

Hematopoietic Stem Cell Transplantation as a Potential Cure for HIV-1

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Abstract

Human Immunodeficiency Virus (HIV) is a harmful disease that destroys T lymphocytes, key cells involved in the immune system. Progression of the disease can lead to the development of Advanced Immunodeficiency Syndrome (AIDS), a chronic, life-threatening illness. For decades, antiretroviral therapy (ART) has been the standard treatment for individuals with HIV infection and has saved millions of lives. However, life-long treatment comes with unwanted consequences, and low adherence to the treatment regimen may decrease its effectiveness, causing patients to become viremic again. The only known individuals cured of HIV were treated using hematopoietic stem cell transplantations. Hematopoietic stem cells (HSC) are multipotent primitive cells that differentiate into various lineages of blood cells. Research has explored utilizing these stem cells to develop a new hematopoietic system in the host that is resistant to HIV. This review outlines the current use, progress, and challenges of allogeneic hematopoietic stem cell transplantation to cure individuals of HIV-1 infection. Current studies examine how genetic engineering tools like CRISPR/Cas9 can manipulate these stem cells to treat HIV.

List of Abbreviations

Advanced Immunodeficiency Syndrome – (AIDS)

Antiretroviral Therapy – (ART)

CC-Chemokine Receptor 5 – (CCR5)

Clustered Regularly Interspaced Short Palindromic Repeats – (CRISPR)

CXC Chemokine Receptor 4– (CXCR4)

Human Immunodeficiency Virus Type 1– (HIV-1)

Hematopoietic Stem Cells–(HSC)

Hematopoietic Stem Cell Transplantation– (HSCT)

Human Leukocyte Antigen–(HLA)

Synthetic Guide RNA – (sgRNA)

Transcription Activator-Like Effector Nucleases–(TALENs)

Introduction

Epidemiology of HIV

Human Immunodeficiency Virus (HIV) is a pathogen that targets the host immune system and interferes with the ability to fight off diseases and infections. This virus is spread by contact with bodily fluids, which most commonly occurs through unprotected sexual activity, the sharing of drug needles, and contact with blood of an infected person [1]. If left untreated, HIV can progress into Advanced Immunodeficiency Syndrome (AIDS) after about 8-10 years. Despite significant progress that has been made in testing and treatment of HIV/AIDS since the beginning of the epidemic in 1981, HIV is still a major global health problem worldwide. HIV-related deaths have claimed more than 30 million lives over the last four decades [2]. According to the World Health Organization (WHO), 38.4 million people globally were infected with HIV at the end of 2021 [3].

Pathogenesis

HIV-1 (Human Immunodeficiency Virus type 1) persists in memory CD4+ T lymphocytes and integrates itself into the host genome [4]. During the beginning stages of HIV-1 infection, the virus binds to coreceptor CCR5 (CC-chemokine receptor 5), and during later stages, binds with CXCR4 (CXC chemokine receptor 4) to enter CD4+ T cells. More specifically, HIV-1 enters via the gp-120 protein coated on the wall of the virus, which binds with the CCR5 receptor of the host lymphocyte. After a longer period of infection, the gp-120 protein mutates and binds with the CXCR4 coreceptor. This binding causes fusion of viral and lymphocyte membranes and cascades into the viral life cycle. The virus integrates a DNA copy of its RNA and integrates into the genome of host cells. Incorporation of viral genome into the host genome allows the virus to remain latent in cellular reservoirs for years, making it difficult for the immune system to eradicate. Overtime, the host lymphocyte produces new HIV viruses that exit the cell via exocytosis. These viruses rupture the plasma membrane as they exit and induce apoptosis of CD4+ T cells. This process greatly reduces the amount of CD4+ T lymphocytes, key cells involved in active immunity of the host. The host immune system is weakened overtime by CD4+ T cell depletion, eventually leading to the development of AIDS (Figure 1).

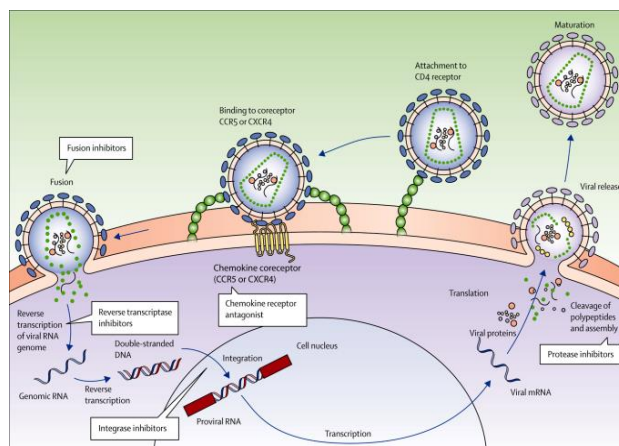


Figure 1: HIV viral life cycle [5].

