HIV Receptors and the Pathogenesis of AIDS

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In a recent radio interview, the 1996 Crafoord Prize winner, Oxford mathematical biologist and chief scientific adviser to the British government Sir Robert May, quipped that if acquired immunodeficiency syndrome (AIDS) researchers wished to understand human immunodeficiency virus (HIV) pathogenesis, perhaps they should not spend their time studying receptors. May's off-the-cuff remark was made after Gallo's group had reported (*1*) that the β-chemokines Rantes, MIP-1α, and MIP-1β act as soluble HIV suppressor factors secreted by $CD8^+$ T lymphocytes and just before Berger's laboratory announced the identification of the coreceptor (LESTR, which Berger called fusin) to the CD4 antigen needed for membrane fusion and entry of T cell line–adapted strains of HIV-1 into cells (*2*). New data from several laboratories (*3*) show that the β-chemokine receptor CC CKR5 serves as a coreceptor for primary HIV-1 strains, including those that infect macrophages, and that the inhibitory effect of the β-chemokines is mediated by blockage of HIV-1 entry. Furthermore, elevated levels of β-chemokine expression are probably involved in controlling HIV load and replication in individuals who do not progress to AIDS and clearly help to explain why some repeatedly exposed, noninfected people manage to escape infection (*4*). The realization that HIV is playing on the keyboard of 7-transmembrane G protein–coupled (7tm) chemokine receptors is giving us new insights into virus–host cell interactions. Receptors have become even more relevant than they formerly were to understanding the dynamics of HIV pathogenesis and transmission (Fig 1).

May's more serious point is that although experimental physicists readily use and rely on the mathematics of their theoretical brethren, experimental biologists all too often shy away from rigorous mathematical models. The theoreticians argue that the enormous complexity of host-parasite interactions necessitates the use of mathematical models. They think experimental virologists exhibit a type of naïve arrogance in believing that their pet molecule is the key to HIV pathogenesis, be it the CD4 receptor, the Nef protein, or the nuclear factor kappa B transcriptional regulator. The virologists retort that theory is all very well, but theoretical biologists should spend less time building castles in the air; more assiduous attention to empirical data might help to establish more plausible premises.

A case in point is Nowak and May's antigenic diversity threshold hypothesis (*5*). Recent observations show that, in apparent contradiction to the theory's prediction, HIV antigenic diversity is inversely related to progression to AIDS (*6*). These findings have generated both a critique and a strong defense of the hypothesis (*7*). One reason why I have always suspected that the battle between the immune system and the virus infecting it (*8*) cannot be the whole story of lentivirus pathogenesis comes from a consideration of maedi-visna virus (MVV) in sheep. MVV does not recognize the ovine CD4 receptor and does not infect T helper lymphocytes, although it infects macrophages and brain tissue (*9*). Infected susceptible sheep do not show the severe immunodeficiency characteristic of AIDS, but they suffer similar wasting and neural syndromes to those seen in AIDS, and disease progression is as inexorable as that of HIV in humans. Antigenic diversity of MVV occurs, no doubt accompanied by immune escape, but it does not affect T lymphocyte dynamics. Because the antigenic diversity threshold hypothesis does not account for the progression to fatal MVV disease in sheep, I question whether it has a central role in human AIDS. Comparative virology has much to contribute to the modeling of pathogenesis, as Hilleman and I have argued elsewhere (*10*, *11*), not only in identifying systems with similarities to AIDS, such as simian immunodeficiency virus in macaques, but in providing insights through examination of key differences.

Elucidation of the cell biology of HIV infection is surely a prerequisite to understanding its replication rate and pathogenesis (*11*, *12*). Each susceptible cell type represents a different ecological niche. The discovery that the CD4 antigen is the principal binding receptor for HIV immediately explained why $CD4^+$ cell depletion is the major feature of immune deficiency in AIDS (*13*). It soon became apparent from expression of human CD4 in animal cells that CD4 is necessary but not sufficient to permit HIV entry into host cells (*14*). Further studies from many groups demonstrated that HIV's ability to adapt to replicate in different cells, such as peripheral blood lymphocytes, macrophages, and established T cell lines, is a property of the variable antigenic loops of the outer envelope glycoprotein gp120 (*15*). Different HIV isolates exhibit selective tropisms for the different types of $CD4^+$ cells, and these tropisms are determined at the level of virus penetration.

The V1/V2 and V3 loops of gp120 are also major determinants of strain-specific neutralization by antibodies (*15*, *16*). Selection of HIV substrains that are resistant to neutralization frequently have mutations in these variable epitopes. However, genetic change in these loops affects cell tropism too (*16*). For example, we recently showed (*17*) that immune escape from neutralizing antibody by means of a V3 loop mutation resulted in a change of tropism from neural cell infection to macrophage infection. More important, the converse was evident too; adaptation to replication in a new cell type resulted in an immune escape phenotype in the absence of immune selection (*17*).

