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MEDICINE

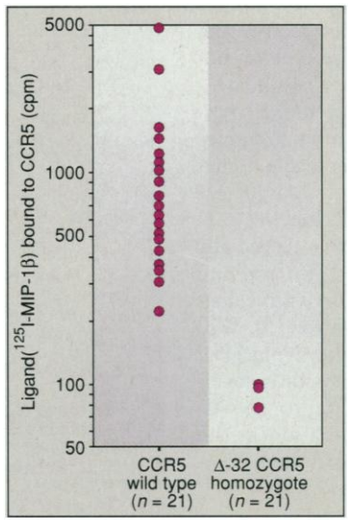
Coreceptors: Implications for HIV Pathogenesis and Therapy

John P. Moore

Human immunodeficiency virus (HIV) cannot enter human cells unless it first binds to two key molecules on the cell surface. The identity of one of these, CD4, has been known since 1984, but only last year did the decade-long search for the second receptor molecules end (*1*). Identification of these coreceptors—CCR5 and CXCR4—has changed the view in several arenas of acquired immunodeficiency syndrome (AIDS) research.

The virology of HIV has now become more understandable. The HIV-1 strains that cause most transmissions of viruses by sexual contact are called M-tropic viruses. These HIV-1 strains (also known as NSI primary viruses) can replicate in primary $CD4^+$ T cells and macrophages and use the β-chemokine receptor CCR5 (and, less often, CCR3) as their coreceptor. The T-tropic viruses (sometimes called SI primary) can also replicate in primary $CD4^+$ T cells but can in addition infect established $CD4^+$ T cell lines in vitro, which they do via the α-chemokine receptor CXCR4 (fusin). Many of these T-tropic strains can use CCR5 in addition to CXCR4, and some can enter macrophages via CCR5, at least under certain in vitro conditions (*1*). Whether other coreceptors contribute to HIV-1 pathogenesis is unresolved, but the existence of another coreceptor for some T-tropic strains can be inferred from in vitro studies. What is occurring in patients? Because M-tropic HIV-1 strains are implicated in about 90% of sexual transmissions of HIV, CCR5 is the predominant coreceptor for the virus in patients; transmission (or systemic establishment) of CXCR4-using (T-tropic) strains is rare (*1*, *2*). However, once SI viruses evolve in vivo (or if they are transmitted), they are especially virulent and cause faster disease progression (*1*, *3*).

The numbers and identity of coreceptor molecules on target cells, and the ability of HIV-1 strains to likely enter cells via the different coreceptors, seem to be critical determinants of disease progression. These factors are major influences on both host- and virus-dependent aspects of HIV-1 infection. For example, a homozygous defect (Δ32) in CCR5 correlates strongly with resistance to HIV-1 infection in vivo and in vitro. Individuals who are heterozygous for a defective CCR5 allele are at best weakly protected against infection and have only a modestly slowed disease progression (*2*). However, other factors can influence the level of CCR5 expression on activated $CD4^+$ T cells and thereby affect the efficiency of HIV-1 infection in vitro (*4*, *5*). For reasons that are not yet clear, the amount of CCR5 expression on the cell surface (as measured by MIP-1β binding) varies by 20-fold on $CD4^+$ T cells from individuals with two wild-type CCR5 alleles (*4*) (see figure). Staining with a CCR5-specific monoclonal antibody indicates a similar large variability (*6*). Such variation may far outweigh any effect of one defective allele for CCR5. The causes of this variation should be the subject of intensive studies, as they point to controllable factors that could increase resistance to disease.



Binding to a coreceptor. The binding of the chemokine ^{125}I-MIP-1β to the coreceptor of activated $CD4^+$ T cells differs markedly in 21 individuals with two wild-type CCR5 alleles and three individuals homozygous for defective CCR5 alleles (*19*).

The state of activation of $CD4^+$ T cells also affects coreceptor expression. Quiescent $CD4^+$ T cells express CCR5 only minimally or not at all, but they do express CXCR4. Activation with interleukin-2 (IL-2) causes strong, sustained up-regulation of CCR5 expression and transient up-regulation of CXCR4 (*5*). Hence, M-tropic strains that only use CCR5 for entry do not fuse efficiently with quiescent T cells, whereas T-tropic primary and lab strains can do so without difficulty (*7*). In assessing antibody effectiveness, assays for virus neutralization that rely on HIV-1 entry into resting cells are badly skewed by these variations in coreceptor expression. Memory T cells ($CD45RO^+$) are susceptible to the effects of β-chemokines that bind CCR5 (*8*) and express much more CCR5 than naive T cells ($CD45RA^+$), but CXCR4 expression appears to be less variable between T cell subsets (*5*). A phenotypic switch (M- to T-tropic) that may be associated with escape from β-chemokines, or reduced production of α-chemokines, can occur during disease progression (*1*, *3*). This could render a whole new set of naive $CD4^+$ T cells susceptible to efficient HIV-1 infection (through CXCR4). Another important but as yet uncharted area is the interaction of CD4 with CCR5 and CXCR4. The specifics of this process will be important for understanding HIV-1 infection and perhaps also for more general immunology studies.

