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Robert W. Doms

It is probably safe to say that at the beginning of 1996, most HIV scientists knew little about chemokines and their receptors, whereas those who studied these molecules had little reason to concern themselves with HIV. This changed dramatically with the publication of Feng et al. (1) in May of 1996, the *Pillars of Immunology* paper that is the subject of this commentary. In linking the chemokine and HIV fields, this seminal paper did much to explain how HIV infects cells and led to the discovery of additional host proteins needed for infection, polymorphisms that influence whether an individual becomes infected or the rate of progression to AIDS, and ultimately to the development of clinically useful antiretroviral agents.

Viruses must deliver their genome into the cytoplasm of the host cell to replicate, making entry a critically important first step in the virus life cycle. For HIV and other viruses enveloped by a lipid membrane, entry can be viewed as a process with several discrete steps. Attachment of the virion typically entails engagement of a specific cell surface molecule by a viral membrane glycoprotein, termed envelope (Env) in the case of HIV. The presence or absence of a viral receptor goes a long way toward explaining viral tropism, the ability of a virus to infect some cells but not others. If the receptor is not expressed on a cell, then it is refractory to virus infection. Once bound to its receptor, the viral membrane must fuse with that of the cell so that the viral genome can gain entry to the cytoplasm. Membrane fusion is invariably mediated by a viral membrane glycoprotein, Env in the case of HIV, with the host cell providing one or more cues that trigger the conformational changes needed for the fusion reaction to occur. At the time of Feng et al. (1), virus-membrane fusion was thought to be triggered either by receptor binding or after delivery of virus to endosomes in which low pH induces conformational changes in the viral fusion protein. As early studies showed that HIV can infect cells in a pH-independent manner (2, 3), it was widely thought that entry would result from receptor binding alone. What was not initially appreciated was that the HIV Env protein would need to sequentially engage two receptors to mediate virus entry.

Shortly after the discovery of HIV as the causative agent of AIDS, CD4 was shown to function as a high-affinity receptor for HIV (4, 5), helping to explain the decline of CD4+ T cells that is characteristic of HIV infection. However, it was soon recognized that CD4 expression by itself did not fully explain HIV tropism; expression of CD4 in otherwise CD4-negative cells sometimes failed to make cells susceptible to virus infection, while at other times, it made cells susceptible to a class of viruses termed T cell-tropic virus strains but not to strains capable of infecting macrophages (M-tropic virus strains) (6–10). Over the years, evidence mounted that: in addition to CD4, the HIV Env protein needed to interact with at least one other cellular component, termed a coreceptor; different virus strains might use different coreceptors; and coreceptor binding was the final trigger needed to unlock the membrane fusion potential of Env (6–10). In retrospect, it is somewhat surprising that more than a decade elapsed between the identification of CD4 as a key HIV receptor and the discovery of the first HIV coreceptor by Feng et al. (1), but even today, the identities of many viral receptors remain elusive.

The key to discovering the first HIV coreceptor was the development by Ed Berger and his colleagues (11) of a new assay that made it possible to rapidly and quantitatively assess HIV Env-dependent membrane fusion. In this assay, HIV Env was expressed in a cell line along with a reporter gene under the control of the T7 promoter. When mixed with HeLa cells expressing CD4 and T7 polymerase, the viral Env protein mediated cell–cell fusion, which in turn led to expression of the reporter gene that could be easily measured. However, if the Env-expressing cells were mixed with a murine cell line expressing human CD4, membrane fusion did not occur. Berger and colleagues (11) concluded that although HeLa cells must constitutively express an HIV coreceptor, the murine cell line did not. This provided the basis for an expression cloning approach in which cDNAs from HeLa cells were introduced into murine cells expressing human CD4 in the hopes of making them permissive for HIV Env-dependent fusion. As described in Feng et al. (1), a single clone was identified that, when expressed along with CD4, rendered murine as well as other nonpermissive cells susceptible to membrane fusion mediated by HIV Env proteins from T cell-tropic but not M cell-tropic virus strains. The cDNA encoded a previously identified seven transmembrane domain receptor that was known to be expressed in human T cells but had no known function (12–14). In light of its ability to support HIV membrane fusion, Feng et al. (1) termed this newly discovered HIV coreceptor “fusin.” However, the identity of the coreceptor used by M-tropic HIV strains, which are the strains responsible for the vast majority of infections, remained unknown.

