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C-C Chemokine Receptor 5 and HIV:
Therapeutic Potentials of the Δ32 Base Pair Deletion

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ABSTRACT

The human immunodeficiency virus, a retrovirus discovered in 1981, has reached pandemic status worldwide. Without an existing cure or vaccine, a majority of the world’s population remains at risk for infection and more than 35 million people to date have died from AIDS. Resistance to the virus, however, has been discovered in about 10% of the world’s population in the form of an allelic base pair deletion, located on C-C chemokine receptor 5. Those homozygous for the base pair deletion are resistant to HIV, while heterozygotes have displayed delayed onset of HIV infection. The CCR5 mutation and observed resistance to HIV in those with the base pair deletion represent exciting possibilities for the prevention and treatment of the virus. A new class of pharmaceuticals termed CCR5 antagonists, as well as CCR5-Δ32 allogenic stem cell transplantation, hold therapeutic promise not just for HIV but also other chemokine mediated inflammatory diseases, including multiple sclerosis, rheumatoid arthritis, cancer and autoimmune myocarditis.
Introduction

Since the discovery of the human immunodeficiency virus in 1981, scientists have explored every aspect of the virus in the hope of finding a cure. Although this cure or vaccine has yet to be discovered, some hope exists in the recent discovery of a genetic mutation that results in resistance to HIV. C-C chemokine receptor 5 (CCR5) is the cellular locus where the HIV virus enters the cell (5). Some individuals, however, have a 32 base pair deletion at the CCR5 receptor site, resulting in complete resistance to HIV in those homozygous for the deletion and partial resistance or delayed onset of infection in those heterozygous for the deletion (5). The absence of these 32 nucleotides at the CCR5 receptor site results in a truncated, non-functional protein, making it impossible for HIV to enter the human host cell without a necessary coreceptor.

Population surveys have found the overall frequency of this allelic mutation to be as high as 10% among those of European descent, but have not found any individuals of African, Middle Eastern or Asian descent possessing the deletion (11). Because the human immunodeficiency virus evolved relatively recently in history, there is strong a suggestion that the mutation was selected for prior to the emergence of HIV by other factors (14). Among these suggestions are the bubonic plague and smallpox, all of which have been hypothesized as historical selective pressures for the mutation.

While the exact historical origin of the CCR5-Δ32 deletion has yet to be confirmed, the ways in which this base pair mutation influences host defenses presents a hope for HIV and AIDS research. By targeting C-C chemokine receptor 5, a new class of pharmaceuticals termed CCR5 antagonists represent potential for the prevention and treatment of HIV, as well as therapeutic potential for other chemokine mediated inflammatory diseases, including multiple sclerosis, rheumatoid arthritis, cancer and autoimmune myocarditis.
Chemokines and Their Receptors: Structure and Function

The C-C chemokine receptor 5 molecule involved in HIV-1 resistance is one in a class of molecules termed chemokine receptors. True to their name, chemokine receptors act as the body’s receptors for chemokines, small cytokine molecules that promote chemotaxis, or movement within the cell (10). Chemokines are divided between two different classes: those involved in inflammation, pro-inflammatory chemokines, and those involved in tissue maintenance, or homeostatic chemokines (16). These pro-inflammatory chemokine molecules play an important role in the immune system, acting as recruiters and activators for a variety of immune system cells, such as lymphocytes, monocytes, macrophages, eosinophils, and basophils (2). Pro-inflammatory chemokines are responsible for directing host responses to foreign particles by mediating inflammation, and as such are one of the first molecules involved in the inflammatory process.

Chemokines are divided into two different classes: CC chemokines, or β-chemokines, which primarily attract neutrophils, and CXC chemokines, or α-chemokines, which attract monocytes and lymphocytes (2). While the structure varies slightly between the two classes of chemokines, what remains common among all chemokines is the transmembrane structure of their receptors. This 7-transmembrane structure on the leukocyte cellular surface contains both extracellular and intracellular loops, allowing the chemokine receptor to bind with glycoproteins, or G proteins. Once bound to a G protein, the chemokine receptor is considered to be activated, meaning that it can transmit signals to the cell (10).

CCR5 Structure

The structure of the CCR5 chemokine receptor, like all chemokine receptors, has the characteristic 7 transmembrane structure, with 3 extracellular and 4 intracellular loops. The CCR5 receptor ligand also contains an extra-cellular N-terminal domain, involved in receptor signaling, and an intracellular C-terminal domain (10). When chemokine molecules bind to the
CCR5 receptor, a conformation change occurs allowing the activation of the G protein coupled to the receptor and the consequential initiation of cellular signaling (10).

