The CCR5Δ32 Mutation's Role in HIV Immunity

Biology 196L Section 001

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Abstract

The CCR5Δ32 mutation provides a protective factor against HIV progression by reducing or eliminating HIV's ability to enter the host cell and replicate. Individuals who are heterozygous for the CCR5Δ32 mutation experience significantly slower than average progression rates to AIDS, while those who are homozygous for the mutation escape HIV infection despite, in some cases, repeated exposure to the virus. Knowledge of the immunity that the CCR5Δ32 mutation confers has led to novel therapeutic treatments designed to suppress expression of CCR5 receptor sites, as well as a cure. However, an incomplete understanding of the interplay between host and viral factors coupled with the virus's ability to mutate has revealed the limitations of focusing solely on inhibiting/eliminating CCR5 receptor sites. Despite these limitations, the CCR5Δ32 mutation will be, with more research, a vital team player in the fight against HIV.

At the close of 2009, HIV and AIDS claimed an estimated 1.8 million lives, orphaned an estimated 16 million children, and infected an estimated 2.6 million individuals worldwide (AVERT, n.d.). These statistics alone accentuate the need for, not only new and effective treatments, but a cure. However, since its discovery in 1981, developing a cure for HIV has proven challenging due to an incomplete understanding of the interplay between host and viral factors, and the virus' ability to rapidly evolve. Despite these difficulties, headway has been made in the development of new treatments, and even a possible cure using clues from those individuals who possess innate immunity to HIV.

HIV, like other viruses, uses the host's machinery to reproduce; its specific targets are $CD4^+$ cells, which are those immune cells that coordinate immune response and the formation of antibodies (Neimark, 2011). Once inside the host, HIV sequesters itself in $CD4^+$ cells, gaining entry via CD4 receptors and CCR5 co-receptors. Now, safely tucked away, HIV reprograms the host's immune cells to produce more of the virus, ultimately killing the host cells in the process. Though HIV is able to successfully hide in the very cells that would normally coordinate its demise, the host body does respond by attacking the virus and replacing the cells that HIV kills (Brown, 1997). However, over time, HIV destroys $CD4^+$ cells at a rate faster than the host can replace; this is when the host's $CD4^+$ cell count begins to drop and the immune system begins to weaken. Once the host's $CD4^+$ count is below $200/mm^3$, and/or the host develops an AIDS-defining illness, such as Kaposi's sarcoma and pneumocystis carinii pneumonia, the disease has officially progressed to AIDS (O'Brien & Dean, 1996). The progression from HIV to AIDS typically takes ten years, but variability in the timeframe exists amongst those infected (Reiche, Bonametti, Voltarelli, Morimoto, & Watanabe, 2007). It is this variability that reveals those rare

individuals who have partial or near complete immunity to HIV due to a mutation in the co-receptor CCR5 gene (Reiche et al., 2007).

The CCR5Δ32 mutation creates a CCR5 co-receptor that is too short and therefore remains intracellular, making it inaccessible to HIV (Reiche et al., 2007). Individuals with one copy of the mutated CCR5 gene have fewer CCR5 receptor sites available to HIV, and therefore progress to AIDS at a much slower rate (Reiche et al., 2007). They remain asymptomatic with normal $CD4^+$ cell counts and low or undetectable viral loads for "prolonged periods" (Reiche et al., 2007, p.1325). Rarer still are those individuals, about 1% of the global Caucasian population, who have two copies of the mutated gene (Neimark, 2011; Reiche et al., 2007). These individuals have no CCR5 receptor sites, and are immune to those HIV strains that use this site. Despite a high risk for infection—defined as repeated exposure to the virus—these rare persons fail to contract HIV (Reiche et al., 2007). This immunity is nothing short of spectacular; however, the challenge is figuring out how to harness this natural immunity for the benefit of the broader population.

Armed with the knowledge of the CCR5Δ32 mutation's role in protecting the host from HIV invasion by blocking the virus' entry into host cells, researchers have devised strategies to confer this resistance to others (Schafer, 2011; Neimark, 2011; Weaver, 2010). Two such strategies are creating compounds that bind to and inhibit CCR5 co-receptor sites and gene therapy (Schafer, 2011; Neimark, 2011; Weaver, 2010). Drugs such as Maraviroc contain small compounds that bind to CCR5 co-receptors, thereby inhibiting HIV's ability to enter the cell (Reiche et al., 2007). The rationale behind this approach is that if HIV cannot get in, then it cannot replicate, wreck the immune system, and progress to AIDS. Another approach is gene therapy with the use of zinc finger nucleases (Schafer, 2011; Neimark, 2011; Weaver, 2010).

Zinc finger nucleases—proteins that cut specific DNA sequences—are used to disrupt the expression of CCR5 co-receptors in host cells (Weaver, 2010). Mature $CD4^+$ cells are extracted from the host, treated with the zinc finger nucleases, and reintroduced to the host body (Weaver, 2010). Research indicates that these modified cells survive in the host, and replenish the host's immune system with cells that resist infection (Weaver, 2010). Both of these approaches have reduced the progression of HIV to AIDS in those individuals infected with the virus, but they are far from cures, as they only stabilize $CD4^+$ counts, and delay or inhibit progression (Weaver, 2010). They do not eliminate the disease. In 2007, Dr. Gero Hütter demonstrated that more drastic measures may be necessary for a complete cure of the disease (Neimark, 2011).

