Journal of Infectious Diseases & Therapy
ISSN: 2332-0877

Rausch ,et al. J Infect Dis Ther 2024, 12:5

Short Communication Open Access

A Short Commentary on HIV Expression in Infected T Cell Clones

Jason W. Rausch* and Mary F. Kearney

HIV Dynamics and Replication Program, Center for Cancer Research, National Cancer Institute, Frederick, USA

***Corresponding author:** Jason W. Rausch, HIV Dynamics and Replication Program, Center for Cancer Research, National Cancer Institute, Frederick, USA, E-mail: rauschj@mail.nih.gov

Received: 26-Jun-2024, Manuscript No. JIDT-24-139866; **Editor assigned:** 29-Jun-2024, PreQC No. JIDT-24-139866 (PQ); **Reviewed:** 12-Jul-2024, QC No. JIDT-24-139866; **Revised:** 19-Jul-2024, Manuscript No. JIDT-24-139866 (R); **Published:** 26-Jul-2024, DOI: 10.4172/2332-0877.1000599

Citation: Rausch JW, Kearney MF (2024) A Short Commentary on HIV Expression in Infected T Cell Clones. J Infect Dis Ther 12:599.

Abstract

Antiretroviral Therapy (ART) can suppress Human Immunodeficiency Virus (HIV) replication almost completely, to the extent that plasma viremia is undetectable by standard clinical tests. Yet this intervention is not curative, as ART withdraw usually results in viremic rebound to pre-ART levels within several weeks. The HIV reservoir, comprised primarily of persistent $CD4^+$ T cells harboring replication-competent proviruses integrated into host cell genomes, is the primary the source of viremic rebound upon ART withdrawal and principal barrier to a cure. Reservoir persistence is enabled by two principal characteristics: T cell clonal expansion and proviral transcriptional suppression, or latency. In a recent authoritative review, select genetic, epigenetic, cellular, and immunological determinants of these reservoir characteristics, interdependencies among these determinants, and implications for HIV-1 persistence were presented and discussed.

Keywords: Human Immunodeficiency Virus (HIV); Persistence; Transcriptional regulation; T cell; Clonal expansion; HIV rebound

About the study

Effective ART suppresses ongoing virus replication, enabling management of HIV infection as a chronic disease and in most cases significantly improving life quality and expectancy. Nevertheless, ART must be administered to people living with HIV regularly and indefinitely, as treatment withdrawal typically leads to viremic rebound and resumption of disease processes. Viremic rebound is seeded by the HIV reservoir, which is primarily comprised of HIV^+ $CD4^+$ T cells harboring replication-competent proviruses. Since around the turn of the 20^{th} century, as successful management of HIV disease became increasingly commonplace, many clinicians and researchers turned their collective attention to understanding the biological basis for HIV persistence despite effective antiretroviral therapy. From these efforts, it was discovered that the HIV reservoir can persist for years or even decades, enabled by two principal reservoir characteristics: (i) the capacity to maintain and expand their numbers through cellular clonal expansion and (ii) transcriptional quiescence, or latency, of the intact proviruses harbored by reservoir cells. These mechanisms are themselves interrelated and enabled by numerous genetic, epigenetic, cellular, and immunological determinants, which are described and discussed in a recent review [1].

HIV expression in infected T cell clones

The composition of the HIV reservoir is overarchingly governed by natural selection, where reservoir cells that that persist or clonally expand despite immune pressures have a selective advantage over those that do not. Such advantage can be conferred by both the capacity of reservoir cells for antigen-driven or homeostatic clonal expansion and suppression of viral gene expression, which might otherwise trigger adaptive immune killing of infected cells. Though these fundamental precepts are themselves simple, their interrelated dynamics are varied, complex, and influenced by genetic, epigenetic, and immunological determinants.

The 5' Long Terminal Repeat (5'LTR) of the HIV provirus harbors recognition sequences for direct or indirect binding of viral and cellular transcription factors. Catalyzed by cellular RNA Polymerase II (RNAPII), viral RNA transcription initiates from the CA/TATAA element in the 5'LTR basal core promoter region. The upstream enhancer region of the 5'LTR harbors tandem binding sites for NF-κB, a cellular transcription factor important for both viral transcription and the biology of T cell activation. Viral transcripts contain the RNA version of the trans-activation response element, which recruits the virus encoded protein Tat to the polymerase complex to enable transition from distributive synthesis of short viral RNAs to efficient synthesis of genome-length viral transcripts [2].

Epigenetic control of HIV transcription is likewise complex and subject to the dictates of natural T cell biology. Assembly and stability of a nucleosome downstream from the HIV transcription initiation site (nuc-1) are thought to influence the Tat-mediated transition from abortive to productive viral RNA synthesis. However, access of cellular transcriptional machinery to the HIV promoter may be more broadly and durably determined by the local chromatin environment of the provirus, i.e., whether it resides in a transcriptionally accessible euchromatic or condensed, inaccessible heterochromatic region of the host cell genome. In the face of cellular epigenetic regulation, the capacity for HIV to genetically control its own transcription may be limited, as local and regional chromatin structure and cellular transcriptional programming are principally determined by natural T cell biological responses to immune signaling and mediated by cell-encoded histone modifiers. However, there is an increasing body of evidence to suggest that proviruses that integrate into regions of the

genome more often associated with euchromatin or heterochromatin have greater or lesser propensities toward viral gene expression, respectively [3,4].

$CD4^+$ T cell epigenetic and transcriptional programs are often manifestations of their adaptive immunological functions, which also influences cellular clonal expansion and, potentially, viral gene expression in HIV^+ T cells. More specifically, antigen-driven T cell activation induces rapid clonal expansion, thought to favor reservoir persistence, while also creating an epigenetic and transcriptional environment that may favor viral gene expression and thus trigger immune recognition and killing of HIV^+ cells. Though coupling between T cell activation and activation of viral transcription is a well-established paradigm *in vitro*, a model of HIV persistence in which reservoir proviruses tend to be unresponsive to antigen-driven activation, perhaps because they are integrated in transcriptionally suppressive chromatin environments, is increasingly gaining acceptance [3,5].

After decades of investigation, our understanding of the governing determinants of HIV persistence, including and especially T cell clonal expansion and proviral latency, is improving. Recent technological advancements, particularly with respect to multi-omics characterization of individual HIV^+ T cells, should allow researchers to develop an increasingly refined and granular model of HIV persistence [6].

Funding

The M.F.K. laboratory is funded by the NIH-National Cancer Institute and the office of AIDS Research.

References

1. Rausch JW, Parvez S, Pathak S, Capoferri AA, Kearney MF (2024) HIV expression in infected T cell clones. Viruses 16:108.
2. Roebuck KA, Saifuddin M (1999) Regulation of HIV-1 transcription. Gene Expr 8:67-84.
3. Lichterfeld M, Gao C, Xu GY (2022) An ordeal that does not heal: Understanding barriers to a cure for HIV-1 infection. Trends Immunol 43:608-616.
4. Verdikt R, Hernalsteens O, Van Lint C (2021) Epigenetic mechanisms of HIV-1 persistence. Vaccines 9:514.
5. Murray AJ, Kwon KJ, Farber DL, Siliciano RF (2016) The latent reservoir for HIV-1: How immunologic memory and clonal expansion contribute to HIV-1 persistence. J Immunol 197:407-17.
6. Wong M, Wei Y, Ho YC (2023) Single-cell multiomic understanding of HIV-1 reservoir at epigenetic, transcriptional, and protein levels. Curr Opin HIV AIDS 18:246-56.