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Molecular Mechanisms and Therapeutic Approaches for HIV-1 Latency: A Current Review

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Abstract

HIV-1 infection remains a global health challenge, with approximately 38 million people living with the virus worldwide. While the advent of highly active Antiretroviral Therapy (HAART) has significantly improved the prognosis and quality of life for individuals living with HIV-1, a complete cure remains elusive due to the persistence of latent HIV-1 reservoirs. HIV-1 latency refers to the ability of the virus to remain dormant in certain cells, evading immune surveillance and antiretroviral drugs. This latent reservoir poses a major barrier to achieving a functional cure for HIV-1. In this review, we delve into the molecular mechanisms underlying HIV-1 latency and discuss current therapeutic approaches aimed at eradicating or controlling this persistent reservoir.

Keywords: DNA methylation • HIV-1 • Latency

Introduction

HIV-1 primarily infects CD4+ T cells, but it can also establish latent reservoirs in other cell types, such as macrophages and dendritic cells. Within the CD4+ T cell population, two main types of latency are recognized: pre-integration latency and post-integration latency. Pre-integration latency occurs when the virus enters a quiescent or resting CD4+ T cell and fails to integrate into the host genome. These cells can harbor viral genetic material as unintegrated circular DNA, known as 2-LTR circles, and remain transcriptionally silent. Post-integration latency, on the other hand, occurs when the virus successfully integrates its genetic material into the host genome but remains transcriptionally silent. This state is largely attributed to the lack of transcription factors and the presence of repressive epigenetic modifications, such as DNA methylation and histone deacetylation, in the proviral DNA. The establishment and maintenance of HIV-1 latency are regulated by a complex interplay of host and viral factors. Epigenetic modifications play a critical role in silencing viral gene expression within latently infected cells [1,2].

Literature Review

Host restriction factors like APOBEC3G and SAMHD1 can limit viral replication by inducing hypermutation or reducing the pool of available dNTPs, respectively. These factors can contribute to the establishment and maintenance of latency. Drugs like vorinostat and romidepsin can disrupt histone deacetylation, leading to chromatin remodeling and viral transcription. Agents like bryostatin-1 and prostratin activate PKC signaling, which in turn activates NF-κB and promotes viral transcription [3]. Combining LRAs with immune-based therapies can maximize the elimination of reactivated cells. In this comprehensive review, we will delve into the molecular mechanisms underlying HIV-1 latency and explore the latest therapeutic approaches aimed at disrupting or eliminating these latent reservoirs. These reservoirs consist of long-lived, quiescent infected cells that are not targeted by current antiretroviral drugs, making it difficult to completely eradicate the virus from the host [4].

Discussion

HIV-1 latency is primarily established in resting memory CD4+ T cells, although other cell types like macrophages and dendritic cells can also contribute. The virus enters these cells via the CD4 receptor and coreceptor, typically CCR5 or CXCR4. Once inside, the viral RNA is reverse transcribed into DNA, and the viral genome is integrated into the host cell's chromosomal DNA. Instead of proceeding with active viral replication, some infected cells enter a state of latency, characterized by transcriptional silencing of the viral genes. The integration of the HIV-1 provirus into the host genome occurs in regions with repressive epigenetic marks, such as DNA methylation and histone deacetylation. These modifications create a closed chromatin structure that prevents transcriptional activation. Tat, a viral protein essential for HIV-1 transcription, is not produced at sufficient levels in latently infected cells. That recruits positive transcription elongation factor (P-TEFb) to stimulate viral transcription, but in latency, P-TEFb is sequestered in an inactive complex [5,6].

Conclusion

HIV-1 latency remains a significant obstacle to achieving a functional cure for HIV/AIDS. Understanding the molecular mechanisms that underlie HIV-1 latency is crucial for the development of effective therapeutic approaches. While progress has been made in the development of latency-reversing agents and immune-based therapies, many challenges remain. The optimal strategy for HIV-1 cure may involve a combination of approaches, including "shock and kill," immune-based therapies, gene editing, and the development of innovative small molecules to maintain latency ("block and lock"). Ongoing research and clinical trials hold promise for a future where HIV-1 can be controlled or eliminated, offering hope to millions of individuals living with this devastating virus.

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Conflict of Interest

None.

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