In 2006, Dr. Hütter gained a new patient, Timothy Ray Brown (Neimark, 2011). Brown had myeloid leukemia and HIV (Schafer, 2011). Brown's HIV was sufficiently controlled; however, because chemotherapy had failed to treat his leukemia, a bone marrow transplant was needed (Neimark, 2011). Because $CD4^+$ cells are produced in the bone marrow, Dr. Hütter, who was familiar with the research surrounding HIV immunity, chose an individual who was homozygous for the CCR5Δ32 mutation to be Brown's donor (Neimark, 2011). After Dr. Hütter destroyed as much of the infected bone marrow as possible, he gave Brown his donor transfusion and directed Brown to stop taking his antiretroviral medications (Neimark, 2011). Over sixty days later, Brown was HIV free, and, to this day, remains so; however, the methods associated with his cure pose significant barriers to expanding this form of treatment to a wider population (Niemark, 2011; Schafer, 2011).

The first barrier is the availability of suitable donors. As previously stated, individuals who are homozygous for the CCR5Δ32 mutation make up approximately 1% of the global Caucasian population, and not everyone in this 1% is a suitable donor (Schafer, 2011; Neimark,

2011; Weaver, 2010). The second, and most prohibitive barrier, is the risk of graft versus host disease (GVHD) (Schafer, 2011; Neimark, 2011; Weaver, 2010). GVHD is a disorder in which donor cells attack the host's cells causing a variety of problems, one of which is death (Neimark, 2011; Schafer, 2011; NCBI, n.d.). In order to combat GVHD, patients are given immunosuppressant drugs, which leave them susceptible to opportunistic infections, thereby potentially defeating the purpose of the transplant (Schafer, 2011). With these barriers in mind, researchers are starting to experiment with gene therapy by modifying the host's own stem cells with zinc finger nucleases designed to disrupt CCR5 co-receptor expression (Schafer, 201; Neimark, 2011; Weaver, 2010). These disrupted stem cells are then multiplied and given back to the host without any risk of GVHD (Neimark, 2011; Weaver, 2010; Schafer, 2011). Therefore, a cure, inspired by Brown's recovery, and made possible by the discovery of the CCR5Δ32 mutation, may one day be made available to the world. However, the CCR5Δ32 mutation, along with its inspired treatments and cures, may not be the panacea that the world is hoping for.

One reason for this is the fact that HIV binds with other co-receptor sites (Reiche et al., 2007). CCR5 may be its favored co-receptor site, but HIV is also capable of recognizing the CXCR4 receptor site (Schafer, 2011). In fact, strains that use the CCR5 co-receptor site in early stages of HIV infection commonly evolve to prefer the CXCR4 co-receptor site (Reiche et al., 2007). In light of this, a treatment or cure that specifically targets the CCR5 co-receptor site would not be effective for all cases of HIV infection. Other concerns suggest that the CCR5Δ32 mutation's ability to regulate viral replication may be underappreciated (Dolan et al., 2007).

Some researchers like Dolan et al. (2007), have become convinced that the CCR5Δ32 mutation's ability to inhibit HIV disease progression by blocking HIV's entry into the cell may only be a part of the picture. Evidence for this belief comes from the observation that some hosts

for the Simian Immunodeficiency Virus (SIV)—the simian version of HIV—with reduced numbers of CCR5 co-receptor sites remain healthy with no decline in $CD4^+$ cells despite high viral loads (Dolan et al., 2007). Further evidence is found in viremic and elite controllers, those HIV infected individuals who, respectively, maintain low or undetectable viral loads in the absence of treatment, and therefore, remain asymptomatic (Niemark, 2011; Dolan et al., 2007). Investigations into how this can be have revealed that the CCR5Δ32 mutation, along with the CCL3L1 gene (of which high expressions of this gene is associated with a lower proportion of CCR5 expressing cells), may affect HIV progression through, not only the restriction of viral replication, but also through a stronger immune response against the virus, and other host factors that are not yet completely understood (Dolan et al., 2007). Therefore, researchers are inclined to believe that simply inhibiting HIV's ability to enter the cell may not slow disease progression as well as previously believed (Dolan et al., 2007). Other researchers, such as Crawford, Angelosanto, Nadwodny, Blackburn, and Wherry believe that inhibiting CCR5 may have unintentional deleterious effects on the host's immune system (2011).

Although individuals homozygous for the CCR5Δ32 mutation do not appear to be adversely affected by the absence of CCR5 co-receptor sites (Reiche et al., 2007), some researchers have found that defects/deficits of CCR5 co-receptor sites disrupts the effectiveness of RANTES, a protein that assists in orchestrating immune response (Crawford, Angelosanto, Nadwodny, Blackburn, & Wherry, 2011). This disruption may leave the host vulnerable to certain chronic viral infections, such as the West Nile Virus and some forms of encephalitis (Crawford et al., 2011). This suggests that CCR5 may have a role in regulating viruses other than HIV, and illuminates the need for a reexamination of the effects of blocking CCR5 co-receptor sites.

A final consideration against the CCR5Δ32 mutation being a holy grail for HIV immunity is the viruses' ability to rapidly evolve. HIV replicates its DNA from RNA with the aid of reverse transcriptase, a process that can create numerous variations of viral DNA, which then leads to mutant strains of HIV (Brown, 1997). These mutant strains can either use the common co-receptor, CCR5, or they can evolve to use other receptors such as the CXCR4, CCR2, and CCR3 co-receptors (Reiche, et al., 2007). Given these facts, the focus on the CCR5 co-receptor is too narrow since HIV may rapidly evolve to circumvent CCR5Δ32-mutation-inspired treatments and cures.

Although the CCR5Δ32 mutation appears to be a very important player in treating and curing HIV, the aforementioned limitations remind researchers that there is no "I" in team. More research is needed to clarify the following: CCR5's role in HIV pathogenesis and immune response; the interplay between host and viral factors; and ways to effectively combat HIV's ability to rapidly evolve. With additional research and advances, researchers may be able to compose a "team" in treating and curing HIV, of which the CCR5Δ32 mutation may, or may not be, the MVP.

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