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CCR5Δ32 mutation and HIV infection: basis for curative HIV therapy

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The C–C chemokine receptor 5 (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 Δ32 mutation in the *CCR5* gene prevents CCR5 cell surface expression and thus confers resistance to infection with CCR5-tropic HIV strains. Transplantation of hematopoietic stem cells from a CCR5Δ32/Δ32 donor was previously successful in eliminating HIV from the recipient's immune system, suggesting that targeted CCR5 disruption can lead to an HIV cure. Therefore, intense work is currently being carried out on CCR5 gene-editing tools to develop curative HIV therapy. Here, we review the natural function of CCR5, the progress made on CCR5 gene editing to date and discuss the current limitations.

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Introduction

Current standard therapy for human immunodeficiency virus (HIV) infection requires the lifelong daily administration of a combination of antiretroviral drugs (combination antiretroviral therapy; cART). Although therapeutic control of viral replication allows the immune system to partially restore and delays disease progression, the cure of HIV infection remains unachievable with the use of the currently available drugs. Individuals who are naturally homozygous for the *CCR5* gene variant Δ32 are resistant to CCR5-tropic HIV infection because of the lack of cellular C–C chemokine receptor 5 (CCR5) surface expression [1]. Previously, we reported the cure of HIV infection in a patient who received hematopoietic stem cells from a donor with this homozygous Δ32 gene variant [2••]. After transplantation and discontinuation of cART, HIV became undetectable and $CD4^+$ T cell counts normalized, demonstrating effective protection from HIV replication [2••,3••]. Unfortunately, this outcome could not be repeated in a later study [4•]. The first case has nevertheless brought a lot of attention to the curative potential of treatment strategies targeting the *CCR5* gene in HIV-infected patients. Consequently, new technologies for gene editing have been developed over the last few years that aim to mimic natural CCR5 deficiency. In this review, we describe the physiological role of CCR5, the recent advances made in developing CCR5-modifying methods and discuss their application towards HIV therapy.

Natural immune functions of CCR5

The chemokine receptor CCR5 is a seven-transmembrane segment protein and can interact with several proinflammatory C–C motif chemokines that are typically released as part of innate or adaptive immune responses. Many of these chemokines are also capable of binding to other chemokine receptors, whereas chemokine (C–C motif) ligand 4 (CCL4) appears to be largely specific for CCR5 [5]. The most potent agonist of human CCR5 yet described is CCL3-like 1 (CCL3L1) [6]. CCR5 is naturally expressed on the surface of a wide range of leukocytes including memory/effector T cells, natural killer cells, B cells, monocytes, and antigen-presenting cells such as dendritic cells and macrophages. Interaction of surface CCR5 with agonist chemokines induces intracellular signaling pathways, which (i) mediate leukocyte migration along the chemokine gradient to the site of inflammation and (ii) enhance local inflammatory immune responses by stimulating the proliferation and effector molecule secretion of leukocytes. CCR5 is thus involved in the regulation of cell migration and local immune activation. For completeness, it should be noted that CCR5 is also expressed on non-hematopoietic cells including osteoclasts, fibroblasts, vascular endothelium, epithelium and vascular smooth muscle cells, liver cells, and neurons where it may have other physiological functions that are not directly related to immune response [7].

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 (CCR5Δ32) introduces a premature stop codon and generates a shortened form of the protein that does not appear on the cell surface. The allelic frequency of the CCR5Δ32 deletion varies in populations from different ethnic groups. In

