UNDERSTANDING HIV:
CO-RECEPTORS – CCR5

discovery of immune cell proteins shows promise for new therapies

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Two new proteins found on immune cells, CCR5 and fusin (also known as CXCR4), play a key role in understanding how HIV infects cells. Though these discoveries may not have immediate impact on people with HIV, they may lead to important advances in HIV treatment, prevention and research in the future.

One way HIV disables the immune system is by infecting and destroying CD4+ T-cells. These cells are critical in managing immune responses and when they are depleted, immune defenses are weakened. When HIV and other pathogens enter the body, CD4+ cells, operating through a network of chemical interactions, instruct other cells to disable the invading organisms. HIV actually attaches to the CD4+ protein on the surface of these and other cells to gain entry.

CD4+ can be likened to a doorway that HIV uses to enter the inner compartments of the cell. However, experiments in test tubes suggest that the CD4+ protein alone is not enough to allow viral entry into cells. Scientists believe they have now identified a second doorway that the virus needs to open to infect a cell, and they have learned that this receptor may be different for different types of cells. One is called CC-CCR5 (CCR5 for short), and another is called CXCR4 or fusin.

Differences between CCR5 and fusin

CCR5 is present on a broad range of cells that can be infected by HIV, including T-cells and macrophages. Fusin on the other hand, is primarily found on CD4+ cells and only appears to serve as a doorway for certain types of HIV. CCR5 appears to be important for NSI strains of HIV (the strains most common in early disease), while CXCR4 appears to be more important for SI strains (a more aggressive strain seen in some people with more aggressive disease).

NSI (non-syncitium inducing) strains of HIV are the most common sexually transmitted form of the virus. This type of HIV preferentially infects macrophages (often found in the skin and mucous membrane) rather than T-cells. Therefore, it is macrophage-tropic, or M-tropic.

When HIV is transmitted sexually, it first establishes itself as an M-tropic virus, later developing into T-cell-tropic viruses in some people. These T-tropic strains that prefer to infect T-cells, are SI (syncitium inducing) viruses and *may* become more prevalent during later stages of the disease. It is unclear why the virus converts from an NSI to an SI strain in some people. About 50% of people who die of AIDS still have a predominant NSI strain of virus.

The SI strain of HIV is more aggressive and its prevalence correlates with more rapid disease progression. Additionally, anti-HIV drugs generally have less activity against SI strains of HIV. The most obvious difference between someone with an NSI versus an SI strain, however, is that people with an SI strain experience more rapid decline in CD4+ counts, as the SI virus preferentially infects and destroys these cells. Also, people with the SI strain tend to have a 3- to 5-fold increase in the rate of disease progression.

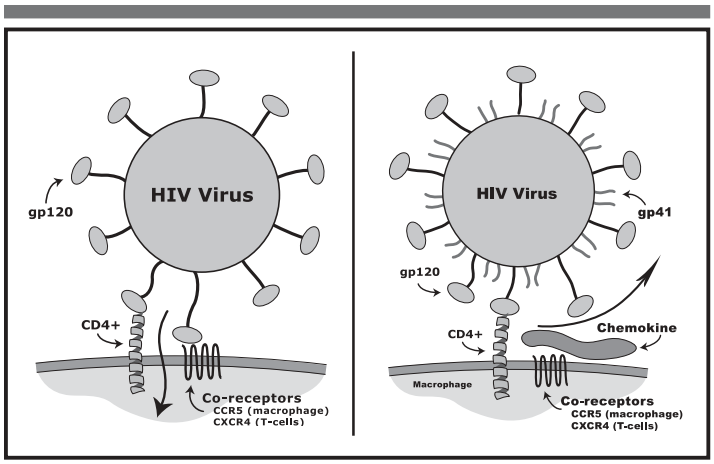


FIGURE 1:
Beta-chemokines block entry of HIV into cells

Chemokines

Coinciding with the discovery of these novel receptors was the discovery that naturally occurring immune chemicals, called beta-chemokines, bind up CCR5 and CXCR4 and help block HIV from infecting cells. This is depicted graphically in **Figure 1** above. For many years it has been supposed that CD8+ cells produce a factor capable of suppressing HIV infection of CD4+ cells.

