Review / Derleme

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Gene-editing of CCR5 for the Treatment of HIV: A Novel Therapeutic Approach

HIV Tedavisi için CCR5 Gen Düzenlemesi: Yeni Bir Tedavi Yaklaşımı

Ramakrishnan Veerabathiran, Shahil Ahamed Mansoor, Iyshwarya Bhaskar Kalarani, Vajagathali Mohammed

Human Cytogenetics and Genomics Laboratory, Faculty of Allied Health Sciences, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Tamilnadu, India

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Corresponding Author: Ramakrishnan Veerabathiran, Human Cytogenetics and Genomics Laboratory, Faculty of Allied Health Sciences, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Tamilnadu, India
Phone: +919840636315 **E-mail:** rkgenes@gmail.com **ORCID:** orcid.org/0000-0002-9307-5428

Abstract

Human immunodeficiency virus (HIV) was thought to be the medical pandemic of the 21st century, infecting 77.3 million people and being the cause of the deaths of 34.5 million people. To date, various studies have deepened our understanding of the structure, variability, and replication of HIV, considered virological and immunological mechanisms associated with the infection and helped design new therapeutic approaches. Antiretroviral treatment has transmuted AIDS from a deadly condition specific to a prolonged, controllable disease. In 1996, CCR5 and CXCR4 were co-receptors for HIV-1 entrance. CCR5 is the most critical chemokine co-receptor for HIV-1 entry. In 2008, allogeneic transplantation of mutant CCR5-d32 homozygous stem cells into HIV-infected people resulted in ongoing viral control and maybe extinction of HIV. Since then, there has been a strong emphasis on expanding this method to a larger population and using gene-editing techniques like transcription activator-like effector nucleases, zinc finger nucleases and clustered regularly interspaced short palindromic repeats in hematopoietic stem cells to make subjects immune to HIV. This research aims to look at the use of gene-editing methods in allogeneic hematopoietic stem cell transplantation as a possible HIV treatment approach. Based on the literature, it is found that subjects infected with HIV who underwent gene-editing methods to edit the *CCR5* gene on hematopoietic stem cells for 32 bp removal in the *CCR5* gene have been proven to enhance positive results of the maximum number of patients.

Keywords: HIV strains, *CCR5* gene, therapeutics, gene editing, stem cells

Öz

İnsan immün yetmezlik virüsünün (HIV) 21. yüzyılın tıbbi pandemisi olduğu, 77.3 milyon insanı enfekte ettiği ve 34.5 milyon insanın ölümüne neden olduğu düşünülmektedir. Bugüne kadar yapılan çeşitli araştırmalar, HIV'nin yapısı, değişkenliği ve replikasyonu, enfeksiyonla ilişkili virolojik ve immünolojik mekanizmalar hakkındaki bilgilerimizi derinleştirmiş ve yeni terapötik yaklaşımların tasarlanmasına yardımcı olmuştur. Anti-retroviral tedavi, AIDS'i ölümcül bir hastalıktan, kontrol edilebilir bir hastalığa dönüştürmüştür. HIV-1 girişi için, 1996 yılında, CCR5 ve CXCR4 ko-reseptör olarak tanımlanmıştır. CCR5, HIV-1 girişi için en kritik kemokin ko-reseptörüdür. 2008'de, mutant CCR5-delta 32 homozigot kök hücrelerinin HIV ile enfekte insanlara allojenik nakli, devam eden viral kontrol ve belki de HIV'in neslinin yok olması ile sonuçlanmıştır. O zamandan beri, HIV'ye bağışıklık kazandırmak için, bu yöntemin daha geniş bir popülasyona yayılmasına ve transkripsiyon aktivatör benzeri efektör nükleazlar, çinko parmak nükleazlar ve hematopoietik kök hücrelerde kümelenmiş düzenli aralıklı kısa palindromik tekrarlar gibi gen düzenleme tekniklerinin kullanılmasına güçlü bir vurgu yapılmıştır. Bu araştırmanın amacı, olası bir HIV tedavisi yaklaşımı olarak allojenik hematopoietik kök hücre naklinde gen düzenleme yöntemlerinin kullanımını incelemektir. Literatüre dayalı olarak, *CCR5* geninde 32bp çıkarılması için hematopoietik kök hücrelerde *CCR5* genini düzenlemek amacıyla gen düzenleme yöntemleri uygulanan HIV bulaşmış deneklerin, maksimum sayıda hastada pozitif sonuçları artırdığı kanıtlanmıştır.