The discovery of fusin initiated an intense period of discovery over the course of the next several months. Although
Fusin had no known function, but it bore sequence similarity to chemokine receptors, which themselves had only recently been described. This observation gave new insight to a paper published at the end of 1995, just 5 mo before the publication by Feng et al. (1). In their study, Cocchi et al. (15) showed that three C-C chemokines were major HIV-suppressive factors secreted by CD8+ T cells. It was logical to infer that the antiviral activity of these chemokines could result from their binding to an as yet unidentified chemokine receptor, likely related to fusin, and that this molecule might also function as an HIV coreceptor. Fortuitously, Marc Parmentier’s laboratory described a new chemokine receptor, CKR5 (now CCR5), just two months before Feng et al. (1) was published. In this study, Samson et al. (16) showed that CCR5 bound precisely the same three chemokines shown by Cocchi et al. (15) to have antiviral activity. Putting the pieces together, five different groups, including the Berger laboratory, showed within 2 mo after the publication of Feng et al. (1) that CCR5 was the coreceptor for M-tropic strains of HIV-1 (17–21). Two of these groups then showed several months later that ~1% of individuals of Northern European decent lacked CCR5 due to a naturally occurring polymorphism in the ccr5 open reading frame and that these individuals were highly resistant to HIV infection (22, 23). The chemokine–HIV connection was further cemented when Bleul et al. (24) showed in August of 1996 that the chemokine SDF-1 is a ligand for fusin, identifying fusin as a chemokine receptor now termed CXCR4.

Feng et al. (1) and related studies provided molecular clarity to the issue of HIV tropism as well as viral pathogenesis. For HIV to infect cells, its viral Env protein must first bind CD4. This induces significant conformational rearrangements in Env that enable it to bind to either the CXCR4 or CCR5 coreceptor, with this in turn triggering the membrane fusion reaction. Most infections result from virus strains that use CCR5 in addition to CD4 to infect cells. Now termed R5 virus strains (25), these typically predominate in the first few years following infection. With time, mutations may accumulate in Env that enable it to use CXCR4 in place of or in addition to CCR5 to infect cells (X4 or R5X4 strains, respectively). The emergence of CXCR4 use is a harbinger of accelerated disease progression, perhaps in part because CXCR4 is expressed on a much greater fraction of CD4+ T cells than is CCR5. The fact that individuals who lack CCR5 are highly resistant to HIV infection ultimately led to the development of CCR5 antagonists that can be used to treat HIV-infected individuals (26).

The story linking HIV and chemokine receptors begun by Feng et al. (1) provides a wonderful example of how asking a basic question—in this case, how HIV enters cells—can lead to the identification of new drug targets and the development of effective drugs and treatment strategies. In fact, the first likely cure of HIV infection has resulted from insight into the HIV–chemokine receptor connection. An HIV-infected patient with acute myeloid leukemia received an allogeneic stem cell transplant from an HLA-matched donor who was homozygous for the ccr5 deletion. Surprisingly, HIV has not been detected in this patient for the more than three years following the transplant even though he has not been treated with antiviral agents during this time (27). Finally, it is interesting to note that the clinical application of CCR5 antagonists represents a fundamentally different approach to treat a viral infection, because it is a host rather than a viral protein that is the antiviral target. This proof of principle has helped spur other efforts to identify host molecules that are critically important for infection by HIV as well as other viruses in the hopes that they, too, can be the targets for new antiviral compounds.

Disclosures
The author has no financial conflicts of interest.

References