**CCR5 and HIV-1**

The CCR5 chemokine receptor is of particular interest to researchers because of its role as a coreceptor for HIV. HIV, the virus responsible for acquired immunodeficiency syndrome (AIDS) was first identified by scientists in 1981 and has since killed more than 35 million people, the majority of which live in Sub-Saharan Africa (3). 33 million people globally are currently living with the virus (15). HIV is divided into two subtypes: the HIV-1 virus, which is responsible for the majority of all HIV infections, and HIV-2, a less frequent, less-readily transmitted variation of the virus, confined mainly to Western Africa (3).

**HIV-1 Pathophysiology**

Although HIV-1 is as an infectious disease, it is not as highly contagious as many other infectious pathogens; it is not transferrable through fomites, or inanimate objects such as door handles, nor can it be spread by insects, such as mosquitoes in the case of malaria or West Nile virus (19). The only way the HIV-1 virus can be spread is through transmission of bodily fluid from an infected individual, namely blood, breast milk, vaginal secretions, and semen containing a sufficient concentration of the virus to result in infection (19).

Once in the human body, the HIV-1 virus attacks the host’s lymphocytes, specifically T-lymphocyte cells. The HIV-1 infectious process can be divided into two different stages, the M-tropic (primary) and T-tropic (latter) stages (2). In the M-tropic stage, two viral glycoproteins on the HIV capsid (gp41 and gp120) bind to a receptor molecule, CD4, on the T-lymphocyte cell (19). When the virus attaches to the CD4 molecule, gp120 undergoes a conformational change that exposes binding sites allowing it to bind to the chemokine receptor CCR5 (10). Once HIV has bound itself to both the CD4 and CCR5 coreceptor molecules, the virus undergoes yet another conformational change, allowing the hydrophobic regions of gp41 to
insert themselves into the membrane of the host cell (10). Gp41 then folds itself into a 6-helix bundle, bringing the viral membrane and the host cell membrane into closer contact, with the two membranes ultimately fusing together and the HIV viral contents entering the host cell (10).

Once inside, the HIV virus matures and replicates in the host cell, ultimately budding off of the host cell in order to infect other T-cells, resulting in the characteristic depletion of T-lymphocytic cells in HIV-1 positive individuals (19). This depletion of T-cells is part of the T-tropic stage, characterized by a continually declining number of T-cells in the body. In an uninfected individual, the T-cell count is typically around 1,000/mm$^3$ of blood; in an infected individual, the count decreases by 40 to 80 cells per year (19). Once the T cell count has reached 400 to 800 cells/mm$^3$ of blood the body’s immune system has been significantly compromised. Opportunistic infections, such as thrush and shingles, set in and the individual is said to have AIDS-related complex (or ARC) (19).

**The CCR5 - Δ32 Basepair Deletion**

When the role of chemokine receptors in the infectious process of HIV was revealed in 1995, genetic variants in the CCR5 chemokine receptor discovered one year later in 1996 proved the HIV-1 virus is not universally infectious (15). A genetic variation of the CCR5 gene showed that certain individuals have a 32 base pair deletion in the molecular structure of the chemokine receptor, a mutation that shifts the allele’s open reading frame, resulting in a truncated protein (15).

For those individuals homozygous for the deletion, that is to say, with two copies of the gene mutation, the chemokine receptor CCR5 is not fully produced by the body and is absent from the cell surface (2). Without CCR5 coreceptor expression at the surface of the host cell, the HIV-1 virus cannot attach to the host cell or insert its viral DNA, making the individual effectively resistant to HIV-1 infection. Individuals heterozygous for the deletion, possessing only one copy of the mutation, have a reduced number of CCR5 coreceptors expressed at the
cellular surface, a reduction which slows the progression of HIV (2). In addition to the delayed progression of HIV, heterozygotes for the Δ32 mutation have also displayed a reduced viral load. The reduction in the number of CCR5 coreceptors at the cellular surface translates to reduced opportunistic portals for the HIV-1 virus, as well as decreased T-cell destruction (15).