Anahtar Kelimeler: HIV suşları, *CCR5* geni, terapötikler, gen düzenleme, kök hücreler

ORCID: R. Veerabathiran 0000-0002-9307-5428, S. A. Mansoor 0000-0002-2050-4543, I. B. Kalarani 0000-0001-9368-3434, V. Mohammed 0000-0003-1342-3689

Introduction

The human immunodeficiency virus (HIV) was considered the medical epidemic of the twenty-first century (1). The very first case of HIV infection was discovered in the summer of 1981 (2). Homosexual people develop immunodeficiency and die due to illnesses that their immune responses should have been able to fend off (3). Additionally, infected patients may develop dark purple tumors caused by Kaposi's sarcoma, infectious cancer (4). In 1982, the Centers for Disease Control and Prevention coined acquired immunodeficiency syndrome (AIDS) (5). Early theories indicated that AIDS was transmitted by environmental factors such as homosexual men and intravenous drug users (6). HIV is a member of lentivirus (LT) genus, retroviruses with variable genomes, and cone-shaped capsid core particles belong to the LT family (7). LT can successfully infect non-dividing cells (8). HIV's retroviral genome is made up of two similar retroviral RNA copies (9). Initially, a virus enters a new host cell, its genome, like that of all retroviruses, is encoded by RNA transcribed into viral DNA by the viral reverse transcriptase (Figure 1) (10). It is mainly grouped into 2 different types, HIV-1 and HIV-2, based on their genomic structure. HIV-1 is the primary group that infected 60 million people and resulted in the deaths of 25 million people (11). The structural genes like a gag, pol, and env are present in both HIV strains (12).

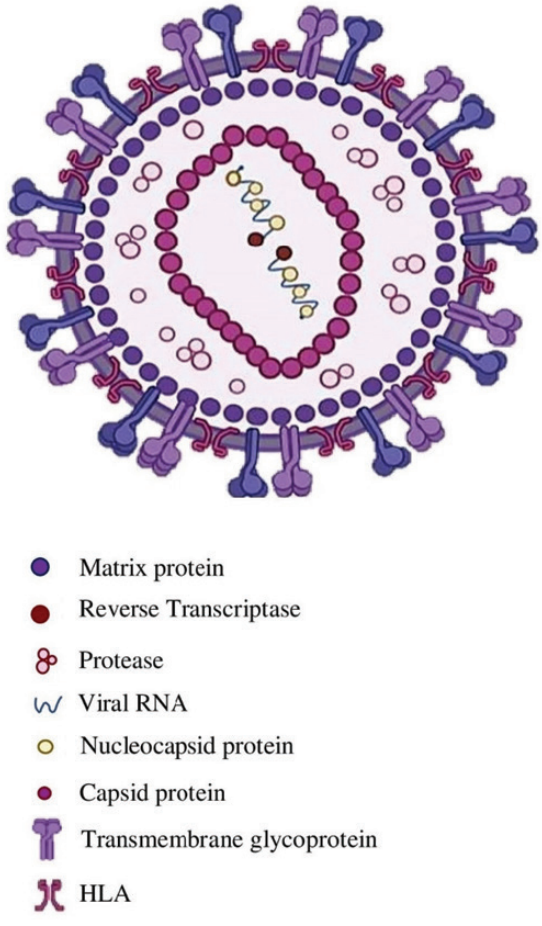

Figure 1. Structure of the HIV genome.

