Novel Methods To Eliminate Dormant HIV Reservoirs

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BACKGROUND

Human immunodeficiency virus type-1 (HIV-1) is a pathogenic retrovirus and the causative agent of acquired immunodeficiency syndrome (AIDS) and AIDS-related disorders. There were 1.7 million new infections globally in 2018, and ~38 million people are currently living with HIV-1. Although the introduction of antiretroviral therapy (ART) has prevented millions of AIDS-related deaths worldwide, patients must continue to receive ART for the remainder of their lives. HIV-1 reservoirs persist even while subjects are on ART, leading to a rapid increase in viral replication when therapy is discontinued. Therefore, eradication of persistent HIV-1 reservoirs remains the main barrier to achieving a cure for HIV-1/AIDS.

The prevailing view of persistence suggests that the virus remains in a latent state in memory CD4+ T cells regardless of plasma viral loads, allowing the virus to establish a life-long infection in the host. Since the latent virus is refractory to existing antiretroviral therapies, curative strategies are now focusing on agents that reactivate viral replication and render it susceptible to conventional therapy. Any strategy aimed at controlling and eradicating viral reservoirs in HIV-1-infected individuals must target such latent reservoirs.

The mammalian genome encodes thousands of long noncoding RNAs (lncRNAs, >200 nucleotides), including intergenic lncRNAs (lincRNAs), which are increasingly recognized to play major roles in gene regulation. The pathophysiological functions and mechanisms of lncRNAs in gene regulation have started to emerge. Work over the last few years has begun to uncover the role of lncRNAs in modulating HIV-1 gene expression.

TECHNOLOGY DESCRIPTION

Researchers at UC San Diego have developed methods and compositions for targeting long noncoding RNA for treating human immunodeficiency virus. Investigators are the first to report the genome-wide expression analysis of lncRNAs in HIV-1-infected primary monocyte derived macrophages (MDMs). They identified an lncRNA, that is upregulated by HIV-1 infection of MDMs, microglia, and T lymphocytes. Peripheral blood mononuclear cells of HIV-1-infected individuals show elevated levels of this lncRNA. Importantly, this serves as a broad enhancer of multiple HIV-1 strains because depletion of this lncRNA inhibited X4, R5, and dual-tropic HIV replications and the inhibition was rescued by lncRNA overexpression. lncRNA forms a complex with the RNAbinding protein FUS, which facilitates HIV replication through at least two mechanisms. Notably, knockdown and knockout of lncRNA mediated by RNA interference (RNAi) and CRISPR-Cas9, respectively, prevent HIV-1 recrudescence in T cells and microglia upon cessation of azidothymidine treatment *in vitro*.

APPLICATIONS

Our results suggest that silencing of lncRNA or perturbation of the lncRNA-FUS ribonucleoprotein complex could provide a new epigenetic silencing strategy to eradicate viral reservoirs and effect a cure for HIV- 1-AIDS

ADVANTAGES

This represents a new approach to targeting and eliminating dormant HIV reservoirs.

STATE OF DEVELOPMENT

While our results are experimental at present, lncRNA knockdown and knockout mediated by RNA interference (RNAi) and CRISPR-Cas9, respectively, prevent HIV-1 recrudescence in T cells and microglia upon cessation of azidothymidine treatment in vitro. Our results suggest that silencing of lncRNA or perturbation of the lncRNA-FUS ribonucleoprotein complex could provide a new epigenetic silencing strategy to eradicate viral reservoirs and effect a cure for HIV-1-AIDS.

INTELLECTUAL PROPERTY INFO

The invention is patent-pending and is available for licensing and collaborations.

RELATED MATERIALS

- Rana, TM. et al. Critical Cellular Player Controlling HIV Reproduction in Immune Cells Identified. GEN. September 26, 2019 - 09/26/2019
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OTHER INFORMATION

KEYWORDS

Cure for AIDS, viral reservoirs depletion, long noncoding RNAs, epigenetic regulation, HIV promoter, Ribonucleoprotein complexes, prevention of HIV-1 recrudescence

CATEGORIZED AS

- **Medical**
  - Disease: Infectious Diseases
  - Therapeutics

RELATED CASES

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PATENT STATUS

Patent Pending

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