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HIV-1 Reservoirs and Latency: Critical Barriers and Clues for HIV / AIDS Cure

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1. Introduction

Human immunodeficiency virus type 1 (HIV-1) infection is still a formidable threat to public health in spite of remarkable therapeutic advances (Adoga et al., 2009; Goselle, 2011). Highly active antiretroviral therapy (HAART) is effective against HIV/AIDS but it is not curative, and hence does not lead to the eradication of HIV-1 infection. Patients on HAART usually have their HIV RNA levels suppressed below the lower detection limit of 50 copies / ml. However, interruption of treatment leads to viral rebound and HIV can be detected again usually within two weeks (Davey et al., 1999; Dahl et al., 2010). This observation led to the initial questions that spurred investigations into the discovery of the critical roles of reservoirs and latency in HIV-1 persistence.

Scientists continue to demonstrate that the major barriers to HIV/AIDS cure are the latently infected CD4⁺ T lymphocytes harbouring replication-competent HIV in lymph nodes, spleen and cells of the CNS (Cordelier, 2006; Dinoso et al., 2009). HIV-infected patients harbour ~ 10⁵ to 10⁶ memory CD4 T-cells that contain fully integrated but transcriptionally silent HIV proviruses, which constitute a reservoir of viruses that show no sensitivity to highly active antiretroviral therapy (HAART), leading to HIV persistence in patients for life (Williams and Greene, 2007).

Latently infected cells may be defined as transcriptionally silent cells that contain integrated HIV DNA, but which are capable of producing infectious virus only upon activation (Lassen et al., 2006; Pace et al., 2011). Based on this definition, it may be deduced that latently infected cells do not transcribe HIV RNA or express HIV proteins. On the contrary, it has been reported that resting CD4⁺ T cells and PBMC (peripheral blood mononuclear cell) from patients taking HAART do contain low levels of HIV RNA (Li et al., 2005; Fischer et al., 2008; Pasternak et al., 2009). However, the low levels of HIV RNA are lower than in activated CD4⁺ T cells, which brings to question as to whether the low levels of HIV RNA is enough for significant expression of protein (Lassen et al., 2004a; Zhang et al., 2004).

Current evidence suggests that HAART suppresses viremia to below clinically detectable limit (50 HIV-1 RNA copies/ml) (Dinoso et al., 2009). It has been reported earlier that

antiretroviral drugs caused increase in CD4⁺ T cell counts and exponential decay in viremia, demonstrating the short lifespan of plasma virus with half life of about 2 days (Wei et al., 1995; Perelson et al., 1996). This led to the earlier idea that, with prolonged use of combination antiretroviral drugs, HIV-1 could be eradicated completely leading to a cure (Perelson et al., 1997). However, we now know that mere prolonged use of HAART cannot cure HIV/AIDS because HIV-1 is capable of persisting in latently infected resting CD4⁺ T cells which constitute a reservoir for the virus (Rong and Perelson, 2009; Jochmans et al., 2010; Margolis, 2010).

This leads to the clear challenge of eliminating the virus in reservoirs or sanctuaries before a cure, hence prompting scientists in this field to devise various strategies or models of purging and eliminating the virus from the reservoir. In this chapter, we discussed HIV-1 persistence and latency, the mechanisms for HIV latency, dynamics of persistent viremia, dynamics of viral decay, and current approaches for purging latent HIV reservoirs *inter alia*.

2. Defining HIV-1 reservoir

A cell type or anatomical site where a replication-competent form of a virus persists for a longer time than in the main pool of actively replicating virus can be termed a viral reservoir. In the case of HIV-1, CD4⁺ T-cells serve as major reservoirs both during HAART and untreated infection. The ultimate goal of HIV therapeutic interventions is to eradicate HIV-1 from persons infected with the virus. The development of potent antiretroviral regimens that greatly suppress HIV-1 replication has witnessed important life-saving advancement.

