The Libyan International Medical University

Faculty of Basic Medical Science

The cure of HIV infection by CCR5Δ32 stem cell transplantation

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Abstract

The human immunodeficiency virus, or HIV, which infects and destroys certain white blood cells that are essential to the body's immune system. That causes acquired Immunodeficiency Syndrome AIDS.When HIV infects the body's cell, it combines with that cell's genetic material and may be inactive for years.The main attachment receptor for HIV is the CD4 molecule that is present on the CD4 positive T (helper) lymphocyte, macrophages, and microglial cells.. The viral gp120 binds initially to this CD4 molecule, which then triggers a conformational change in the host-cell envelope that allows binding of the co-receptor (either CCR5 or CXCR4).Procedure that replace unhealthy cells with healthy ones is called stem cell transplantation.The major types or techniques are allogeneic and autologous transplants.Chemokine and their receptors are vital modulators of the immune response. CC-chemokine receptor 5 (CCR5)has been identified as a co-receptor for the human immunodeficiency virus-1 (HIV-1) the gene encoding CCR5 is located on chromosome 32. Absent cell surface expression of CCR5 and mediates resistance to HIV strains that use CCR5 for cell entry these observations have inspired the development of anti-HIV therapies.

Introduction:

The human immunodeficiency virus, or HIV, which infects and destroys certain white blood cells that are essential to the body's immune system. That causes acquired Immunodeficiency Syndrome AIDS. (1)

When HIV infects the body's cell, it combines with that cell's genetic material and may be inactive for years. Most people infected with HIV can live for years with no symptoms or only minor illnesses but they do not have AIDS After period of time the virus becomes activate and then leads to the serious infections and other conditions that characterize AIDS. Although there are treatments that can extend life, AIDS is a fatal disease.(1)

The human immunodeficiency viruses are 100 nm in diameter. HIV has a lipid envelope, in which are embedded the trimeric transmembrane glycoprotein gp41 to which the surface glycoprotein gp120 is attached. These two viral proteins allow for HIV attach to the host cell and are encoded by the env gene of the viral RNA genome.(2)

The main attachment receptor for HIV is the CD4 molecule that is present on the CD4 positive T (helper) lymphocyte, macrophages, and microglial cells. The viral gp120 binds initially to this CD4 molecule, which then triggers a conformational change in the host-cell envelope that allows binding of the co-receptor (either CCR5 or CXCR4).Which is required for fusion between virus envelope and cell membrane Macrophage carry the CCR5 co-receptor.Hence, HIV strains requiring the CCR5 co-receptor for entry and are also referred to as 'macrophage-tropic' although they also infect lymphocytes. Recombination between these two RNA strands during viral replication.Viral replication occurs along with cellular replication and is enhanced by various factors, including coinfection with other organisms, the presence of inflammatory cytokines and cellular activationduring cellular replication. Thehost-cell RNA polymerase II enzyme transcribes the provirus, and the viral messenger RNA (vmRNA) and genomic RNA, are carried with the cellular mRNAs, to be translated into proteins. The viral proteinstogether with the replicated diploid viral genomic RNA,and are assembled and enveloped by budding through the host- cell membrane. Producingis complete HIV vision. (1,2,3)

Procedure that replace unhealthy cells with healthy ones is called stem cell transplantation (SCT). The major types or techniques are allogeneic and autologous transplants. In autologous transplants, stem cells are taken from patients' own bone marrow or peripheral blood.(4)

In allogeneic transplants the hemopoietic stem cells (HCT) are taken from the bone marrow, peripheral blood, or umbilical cord blood of a healthy donor matched for HLA type.(4)

Allogeneic transplantation isusing to treat congenital immune deficiencies, bone marrow failure and hematologic malignant lesions and can be used to enhance the CD4+count.Therefor these methods play a vital role in modern HIV immunotherapy. (4)

CCR5 is defined as a seven transmembrane-helix architecture protein belonging to GPCRs family and its gene is located on the short arm of chromosome 3 (3p21). Evidence demonstrated that several pro-inflammatory cytokines up regulate CCR5 expression in the immune cells via action of NF-MAP kinases and other tyrosine kinase cascades such as FAK and Pyk2.These molecules play important roles in immune cell migration and activation .(5,6)

Chemokine and their receptors are vital modulators of the immune response. CC-chemokine receptor 5 (CCR5) is a receptor that is shared by several b-chemokines, includingCCL5 and CCL3. Moreover, CCR5 has been identified as a co-receptor for the human immunodeficiency virus-1 (HIV-1) The gene encoding CCR5 is located on chromosome 32.(5,6)

