HIV: Current Research

Extended Abstract

Expression Analysis of Cell Surface Markers: Cluster of Differentiation 4, Chemokine Receptor 5 and C-X-C Chemokine Receptor Type 4 in Different Cell Lines after Infection with HIV

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Abstract

In the last three decades, extensive research on human immunodeficiency virus (HIV) has highlighted its capability to exploit a variety of strategies to enter and infect immune cells. Although CD4+ T cells are well known as the major HIV target, with infection occurring through the canonical combination of the cluster of differentiation 4 (CD4) receptor and either the C-C chemokine receptor type 5 (CCR5) or C-X-C chemokine receptor type 4 (CXCR4) coreceptors, HIV has also been found to enter other important immune cell types such as macrophages, dendritic cells, Langerhans cells, B cells, and granulocytes. Interestingly, the expression of distinct cellular cofactors partially regulates the rate in which HIV infects each distinct cell type. Furthermore, HIV can benefit from the acquisition of new proteins incorporated into its envelope during budding events. While several publications have investigated details of how HIV manipulates particular cell types or subtypes, an up-to-date comprehensive review on HIV tropism for different immune cells is lacking. Therefore, this review is meant to focus on the different receptors, coreceptors, and cofactors that HIV exploits to enter particular immune cells. Additionally, prophylactic approaches that have targeted particular molecules associated with HIV entry and infection of different immune cells will be discussed. Unveiling the underlying cellular receptors and cofactors that lead to HIV preference for specific immune cell populations is crucial in identifying novel preventative/therapeutic targets for comprehensive strategies to eliminate viral infection.

Human Immunodeficiency Virus (HIV) is a retrovirus that causes Acquired Immune deficiency Syndrome (AIDS). One of the principal cellular targets of HIV infection is the cluster differentiation 4 positive (CD4+) T lymphocytes [1]. HIV leads to the loss of T lymphocytes are a central factor in the progression of the disease, due to their central role in controlling immune responses. HIV infects T cells via interaction between glycoprotein gp120 and the CD4 molecule [2]. Infection of T cells is assisted by the interaction of T cells with C-X-C Chemokine receptor type 4 (CXCR4) and C-C Chemokine receptor type 5 (CCR5) co-receptors. The envelope of HIV-1 mediates virus entry into cells, which comprises surface gp120 glycoproteins non-covalently linked to transmembrane gp41 glycoprotein that/which embed the complex into the viral membrane. HIV-1 entry is initiated by gp120 binding to cellular CD4 [3], which is a high-affinity interaction that facilitates the initial attachment of virus to the target cell. The binding of gp120 to receptor CD4 results in a conformational change in gp120 which exposes the binding site for chemokine receptors CCR5 or CXCR4 [4,5].

Cluster of differentiation 4 (CD4) was demonstrated to be the principal receptor of HIV on T helper cells in 1986 when the virus was tentatively named lymphadenopathy-associated virus.23 In this study, McDougal et al. used radiolabeling techniques in experiments that exposed CD4+ T cells to HIV and found that one of two monoclonal antibodies (mAbs) recognizing different CD4 epitopes was unable to bind HIV-treated cells. Then, through antibody–antigen complex analyses, the authors demonstrated that the CD4 molecule binds to the viral glycoprotein gp120, thus providing evidence that CD4 plays a major role in HIV infection. Other studies utilizing mAbs against CD4 have showed that HIV infection of target CD4+ T cells could effectively be blocked.24–26 In accordance with these results, the forced expression of CD4 through gene transfection into CD4− human cell lines conferred susceptibility to HIV infection. However, forced CD4 expression in other mammalian cells lines, such as those from mice, yielded nonproductive viral infections.27 These conflicting results led to the conclusion that there were proteins specific to human cell lines, in addition to CD4, responsible for viral infection and propagation, and systems deficient in these factors do not support HIV replication.The knowledge gained from studying HIV tropism provides researchers with unique targets to inhibit infection of specific immune cell subsets and target different stages of disease progression, and thus increase the chances of finding useful combinations of antiviral compounds.14,15 Moreover, as resistance to current HIV-1 therapies continues to emerge,16 inhibitors of HIV-1 attachment/entry provide a different mechanism of action than those of the current standards of care, and are potentially of great value in populations where drug resistance is more prevalent. Furthermore, during the pathogenesis of HIV infection, the virus evolves, in part, due to genetic drift of neutral mutations followed by brief episodes of natural selection during the infectious process, changing

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with it the cell subtype preference of the virus, which is dictated by coreceptors expressed by target cells.