The role of chemokine receptors in HIV infection

Sarah Rowland-Jones

A major breakthrough in HIV research 3 years ago was the identification of the elusive second receptors that the virus needs in addition to the CD4 molecule to get into human cells. A flurry of landmark papers in late 1995 and 1996 showed that members of the chemokine receptor family could be used by different HIV isolates for entry in to CD4+ cells (reviewed in Moore et al and Horuk), and that the chemokines which normally use these receptors can inhibit HIV replication in vitro, presumably by competing with HIV for the receptors. These observations opened up the possibility that the receptors or their ligands could provide new targets for antiretroviral therapy. Over the past few years awareness that the genes encoding these receptors can vary between individuals has led to studies of how such host gene polymorphisms shape the natural history of HIV infection (see fig 1). What now is our understanding of the role of chemokine receptors in HIV infection, and how can this information be used in clinical practice?

In early HIV infection, the vast majority of HIV isolates use the CC chemokine receptor, now referred to as CCR5, which in the blood is expressed predominantly on memory CD4+ T cells, such as those which have responded to a previously encountered pathogen. Moreover, CCR5 is largely expressed on the subset of CD4+ T cells which produce interleukin 2 (IL-2) and interferon gamma (IFN-γ); these are referred to as type 1 helper cells, and make a major contribution to the generation of cellular immune responses. Thus, from the earliest stages of infection HIV is undermining both the immunological memory of its host and the ability to coordinate a cellular immune response to a pathogen.

CCR5 is the major chemokine receptor expressed throughout the genital tract. The first targets of HIV infection acquired by sexual exposure are thought to be the CCR5 expressing dendritic cells in the mucosa. Dendritic cells are specialised cells of the immune system which are designed to pick up foreign antigens in the periphery and transport them to the lymph nodes, where they recruit T cells and initiate an immune response (reviewed in Austyn). This system appears to have been subverted by HIV, which can infect dendritic cells at the mucosal surfaces and then hitch a ride to the lymph nodes. Once in the nodes, the virus is introduced by the dendritic cell to an array of activated susceptible T cells, and the infection of CD4+ T cells then takes off in an explosive manner (reviewed in Rowland-Jones). It is probable that the requirement to infect dendritic cells at the very earliest stages of HIV infection is linked to the very restricted CCR5 usage of infecting isolates, even though the infection may have been acquired from a partner whose dominant virus populations use other coreceptors. This is supported by the observation that people who are homozygous for a 32 base pair deletion in their CCR5 gene (referred to as CCR5-Δ32), which means their cells do not express this...
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1 The role of chemokine receptors in HIV infection is complex and multifaceted. Chemokine receptors play a critical role in HIV infection and disease progression. The virus uses chemokine receptors to enter host cells, and these receptors can also modulate the immune response and disease outcome. Understanding the interactions between chemokine receptors and HIV is essential for developing effective therapies and vaccines.

2 The CCR5 and CXCR4 receptors are particularly important in HIV infection. CCR5 is the primary coreceptor for R5 viruses, which predominate in the early stages of infection. CXCR4 is the primary coreceptor for X4 viruses, which are associated with more advanced disease stages.

3 In HIV-infected individuals, the CCR5 receptor is increasingly being used by the virus, leading to a shift in the viral phenotype from R5 to X4. This change in phenotype is associated with a decrease in viral susceptibility to certain antiretroviral drugs and a delay in disease progression.

4 The CCR5 receptor is found on various cell types, including T cells, monocytes, and macrophages. This receptor is also expressed on neurons, where it may play a role in neuroinflammation and neurodegeneration.

5 CCR5 polymorphisms have been extensively studied in relation to HIV susceptibility and disease progression. Several CCR5 polymorphisms have been identified, including the 32 mutation, which is associated with a reduced risk of HIV infection and a slower disease progression.

6 The CXCR4 receptor is a G protein-coupled receptor that binds to several chemokines, including SDF-1 and MIP-1alpha. The CXCR4 receptor is expressed on T cells, monocytes, and other immune cells. CXCR4 is also found on neurons, where it may play a role in neuroinflammation and neurodegeneration.

7 CXCR4 polymorphisms have also been studied in relation to HIV susceptibility and disease progression. One polymorphism, the 64I mutation, is associated with a decreased risk of HIV infection and a slower disease progression.

8 Understanding the role of chemokine receptors in HIV infection is crucial for developing novel therapeutic strategies. Targeting chemokine receptors with small-molecule ligands or antibody therapies may provide a new avenue for HIV treatment and prevention.
progression was described early in 1998. This is a point mutation in the 3′ untranslated region (UTR) of the SDF-1u gene, for which homozygous approximately 1% of white people showed a striking delay in the onset of AIDS and time to death. Although the effect of this mutation on SDF-1 expression and function is not known, a potential mechanism could be increased production of SDF-1, which then blocks the interaction of the virus with CXCR4. However, protection from disease was not confirmed in another study; in fact, homozygotes for the mutant allele appeared to progress more rapidly to AIDS, so the role of this mutation is controversial.

Although many of these genetic effects remain controversial or confusing, it is feasible that much of the heterogeneity that clinicians observe in the outcome of HIV infection in different people will ultimately be explained by their particular combination of coreceptor and chemokine genes. What are the therapeutic implications of this rapidly expanding area of research? Since CCR5-A32 homozygotes are apparently otherwise entirely healthy, it was reasonable to assume that agents which block CCR5 could be valuable both in HIV therapy and post exposure prophylaxis. Direct use of the CCR5 using chemokines (approximately 1% of white people) showed a striking delay in the onset of AIDS, so the role of this mutation is controversial.

In conclusion, in the 3 years since the identification of the chemokine receptors as coreceptors for HIV entry, many of the mysteries of HIV pathogenesis have become clearer, while the potential of these discoveries for therapy remains to be tapped.


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