Despite these therapeutic advances, major obstacles remain to eradicating HIV-1. Reservoirs of HIV-1 have been identified that represent major impediments to eradication. Conceptually, there are 2 types of sanctuaries or reservoirs for HIV-1, cellular and anatomical. Cellular sanctuaries or reservoirs may include latent CD4⁺ T cells containing integrated HIV-1 provirus; macrophages, which may express HIV-1 for prolonged periods; and follicular dendritic cells, which may hold infectious HIV-1 on their surfaces for indeterminate lengths of time. HIV-1 infected patients harbor $\sim 10^5 - 10^6$ memory CD4⁺ T cells that contain fully integrated but transcriptionally silent HIV proviruses. The key anatomical reservoir for HIV-1 appears to be the central nervous system. Critical clues for HIV-1 eradication lie in the understanding of the dynamics of HIV-1 within these reservoirs (Schrager & D'Souza, 1998; Williams & Greene, 2007).

2.1 Resting CD4⁺ T cells are the main contributors to the reservoir

The description of latently infected resting CD4⁺ T cells was first done by Chun and his colleagues (Chun et al., 1995). Latently infected CD4⁺ T cells are resting CD4⁺ T cells that lack activation markers including CD25, HLA-DR and CD69. Resting CD4⁺ T cells are in the G0/1a stage of the cell cycle, express limited levels of the transcription factors NFAT and NF- κ B, and have limited pools of deoxynucleosides, which are important for the efficient expression of the HIV LTR. Besides, resting CD4⁺ T cells have been shown to be enriched for microRNAs involved in HIV latency (Han et al., 2007; Huang et al., 2007; Colin & Van Lint, 2009; Margolis, 2010). In addition, studies have shown that during acute infection when reservoir establishes, the most prominently infected cell types are the resting CD4⁺ T

cells; and CD4⁺ T cells are the most frequently infected before or during HAART. An in vitro study with enhanced HIV-1 integration assay has also reported that HIV-1 integrates into resting CD4⁺ T cells even at low viral inoculum, suggesting that there is no threshold number of virions required for integration into resting CD4⁺ T cells (Schacker et al., 2000; Li et al., 2005; Agosto et al., 2007). Figure 1 illustrates dynamic patterns of the infection of CD4⁺ T cells.