How does the new information about coreceptors affect the prospects for a successful vaccine for HIV? It may be possible to create a human $CD4^+$, $CCR5^+$ transgenic mouse or rabbit for vaccine testing. However, the infectious inoculum that would be required in such animals might prove problematically high, because HIV-1 replication in nonhuman cells is not very efficient, even if entry blocks are overcome. Among the existing primate models, CCR5 is an important coreceptor for simian immunodeficiency virus (SIV) stocks used for experimentation, but another (as yet unreported) coreceptor is probably the simian counterpart of CXCR4 (CXCR4 does not usually function with SIV) (*9*). It will be important to completely characterize the coreceptor us-

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age of all the available SIV stocks, for it would be desirable to use as an HIV-1 vaccine model an SIV strain that enters cells via CCR5. Many SIV stocks seem to more closely resemble HIV-1 laboratory or T-tropic primary strains than M-tropic strains in that they use multiple coreceptors to enter $CD4^+$ T cells, whereas M-tropic (HIV-1) strains exclusively use CCR5. This preference of SIV presumably reflects the common practice of passing this virus in human cells in vitro and the understandable tendency to select for virulent strains in vivo.

CCR5 is the major coreceptor for M-tropic HIV-1 strains from all genetic subtypes tested (*10*). The interaction of HIV-1 gp120 with CCR5 is sensitive to neutralizing antibodies; many antibodies that do not inhibit the binding of gp120 to the CD4 molecule prevent subsequent interactions with CCR5 (*4*, *11*). Because HIV-1 entry is fundamentally the same for all genetic subtypes, the gp120 proteins of all HIV-1 strains are likely to conserve binding sites for both CD4 and CCR5 (or CXCR4). The structural changes that occur as these molecules function during virus-cell fusion will also be broadly common. Hence, the HIV-1 envelope tertiary and quaternary structures may be rather similar among the genetic subtypes (although subject to some sequence variation). The gp120 variable loops probably shield critical, conserved structures from antibody attack (*11*, *12*), and antibodies to these loops may complicate the interpretation of studies of neutralization serotypes (*13*). The more conserved structures probably become exposed only transiently during fusion, limiting the chances of the virus being neutralized (*4*, *11*), which would make sound sense from the virus' perspective. Because neutralization of other subtypes by human antibodies can occur (*13*, *14*), a cross-reactive, antibody-based vaccine is possible—if only we could learn how to induce such antibodies. The CCR5 molecule itself is poorly immunogenic and so may not be a good candidate to use as a vaccine.

In principle, the coreceptors (especially CCR5) are an attractive target for antiviral therapy, and a β-chemokine derivative does inhibit HIV-1 infectivity in vitro (*15*). Will the β-chemokines be exploitable in practice? Beyond the traditional hurdles of drug development will be ones specific to the β-chemokines, among them variation in the sensitivity of different strains to these compounds and the particular ease with which HIV-1 might escape their effects. M-tropic primary strains tend to be sensitive to β-chemokines, T-tropic ones insensitive, but even among M-tropic primary viruses that use only CCR5 (*1*, *16*), there can be extensive variation (50-fold) in β-chemokine inhibition (*17*). It will be important to test lead compounds on a spectrum of primary HIV-1 strains. This lesson was learned during studies of the soluble CD4 inhibitors of the interaction of HIV-1 with its primary receptor, CD4; soluble CD4 inhibited laboratory strains but not primary viruses (*18*). The extensive plasticity of the HIV-1 binding sites on the coreceptors, combined with the virus' notorious mutability, might facilitate escape from coreceptor antagonists. It is even feasible that blockade of CCR5 during established infection might drive HIV-1 evolution toward the use of CXCR4 (or other coreceptors) and, hence, the development of the more virulent T-tropic phenotype. These issues and more will need to be addressed in a field that continues to evolve at the frenetic pace that accompanied its birth in 1996.

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WEBWATCH

Chicken and egg

http://www.ucalgary.ca/~browder/

The Virtual Embryo ("The site that keeps on developing") at the University of Calgary is a full-service Web resource for developmental biology. Along with the latest news about mammalian cloning, there are essays in the "journal club" discussing the current literature and a large number of links to databases and molecular biology tools. Links to the essential journals, meetings, and scholarly societies stand alongside copious educational pointers, including a Web version of the textbook *Developmental Biology* by the site's creator, Leon Browder.

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Edited by David Voss

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