HIV Infection and Mechanism

The most common method of HIV transmission is sexual transmission (ST) (13). It is contracted by contact with cell-free or cell-associated infectious viruses in the sperm or mucosal surfaces (14). Transfer of HIV through injective drug use, exposure to contaminated blood and blood products through blood transfusion, and transmission of HIV to a fetus or child from an infected mother are among the less prevalent modes of infection (15). Under one week after exposure, partly activated $CD4^+$ T-cells in the vaginal mucosa were identified as the first sites of productive viral replication in early studies of ST in the SIV model (16). After total exposure, $CD4^+$ T-cells become more activated, with SIV spreading locally a few days later in the less numerous but more vulnerable activated $CD4^+$ T-cells (17). According to a more recent study on SIV infection in macaques (18), the virus subsequently travels swiftly to gut-associated lymphoid tissue, most likely through draining, in the gastrointestinal lamina propria, where it causes a significant loss of memory $CD4^+$ T-cells. A comparable cellular decrease appears to occur (19,20). The replication cycle of HIV bears a substantial similarity to that of other LTs (21,22).

HIV and SIV have unique binding receptors and co-receptors, unlike other LTs (23). HIV replication has 2 phases; early and late (8). The early phase is marked by recognizing targeted cells by the mature vision and the process leading to and including the genomic DNA into the host cell's chromosome. The late phase is marked by the controlled expression of the incorporated pro-viral genome (24). It can be summed up in seven steps; I) attachment and entry; II) reverse transcription III) nuclear import; IV) integration; V) transcription; VI) nuclear export; VII) synthesis and packaging of viral proteins (25,26). It encompasses the whole process, from the virus budding to viral maturation (27). Most provirus-carrying cells were discovered to be of clonal origin, with defective provirus being the most habitual. HIV incorporates actively transcribed genes, mainly oncogenesis, and cell-cycle control genes. According to a report, 99 percent of infected cells belong to a clonal population. Figure 2 demonstrates the mechanism of HIV in the human body.

HIV Strains and Chemokine Receptors

A co-receptor is a surface cell receptor to which a signaling molecule binds to other than the primary

receptor to assist ligand recognition and initiate biological processes, such as entering a pathogen into a host cell (28). This receptor classification is based on structure, disulfide-like cysteine residues, and angiogenic effects (29). There are 17 known co-receptors for these chemokine ligands (30). CCR5 and CXCR4 are the most critical co-receptors in HIV infection (31). Tropism refers to a virus's capacity to connect to certain co-receptors (32). Based on the dominant co-receptor in the early stages of infection, HIV is divided into three major tropic strains (33). B-chemokine CCR5 is the most prevalent co-receptor in the HIV-1 genetic grouping (33). This strain is also known as macrophage or m-tropic (34). CXCR4 acts as the co-receptor in other isolates for entry and replication and is also known as T-lymphocytic or T-tropic. HIV can attach to CCR5 and CXCR4 receptors, a dual tropic or X4R5 strain (35). Knowledge of the structure, variability, and replication of HIV is essential for understanding virologic and immunological mechanisms associated with the infection and helps designing new therapeutic approaches (36). This review focuses on therapeutic methods that act as a potential treatment for HIV-1 infection using CCR5 b32 silencing as an alternative to traditional treatments like Highly Active Antiretroviral Therapy (HAART). Table 1 shows the types of HIV strains and structural genes.

Traditional HIV Treatments and Side Effects

In 1996, triple drugs were introduced into antiretroviral medication regimens comprising a varied blend of nuclear and non-nucleoside and protease inhibitors-widely known as HAART, a triple-combination antiretroviral treatment (ART) with two nucleoside-reverse transcriptases (NRTIS) suppresses and prevents the development of viral replication (37). It also includes triple-combination ART with a protease inhibitor (PI), a non-nucleoside-reverse transcriptase inhibitor (NNRTI). Although the routines were complex and frequently challenging to monitor, HAART has transformed AIDS to a protracted and controlled illness (38). However, these effective agents result a toxicity rate ranging from endocrinological, hematologic, and cardiovascular problems to fat loss and redistribution syndromes (39). In a study of 862 HIV-infected individuals on treatment, toxicity was the most common reason for cessation, with 312 patients (36.2%) reported it as the reason (40). Non-adherence and failure to complete the treatment (including immunologic, virologic, and clinical failure) led to treatment discontinuation in 19.6% and 14.1% of these patients, respectively (41). Lipodystrophy is a type of fat cell maldistribution that comprises lipoatrophy, and lipid accumulation is associated with several negative consequences. PI and NRTIS-based art regimens have been linked to lipodystrophy (42). Rash has been recorded in 10-17% of individuals who have used the NNRTIS system (43). IDV usage is associated with retinoid-like symptoms, including baldness, dry skin, dry lips, and ingrown nails, in roughly 30 percent of patients who received t16 (44).

