higher animals. Fautin¹¹ points out that varied reproductive strategies and the heritability of somatic mutations may result in considerable genetic variability, even within the presumed single clone of a large colony. So, many (if not all) coral 'species' represent a palaeontologically stable 'morphospecies', with genetic, symbiotic and niche variabilities that make a mockery of attempts to apply the species concepts that are associated with higher animals and terrestrial organisms.

The significance of these findings goes well beyond the level of depressing (but enlightening) news for organismic coral researchers — whether their bailiwick is the past or the present. The mechanisms by which corals calcify are not well understood, but it has long been known, for example, that skeletal morphology changes in many species as a function of the levels of light. Moreover, the isotopic and chemical composition of the exoskeleton may vary with the rate of growth (extension). Similar variations in how the taxa of the algae that mediate calcification are distributed within a colony constitutes a map for future research — not just an interesting, but frustrating, anomaly. Even more fundamental to the relationship between light, temperature and calcification are studies that seem to uncouple coral calcification¹² or extension¹³ from symbiosis or light, despite earlier experiments which showed that light/dark calcification ratios in symbiotic corals are much greater than unity¹⁴.

The discovery of many labile symbioses by Rowan *et al.* may help to resolve the apparent paradox: if reef-building corals retain the same, genetically hard-wired calcification mechanism that allows their asymbiotic cousins to build skeletons in dark, cold, undersaturated water, this may be reflected in the 'dark calcification' that builds the skeletal template¹³. In the light, photosynthesis by a 'tunable' suite of algal symbionts helps to optimize the harvest of calcium carbonate from supersaturated waters. This calcification component may even be as important as temperature in explaining why reefs are mainly in the tropics (Fig. 1). And the concept of dual-process calcification is a diel analogue of the differential extension-thickening model that explains variations of skeletal density on a seasonal basis¹⁵.

The present spate of exciting and unsettling findings highlights the roles of acclimatization and adaptation in explaining how the consistent metabolism of coral communities over space and structure¹⁶, and the consistent structure of these communities over time¹⁷, can be achieved by evolutionarily stable taxa in a highly variable environment. And these seemingly arcane questions are central to more immediate and practical issues, such as natural controls on carbon cycles and the survival of ecosystems and

biodiversity during global change. Whether they like it or not, coral researchers are living in interesting times. □

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Immunodeficiency viruses

Spoilt for choice of co-receptors

Paul R. Clapham and Robin A. Weiss

As intracellular parasites, viruses need first to attach to and then gain entry into cells. The human and simian immunodeficiency viruses (HIV, SIV) carry out these steps through surface glycoproteins which interact with different molecules displayed by the host cell. All immunodeficiency viruses bind with high affinity to the CD4 cell-surface receptor of T lymphocytes, which attaches them to the cell under attack, but different strains use distinct co-receptors to trigger viral entry (see Fig. 1 and our previous News and Views article¹ on the topic).

In papers on pages 296 and 238 of this issue^{2,3}, and elsewhere^{4,5}, several groups announce the discovery of further co-receptors for SIV and HIV infection; indeed, a receptor molecule encoded by cytomegalovirus is also reported to serve as an HIV co-receptor⁶, although this may not hold for all cytomegalovirus strains. The ability of immunodeficiency viruses to use so many receptors has provoked much thought about HIV pathogenesis and how it might be prevented.

CD4 was identified in 1984 as the receptor for HIV, but it soon became apparent that its presence alone was not sufficient to permit viral entry. The identity of second receptors remained elusive until 18 months ago, but since then it has become clear that there is a growing family of them, used by different HIV and SIV strains. Their expression on different (but often overlapping) cell populations, along with selective use by particular virus strains, makes them a major determinant of which cells HIV can infect.

All the co-receptors so far identified are members of, or related to, the seven-transmembrane, chemokine-receptor family. These are G-protein-coupled signalling receptors which bind the chemoattractant proteins, known as chemokines, that are involved in controlling activation and

migration of various leukocytes. All HIV-1 strains so far tested use the CCR5 or CXCR4 co-receptors, or both, and therefore these two are likely to be crucial to HIV infection and pathogenesis *in vivo*. Many HIV-1 strains, however, are able to use other co-receptors — including CCR3, CCR2b (refs 7, 8) and three of the four newly identified ones (see Table 1) — as well as CCR5 or CXCR4.

The CCR5 co-receptor is targeted by the so-called non-syncytium-inducing (NSI) viruses of HIV-1, those that don't induce cell-to-cell fusion in T-cell lines. It seems crucial for viral transmission because people who are homozygous for a CCR5 gene deletion are largely protected from HIV-1 infection⁹. CCR5-using strains are usually present throughout the course of infection. Syncytium-inducing (SI) viruses, by contrast, use the CXCR4 co-receptor, and often emerge later in the course of infection; they can be isolated from about half of AIDS patients.

In the co-receptor context, SIV presented a puzzle because some strains infect several CD4-positive human and non-human cell types that are resistant to HIV-1 (ref. 10). That puzzle grew more complex earlier this year when it was found that SIV used CCR5 but not CXCR4 (refs 11–13), yet could infect the CCR5-negative human T-cell lines Hut 78 and CEM × 174, as well as the astroglial cell line U87.CD4. Clearly, these strains used different and unidentified co-receptors.