CCR5 deficiency and natural HIV resistance CCR5 is one of the major co-receptors for HIV entry into CD4+ target cells. A natural occurring 32-base pair deletion in the CCR5 open reading frame (CCR5D32) introduces a premature stop codon and generates a shortened form of the protein that does not appear on the cell surface. leads to permanent absent cell surface expression of CCR5 and mediates resistance to HIV strains that use CCR5 for cell entry These observations have inspired the development of anti-HIV therapies.(3,4,9)

A homozygous D32 mutation in the CCR5 gene prevents CCR5 cell surface expression and thus confers resistance to infection with CCR5-tropic HIV strains.(4)

Aim of the study

Studies on HIV virology and pathogenesis address the complex mechanisms that result in the HIV infection of the cell and destruction of the immune system. These studies are focused on both the structure and the replication characteristics of HIV and on the interaction of the virus with the host . Stem cell transplantation immunotherapy for HIV. CCR5, is a necessary precondition for maintaining HIV-1 infection. Individuals with the CCR5-delta32 deletion who lack this receptor are highly resistant to infection by the most common forms of HIV-1.studies on the successful transplantation in an HIV-1-positive patient of allogeneic stem cells homozygous for the CCR5-delta32 allele, which stopped viral replication.

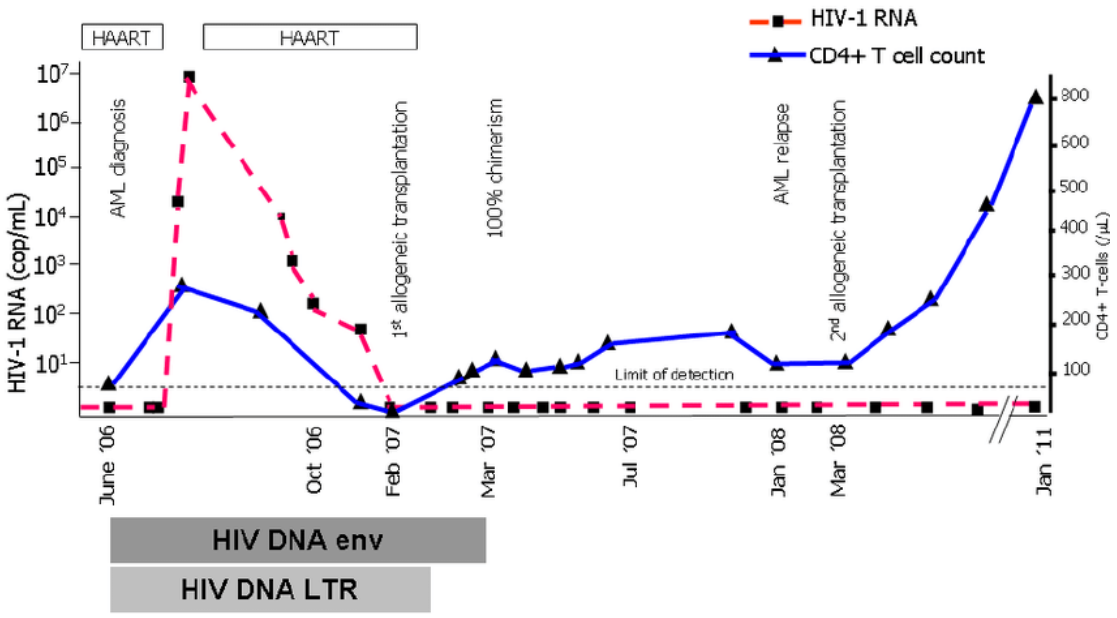
Material and method

The first patient is 37-year-old patient with HIV-1 infection and aggressive lymphoma who had disease progression after five lines of radiochemotherapy.includingan received an allogeneic HCT with four of six HLA-matched CCR5 Δ32 homozygous cord blood cells. Blood or tissue samples were obtained before and weekly after HCT to monitor transplant and HIV infection, including chimerism analysis,CCR5 genotyping and viral tropism,viral isolation and sequence and viral reservoir analysis.Immune activation and proliferation .combined antiretroviral therapy (HAART) continued during the procedure. (8)

The second patient was in Berlin 2007.He presented with leukaemia and HIV. Replaced his bone marrow with a bone marrow bares CCR5-delta32 mutation. (9)