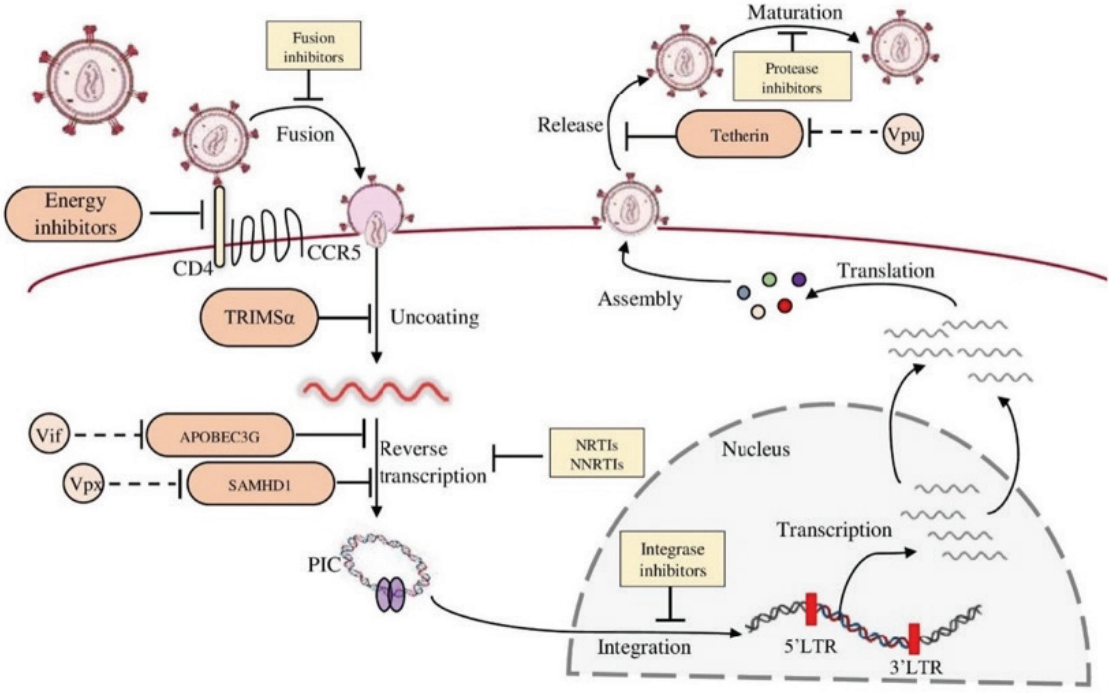

Figure 2. Replication cycle of HIV.