Global Distribution of the CCR5 - Δ32 Mutation

When examining the global distribution of the Δ32 deletion, certain geographical trends become very obvious. The Δ32 mutation is found only in those of European and Western Asian (Russian) origin and exhibits a north-south cline, meaning frequencies of the allele are highest in northern Europe and gradually decline towards the more southern regions (14). For example, the frequency of the allele ranges from 16% in northern Europe (Sweden, Finland, Belarus, Estonia and Lithuania) to 4% in Greece (14). The highest observed frequency of the allele, 20.93%, can be found amongst Ashkenazi Jews, but is most likely a founder effect due to the fact that the Ashkenazi population is highly endogamous (12,14).

The frequency of the Δ32 deletion in European populations, as well as its total absence in Asia, Africa, and the Middle East, is important not only in understanding the origins of the mutation but for discovering ways in which population genetics can be used to understand how the gene was selected for. The absence of the allele in Asian, African and Middle Eastern populations suggests that the mutation arose after these populations diverged (10), and the high allelic frequency observed in certain populations indicates selective advantages for the Δ32 deletion other than HIV (10).

Origins of the Mutation

Because of the way the CCR5 - Δ32 allele is globally distributed, evidence points to a single mutation event as the origin for the mutation (7). Since allele frequencies are highest in Caucasian population and nonexistent in others, the Δ32 deletion indicates an origin dating to sometime after the divergence of various populations from their shared African origin.
Additional evidence in support of the single mutation event theory stems from the size of the deletion – a 32 base pair deletion is a large deletion, meaning that it is highly unlikely to have occurred more than once within the last 1,000 years (7).

**Age of the Allele**

While a single origin of the allele is almost universally agreed upon by researchers, the exact age of the mutation has been a subject of mass debate. Inferences as to the age of the allele have been drawn from the archeological findings from a burial site in Lichtenstein, France – here, a Bronze Age skeleton dating to 900 B.C. The remains of 17 individuals at this site were genetically analyzed and found to demonstrate an allele frequency of 11.8% for the Δ32 deletion (8), indicating that the CCR5-Δ32 allele was prevalent among prehistoric populations of central Europe (8).

Another popular hypothesis regarding the age of the Δ32 deletion has centered around the possible role of the Vikings in its dispersal. The frequency of the allele in Nordic countries such as Norway, Sweden, and Iceland (as high as 16%), suggests that the Vikings may have disseminated the mutation during the raiding of Northern Europe from the 8th to 10th centuries (11).

**Historical Selective Pressures for the Δ32 Mutation**

Because approximately 85-95% of human genetic variation is shared among African, Asian and European populations, the genetic variation seen between these populations regarding the CCR5-Δ32 deletion suggests not only the recent origin of the allele but also influence from a historical selective pressure (22). The frequencies of the allele observed in Europe also indicate the presence of selective pressures – for the Δ32 mutation rate to reach a rate of 10% without any influence from selective pressures would take 127,500 years (7). Additional support for the selective pressure hypothesis stems from the fact that genes encoding proteins for reproductive and developmental functions that maximize survival fitness are shared among various ethnic
populations; those encoding immunological functions are usually pathogenically or historically selected for (22).

_Bubonic Plague and Small Pox_

Because the HIV-1 virus is believed to have evolved relatively recently in human history, it has not been a exerting selection on the human genome long enough to be considered as selective pressure for the Δ32 mutation (7). The two most commonly suggested historical selective pressures for the CCR5 - Δ32 deletion are smallpox and plague.

_Bubonic Plague_

Because of the relatively young age of the allelic mutation, many have suggested that bubonic plague, namely the outbreak that caused the Black Death of 1346 – 1352 is responsible for the frequencies seen in European populations (1,17,18,21). The bubonic plague, caused by the bacterium _Yersina pestis_ (Y. pestis), is a diseases caused by rodents. Outbreaks of the disease must first originate with an epizootic within a rodent population (1). Once large numbers of rodents have died off, the fleas that normally feed off of the rodent populations move to humans in order to obtain blood (1). For bubonic plague to result from the flea bite, the flea must regurgitate the _Y. pestis_ bacillus into the blood stream of the human which it is feeding upon (1).

Because the success rate for the transmission of the _Y. pestis_ bacillus into the human blood stream from a flea bite is less than 20%, the disease spreads through populations slowly (1), and is wholly dependent on the activity levels of the fleas spreading the disease (4). The rodents so commonly associated with the disease, therefore, are simply intermediaries – for bubonic plague to spread, the infected wild rodent population must die and then pass on the fleas carrying the infection (4).

