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CCR5: A Cellular Doorway for HIV-1 Entry

Abstract

The CCR5 chemokine receptor plays a crucial role in HIV-1 infection, acting as the principal coreceptor for viral entry and transmission, and as such offers an important potential therapeutic target. Studies have suggested that CCR5 surface density and its conformational changes subsequent to virions engagement are rate limiting for virus entry. Several small molecule antagonists have been developed that target the HIV-1 coreceptor CCR5. CCR5-tropic (R5) viral strains are by far the most prevalent and are the predominant transmitted types. Not all existing CCR5 blockers fully inhibit HIV-1 infection, suggesting a need for more potent reagents. This review will discuss some of the CCR5 blockers, their development, and existing or potential future clinical usage.

Keywords: CCR5; HIV-1 Entry; CCR5 Antagonists; Maraviroc; CCR5 mAbs; Fusion protein

Mini Review

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Latinovic OS [1,2]*, Redfield RR[1,2,3]

[1]*Institute of Human Virology, University of Maryland School of Medicine, USA*

[2]*Department of Microbiology and Immunology, University of Maryland School of Medicine, USA*

[3]*Department of Medicine, University of Maryland School of Medicine, USA*

***Corresponding author:** Olga S Latinovic, Institute of Human Virology, University of Maryland School of Medicine, 725 West Lombard Street, Baltimore, Maryland 21201, Tel: 4107062769; Email: olatinovic@ihv.umaryland.edu

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Abbreviations: CCR5: C-C Chemokine Receptor Type 5; MVC: Maraviroc; FLSC IgG1: Full Length; Single Chain IgG1

Introduction

Viruses, unlike fungi and bacteria, require host cells and cellular proteins for infection and replication. HIV-1 requires two cellular proteins for cell entry, the primary receptor CD4 and co receptors CCR5 or CXCR4 [1-3], such cellular targets are attractive for antiviral therapy because they do not readily mutate under therapeutic pressure as viral proteins do [4-6]. Each step during the HIV-1 replication cycle depends upon cellular factors, which are thus potential targets for antiviral therapy. Pharmacology/biotechnology companies have developed 13 drugs that inhibit reverse transcription, 12 protease inhibitors, and 3 integrate inhibitors, but there has been less development in the area of virus entry inhibition, a potential critical target in anti-viral therapy. New drugs are much needed because of the side effects, costs, and existing drug resistance to current antivirals. There are two entry inhibitors licensed for patients with drug-resistant HIV-1, one virus/cell fusion inhibitor (Enfuvirtide, T-20 [7]) and one CCR5 coreceptor antagonist, Maraviroc [8]. Entry inhibitors target HIV-1 extracellular thereby potentially sparing cells from both viral and drug-induced intracellular toxicities. In addition, these inhibitors are especially attractive since they act at the earliest step of viral life and immobilize HIV-1 within the extracellular environment, where it is accessible to the immune system [9].

The discovery of the HIV-1 inhibitory activity of the CCR5 β-chemokines [10] led to the identification of CCR5 as the major HIV-1 receptor during virus binding and entry [11-13] and there has since been a strong interest in blocking the coreceptor for infection prevention and treatment. The CCR5 coreceptor is expressed on a number of cells, including activated T lymphocytes, dendritic cells and macrophages [14]. It is one of a family of chemokine receptors within the G protein-coupled receptor family [15], and CCR5-tropic HIV-1 strains are the predominant forms involved in viral transmission [16]. The chemokine receptors consist of seven transmembrane helices, an extracellular N-terminus, and three extracellular loops (ECLs). Elements located in the N-terminus and second ECL of CCR5 is crucial for interactions with HIV-1, making them appealing targets for antiviral therapy; therefore, they are the main targets for blocking HIV-1 entry. This has led to efforts to develop effective antiviral CCR5 inhibitors, including CCR5 antagonists [16-18] and fusion proteins that target the N-terminus and other relevant sites in CCR5 [19], as well as CCR5 antibodies [20-22]. Some CCR5 blockers have achieved remarkable suppression of HIV-1 entry both in vitro and in vivo [16,17,22,23].