CCR5 Gene

This gene has G protein-coupled receptor, includes seven transmembrane domains and is located on monocytes/macrophages, B-cells, T-cells, and microglia (45). RANTES and MIP are two chemokines that attach to and are secreted (regulated on activation, normal T-cell expressed and secreted) (46). CCR5 is located on chromosome 3p21, near the *CCR2* gene. *CCR5* gene variants have been linked to an increased risk of HIV infection, according to several studies (47). In Europe, 10% of people carry the CCR5-delta32 (CCR5d32) allele (48). Homozygote frequency in the population is around one percent (49). Several diseases, especially those affecting the nervous system, have been linked to CCR5 (50). Tissue-resident macrophages, microglia, dendritic cells, langerhans cells, and osteoclasts are among the cell types that express CCR5, 76 times higher than the expression in $CD4^+$ T-cells in NK cells (22). Other cells that express CCR5 include langerhans cells and osteoclasts (51). Additionally, researchers have discovered CCR5 expression in various non-hematopoietic cells, including neurons, endothelial cells, smooth muscle cells in the arteries, and hepatic stellate cells (52). R5 tropic strain, the most predominant strain transmitted in the initial stages of infection, binds to CCR5 and makes CCR5 act as a predominant chemokine co-receptor in HIV-1 infection (53). CCR5 is the significant co-receptor in 51% of HIV-1 infections (54). Non-hematopoietic cells, including osteoblasts, fibroblasts, vascular endothelium, epithelium, vascular smooth muscle cells, liver cells, and neurons, express CCR5 with other physiological symptoms functions that are not related to the immune response (55). However, editing CCR5 does not meet the 1st criterion because that homozygosity for the CCR5d32 mutated gene has unusual adverse events (56), a four-fold increased risk due to influenza related death (57), and impaired bone resorption activity (58). Furthermore, CRISPR-Cas9 has been linked to several articles documenting unintended off-target alterations (59). Some infrequent but significant alterations were reported (60), others detected substantial reductions (61,62), and further revealed inexplicable complicated deletions and substitutions in rodents created using CRISPR-Cas9 (63). As a result, the CCR5 twins must be closely examined for some expected outcomes, including greater vulnerability to influenza infection, aberrant bone formation, and other inflammatory problems (64).

Mutation in CCR5

The CCR5d32 mutation was found in few people who were immune to HIV-1 infection after being regularly exposed to it (65). In the CCR5 chemokine receptor locus, the CCR5d32 allele produces a premature stop codon of 32 base pairs, leading to receptor obliteration (66). It confers resistance to HIV-1 infection (67). Due to inefficient HIV binding on targeted cells, subjects with the CCR5 mutation are comparatively strongly HIV-resistant 1 (68). CCR5d32 mutation was reported as a rare event (69). CCR5d32 mutations have been identified in pre-historic skeletons dating over 5000 years (70), long before smallpox and plague became common human illnesses. People with a homozygous *CCR5*-32 bp gene may have evolved a chemokine system to compensate for the lack of a functional CCR5 (71).

Gene Editing Techniques and Their Application

Cellular monitoring, gene expression control, epigenetic change, pharmaceutical drug innovation, structural gene testing, and genetic identification have benefited from gene editing technologies (Table 2) (72). Even though the out-of-target impact of genome-editing technique implementation is still expected to be strengthened, next generation sequencing and quite specialized nanomaterials have enhanced productivity generating genome editing methods closer to the treatment center (73,74). Synergistic T-cells and allogeneic stem cells (STC) have been examined as an alternative to HAART therapy to treat HIV infection (75). The initial recipients of hematopoietic STC transplantation

Table 1. Structural genes and different tropic strains on HIV.

Gene	Primary protein	Function
Glycosaminoglycan (gag)	Gag poly-protein	The gag gene encodes The structural proteins of the core
Polymerase (pol)	Pol poly-protein	Env gene encodes glycoproteins gp120 and gp41, recognizing cell surface receptors
Envelope (env)	Gp160	The pol gene encodes enzymes crucial for viral replication, which are the reverse transcriptase that converts viral RNA into DNA, the integrase that incorporates the viral DNA into host chromosomal DNA (the provirus), and the protease that cleaves large gag and pol protein precursors into their components
HIV strains		
Strain	Predominant co-receptor	Tropic strain
HIV tropic strain-1	CCR5	R5 tropic
HIV tropic strain-2	CXCR4	X4 tropic
HIV tropic strain-3	CCR5 and CXCR4	Dual tropic

(HSCT) were HIV-positive lymphoma patients (76). The frameshift mutation generated by the 32-bp deletion in the *CCR5* gene hinders HIV-1 infection because the shortened protein does not enable effective gp120 binding (77). People who are homozygous for this gene are immune to the r5-tropic HIV-1 strain (78). However, the small number of individuals homozygous for b32 mutation is a step back for HSCT. Therefore, using gene-editing technologies to generate gene-editing tools to Silence CCR5 in autologous cells' genomes is highly recommended (79). By using designer nucleases, DNA may be cleaved at specific locations (80).