Deng *et al.*² now describe two new co-receptors for SIV. They have been identified through screening complementary DNA libraries for their capacity to allow SIV entry into cells, and are termed Bonzo and BOB (standing for 'brother of Bonzo'; alas, the names will change to the more conventional terminology when their natural ligands are identified). Both receptors were used by the

Table 1 Immunodeficiency virus receptors

	CD4	CCR5	CXCR4	CCR3	CCR2b	Bonzo STRL33	BOB GPR15	GPR1	US28
HIV-1 NSI	+	+	-	+	-	+	+	-	+
SI	+	+	+	+	+	(+)	+	-	+
SIV _{mac}	+	+	-	-	-	+	+	+	?
Natural ligands	MHC class II	MIP-1 α MIP-1 β RANTES	SDF-1	Eotaxin RANTES MCP-3 MCP-4	MCP-1 MCP-2 MCP-3	?	?	?	?

All strains of HIV and SIV bind to CD4. Eight co-receptors are shown that bind different HIV and SIV strains. +, indicates that the appropriate co-receptor is active for at least one virus strain. -, means that no viruses have yet been shown to use that co-receptor. ?, means not yet tested or unknown. The known natural ligands of co-receptors are all chemokines. NSI, non-syncytium-inducing, SI, syncytium-inducing. The newly identified co-receptors are Bonzo/STRL33 (refs 2-4), BOB/GPR15 (refs 2, 5), GPR1 (ref. 5) and US28 (ref. 6).

three strains of SIV tested, and by several HIV-1 and HIV-2 strains. BOB is identical to a receptor (GPR15) described in 1996 (ref. 14), but not hitherto linked to HIV/SIV infection. Bonzo is identical to a co-receptor (STRL33), described last month by Liao *et al.*⁴, which functioned as a co-receptor for all of eight HIV-1 strains tested (both NSI and SI). The same group³ now add that the Rhesus macaque SIV (SIV_{mac}) uses STRL33/Bonzo. In addition, Farzan *et al.*⁵ show that two orphan molecules^{14,15}, resembling chemokine receptors, are used by SIV_{mac}. GPR15 (from CEM $\times$ 174 cells) is the same as BOB, whereas GPR1 (from U87.CD4 cells) is novel as a virus receptor.

In all, then, three new human co-receptors for immunodeficiency viruses have been identified — BOB/GPR15, Bonzo/STRL33 and GPR1. Each can be used by the SIV_{mac} strains tested, but although GPR1 is, so far, specific for SIVs, BOB and Bonzo can be used by several HIV-1 strains. Farzan *et al.*⁵ and Deng *et al.*² agree that only certain HIV-1 strains target BOB. Deng *et al.* report a more restricted use of Bonzo than do Liao *et al.*⁴, with entry by some but not all primary HIV-1 isolates. Despite this minor discrepancy, Bonzo and BOB could be important in both HIV and SIV infection *in vivo*. BOB and Bonzo are expressed widely in lymphoid tissue, the main site for HIV and SIV replication². Bonzo but not BOB messenger RNA was present in monocytes, whereas GPR1 was detected in alveolar

macrophages but not T cells⁵. High levels of BOB mRNA were detected in colon tissue, prompting Deng *et al.* to speculate on a possible role in HIV or SIV transmission to or from this site.

What are the implications of these new results? First, the lack of CXCR4 use by SIV strains, along with the possibility that BOB, Bonzo and particularly GPR1 might be more significant for infection by SIV than by HIV-1, mean that SIV may target distinct haematopoietic cell populations; if so, some caution is called for in extrapolating from SIV infection of macaques to HIV-1 infection of humans. But it is still unclear how many HIV-1 strains infect cells through BOB and Bonzo, and whether GPR1 is

used at all. Moreover, many HIV-positive patients, like SIV-infected macaques, develop AIDS without the appearance of CXCR4-using SI strains.

Second, there are the implications for drug development. The discovery of co-receptors has brought hope that new drugs can be developed that block HIV-1 entry into cells. Modified chemokines can indeed inhibit HIV infection by competing with HIV for specific co-receptors, apparently without activating the immune system^{16,17}. But the growing number of HIV-1 co-receptors being identified implies that targeting specific co-receptors may simply mean that other HIV strains using alternative co-receptors emerge and come to predominate. It should not be forgotten, though, that whereas we can assess the extent of co-receptor use in cell culture, we cannot yet do so *in vivo*; and that we don't fully understand the selective *in vivo* pressures (innate or immune) that act for or against the use of individual co-receptors.

Six human co-receptors that are active for HIV-1 strains are now known (see Table 1). More will probably follow. The capacity of evolving HIV/SIV strains to use additional co-receptors is likely to provide them with new cell populations to target, as seen for SI viruses that use the CXCR4 co-receptor and tend to emerge late in disease. CXCR4 expression is more widespread, and includes naive T cells, while CCR5 is mainly expressed on macrophages and memory T cells¹⁸. It remains controversial whether this change in co-receptor use (to CXCR4), and therefore type of T cell infected, results in the precipitous drop in CD4-positive T cells that often follows the emergence of SI HIV-1. Much careful work is now required to establish the contribution of each co-receptor to HIV infection and pathology.

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Figure 1 HIV and SIV attachment and entry into cells. Spike glycoproteins (gp) on virus particles are made up of surface gp120 noncovalently attached to transmembrane gp41. Each spike contains three of each. a, gp120 binds to CD4 at the cell surface to attach virus particles to the cell. b, Conformational changes in the spike glycoproteins generated by their interaction with CD4 result in co-receptor binding. Further rearrangements in the spike glycoprotein induce the exposure of a hydrophobic domain at the amino terminus of gp41, and insertion of this region into the cell membrane initiates fusion of the cell and viral membranes (see ref. 19). c, After fusion, the virus core containing the RNA and reverse transcriptase enters the cytoplasm of the cell.