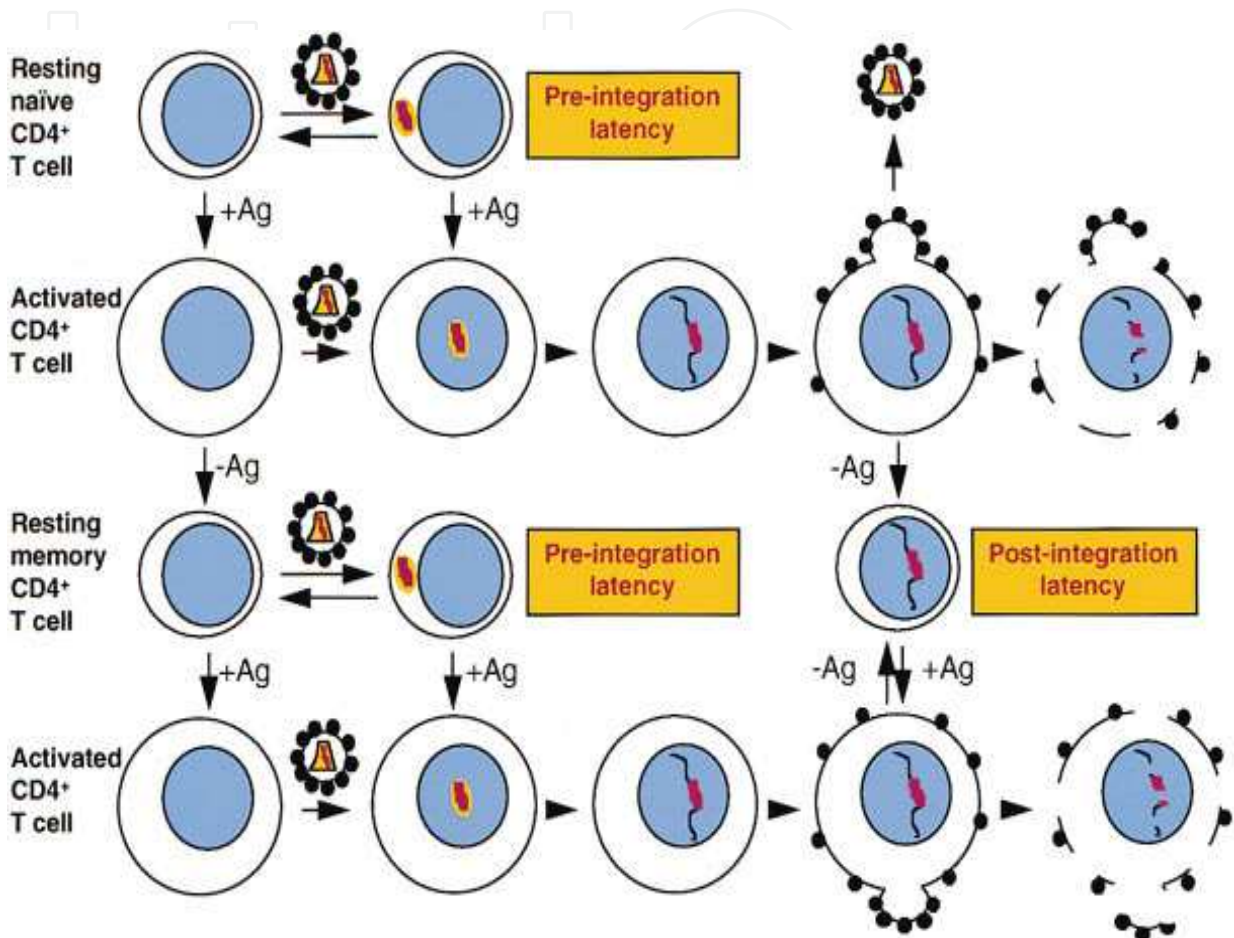


Fig. 1. Dynamics of HIV-1 Infection of CD4⁺ T lymphocytes: The horizontal arrows show the successive steps in the life cycle of the virus; while the vertical arrows show the transitions between resting (small) and activated (large) CD4⁺ T cells. X4 isolates of HIV-1 can infect resting and activated CD4⁺ T cells, but replication does not occur in resting cells due to a block prior to the stage of nuclear import of the pre-integration complex containing the reverse-transcribed HIV-1 DNA. R5 isolates can infect activated CD4⁺ T cells, but may infect only the subset of resting CD4⁺ T cells that express sufficient amounts of CCR5 (Finzi & Siliciano, 1998).

3. Dynamics of HIV-1 infection, decay characteristics and latency

The dynamics of viral replication in vivo offer the best context to consider the pathophysiology of HIV-1 infection and the mechanisms of viral persistence.

Understanding viral dynamics requires a steady state (in which continuous virus production is balanced by virus clearance) analysis of the amount of free virus and the

number of virally infected cells present in infected individuals (the viral load) and a dynamic analysis of the rates at which virus particles and virally infected cells are generated and cleared. Substantial progress has been made in understanding key elements of HIV-1 dynamics, and the perspectives developed have already proven useful in understanding the pathogenesis of other infectious diseases.

Several studies have described the dynamics of HIV-1 infection, decay characteristics and latency. In one of such studies, Perelson and colleagues used a set of differential equations and described the dynamics of cell infection and virion production and by fitting the decay data to the derived model. This way they were able to examine plasma viral levels early after the initiation of therapy in an effort to measure separately the two processes that contribute to the rapid initial decay of the plasma virus: the clearance of free virions and the loss of the infected cells that produce most of the plasma virus. They found out that corresponding half life ($t_{1/2}$) values for free virions ranged from 0.18 to 0.34 days, with a mean of 0.24 ± 0.06 days (~ 6 hours).