Once the human has been bitten by the _Y. pestis_ carrying flea, they enter an incubation period of two to six days (4). Around the sixth day they experience chills and a fever, as well as severe headaches and body aches (4). The infected person then becomes very confused and
restless, often slurring their speech – within two days of these symptoms setting in, they are prostrate with the symptoms of shock, and will usually die sometime between the third and the sixth day (4).

The aggressive pathology of the bubonic plague explains the high mortality rates observed in Europe at the time of the outbreaks. At least a third of Europe’s population died during the *Y. pestis* outbreak of 1346 – 1352, and some cities, such as Florence, experienced a 75% decline in their population owing to plague mortality (1). In an attempt to explain high levels of the CCR5-Δ32 base pair deletion among Europeans, some scientists have argued that this Black Death outbreak caused a genetic shift in the population of Europe resulting in the HIV-1 resistance observed today (4).

While theories connecting the Black Death to the frequency rates of the Δ32 mutation have been proposed, modern research regarding bubonic plague’s roles in the mutation prove that it most likely was not the cause behind the rise in Δ32 allelic frequencies. In recent laboratory experiments, the connections between *Y. pestis* and CCR5 have been tested to see if a correlation between the two does exist. In these experiments, CCR5 deficient mice, a deficiency that mirrors the absence of the CCR5 chemokine receptor on human cell surfaces in the presence of the Δ32 mutation, were inoculated with Pgm, the *Y. pestis* KIM substrain D27 (13). Two to four days post-inoculation, there was no difference between bacterial load in CCR5 deficient mice and CCR5 expressing mice (13). These laboratory results proved that not only does the *Y. pestis* bacterium not use the CCR5 receptor (4), but also that CCR5 deficiency in mice does not reduce the chance of infection or death from *Y. pestis* infection, meaning it is unlikely that the Δ32 allelic mutation provides plague protection.

Evidence suggesting a selective factor other than bubonic plague also cites plague rates during the 14th through 17th centuries. The Black Death outbreak infamous for killing one third of the European population was a single pandemic – no other large outbreaks of the plague (with
the exception of one in 1665) occurred in Europe after the 14th century, meaning that at most allelic frequency for the CCR5 - Δ32 mutation would have increased from a frequency of $5 \times 10^{-5}$ to $5 \times 10^{-4}$ (5). Using a model combining population genetics with the dynamic of bubonic plague, two researchers, Galvani and Slatkin, developed a model proving that the intermittent nature of the plague epidemics in Europe were not a strong enough selective factor to drive allelic frequencies to that rates of ~ 10% observed in Europe today (6,7).

Smallpox

Because bubonic plague and the *Y. pestis* bacillus were not present in Europe long enough to be considered as a selective factor for the CCR5-Δ32 mutation, it is likely that selection in favor of the base pair deletion occurred because of a disease that *was* endemic to the European population. Smallpox, a disease that occurred in epidemics in Europe at least once every five years from 1347 to 1979, was once such endemic disease (5). While the Black Death may have killed 23 million people during the main outbreak of the disease in the 14th century, smallpox killed more than 300 million people until it was eradicated in 1979 (2).

In addition to its status as a disease endemic to Europe during the time period during which Δ32 was being selected for, it is also necessary to consider the way in which smallpox is transmitted. Because smallpox is transmitted directly between humans (as opposed to the flea-to-human transmission observed for bubonic plague), it was continuously transmitted between the population of Europe during the time (6). The frequency of smallpox outbreaks meant that children were typically the only immunologically naïve individuals in a community – most Europeans experienced a smallpox infection before the age of 10 (7), with only 70% surviving an infection (6). Smallpox, therefore, was exerting continuous selection for the CCR5 - Δ32 mutation over the European population (6) – only those children that survived the childhood outbreaks of smallpox went on to reproduce and pass on selective factors to future generations.
Other evidence pointing in favor to smallpox as the European disease that selected for Δ32 is the similarities between the etiologies of smallpox and HIV (2). Both smallpox and HIV are viruses (as opposed to Y. pestis, which is a bacterial disease). The infectious process in both HIV and smallpox uses chemokine receptors in order to infect lymphocytes, and the gene products from pox viruses actually inhibit chemokine receptors (7). Indeed, one member of the pox virus family, Myxoma virus, specifically targets the CCR5 receptor (2). Although the specific receptors for smallpox have yet to be identified, it is possible that the similarities between the pox viruses could translate to a shared inhibition of the CCR5 receptor, making smallpox a definite candidate as the historical selective factor for HIV.

