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Targeting viral latency: Strategies for eradicating persistent infection.

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Introduction

Viral latency represents one of the most formidable challenges in infectious disease management. Unlike acute infections, latent viruses evade immune surveillance and persist in host cells without producing detectable viral particles. This silent persistence allows viruses to reactivate under favorable conditions, leading to recurrent disease and transmission. Latency is a hallmark of several clinically significant viruses, including HIV, herpesviruses (HSV, CMV, EBV), and hepatitis B virus (HBV). Eradicating these infections requires innovative strategies that go beyond conventional antiviral therapy. This article explores the mechanisms of viral latency and emerging approaches to disrupt and eliminate latent reservoirs [1].

Latency is a state in which a virus remains dormant within host cells, often integrating into the genome or existing as episomal DNA. During latency, viral gene expression is minimal or absent, allowing the virus to escape immune detection and antiviral drugs that target active replication. HIV establishes latency in resting CD4+ T cells, forming a reservoir that is unaffected by antiretroviral therapy (ART) [2].

Herpesviruses persist in neurons (HSV), monocytes (CMV), and B cells (EBV), reactivating during immunosuppression or stress. HBV maintains covalently closed circular DNA (cccDNA) in hepatocytes, serving as a template for viral replication even after clinical resolution. These reservoirs are the primary barrier to viral eradication and necessitate targeted interventions. One of the most studied approaches to eliminating latent viruses is the "shock and kill" strategy, particularly in HIV research. This method involves: Compounds that reactivate latent virus, making infected cells visible to the immune system [3].

Once reactivated, infected cells are targeted for destruction by cytotoxic T lymphocytes or therapeutic agents. LRAs include histone deacetylase inhibitors (HDACi), protein kinase C agonists, and toll-like receptor agonists. While promising, this strategy faces challenges such as incomplete reactivation, toxicity, and immune exhaustion. In contrast to "shock and kill," the "block and lock" strategy aims to reinforce latency and prevent viral reactivation indefinitely. This approach uses: Tat inhibitors in HIV to suppress transcriptional activation. Epigenetic modifiers to silence viral promoters. RNA interference to degrade viral transcripts. "Block and lock" may be more feasible for patients with stable viral suppression, offering a functional cure without complete eradication [4].

CRISPR-Cas technology has revolutionized gene editing and holds promise for targeting latent viral genomes: CRISPR-Cas9 has been used to excise proviral DNA from host genomes in vitro and in animal models. CRISPR systems targeting cccDNA have shown potential to reduce viral replication. Editing latent viral DNA in neurons remains challenging but is under investigation. Despite its potential, CRISPR faces hurdles such as off-target effects, delivery mechanisms, and immune responses to Cas proteins. Designed to boost T-cell responses against latent antigens. Examples include CMV and EBV vaccines in transplant recipients. Drugs like anti-PD-1

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antibodies may rejuvenate exhausted T cells in chronic infections. Engineered T cells targeting HIV-infected cells have shown promise in preclinical studies. These approaches aim to enhance immune surveillance and eliminate reactivated or persistently infected cells. Viruses rely on host cellular machinery to maintain latency. Host-targeted therapies may reduce the risk of resistance but require careful evaluation to avoid toxicity [5].

Conclusion

Viral latency remains a formidable obstacle to curing persistent infections. From “shock and kill” to CRISPR-based editing, researchers are exploring diverse strategies to disrupt and eliminate latent reservoirs. While no single approach has yet achieved complete eradication, the convergence of molecular biology, immunology, and nanotechnology offers hope. Continued innovation, ethical oversight, and equitable access will be key to transforming these strategies into viable cures.

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