Standard of Care

HIV-1 has no curative treatment to date. In 1996, the development of antiretroviral therapy (ART) proved to be an effective method to control HIV infection [6]. This biomedical breakthrough in treatment changed the course of the epidemic – HIV went from a life-threatening illness to a manageable, chronic condition. ART therapy regimen consists of three antiretroviral drugs conformed into one drug, taken once a day, every day. ART works by suppressing HIV replication in host lymphocytes [7]. While therapy has increased survival rates, it does not go without drawbacks. ART medications are not made available to everyone, and lifelong side effects give rise to challenges. High cost of care prevents the administration of ART on a global scale. Frailty, major depressive disorder (MDD), HIV-associated neurocognitive disorder (HAND), and end-organ disease, specifically myocardial infarction, and stroke, are all associated with long term use of ART. HIV treatment does not fully eliminate the virus, nor does it fully restore health [8]. Neurological, cardiovascular, and renal toxicities stem from long term use of treatment. Additionally, low adherence to the medication regimen, or “treatment fatigue”, presents another major barrier to its success [7]. Negative side-effects, drug-to-drug interactions, and the requirement to be administered everyday throughout a patient’s life, reduces full adherence to the regimen and effectiveness. Latent viral reservoirs persist in patients with ART, and interruption or cessation of treatment cause patients to become viremic again [8].

A practical approach to effectively control and eradicate HIV infections would be the development of a vaccine. However, HIV vaccine development has not come to fruition after 30+ years of research and trials [9]. The HIV replication process is fast and prone to error. The virus produces mutated copies of itself at a rate exceeding the ability to produce new vaccines. Thus, the diversity of HIV sequences differs from person-to-person, presenting a large challenge to developing a vaccine. The virus also remains hidden, integrated in the host genome, and is difficult for the immune system to eradicate from these latent reservoirs. Overall, barriers in the current standard of care and development of a vaccine for HIV spark hope to find a cure. A potential cure would reduce the burden and cost associated with a lifetime of treatment and health challenges.

Hematopoietic Stem Cells

Hematopoietic Stem Cells (HSC) are multipotent primitive cells that originate in the peripheral blood, bone marrow, and umbilical cord blood and can differentiate into red blood cells, white blood cells, and platelets [10]. Blood cells derived from HSCs are divided into two lineages: lymphoid cells and myeloid cells. HSCs divide into lymphoid cells through a process called lymphopoiesis. Lymphoid cells- T cells, B cells, and natural killer (NK) cells, are the prominent white blood cells involved in innate and adaptive immunity. Myeloid cells, generated from HSCs via myelopoiesis, include all other blood cells: monocytes, erythrocytes, platelets, and granulocytes. The ability of HSCs to differentiate into multiple cell types has made it an effective tool in regenerative medicine (Figure 2).

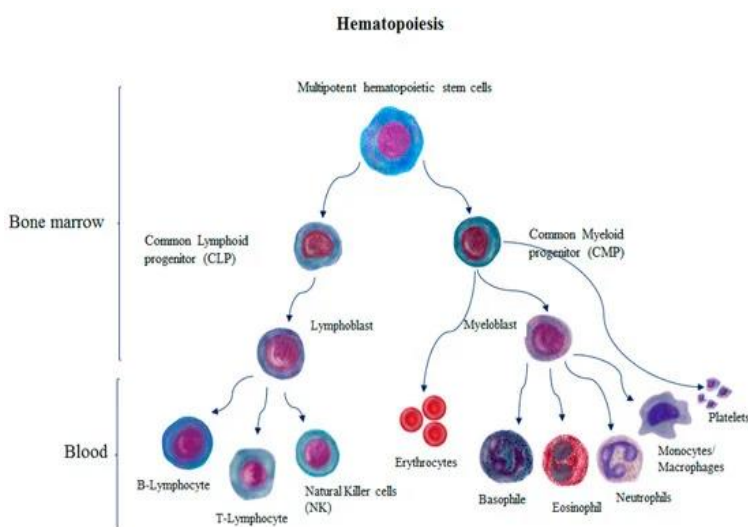


Figure 2: Hematopoietic Stem Cell Differentiation Pathways [11].