The b32 deletion was initially identified as a natural resistance to HIV transmission in 1996 (81). Since then, several methods have been used to tune this HIV-1 "major vulnerability" to produce novel CCR5-targeted ART (82). CCR5 knockout caused duplicating the naturally occurring CCR532 deletion (83). There have been significant advances in gene editing techniques and tools, including ZFNs, TALENs, and CRISPR (84). Transplantation of CCR5d32 homozygous STCs into an patient with HIV in 2008 led to long-term viral control (85). Since then, there has been much interest in applying this technique to a larger population to induce immunity to HIV (86). ZFNS have shown versatility for genome editing, and the use of ZFNS is now well dependable in several organisms and human cells (87). Because of the double-strand break caused by engineered ZFNS targeting CCR5d32, the natural CCR5d32 mutation is successfully eliminated (88). Primary human $CD4^+$ T lymphocytes revealed identical results to the animal model *in vitro* and an HIV-1 infection model in mice (89). A study regarding ZFN nucleases included 12 HIV-infected patients who received 10 $CD4^+$ T-cells with b32 deletion and were administered HAART for four weeks (90). HAART was restarted in two patients after increasing HIV RNA levels (91). After a 12-week break from HAART, the viral load was reduced in four patients, indicating the relative survival of modified $CD4^+$ T-cells (92).

In contrast, an undetectable viral load was found in a patient who was found to be heterozygous for the CCR5d32 allele, most likely due to suboptimal engraftment and the small number of cells containing a bi-allelic disruption (35). Another study enrolled 10 subjects heterozygous for CCR5d32 (35). Three of 8 subjects had low-level viral content below the detection limit after discontinuation of HAART for 20 weeks (35). Figure 3 represents the *CCR5* and *CXCR4* gene functions in HIV.

HIV Antagonists - Early Inhibitors

Gp120 co-receptor blockers interfere with HIV viral attachment to the CD4 surface, preventing viral infection by preventing the virus from fusing with the cell's membrane (93). The targeted co-receptors are part of a seven-transmembrane GPCR that binds to chemotactic chemokines, creating cell signals and sustaining the immune response (94). RANTES, mip-1, and mip-1, maraviroc, vicriviroc, cencriviroc, and maraviroc are all CCR5 inhibitors (95). Plerixafor, alx40-4c, t22, and other highly cationic compounds are the agents that act on CXCR4 nsc651016, a distamycin analog, inhibits both CCR5 and CXCR4 receptors (96). CXCR4 and CCR5 are the most commonly employed chemokine receptors as co-receptors in HIV-1 entrance, and their increased transcription is critical for regulating virus tropism (97). During T-cell stimulation and IL-2 response, CXCR4 and CCR5 transcription is differently modulated. In T-cells, extended stimulation with IL-2 enhances CC-chemokine receptor transduction and sensitivity to CC-chemokines (98). CXCR4 activation following T-cell stimulation, on

Table 2. Advantages and disadvantages of gene-editing techniques.

Gene editing techniques	Advantages	Disadvantages	References
Mega-nucleases	It is the potential to detect large segments of 14-40 bp DNA enhanced earlier the gene-editing performance.	Since each protein has distinctive identification pattern, the likelihood of discovering an appropriate mega nuclease to consider a valuable target had been minimal.	(47)
ZFNs	There was an improvement in selective homologous rearrangement in experimental organisms and human cells.	Every target location will need time-consuming enzyme synthesis for DNA identification.	(48,49)
TALENs	The identification tendency of each base rather than three bp TALE enzymes around each other with a combination of the FOK I endonuclease segment provided it as an optimum gene-editing method.	Protein determines how DNA is recognized.	(50)
CRISPR/CAS9	Technological convenience, the flexibility of operation, and excellent efficiency It is not only for gene editing but also for regulatory disruption, epigenetic control, and genome visualization.	Out of target and unusual genetic changes.	(51-53)

the other hand, shows a different pattern (99). After simultaneous PHA activation and IL-2 response, CXCR4 quickly increases, attaining its peak. However, this contradictory expression of CXCR4 cannot inhibit the virus entirely and limitations for treating HIV (100).