In 2001, Dr. Robert Gallo's group identified such a factor, which appears to be a combination of chemicals (called chemokines): MIP-1-alpha, MIP-1-beta and Rantes. The fact that CCR5 not only allows HIV entry into CD4 bearing cells, but is also a receptor for these chemokines explains two important aspects of the interaction between the immune system and the virus. When the CD8+ cells effectively make a large quantity of the chemokines, they may fill up and block the "doorway" for infection provided by the CCR5 protein. Conversely, when levels of the chemokines are low or absent for any reason, the virus is free to more easily infect cells because the CCR5 receptor protein is readily available to it.

Collectively, the back-to-back discoveries of the role of the chemokines and the CCR5 receptor site shed important new light on how HIV infects cells and may explain why the disease process differs from person to person. It should also be noted that another CD8+-derived antiviral factor (CAF), documented first by Dr. Jay Levy (co-discoverer of HIV), has been shown to inhibit HIV replication, but the origin of this factor remains unidentified.

Clinical implications

While these findings may not have direct therapeutic relevance at present, they do have some interesting clinical implications for research and treatment in the future. Studies have suggested that some long-term non-progressors have defects in the CCR5 receptor protein and appear to have some immunity to HIV infection.

The study showed that when people inherited a defective version of CCR5 from both parents, they appeared to be resistant to infection with HIV. (The gene is considered defective because a portion of it is missing, and it thus cannot produce a functional CCR5 receptor.) Some people may inherit a single defective version of the gene from one parent, but there is insufficient information to know whether this confers partial protection against infection.

It has been shown that people with the partial CCR5 defect may progress to HIV disease more slowly than someone without the CCR5 defect. This study was extremely small, however, and the defective receptor was found in only two of fifteen people who were thought to be exposed to HIV, yet remain uninfected.

Researchers are already experimenting, in test tubes, with approaches that may be useful in blocking the CCR5 and CXCR4 receptors. Two approaches are possible. One is to artificially give more of the chemokines to people whose CD8+ cells are not producing these chemicals in adequate quantities. The other is to develop methods for directly blocking the receptor sites. Both therapies should help prevent HIV from infecting new cells.

The challenge of either approach is to do this without interfering with the normal function (whatever it is) of the chemokines and the CCR5 receptor sites. Thus far, no known harmful side effects have resulted from the defective gene, in humans, as well as in animal studies. The CCR5 receptor appears to be 'non essential', meaning that binding up the receptor is not expected to interfere with normal immune function. CXCR4, on the other hand, may be more critical. Mice with cells engineered to be CXCR4 deficient died during gestation.

Another potential therapeutic use of these defective CCR5 genes is in stem cell transplantation, where stem cells (the mother of all cells, which divide into the entire spectrum of immune cells) are removed from an individual who has the defective gene and then reinfused into a person with HIV who does not have the defective gene. If stem cells with two copies of the defective CCR5 gene could be successfully transplanted into an HIV-infected individual, they would produce blood cells (lymphocytes and macrophages) that would be naturally immune to HIV infection, although only to infection by NSI strains of HIV.

Another application for these discoveries is the development of better animal models to study HIV disease. A limitation in studying the disease and potential therapies in animals has been that HIV does not infect many animals, and in those species which are infected, HIV rarely causes the immune decline and disease as it does in humans. Engineering animal cells with CCR5 and CXCR4 may provide a way to better research the disease and study potential therapies more efficiently.

the continuing saga

In the fray of excitement over these series of discoveries, the picture was becoming over simplified. More recent information provides a reality check for everyone about the complexity of both the virus and the immune system.

A group from Texas has shown that resting CD4+ cells, despite bearing the CCR5 gene, are resistant to infection by HIV. Another group identified a type of cell, called a stem cell, which had CD4+ and both co-receptors on its surface, yet remained resistant to infection by HIV. What this implies is that there are other factors, beyond the expression of CD4+ and the newly identified co-receptors, which come into play with regard to HIV entry into cells.

A number of research groups show that inheriting the CCR5 deletion from one parent was not the only factor associated with long-term non-progression. An Italian group has presented information on 52 long-term non-progressors. They are defined as people who had been HIV-positive for seven years or longer, consistently had CD4+ cell counts above 500, never experienced symptoms of HIV disease and had never used anti-HIV therapy to maintain their CD4+ cell counts. Among those studied, only 10 of these individuals had the single inherited CCR5 deletion. Thus long-term non-progression is a multifactorial process, with several possible collaborating and independent causes.

