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CCR5: HIV-1 Entry, Therapies, Resistance

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Introduction

CCR5 acts as a crucial co-receptor for Human Immunodeficiency Virus type 1 (HIV-1) entry, and CCR5 antagonists hold therapeutic potential in managing HIV infection. This understanding extends to CCR5's role in other diseases, pointing to broader therapeutic applications beyond just HIV [1].

Various strategies for targeting coreceptors like CCR5 are critical for preventing HIV-1 entry. These approaches delve into the mechanisms by which coreceptors facilitate viral fusion, highlighting current therapeutic interventions, including small molecule inhibitors and monoclonal antibodies that specifically block CCR5 function [2].

Structural insights are paramount for understanding how the HIV-1 envelope glycoprotein (Env) interacts with CD4 and co-receptors such as CCR5 and CXCR4. This interaction is a critical step for viral entry, and grasping these atomic-level details is crucial for designing more effective antiviral drugs and vaccines aimed at preventing the initial stages of infection [3].

Broadly neutralizing antibodies (bNAbs) that target the HIV-1 Env glycoprotein, which mediates entry via CCR5, represent a promising avenue. These antibodies can effectively interfere with the binding and fusion process, offering significant potential for both prophylactic and therapeutic interventions against HIV [4].

A growing concern in HIV therapy involves antiretroviral drug resistance, specifically resistance to CCR5 antagonists. Viral mutations can lead to altered co-receptor usage or reduced drug sensitivity, underscoring the vital need for ongoing surveillance and the continuous development of new anti-retroviral compounds [5].

Chemokine receptors, including CCR5, have multifaceted roles in the entry and pathogenesis of various viruses, not solely HIV. Delving into the diverse mechanisms by which viruses exploit these receptors for cellular entry can lead to the development of broad-spectrum antiviral strategies [6].

The dynamic conformational changes occurring in the HIV-1 Env glycoprotein and co-receptors like CCR5 during the viral entry process are highly significant. These molecular movements are crucial for successful membrane fusion and represent critical targets for novel antiviral inhibitors [7].

An updated perspective on HIV-1 entry inhibitors particularly highlights compounds that target CCR5. This area of research summarizes the development and clinical status of these inhibitors, outlining their effectiveness and challenges, including the emergence of resistance and the persistent need for new generation drugs [8].

The concept of allosteric modulation for chemokine receptors, including CCR5, which is critical for HIV entry, offers new possibilities. Allosteric modulators can alter receptor conformation to inhibit viral binding and fusion, providing a distinct advantage over orthosteric ligands and opening innovative avenues for drug discovery [9].

The impact of CCR5 genetic polymorphisms, notably the CCR5-Δ32 mutation, on susceptibility to HIV-1 infection and disease progression has been systematically investigated. Studies confirm that individuals with certain CCR5 variants exhibit altered resistance or progression rates, highlighting the crucial role of host genetics in viral entry and pathogenesis [10].

Description

The human immunodeficiency virus type 1 (HIV-1) relies heavily on the chemokine receptor CCR5 to mediate its entry into host cells, making CCR5 a primary target for therapeutic interventions [1]. Strategies for targeting co-receptors like CCR5 are central to preventing HIV-1 entry, encompassing various mechanisms by which these co-receptors facilitate viral fusion [2]. Current therapeutic approaches include the development of small molecule inhibitors and monoclonal antibodies specifically designed to block CCR5 function, thereby impeding viral infection [2]. These CCR5 antagonists show promise not only in managing HIV infection but also in exploring broader therapeutic applications in other diseases where CCR5 plays a role [1].

Understanding the structural aspects of how the HIV-1 envelope glycoprotein (Env) interacts with CD4 and co-receptors such as CCR5 and CXCR4 is critical for viral entry [3]. This atomic-level comprehension is essential for designing more effective antiviral drugs and vaccines that can prevent the initial stages of infection [3]. In this context, broadly neutralizing antibodies (bNAbs) that target the HIV-1 Env glycoprotein have emerged as a promising avenue. These antibodies can interfere with the viral binding and fusion process, offering significant potential for both prophylactic and therapeutic interventions against HIV [4].

A notable challenge in HIV therapy is the emergence of drug resistance, particularly to CCR5 antagonists. Viral mutations can lead to altered co-receptor usage or diminished drug sensitivity, emphasizing the continuous need for robust surveillance and the development of new anti-retroviral compounds [5]. An updated perspective on HIV-1 entry inhibitors highlights compounds targeting CCR5, outlining their development, clinical status, and effectiveness, while also addressing the challenges, including the emergence of resistance and the persistent demand for new generation drugs [8].

Chemokine receptors, including CCR5, possess multifaceted roles in the entry and pathogenesis of various viruses beyond HIV. Exploring the diverse mechanisms by which viruses exploit these receptors for cellular entry can inform the creation of broad-spectrum antiviral strategies [6]. Furthermore, the dynamic conformational

changes that occur in the HIV-1 Env glycoprotein and co-receptors like CCR5 during the viral entry process are crucial for successful membrane fusion [7]. These molecular movements represent significant potential targets for novel antiviral inhibitors, offering new avenues for therapeutic development [7].

The concept of allosteric modulation for chemokine receptors, including CCR5, offers a distinct advantage in drug discovery. Allosteric modulators can alter receptor conformation to inhibit viral binding and fusion, opening innovative pathways for drug development over traditional orthosteric ligands [9]. Concurrently, host genetics play a crucial role, with genetic polymorphisms of CCR5, such as the well-known CCR5-Δ32 mutation, significantly impacting susceptibility to HIV-1 infection and disease progression. Systematic reviews confirm that individuals with certain CCR5 variants exhibit altered resistance to infection or the rate of disease progression, highlighting the profound influence of host genetics on viral entry and pathogenesis [10].

Conclusion

Research highlights CCR5 as a crucial co-receptor for HIV-1 entry, forming the basis for therapeutic strategies such as CCR5 antagonists, with potential applications extending beyond HIV infection. Scientists are actively targeting coreceptors like CCR5 with small molecule inhibitors and monoclonal antibodies to prevent viral fusion. Structural studies provide atomic-level understanding of HIV-1 Envelope Glycoprotein (Env) interactions with CD4 and CCR5, essential for designing effective antiviral drugs and vaccines. Broadly neutralizing antibodies targeting HIV-1 Env offer promising avenues for both prophylactic and therapeutic interventions. However, drug resistance to CCR5 antagonists, arising from viral mutations, poses a significant challenge, necessitating continuous surveillance and the development of new antiretroviral compounds. Chemokine receptors, including CCR5, play multifaceted roles in the entry and pathogenesis of various viruses, not just HIV, paving the way for broad-spectrum antiviral strategies. The dynamic conformational changes in HIV-1 Env and co-receptors during entry are critical for membrane fusion and serve as key targets for novel inhibitors. The evolving landscape of HIV-1 entry inhibitors, particularly those targeting CCR5, continuously faces challenges like resistance, driving the need for new generation drugs. Innovative approaches, like allosteric modulation for chemokine receptors, aim to inhibit viral binding and fusion by altering receptor conformation. Furthermore, host genetic factors, such as CCR5 polymorphisms like the CCR5-Δ32 mutation, significantly influence susceptibility to HIV-1 infection and disease progression, underscoring the crucial role of host genetics in viral pathogenesis.

Acknowledgement

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Conflict of Interest

None.

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