VIROLOGY

Nosing ahead in the cold war

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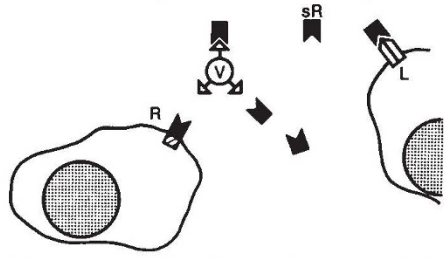
As viruses are intracellular parasites, the ideal anti-viral agent would prevent entry of the virus into a potential host cell, so minimizing the tissue damage caused by the virus and by the immune response to it. Most existing anti-viral agents, such as α-interferon, acyclovir, AZT and ribavirin, act only after penetration of the cell by the virus. But on page 70 of this issue, Marlin *et al.*[1] describe a novel method of preventing infection of cells by the common cold virus (rhinovirus) using an agent that targets the virus 'receptor' — the cell-surface molecule that binds the virus and allows its entry into the cell.

The recent identification of the cell-surface receptors for Epstein–Barr virus[2], HIV (refs. 3, 4), poliovirus[5], rhinovirus[6,7] and the murine ecotropic leukaemia virus[8] has focused research on receptor targeting as a strategy for new anti-viral drugs. In particular, the discovery that the CD4 molecule is the main cellular receptor for HIV (refs 3, 4) has raised hopes of using either soluble CD4 (ref. 9) or a CD4-Fc chimaeric molecule[10] to prevent infection by the AIDS virus. Marlin *et al.*, one of the groups that identified[7] ICAM-1 — intercellular adhesion molecule-1 — as the main receptor for human rhinoviruses, have now used this principle to block rhinovirus infection of cells *in vitro*.

They have produced a soluble form of ICAM-1 (sICAM-1) by introducing a stop codon just outside its predicted membrane-spanning region. They then transfected this mutated gene into Chinese hamster ovary cells, amplified it by dihydrofolate reductase/methotrexate selection, and selected those clones that produced large amounts of sICAM-1. The immunoaffinity-purified molecule retained the ability to bind three anti-ICAM-1 monoclonal antibodies, indicating that the structure of the soluble molecule was at least broadly similar to the membrane-bound (native) form. sICAM-1 specifically inhibited the cytopathic effect induced by a member of the major rhinovirus subgroup (HRV54), but did not moderate the effect induced by non-ICAM-1-binding rhinoviruses (of the minor subgroup), other picornaviruses or the unrelated herpes simplex virus (HSV-1). sICAM-1 also inhibited binding to cells of radiolabelled rhinovirus particles in a dose-dependent manner.

The structure of picornaviruses (which include rhinoviruses) is known to a high level of resolution[11]. There is some evidence[12], as yet unproved, that deep pits or 'canyons' in the surface of the virion contain the receptor-binding domains of the virus. If such receptor-binding canyons are inaccessible to antibodies, as their dimensions indicate, this could explain the failure of antibodies against one rhinovirus strain to neutralize another strain[11]. The protein sequence in the canyon wall is highly conserved, presumably because there is strong selective pressure to maintain the receptor-binding capacity. Soluble receptor molecules (or their analogues) should have the virtue that they attack this highly-conserved Achilles' heel of the virus, which other anti-viral agents cannot reach.

Marlin *et al.* mention the possibility of using sICAM-1 or an analogue as an anti-viral drug. But several important



The virus particle (V) adsorbs to a cell by binding to the cell-surface receptor (R). The soluble receptor analogue (sR), made by deleting the transmembrane and cytoplasmic domains of the receptor molecule, binds to the virion and so prevents adsorption of the virus to the cell. If the receptor is an adhesion molecule, the soluble receptor analogue will also bind to its ligand (L), and so may interfere with normal cell–cell interactions.

hurdles will have to be surmounted before such a drug could be used in humans. First, the efficacy of the soluble receptor analogue must be demonstrated *in vivo* in an animal model; it must be efficient in concentrations that can be achieved and maintained on the nasal mucosa. Second, frequent doses of any substance, especially a protein, may cause sensitization in the nasal mucosa, inducing an immediate (anaphylactic) immune response, or an immune-complex-mediated hypersensitivity response such as pituitary snuff takers' lung. If a close analogue of a native protein is used, autoreactive antibodies might also be produced.

Third, as Marlin *et al.* observe, the effects of soluble receptor analogues on normal cell– cell interactions must be studied. This is particularly important when the virus receptor is an adhesion molecule responsible for binding to a specific ligand on another cell. Intriguingly, three of the recently described cell-surface receptors (those for HIV, poliovirus and rhinovirus) are members of the immunoglobulin 'superfamily'[13] of proteins, the largest known family of cell-adhesion molecules. We know a little about the immunological importance of the interaction of ICAM-1 with its ligand, LFA-1, from the study of patients with congenital deficiency of LFA-1 (ref. 14). Such patients suffer from indolent bacterial and fungal infections and most die before the age of two years. But these patients usually have a defect in the β-chain of the LFA family (CD18), and so lose the function not only of LFA-1 but also of two related glycoproteins (CD11b and CD11c). As these do not bind to ICAM-1, blocking the function of ICAM-1 with sICAM-1 may have less effect. Furthermore, LFA-1 is known to interact with at least one other ligand, ICAM-2 (ref. 15).

These results will also encourage efforts to clone the cell-surface receptors of other viruses, both to develop similar anti-viral drugs and to understand better the tissue specificity and infectivity of certain viruses. A typical strategy has involved antibody blocking of virus binding (of rhinovirus and HIV for example), but this depends on large panels of monoclonal antibodies (which are incomplete), and has not been uniformly successful. New approaches are needed. These might include expression cloning systems[16], whereby the putative receptor-binding protein of the virus, such as the envelope protein of retroviruses, is used as a ligand to select transfected cells expressing the receptor molecule. This could lead directly to cloning of the receptor, unless it is a complex protein encoded by two distinct messenger RNAs.

The success of receptor analogues as anti-viral drugs will of course also depend on whether the virus can enter the cell by other routes. But the identification of virus-receptor molecules has opened a new age in virology. At the least, we shall understand more of the behaviour and evolution of viruses; at best, it makes possible a new approach to the rational design of anti-viral drugs. □

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