In a group of people living with hemophilia and HIV, having inherited a single CCR5 deletion suggested longer-term survival. This doesn't mean that people with the single CCR5 deletion never progressed to AIDS, but rather in general they progressed more slowly. Interestingly, in the group of people living with hemophilia, a deletion in a gene for a newly identified co-receptor, called CCR2, was related to even greater improved survival. What this tells us is that there may be many co-receptors for HIV entry into cells and the field is only just beginning to open up.

For the short term, there will undoubtedly be more questions than answers, though it's encouraging that new information is coming out so quickly. For now, it's wise to anticipate that we'll hear conflicting reports as well as findings of new co-receptors. We can expect some confusion before this field comes into focus.

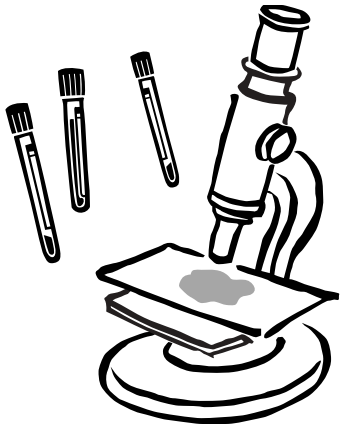
For example, there were a number of reports of identified individuals who had inherited the deletion in the CCR5 gene from both parents and were nonetheless infected with HIV. According to previous reports and identified cases, those who inherited the gene from both parents were assumed to have some natural immunity to HIV infection.

To the contrary, rather than being infected with the most common strain of HIV, the individuals were infected with the type of virus typically only found in some people with advanced stages of HIV disease, that rely on the CXCR4 protein to support entry into the immune cell. This type of virus is associated with dramatic and rapid loss of CD4+ cells and more rapid progression of disease. In line with this, these reported individuals suffered a very rapid course of disease.

With regard to the implications of all these findings to future therapies, a research team in New York has shown that in the laboratory setting, the use of GM-CSF (Leukine) can decrease cell expression of both CCR5 and CXCR4, and thus protect cells from HIV infection. Moreover, chemicals released by the GM-CSF treated cells protected other cells from becoming infected with HIV.

While these observations have only been noted, thus far in the laboratory, GM-CSF is an approved therapy and is being researched in a large clinical trial for its ability to prevent opportunistic infections in people with HIV. It should be relatively easy to start exploring if this effect is seen in humans as well. Several groups are screening for antibodies to block CCR5 and several look promising, although it may be some time before they're ready to be tested in humans.

Commentary on co-receptors



The take home message from discussions of the newly identified co-receptors is that there is a long road ahead before the picture is complete. Undoubtedly new co-receptors will be identified, and already a third receptor, CCR2 has been discovered. Based on these discoveries, therapies that interfere with the virus' ability to infect cells are already being explored. Some of these therapies, like GM-CSF, could be tested in human studies very quickly.

These discoveries are still very new, however, and everyone should be cautious not to over interpret their meaning. Viatical Settlement companies have offered free screening for a CCR5 deletion and some people, who have had potential exposures to HIV yet remain uninfected, are making assumptions that they have natural immunity when perhaps they simply had good luck. To date, the real world implications of these findings are that some people with HIV who have an inherited CCR5 deletion from one parent may be at less risk for disease progression, but clearly less risk doesn't mean no risk.

Certainly there are people with an inherited deletion who have progressed to AIDS and died. CCR5 deletion or not, monitoring health, making wise treatment choices and keeping the virus in check is critical to managing HIV disease. Moreover, CCR5 deletion or not, the factors in long-term non-progression are numerous. There are hundreds of people who have been categorized as long-term non-progressors who have fully intact CCR5 genes.

Finally, no one should assume that they have immunity to HIV infection. Even if someone has inherited the CCR5 deletion from both parents, findings at this conference demonstrate that HIV infection in the face of these deletions may favor a much more aggressive type of HIV, leading to a more rapid course of disease progression.

the bottom line

The bottom line is that these discoveries may some day be important in HIV therapies. At the current time, however, further research is necessary to confirm the findings and develop new ways to interfere with the cellular proteins.