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The relationship between CCR5 gene and resistance to cellular HIV infection

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Abstract

The (CCR5) is expressed on potential human immunodeficiency virus (HIV) target cells and serves as the predominant co-receptor for viral entry during initial transmission and through the early stages of infection. A homozygous D32 mutation in the CCR5 gene prevents CCR5 cell surface expression and thus confers resistance to infection with CCR5-tropic HIV strains. Berlin patient is the first patient who's cured from HIV by transplanting a bone marrow with mutation CCR5 delta 32/ delta 23 Therefore, intense work is currently being carried out on CCR5 gene-editing tools to develop curative HIV therapy.

Introduction

The human immunodeficiency virus is the lentivirus and one of the member of retroviridae family

On the genatic basis of the viral antigen HIV classified into two major types HIV_1 AND HIV_2 , HIV-1 is the most important type ; HIV-2 is a variant that originated in West Africa and has spread to Central Africa, Europe and South America (1) There are many route for transmission of HIV one of them is by sexual intercourse: male to female and female to male. Or can be transmitted from mother to fetus through the placenta, during delivery or by breast-feeding , IV drug abusers , for example by multiple use of needles for injection of drugs, also transmits HIV. The virus can be enter the cells by binding (glycoprotein of 120 kDa) which is surface molecule for HIV to CD4 on T_helper cells and macrophages . also required a co-receptor for infection of target cells: the co receptor for T cell is CXCR4; while the co receptor for macrophage is CCR5 . Viral gp41 fuses with the membrane of the cell and injection into the target cell of two strands of viral genetic information , which is RNA. One strand is destroyed by ribonuclease H enzyme and viral reverse transcriptase converts the surviving strand into a copy of DNA . This forms the template for synthesis of the complementary second strand by cellular enzyme called DNA polymerase. The double-stranded DNA is then integrated into host cell DNA by viral integrase . when infected macrophages enter the new host, they are destroyed, discharging HIV. Dendritic cells transport HIV to draining lymph nodes where they infect CD4+ cells (2) . A well described functional polymorphism in the CCR5 gene comprises a 32-bp deletion (called CCR5_32) which results in a lack of the last three transmembrane domains of the CCR5 gene resulting in the presences of abnormal protein in the cytoplasm and complete lack of CCR5 cell surface receptor. In the nonappearance of this co-receptor binding site, HIV-1 is incapable to enter the cell , individuals homozygous for CCR5-_32 display complete resistance to HIV-1, whereas heterozygotes have a delayed onset of AIDS (3)

AIM

The aim of this study is to discuss the relationship between the CCR5 gene and resistance to cellular HIV infection .

Methods and materials

The first study in this paper showed , Transplantation of hematopoietic stem cells from a CCR5D32/D32 , genomic DNA was extracted from heparinized peripheral-blood monocytes obtained from the patient and the prospective donor, Screening of donors for the *CCR5* delta32 allele was performed with a genomic polymerase-chain-reaction (PCR) assay, resulting in a PCR fragment of 200 bp for the *CCR5* allele and 168 bp for a delta32 deletion . (4)

And the second showed the gene editing technology in two baby girls by using the CRISPR design tool , the nearest possible CRISPR target site from the CCR5 start codon was chosen for testing (5)

Results

resulting from the first study , Genomic DNA from 62 of 80 potential HLA-identical stem-cell donors registered at the German Bone Marrow Donor Center was sequenced in the *CCR5* region. The frequencies of the delta32 allele and the wild-type allele were 0.21 and 0.79, respectively. Only one donor was homozygous for the*CCR5* delta32 deletion in this cohort. (4)

Resulting from the second study , The CRISPR-sgRNAs-Cas9 could successfully induce editing of CXCR4 and CCR5 genes in various cell lines and primary CD4 T cells. Using HIV-1 challenge assays, they demonstrated that CXCR4-tropic or CCR5-tropic HIV-1 infections were significantly reduced in CXCR4- and CCR5-modified cells, and the modified cells exhibited a selective advantage over unmchanged cells during HIV-1 infection . (5)

Discussion

All studies reviewed in this paper agreed about the mutation in the CCR5 gene and the gene editing for ccr5 gene can cause resistance to cellular HIV infection .

A well described polymorphism in the CCR5 gene (CCR5D32) produces a form of the protein which is shorter than the normal , that does not show up on the surface of the cell . The allelic recurrence of the CCR5D32 deletion varies in populations from different ethnic groups , African and Asian people CCR5D32 is about non-existent, while in Caucasians, the frequency

of the CCR5D32 allele is 10–20% and the predominance of the homozygous mutation is 1–2% .

The homozygous genotype which is lead to permanent absent cell surface expression of CCR5 co receptor and mediates resistance against HIV strains that utilize CCR5 for entering the cell (3 the first study is talk about eliminating of HIV infection by transplantation of actually CCR5-deficient hematopoietic stem cells which is the co-receptors for HIV entry into CD4+ target cells , in a patient with long-known HIV infection and recently diagnosed with acute myeloid leukemia . After exhaustions of the patient's CCR5D32/wild-type immune system, CCR5D32/D32 donor progenitor cells engrafted, expanded, and differentiated into mature lymphoid and myeloid cells that are safe to HIV infection via CCR5. The patient remained off cART following the transplantation and HIV in peripheral blood and certain tissues remained continuously imperceptible . Today, this patient is respected as cured of HIV infection and known as the 'Berlin patient'. Because of this remarkable success in clearing HIV from the immune system, permanent substitution of CCR5-expressing cells by CCR5-deficient cells is considered as the most promising approach to efficiently interrupt the interaction of HIV with its host cells. (6)

and The second study is showed the CRISPR/Cas9 gene editing technology in twin baby girls . gene altering of the CCR5 gene in the embryo would knock out the CCR5 gene, All the male members were positive for HIV, and all female members were negativefor HIV. The participants' sperm was washed off to get rid of HIV and then injected into eggs collected from the female participants. By using clustered regularly interspaced short palindromic repeat (CRISPR)-Cas9, a gene editing technique, they disabled a gene called CCR5 in the embryos, aiming to close the protein enteryway that allows HIV to enter a cell and make the subjects immune to the HIV virus. The process led to at least one successful pregnancy and the birth of the twin baby girls , There are another modifying techniques: zinc-finger nucleases (ZFNs), transcription activator like effectors nucleases (TALENs), to modify the babies germline gene . targeting efficiency of CRISPR CAS9 technique is still insufficiency. For example, the efficiency of CRISPR-Cas9 is 20%– 30% on monkey zygotes and less than 5% in mice). The human embryo editing shows an efficiency rate of 15% for single gene correction Besides inefficiency, there are other technical problems with CRISPR-Cas9, including off-target

mutations, mosaicism, and on-target mutations with unwanted consequences. Researchers have found that off-target mutations could cause defects, disabilities or even cancer in some cases (7)

Conclusion

concluded that individuals that are homozygous for this mutation are resistant to infection by the HIV-1 virus while those heterozygous for this allele who are HIV-positive have a delayed onset to AIDS and the Gene editing techniques that are used in the second study to test this idea showed that this techniques not sufficiently safe or effective to be used on human reproductive cell lines , because the genatic modifications are transmittd to the offspring , and also the gene editing on the germ cells is non ethical issues .

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