Just as the model used by Galvani and Slatkin to disprove the likelihood of bubonic plague as a selective factor for the Δ32 mutation, the smallpox virus reaches allelic frequencies of 10% in 680 years (2), almost the exact time period for which smallpox has been endemic in Europe. This model, in combination with the similarities between smallpox and the HIV virus, makes smallpox the more likely disease in European history presently serving as a selective factor for the CCR5 - Δ32 deletion and HIV-1 resistance.

Potential Therapies Involving the CCR5 - Δ32 Deletion: HIV-1

Insight into the historical selective factors not only answers questions regarding how and when the Δ32 mutation was selected for, but also a better understanding of why it was selected for. Using the knowledge gained from these examinations, particularly connections to smallpox etiology, provides information to researchers regarding the ways Δ32 can be used for potential therapies for HIV or other diseases using chemokine receptors as disease pathways.

Current drug therapies for HIV involve a variety of pharmaceuticals. These antiretroviral drugs (ARVs) include nucleoside/nucleotide reverse transcriptase inhibitors, non nucleoside reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors and entry inhibitors (3).
Recent pharmacological research, however, has focused on the ways in which chemokine inhibition, similar to that observed in those homozygous for the Δ32 base pair deletion, can be used to develop new therapies for HIV. Because the main mechanism of entry for the HIV virus involves the CC chemokine receptor CCR5, it is the hope of researchers that two new CCR5 inhibitors (antagonists), maraviroc and vicriviroc, will help slow the progression of HIV to AIDS by inhibiting viral entry into the host cells.

*Maraviroc and Vicriviroc*

Maraviroc, a CCR5 co-receptor antagonist, was first approved by the FDA in 2007, while vicriviroc, also a CCR5 antagonist, is currently in phase III clinical trials (3). Maraviroc’s mechanism of action centers around the host T-cell membrane, where the CCR5 receptor is expressed. By inhibiting chemokine sub-type ligands CCL3 and CCL4, cystine groups at the N-terminal region of the CCR5 receptor, maraviroc blocks intracellular signaling and prevents the interaction between the CCR5 receptor and the gp120 G-protein on the HIV-1 virus necessary for insertion of viral information to the host cell (3). Vicriviroc, as a CCR5 antagonist, works in a similar way to maraviroc, but has yet to be approved for public use by the FDA.

Aside from these two pharmaceuticals, other research has focused on ways to inhibit HIV entry into the host cell by blocking or disrupting the synthesis of the CCR5 chemokine receptor protein (3). Some of the ways in which researchers have decreased CCR5 expression at the cellular surface have ranged from RNA interference (RNAi), a process that cleaves RNA in cells to decrease the expression of certain proteins (3), to the use of zinc fingers, proteins that insert themselves into DNA in order to block protein synthesis, such as the synthesis of the CCR5 receptor protein (3).
Allogenic Stem Cell Transplantation

In addition to the development of CCR5 antagonists, researchers have also recently discovered stem cell transplantation as a therapeutic option for HIV-1 patients. Because R5 tropic strains of HIV-1 must use the CCR5 coreceptor in order to enter the host cell, transplanting stem cells from a donor homozygous for the Δ32 base pair deletion into an individual without the deletion should result in the recipient acquiring the HIV-1 resistance observed in the donor. In recent experiments with the procedure, a HIV-1 positive patient received stem cells from an HLA matched Δ32 homozygous donor. The patient’s HAART antiretroviral therapy was discontinued prior to transplantation (9). Cellular analysis post-transplantation revealed HIV-1 to be undetectable (9). In just 61 days, the patient’s genotype changed from homozygous for absence of Δ32 base pair deletion(-/-) to a +/+ Δ32 homozygous state in which the CCR5 receptor was completely absent from mucosal T-cells (9). At the time of release of the study (2009 – 20 months post-transplantation), the patient still remained without viral rebound (9).

Potential Therapies Involving the CCR5 - Δ32 Deletion: Chemokine Mediated Disease

While research into the Δ32 base pair deletion has provided many viable therapeutic options for the HIV-1 virus, it has also demonstrated the ways in which other chemokine related diseases can be manipulated. Like HIV, many other diseases - such as multiple sclerosis, rheumatoid arthritis, cancer and autoimmune myocarditis – also use chemokines and chemokine receptors as mediators of inflammation. By exploring the role of CCR5 in HIV-1, researchers have gained a better understanding of how this receptor impacts the pathologies of numerous other autoimmune diseases.
Multiple Sclerosis

Multiple sclerosis is one such autoimmune disease that displays significant chemokine involvement in its pathology. The demyelination of neuronal axons that causes the neurological symptoms associated with the disease (muscle tremor, loss of sensation in the periphery, difficulties with coordination, etc) is caused as a result of leukocyte infiltration into the central nervous system (16). The CCR5 receptor was found on the lymphocytic cells in brain lesions of MS patients, and was expressed at heightened levels by the T-cells in their cerebrospinal fluid (16). The increased expression of CCR5 in CSF fluid of MS patients suggests an active role of CCR5 in the immune response that causes neuronal demyelination.