Result

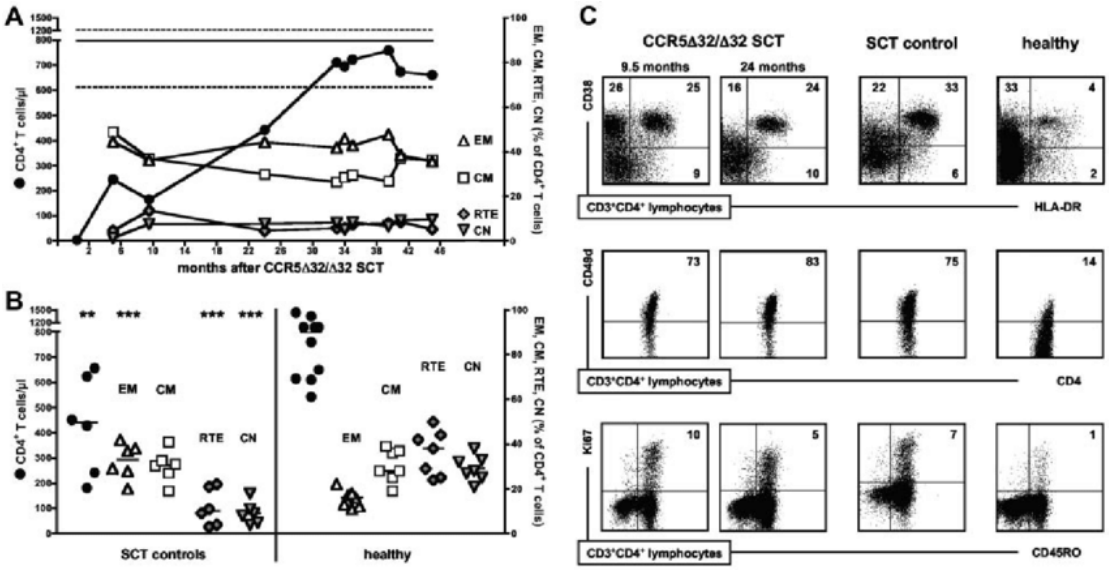
1. Result of the first patient:



(**Figure 1**)(7)

The patient's HIV was CCR5-tropic by genotypic and phenotypic analyses. Baseline latent reservoir tests showed HIV DNA copies in bulk and resting CD4 T cells and in gut-associated lymphoid tissue, CD4 T-cell-associated HIV RNA, replication competent viral size of 2•1 copies per 107 CD4 T cells, and single copy assay of 303 copies per mL(Showing in **Figure 1**). After HCT, the patient's CCR5 Δ32 homozygous CD4 T cells responded to proliferation and activation stimuli and became resistant to infection by the patient's viral isolate and by laboratory-adapted HIV-1 strains.(8)

2. Result of second patient :



(Figure 2)(7)

Berlin patient after CCR5D32/D32 stem cell transplantation.CCR5D32/D32 donor progenitor cells engrafted, expanded and differentiated into mature lymphoid and myeloid cells that are resistant to HIV infection via CCR5. (Showing in**figure 2**) (9)

Discussion

These results show that systemic recovery of CD41 T cells after CCR5D32/ D32 SCT and discontinuation of ART was not impaired compared with that of SCT control patients. In accordance with previous studies, repopulation of the CD41 T-cell compartment was associated with peripheral expansion of donor-derived memory CD41 T cells, generally. this homeostasis-driven expansion of activated memory CD41 T cells leads to an enrichment of the preferential targets for productive infection with HIV and likely contributes to the rapid dynamic of HIV rebound after conventional SCT in HIV-infected patients.(9)

These findings argue for the absence of HIV disease progression in the largest component of the lymphoid organ system. Surprisingly, compared with healthy control patients, mucosal CD41 T-cell numbers in both the CCR5D32/D32 SCT patient and the SCTcontrol patients were increased. (7, 8, 9)

These findingsmay likely be explained by the high prevalence of activated/effector memory CD41 T cells in the circulation, for which we have previously found enhanced gut-homing capacity. In addition, the normalized frequency of central memory cells within circulating CD41 T cells suggests that recovered CD41 T cells have been efficiently directed to peripheral lymph nodes. (8,9)

These results demonstrate that the process of immune reconstitution has successfully restored both the central and the mucosal immune system with CD41 T cells that lack CCR5 surface expression but have susceptibility to productive HIV infection.(9)

Conclusions

These studies suggest that principles can be further explored to utilize multiple antibodies against HIV. Genetically modified B cell responses may be useful to uplift cellular immune responses specifically in the innate and mucosal immune compartments.

Future work

CCR5 Δ32 homozygous cord blood reconstitution can successfully eliminate HIV-1 and render the allogeneic graft recipient's T lymphocytes resistant to HIV infection. Thus, they build on the evidence available to strongly support the use of cord blood as a strategic platform for a broader application of CCR5 transplantation to other infected individuals.

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