Maraviroc

Maraviroc is a small, reversible CCR5 antagonist molecule (101). At present, r5-tropic HIV-1 infected patients are approved for treatment. It is an allosteric non-competitive antagonist that blocks chemokine and HIV gp120 binding by targeting and altering CCR5 chemokine identification site 2 (102). Therefore, a susceptible tropism test should be used to identify which HIV strain is infecting the patient before starting Maraviroc (22). Maraviroc injection to individuals infected with the x4 tropic strain of HIV is the most prevalent reason for treatment failure (22). It is a CCR5 inhibitor that prevents HIV-1 transmission in humanistic RAG-hu rodents and chimps by interfering with HIV-envelope adherence to CCR5 through dynamic modification (103). In an *ex vivo* test, though, a single 300-mg dosage was insufficient to inhibit rectal or vaginal HIV-1 transmission (104,105).

In contrast to CCR5 antagonists, the drug resistance profiles of HIV protease, reverse transcriptase, and integrase inhibitors are unique (106). Maraviroc can therefore be provided to HIV-1-positive patients who have developed medication resistance to other antiviral authorized drugs beneficially (107). Additionally, Maraviroc is effective against CCR5-tropical HIV-2 addition HIV-1 (108). Although this approach should be tested in large-scale clinical trials (109); *in vitro* studies have shown that dual-r5x4-tropical HIV-1 strains are genetically and phenotypically identical to the R5 strain and they can inhibit MVC 163. As a consequence of engaging CCR5, Madrid-Elena et al. (110) discovered that Maraviroc might possess a role in stimulating persistent viral expression by activating NF-kB. Their findings suggest that Maraviroc might be used as a possible delayed restoration medication in HIV-1 affected individuals (111).

P140 (Leronlimab)

P140 is a monoclonal CCR5 antibody that binds to a complex epitope on CCR5 that spans several extracellular domains (112). Pro140 inhibits the HIV r5 tropic strain (113). P140 may have reliable, dose-dependent, significant antiviral activity with comparatively few side effects, according to two small trials (114). While the US food and drug administration has given P140 fast track approval, broader studies on its efficacy yet to be conducted. A single 5-mg/kg or 10-mg/kg intravenous infusion of P140 showed significant, influential, and long-lasting antiviral efficacy in patients with CCR5-tropic HIV (115). P140 has also been shown to inhibit several r5x4 viruses (113). P140 reduced HIV-1 RNA levels by 1.51 log10 copies/mL compared to 0.15 log10 copies/mL in the control group (116). A phase 2b/3 clinical research is currently underway to investigate the effect of once-weekly subcutaneous injection of leronlimab (117). The clinical trial (NCT00642707) reported that diarrhea, headache, enlarged lymph nodes, and elevated blood pressure were the most prevalent adverse effects related to leronlimab (115). Strengthening of the muscle, discomfort, and inflammation were all minor and transitory adverse symptoms that occurred at or near the site of injection. Dhody et al. (115) reported that the host and virologic markers that indicate therapeutic efficacy on PRO 140 treatment could be established, PRO 140 has the option to satisfy an unfulfilled requirement for a more