Several recent studies have focused on how CCR5 suppression in MS patients via CCR5 antagonism could produce therapeutic benefits. While no study has been conclusive, CCR5-Δ32 homozygous individuals with the disease provide clues as to how antagonism at the CCR5 receptor site could be beneficial to MS patients. The Δ32 deletion has not been shown to prevent onset of the disease, but it has been shown to delay it, with Δ32 homozygous individuals developing the disease up to 3 years later than their CCR5 expressing counterparts (16).

Rheumatoid Arthritis

Like MS, rheumatoid arthritis is also an autoimmune disease. While MS inflammation centers around the myelin sheaths of neuronal axons, rheumatoid arthritis is characterized by inflammation of the synovial joints, resulting in extreme difficulty and pain when moving these joints. The inflammation of the synovial joints is caused by T lymphocyte infiltration, a process mediated by chemokines (16). CCR5 has been found in the synovial fluid of patients with rheumatoid arthritis - fibroblasts in the synovial joint upregulate CCL5, a ligand of the CCR5 receptor (16).

As with multiple sclerosis, heightened CCR5 expression at the inflammatory site suggests the therapeutic benefits of CCR5 antagonism. Since the Δ32 deletion has been associated with
decreased severity of the disease, CCR5 antagonists represent definite promise for rheumatoid arthritis patients.

Cancer

Cancer cells, particularly pancreatic and prostate cancer cells, have also proved to be possible sites where CCR5 antagonism would prove beneficial. Because cancer cells can induce inflammation via chemokines (3), antagonism at the chemokine receptor site would reduce this inflammation and prevent further tumor growth and metastasis (3). Some types of breast cancers have also demonstrated increased metastasis in response to chemokines (3). CCR5 antagonism could block the signaling associated with inflammation, preventing tumors from growing or spreading to other areas of the body. One CCR5 antagonist, TAK-779, has proved especially effective in preventing tumor proliferation and metastasis in prostate cancer cells (3). Further research into the use of these drugs could potentiate future therapies for many other types of cancers.

Autoimmune myocarditis

Autoimmune myocarditis is an autoimmune disease in which T cell infiltration promotes inflammation of heart muscle tissue. In dissections of inflamed myocardial tissues, CCR5 was found to be upregulated, once again suggesting its role in the disease’s pathology (3). In experiments done with mice, CCR5 antagonism proved to reduce the severity of myocardial inflammation, and those mice that lacked CCR5 expression (Δ32 homozygous) showed decreased incidence of the disease (3). Should these results were to carry over to humans in further research, CCR5 antagonism could hold great therapeutic promise for patients with the disease.

Conclusions

The CCR5 - Δ32 base pair deletion, in addition to providing HIV-1 resistance in individuals homozygous for the mutation and delayed onset of AIDS in heterozygotes, holds
promise for future research not only in HIV but also other chemokine-related disorders. By studying the ways in which the Δ32 deletion affects chemokine mediated diseases, researchers can gain a better understanding of the process of inflammation and intercellular chemotactic signaling that results in disease. Manipulation of the chemokine system and resulting inflammation through CC5R receptor antagonism has the potential to propagate a cure for multiple autoimmune related diseases as well as inflammatory-based disease as a whole.
**Figure 1**: The Structure of the CCR5 Chemokine Receptor. Here, the 7 transmembrane structure of the CCR5 receptor is displayed, with 3 extracellular and 4 intracellular loops, as well as the extracellular N-terminal domain used for receptor signaling.

Figure 2: Entry of the HIV-1 Virus Into the Host Cell. The HIV-1 virus, via gp120 and gp41, binds to coreceptors CD4 and CCR5, undergoing conformational changes until the ultimate fusing and insertion of viral information into the host cell.

Figure 4: Map Showing the Distribution of the CCR5-Δ32 Allele.

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LITERATURE CITED