The cell tropism of HIV is also relevant to HIV transmission. Langerhans or dendritic cells may be the first port of call in the vagina (*18*, *19*); the virus is then rapidly transported to the draining lymph node, where interaction with $CD4^+$ T lymphocytes may lead to active replication (*20*). In parenteral infection, the $CD4^+$ lymphocytes may become directly infected. Soto-Ramirez and colleagues (*19*) claim that the dominant mode of transmission may determine the spread of different HIV subtypes according to their preferred cellular tropism. In turn, the tropism is determined by the interaction of the V1/V2 and V3 loops on gp120 in some unknown way permitting interaction with cell surface receptors. Later in the course of infection, we can see that the frequent emergence of syncytium-inducing (SI) variants is probably the result of a change in coreceptor usage, from the CC CKR5 receptor used by lymphocyte- and

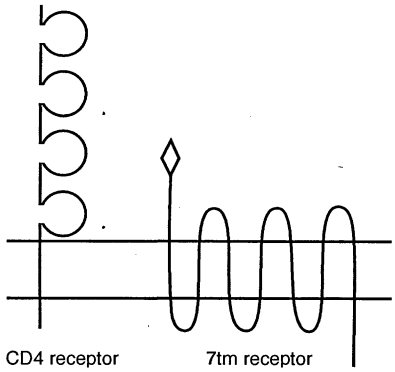

Fig. 1. Co-operating coreceptors for HIV entry.

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macrophage-tropic non-SI HIV to the LESTR receptor used by T cell line adapted strains.

To speculate one step further, I postulate that the "antigenic" diversity of the HIV envelope is driven primarily by adaptation to new coreceptors and only secondarily by immune selection. The coreceptors delineated thus far (*2*, *3*) belong to the 7tm family. Thousands of these receptor genes exist in the human genome; for example, the nasal epithelium alone expresses several hundred such receptors, which serve as chemoreceptors in the discrimination of odor (*21*). Receptors for β-adrenergic neuropeptide transmitters, some cytokines (interleukin-8), and chemokines triggering chemotaxis and allergic responses also belong to the 7tm family (*22*). Some members of the 7tm receptor family are restricted to strictly defined cell subsets, such as basophils or macrophages (*23*). It is becoming evident from the subtle changes in HIV tropism that LESTR (*2*) and CC CKR5 (*3*) are not the only coreceptors exploited by HIV. HIV-2 can infect a broader range of CD4-positive cells than HIV-1 can (*24*) and may use a number of different coreceptors. Some HIV-1 strains can adapt to novel cell types in culture (*16*, *17*). During the long period of infection in each person, the HIV "quasispecies" has the opportunity to colonize new cellular environments, possibly by adaptation to an array of 7tm receptors, thus gradually invading different subsets and clones of hematopoietic cells as well as the brain.

The discovery of this new class of HIV receptor is opening up a field in which many questions can now be addressed at the molecular level. Do the V1/V2, V3, and other domains of gp120 interact directly or indirectly with 7tm receptors? Which epitopes on the receptors are crucial for gp120 recognition? Do the conformational changes that follow binding to CD4 expose 7tm-interacting domains? Does gp120 interaction with 7tm receptors affect their downstream signaling? Does the limitation on the number of infectible T cells at any one time (*25*) reflect receptor expression as a marker of immune activation? Could variation between individuals' CD4 lymphocytes in susceptibility to HIV infection (*26*) be due to blocking by β-chemokines (*3*) or to genetic polymorphism of the coreceptor? Will small animals transgenic for both human CD4 and human coreceptors be useful for AIDS research (*2*) (but if my hypothesis is correct, such animals may not generate such a high degree of HIV variation)? Will ways of blocking HIV and coreceptor interaction be found that will lead to new therapeutic approaches to control of HIV infection?

Many years ago, Sir David Smithers wrote, "Cancer is no more a disease of cells than a traffic jam is a disease of cars. A lifetime of study of the internal combustion engine would not help anyone to understand our traffic problems" (*27*). Yet it was just those studies of internal workings of the cell that revealed the dysregulation of oncogenes, tumor suppressor genes, signal transduction pathways, cyclins, DNA repair, and apoptosis. In AIDS as in cancer, cell biology illuminates the population dynamics of pathogenesis.

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HIV Therapeutics

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After years of small but measurable advances that temporarily delayed disease progression, the chemotherapy of human immunodeficiency virus (HIV) infection now promises to suppress indefinitely the progression of disease, and conceivably to eradicate it altogether. Three factors have converged to provide important advances in antiretroviral chemotherapy: (i) improved understanding of the pathogenesis of HIV infection, (ii) the availability of standardized reliable quantitative assays of HIV RNA in the plasma (present as genomic RNA in virions), and (iii) more potent antiretroviral drugs. Each of these three factors has affected the others.

Surprisingly large amounts of virus are present in the extensive lymphoid tissues of HIV-infected individuals, even in asymptomatic patients early in the disease process (*1*, *2*). The levels of virus in blood are less than in lymphoid tissues and almost certainly reflect the spillover from replication in that tissue. This large amount of virus turns over rapidly, as measured in blood, with a virion half-life of approximately 6 hours and an estimated 10 billion (10^{10}) virus particles generated daily (*3*). Within a year after seroconversion, each infected individual establishes his or her own "set point" of quasi–steady-state levels of plasma HIV RNA (between 10^2 and 10^6 copies per milliliter of plasma) that largely determines the rate at which CD4 T lymphocytes are lost. At sufficiently low levels of CD4 cells, patients are susceptible to opportunistic infections, malignancies, and death. Levels of HIV replication, measurable as plasma HIV RNA, thus drive the rate of immune destruction and in fact can be used to predict the natural history of the disease (*4*).

The measurement of plasma HIV RNA has been instrumental in elucidating this pathogenetic process, as well as in characterizing the magnitude and durability of antiviral activity of investigational drug regimens (*5*). Moreover, this reduction in measured viral "load" appears to account for most of the clinical benefit as measured by opportunistic events or death in study patients (*6*, *7*). With the regimens of nucleoside analogs, even a reduction of plasma HIV RNA by severalfold corresponds to

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