Hematopoietic stem cell transplantation (HSCT) is the intravenous infusion of stem cells commonly used to treat various types of hemato-oncological, immunological, and hereditary conditions [12]. The infusion of stem cells into a patient, typically following chemotherapy or radiation treatment, generates a new hematopoietic and immune system. Two main methods for hematopoietic stem cell transplants are autologous or allogeneic transplantation. Autologous transplantation occurs when stem cells are collected from the recipient themselves and reinfused later, whereas allogeneic transplantation collects stem cells from a different (related or unrelated) donor. HSCT is the standard treatment for diseases such as, acute myeloid lymphoma, acute lymphoblastic lymphoma, and non-Hodgkin's and Hodgkin's disease. Given that hematopoietic stem cells develop in the thymus to differentiate into progeny T cells, there is potential of HSCT to regenerate CD4+ T cells to cure the body of HIV-1 [13].

Discussion

Current research has explored the use of allogeneic hematopoietic stem cell transplantation as treatment for HIV-1. Hematopoietic stem cells can be modified so their progeny T cells are resistant to HIV infection. After transplantation of these HSCs, the host becomes repopulated with a new HIV-resistant hematopoietic system. Two cases of a cure for HIV-1 to date have been treated via allogeneic HSCT.

The Berlin Patient

In the early 2000s, a 40-year-old white male, Timothy Ray Brown, commonly known as “the Berlin patient”, was the first person in the world to be cured of HIV infection. Diagnosed with both acute myeloid lymphoma and HIV-1, the patient underwent 2 allogeneic HSC transplantation procedures as cancer treatment [14]. HIV initially binds to CCR5 receptors on CD4+ T cells to enter and invade cells. However, cells with a homozygous mutation in the CCR5 allele (CCR5delta32), present in approximately 1% of the white population, provide resistance to HIV-1 infection. The CCR5delta32 variant is characterized by the 32-bp deletion in the CCR5 allele’s coding region, preventing the formation of a functional protein and the ability for HIV to enter the cell [14]. Researchers sequenced DNA from potential human leukocyte antigen (HLA)-identical stem cell donors and found one matching donor homozygous for CCR5delta32 deletion. They successfully transplanted HSCs from the donor into the recipient. 20 months post transplantation, the patient remained without viral rebound and was able to discontinue ART therapy. No active, replicating HIV was detected in any reservoirs. While there have been previous attempts of using HSC transplantation with donor stem cells, they were unsuccessful since the CCR5delta32 status was not accounted for [15]. With this mutation, a host is left with no susceptible CD4+ T cells to infect. 8 years post treatment, the Berlin patient remains HIV free [16]. In 2020, Timothy Ray Brown died due to a relapse of his acute myeloid lymphoma, yet he remained HIV-free.

The London Patient

Based on the success of the Berlin patient, a study published in the Lancet reported the second patient cured of HIV using the same method. “The London patient” underwent allogeneic hematopoietic stem cell transplant with donor cells that did not express the CCR5 receptor (CCR5delta32/delta32). 18 months post transplantation, researchers tested plasma and circulating peripheral CD4+ T cells and found no traces of HIV [17]. 30 months post-transplant, the patient underwent extensive tissue sampling, testing the plasma, semen, CSF, intestinal tissue, and lymphoid tissue, to find evidence for a cure. No detectable virus was found, and the patient was determined to be in remission. To date, the London patient is living and remains free from HIV. According to authors, patient findings represent an HIV-1 cure [17].

Although both the Berlin patient and London patient show evidence for long-term remission of HIV-1 infection, many barriers remain before allogeneic-HSCT can be used on a larger scale. First, only a small percentage of the population naturally carry the homozygous CCR5delta32 deletion. The mutation is present in approximately 5-14% of the European descent population and is even more rare in individuals of African and Asian descent [18]. Additionally, allogeneic HSCT requires human leukocyte antigen (HLA) matching of the donor and recipient, making less than 1% of patients eligible for treatment [19]. Secondly, allogeneic stem cell transplantation presents potential morbidity and mortality risks [18]. Therefore, the limited availability of donors and possibility of immunological rejection pose drawbacks from using allogeneic HSCT as a practical alternative to ART therapy.

The Third Individual Cured

The third person to be cured of HIV-1 was a woman of mixed-race receiving treatment for acute myeloid lymphoma. Unlike the Berlin and London patients, the woman received a dual stem cell transplant, a

strategy that infuses umbilical cord hematopoietic stem cells from neonates, combined with additional adult stem cells from bone marrow [20]. Umbilical cord HSCs are more available than bone marrow HSCs and do not need to be matched as closely, increasing the likelihood of finding a suitable donor. Months after treatment, no recorded trace of the virus was found. “The New York Patient”, since she is being treated at New York Presbyterian Weill Cornell Medical Center, was able to discontinue HIV treatment and is in full remission of her cancer [21]. According to the patient’s physician Dr. JingMei Hsu, unlike the Berlin and London patients, this patient experienced no graft versus host disease or other negative side effects from the treatment.