Discussion

Among all cellular partners needed for HIV-1 entry, CCR5 has a further advantage as a cellular target because it is relatively dispensable for normal immune function, in contrast with CD4 and the minor viral receptor CXCR4 [24], both of which have important roles in immune function [25,26] that limit their utility as antiviral therapy targets. Individuals homozygous for the Δ32 mutation in CCR5 are highly resistant to HIV-1 infection [27,28]. Heterozygous individuals' progress to AIDS more slowly than do those homozygous for the wild-type gene [29,30]. Moreover, CCR5 density levels (molecules/cell) on CD4+ T cells correlate with RNA viral load [31] and progression to AIDS [32] in untreated HIV-1-infected individuals. The direct impact of CCR5 surface density on the antiviral activity of CCR5 antagonists was clearly established, showing that CCR5 levels inversely correlate with HIV-1 entry inhibition [33,34], thereby establishing that the potency of entry inhibitors is directly associated with and dependent upon CCR5 surface density [16,22]. All of these and the curative impact seen from Δ-32 mutation hematopoietic stem cells transplantation to the Berlin patient with AIDS and leukemia [35] have given strong stimulus for the use of CCR5 blockers for fighting HIV-1 infection.

Several small molecule CCR5 inhibitors have been developed in the last decade [16,17,22,36] which, unlike natural β–chemokines, do not induce coreceptor internalization. Antagonist

bound CCR5 does not signal and stays on the cell surface. One of these, CCR5 antagonist Maraviroc (MVC), is an allosteric, non-competitive inhibitor of the receptor [32,33] and is the only clinically approved CCR5 antagonist (Pfizer, 2007) [8]. It has been licensed for patients infected with only CCR5-tropic HIV-1 [37], due to its novel mechanism of action, excellent tolerance and potent capacity to reduce HIV-1 entry. Oral administration of MVC has yielded dramatic reductions in viral loads [38]. MVC and other small molecules have great in vitro synergy with other CCR5 blockers, including CCR5 monoclonal antibodies (mAbs) [19,21,22,35,39], inhibiting HIV-1 entry into physiologically relevant primary cells. An experimental drug candidate for inhibiting CCR5 receptors, Cenicriviroc, is in the Phase II clinical trials [40]. Ongoing efforts on blocking CCR5 function are related to the Zinc Finger Nuclease (ZFN) proteins that can delete CCR5. Recently, a completed Phase I clinical trial study (March, 2015) had an aim to find out whether "zinc finger" modified CD4+ T-cells are safe to give to humans and find how "zinc finger" modified T-cell affects HIV-1 (www.clinicaltrials.gov).

Resistance to MVC has been reported previously [41-43], and is due to several mechanisms, including selection of pre-existent minor HIV-1 variants that use CXCR4 as a coreceptor [41], selection for mutants that use inhibitor-bound CCR5 for entry [42], and selection for mutations, primarily in the V3 loop of gp120, that switch coreceptor use from CCR5 to CXCR4. The latter has been reported in vitro [43], but is rare in infected patients treated with MVC [37]. A potential solution for this problem is to combine MVC and CCR5 Abs with distinct patterns of resistance and different mechanisms of action. A new potential synergistic partner to MVC targeting CCR5 that has been identified is FLSC IgG1, a fusion protein containing gp120BAL, the D1 and D2 domains of human CD4 [44,46] and the hinge-CH2-CH3 region of human IgG1. Efficiently binding to CCR5, FLSC IgG1 inhibits efficiently by R5 HIV-1 [39,44, 45,46,47]. The IgG1 moiety provides protein dimerization, which confers bivalency (reducing the concentration required for half maximal binding to CCR5 by more than an order of magnitude) [39,47] and increases protein stability and serum half-life [47-48]. Importantly, FLSC IgG1 does not induce calcium mobilization or chemotaxis subsequent to CCR5 binding [44]. Its binding is inhibited by CCR5 ligands RANTES, MIP-1α, and MIP-1β, which also block R5-gp120 interactions by direct competition [49,50]. It seems possible that FLSC IgG1 represents a potential therapeutic agent to synergistically block HIV-1 entry in combination with MVC, and that it may synergize with other CCR5 blocking agents.

Conclusion

The success of the current HAART therapies is limited by the emergence of drug-resistance, potential drug toxicity, the need for sustained adherence and costs. CCR5 blockers have great therapeutic potential for prevention and treatment of HIV-1 infection.

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