual pair of membrane anchors[6]. The central portion of the protein faces the outside of the cell[6] and seems to interact with the same region of another tetherin molecule[7]. Thus, assuming that tetherin is incorporated into the membrane enveloping Vpu-deficient HIV-1 particles, Neil *et al.*[1] envisage a situation in which tetherin molecules that end up in the viral envelope hold the virus back by interacting with tetherins that are associated with the cell surface (Fig. 1b). Tetherin also interacts with the cell's endocytotic — or internalization — machinery[8], which might play a part in the reuptake of the trapped viruses into the cell and their degradation in intracellular compartments[3] (Fig. 1c).

How does Vpu counteract the effects of tetherin? Neil *et al.*[1] did not detect reduced tetherin levels in the presence of Vpu, although this could have been due to experimental overexpression of tetherin. A previous study[9], however, found that levels of the protein now identified as tetherin are reduced by an entirely unrelated human virus, Kaposi's sarcoma-associated herpesvirus (a finding that also hints at the broad antiviral activity of this protein.) The viral protein responsible in this case, K5, is a ubiquitin ligase enzyme, which adds the molecular tag ubiquitin to proteins, marking them for degradation. K5 is structurally similar to a family of human ubiquitin ligases, at least one of which can strongly reduce the cellular levels of tetherin.

With what turns out to be remarkable foresight, the authors of this earlier study[9] also tested Vpu and found that it, too, decreases the normal cellular levels of tetherin. These observations raise the possibility that Vpu uses a cellular ubiquitin ligase to dispose of tetherin, as it does for CD4. But other possibilities, such as tetherin relocalization by Vpu, rather than its degradation, are also possible.

Only HIV-1 and a handful of its cousin viruses make Vpu, which poses the question of how other related viruses deal with tetherin. For HIV-2 (the less virulent human AIDS virus), a protein that mainly facilitates viral entry substitutes for Vpu, promoting virus release[10], and we will probably soon learn whether this protein also antagonizes tetherin.

Because the amino-acid sequence of tetherin differs considerably among mammals, some HIV-1-related animal viruses might find it difficult to overcome human tetherin, preventing them from becoming human viruses. Conversely, it is worth investigating whether tetherin contributes to the inability of HIV-1 to efficiently escape from most rodent

50 YEARS AGO

"Symmetry of snow crystals" — Despite an infinite variety in the patterns which appear, there does often exist a remarkable symmetry in the six rays [of snowflakes]... Since each of the six arms of the crystal would appear to be growing independently, this symmetry poses a problem in crystal growth, for it almost seems as if each arm of the six-ray star 'knows' what the other five are doing and follows suit... I conjecture that the crystal is vibrating mechanically as a flat plate, in fact as a Chladni plate, with of course a hexagonal symmetry... When the molecules adhere to achieve growth at any particular region on one arm, this immediately introduces a localized damping action on the vibrations... But this very damping is at once felt simultaneously at the corresponding positions on the other five arms. Thus molecules arrive and adhere easily at the other five arms in precisely the same situations as on the first arm; in other words, what happens on any one arm tends to be repeated on the others...
From *Nature* 25 January 1958.

100 YEARS AGO

The product of the world's gold mines for the year 1906 could all be packed in a room 10 feet square and 9 feet high... The value of this 90 cubic feet of gold was nearly eighty-one and a half millions sterling, and its weight nearly 674 tons... Eighty-three per cent. of the total output was secured by the Anglo-Saxon world. According to calculations and estimates made in 1900 by the director of the United States mint, the gold taken from the mines of the world since the discovery of America has amounted in quantity to about 21,424 tons... Nineteen per cent., or nearly one-fifth of the whole, has been mined in the last ten years, and nearly 30 per cent. in the last twenty years.
From *Nature* 23 January 1908.

50 & 100 YEARS AGO