1 in 4 cases of HIV in the United States are women; however, only 11% of these women are included in clinical trials and research for HIV treatment [22]. Additionally, African Americans make up a higher proportion of new HIV diagnoses compared to other races [23]. Researchers believe that the use of umbilical cord hematopoietic stem cells may provide a more accessible option for women and individuals of African or mixed ancestry. There is a clinical trial being performed with 25 patients who will undergo umbilical cord stem-cell transplants as treatment for HIV-1.

Genetic Engineering of Hematopoietic Stem Cells

While donors with the naturally occurring HIV-resistant mutation are limited, the genetic modification of HSCs to be transplanted into patients is currently being explored. Gene editing tools can be used to modify the CCR5 gene in hematopoietic stem cells. Initial studies have used Zinc Finger Nucleases and TALENs gene-editing tools, but have presented many limitations, such as low gene editing efficiency, high off-target rate, and costly vector construction [24]. Despite the presence of other gene-editing techniques, CRISPR has been proven to be the most reliable and effective method [25]. Over the past few years, clustered regularly interspaced short palindromic repeats (CRISPR) and the Cas9 protein have been used to modify genes in mammalian cells. Xiao et al. (2020) demonstrated the successful use of type II CRISPR/Cas9 technology in a group of mice to edit the CCR5 gene and disrupt the expression of the CCR5 co-receptor. Using a lentivirus for delivery, synthetic guide RNA (sgRNA), and the Cas9 protein, researchers effectively induced CCR5 editing of CD4+ T cells and CD34+hematopoietic stem cells [26]. Mice engrafted with the modified CD4+ T cells showed resistance to HIV-1 infection. In addition, CCR5 gene editing of CD34+ hematopoietic stem cells had no effect on cell differentiation. The authors suggest that transplantation of CRISPR gene edited allogeneic hematopoietic stem cells may be a safe and an effective tool for HIV resistance. The most effective, long-term solution would be a successful bone marrow transplantation with CRISPR/Cas9 CCR5 edited hematopoietic stem cells [27,28]. However, further exploration and precision of CRISPR/Cas9 technology is needed prior to clinical trials (Figure 3).

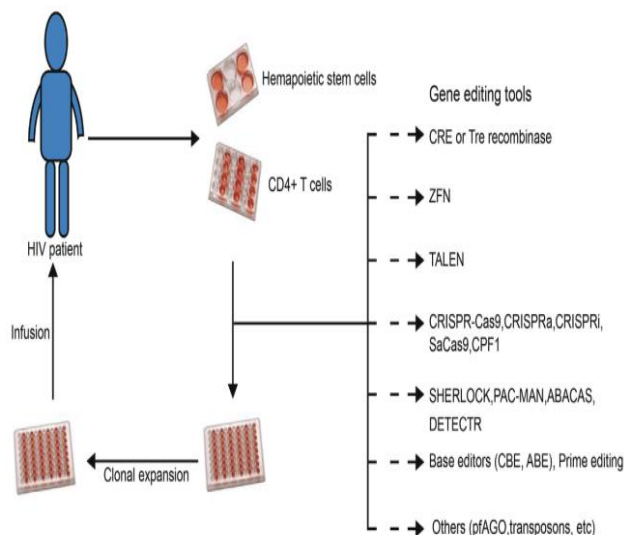


Figure 3: The use of gene-editing tools and allogeneic transplantation of HSCs [28].

Conclusion

HIV/AIDS continues to be one of the most severe global health threats today. While ART therapy is an effective method to control HIV infection, low adherence to the daily regimen, harmful side effects, and high cost of treatment present significant barriers. Thus, there is hope for a cure to mitigate the need for lifelong treatment. Allogeneic hematopoietic stem cell transplantation has been the only method to show a cure for HIV-1. Both the Berlin and London patients underwent successful HSC transplantations with donor cells that did not express the CCR5 receptor (CCR5 Δ 32/ Δ 32). However, with only a small percentage of the population carrying the homozygous CCR5 Δ 32 deletion, plus the need for HLA matching of the donor and recipient, allogeneic HSC transplantations may not be a practical and universal cure. The New York patient was the third individual cured using a dual stem cell transplant. This strategy infuses umbilical cord hematopoietic stem cells from neonates and additional adult stem cells from bone marrow. Umbilical cord stem cells are more available than bone marrow HSCs and do not need to be matched as closely. Therefore, the use of umbilical cord stem cell transplantation as treatment for HIV is currently being explored in clinical trials. The use of CRISPR/Cas9 to genetically engineer hematopoietic stem cells in the CCR5 gene has the potential to be an effective and accessible tool. Genetically engineered HSCs could be infused into patients to build a hematopoietic system resistant to HIV infection. Further research should focus on improving the effectiveness of the CRISPR/Cas9 system and exploring this treatment option in mice prior to clinical trials.

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