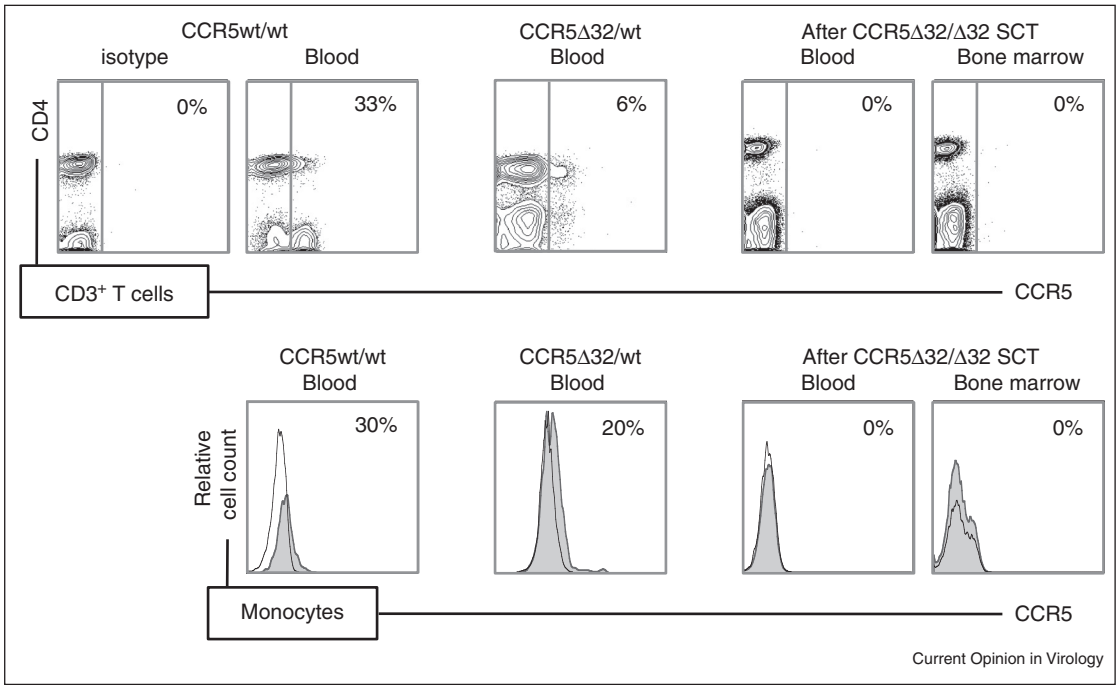
African and Asian people CCR5Δ32 is nearly non-existent, while in Caucasians, the frequency of the CCR5Δ32 allele is 10–20% and the prevalence of the homozygous mutation is 1–2% [8–10]. The homozygous genotype (CCR5Δ32/Δ32) leads to permanent absent cell surface expression of CCR5 and mediates resistance to HIV strains that use CCR5 for cell entry [11,12]. These observations have inspired the development of anti-HIV therapies that interrupt the interaction between the virus and CCR5.

Individuals with natural CCR5 deficiency are largely in healthy clinical conditions, except for impaired immune responses to some pathogens [13–16]. Absence of CCR5 surface expression may also exert a protective effect in inflammatory conditions including atherosclerosis and related cardiovascular disease, arthritis, and endotoxemia because of a defect in leukocyte and monocyte/macrophage trafficking [17–19]. In general, CCR5 seems to be dispensable for the proper function of the immune system, turning it into an excellent target for HIV therapy including cure approaches.

HIV cure by CCR5Δ32/Δ32 stem cell transplantation

Evidence for the curative potential of CCR5 disruption in HIV-infected persons comes from the success in eliminating HIV infection by allogeneic transplantation of naturally CCR5-deficient hematopoietic stem cells in a patient with long-known HIV infection and newly diagnosed acute myeloid leukemia that we have first reported about six years ago [2••,3••]. After depletion of the patient's CCR5Δ32/wild-type immune system, CCR5Δ32/Δ32 donor progenitor cells engrafted, expanded, and differentiated into mature lymphoid and myeloid cells that are resistant to HIV infection via CCR5 [2••] (Figure 1). The patient remained off cART following the transplantation and HIV in peripheral blood and certain tissues remained continuously undetectable. Today, this patient is regarded as cured of HIV infection and known as the 'Berlin patient'. Because of this remarkable success in clearing HIV from the immune system, permanent replacement 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. However, transplantation of naturally resistant donor cells for curative HIV therapy cannot find widespread application in clinical practice because allogeneic stem cell transplantations themselves are risky, with a 40–55% mortality rate [20–23], and are therefore only ethically acceptable in cancer patients without treatment alternatives. Also, the low prevalence of the CCR5Δ32/Δ32 gene variant in the general population limits the availability of naturally CCR5-deficient donor cells for stem cell

Figure 1



CCR5 surface expression on T cells and monocytes of individuals with the CCR5 wild-type genotype or heterozygosity for the CCR5Δ32 mutation and the Berlin patient after CCR5Δ32/Δ32 stem cell transplantation. T cells (upper part) and monocytes (lower part) in peripheral blood or bone marrow were analyzed for CCR5 surface expression. The frequency of CCR5-expressing cells is calculated by differences between the level of staining with a specific antibody (solid histogram) and the corresponding isotype control (open histogram).