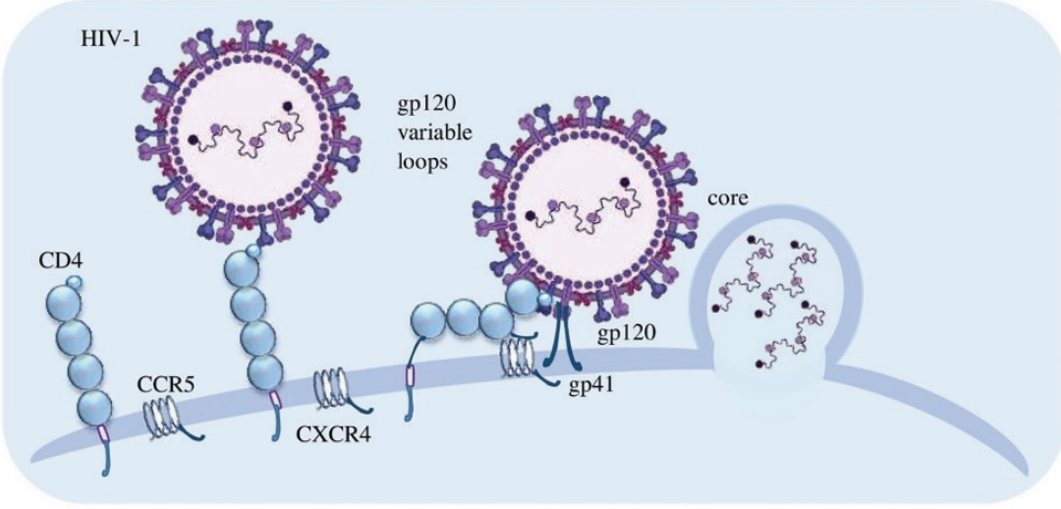

Figure 3. *CCR5* and *CXCR4* gene functions in HIV.

straightforward, lengthy, solitary treatment strategy for HIV transmission (118).

Outcomes of Allogenic STC Transplantation

Berlin Patient

In a 2009 case report of an 1 infected individual with HIV, the so-called Berlin patient was on suppressive ART (118). He underwent a myeloablative allogeneic HSCT. When he developed acute leukemia. The matching donor selected was a homozygous CCR5 d-32 individual, a base pair 32 deletion, which results in a non-functional gene product that inhibits the expression of CCR5 at the cell surface leading to inefficient binding of HIV to targeted cells. Additionally, when the Berlin patient's leukemia reappeared, he had whole-body irradiation, chemotherapy, and a second transplant from the same donor. It is impossible to detect HIV-1 RNA in plasma, which is valid for HIV-1 DNA in peripheral CD4 T-cells. With 24 million resting CD4 T-cells, quantifiable viral development tests from peripheral CD4 T lymphocytes revealed no reactive viruses CD4 T-cells from the patient had CCR5-tropic but not CXCR4-tropic HIV-1 viruses in their HIV-1 DNA before the transplant. One allogeneic HSCT with homozygous CCR532 donor cells might be adequate for the remission of HIV-1, and the findings promote the growth of HIV reduction techniques based on inhibiting CCR5 expression according to these findings (119). The Berlin patient remained free of HIV without ART for 10+ years, considering him free of HIV.

London Patient

For 18 months after discontinuing ART, the London patient had an undetectable plasma viral load and HIV DNA in peripheral $CD4^+$ T-cells, as determined using an ultrasensitive technique (120). Allogeneic HSTC from a CCR5d32 homozygous donor was performed for Hodgkin's lymphoma in this patient. HIV remission might be achieved with a less rigorous treatment strategy for the London patient, who had one transplant and received low-dose whole-body radiotherapy (121). According to these case reports, hematological malignancies and HIV-1 infection may benefit from HSPC transplantation. None of those patients have been found positive for HIV. However, this is an optimistic approach since the frequency of homozygous CCR532 is rare accounting for less than 1% of the Caucasian population (122).

Conclusion

HAART has transformed AIDS to a chronic disease. However, tthose agents may cause a number of adverse events such as endocrinological, hematologic and cardiovascular side effects. On the other hand, CCR5d32 silencing therapies promise better results with fewer side effects. The most dominant co-receptors in HIV infection are CCR5 and CXCR4. HIV-1 susceptibility might be related to homozygosity in the chemical receptor CCR5 for the natural D32 deletion. Subjects with the mutation of *CCR5* gene are comparatively highly resistant to HIV-1 due to the inefficient binding of HIV on targeted cells. *HSPC* gene therapy to HIV-1 infected patients with b-32 homozygous donors may be a potentially curative therapy. The latest advancements in gene editing technologies and methods have enabled us to show this naturally occurring b32 mutation as a potential treatment for possible eradication of HIV as an alternative therapeutic method to traditional methods like HAART.

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