Total daily virion production and clearance rates range from 0.4×10^9 to 32.1×10^9 virions per day, with a mean of 10.3×10^9 virions per day released into the extracellular fluid. The average life span of a virion in the extracellular phase is 0.3 ± 0.1 days, while the average life span of a productively infected cell (presumably an activated CD4+ T cell) is 2.2 ± 0.8 days. Productively infected CD4+ T cells are lost with an average $t_{1/2}$ of about 1.6 days. The average life span of a virion in blood was calculated to be 0.3 days. Therefore a population of plasma virions is cleared with a $t_{1/2}$ of 0.24 days. This implies that, on the average, half of the population of plasma virions turns over in about every 6 hours. The average generation time of HIV-1, defined as the time from the release of a virion until it infects another cell and causes the release of a new generation of viral particles, was determined to be 2.6 days (Perelson et al., 1996; Finzi & Siliciano, 1998; Pierson et al., 2000; Dahl et al., 2010).

4. How HIV-1 reservoirs are formed

Several mechanisms may be involved in the formation of reservoirs. One mechanism is the direct infection of resting CD4+ T cells. This is supported by the fact that resting cells are the prominently infected cells during early infection (Li et al., 2005). Still in support of this mechanism, data from in vitro studies have also demonstrated that it is possible to infect resting cells directly (Agosto et al., 2007; Plesa et al., 2007; Dai et al., 2009).

In addition, a cytokine-rich environment and the presence of macrophages may play some roles in enhancing the formation of reservoir through some mechanisms (Eckstein et al., 2001; Swingler et al., 2003).

Another idea is that latently infected CD4+ T cells may originate from activated CD4+ T cells that return to a resting state after becoming infected. The fact that memory CD4+ T cells contribute the most to latently infected CD4+ T cells lends credence to this idea (Chun et al., 1997; Han et al., 2007).

4.1 How to measure HIV-1 reservoirs

The assay used in measuring latently infected cells was developed by Siliciano and Wong with their colleagues, and is referred to as the Infectious Units Per Million (IUPM) assay.

This assay involves the serial dilution and subsequent activation of resting CD4⁺ T cells from HIV-infected patients on HAART in the presence of allogeneic susceptible T blasts as targets to allow spreading infection (Finzi et al., 1997; Wong et al., 1997; Siliciano & Siliciano, 2005). Determining the number of latently infected cells is made possible by enumerating the number of wells that demonstrate positive results for spreading infection under limiting dilution conditions. The IUPM assay, though costly and laborious, has proved highly invaluable for the characterisation of reservoir cells. Using this assay, latently infected cells are defined as cells that contain HIV DNA but do not produce infectious virions until they are stimulated to enter the cell cycle. Perhaps a better description is to define latent cells as those cells that contain integrated DNA that do not release virions until stimulated, if steps are taken to remove pre-integration complexes (Lassen et al., 2004a; Lassen et al., 2004b).

Studies have shown that measurement of integrated HIV DNA is a useful surrogate marker of latently infected cells. However, studies that involved measuring latently infected cells over a period of time demonstrated constant level of both IUPM and integrated HIV DNA. This observation suggests that changes in the levels of integrated HIV DNA would be a good surrogate marker for changes in reservoir size (Brussel et al., 2003; Brussel et al., 2005; Koelsch et al., 2008; Chomont et al., 2009; Richman et al., 2009).

The integration assay appears to be more sensitive and easier to perform than the IUPM assay, but the IUPM assay will best determine if any cells are capable of producing viable HIV particles. Some studies have demonstrated the superiority of integration assay over the IUPM assay. For instance, the levels of latently infected cells are so low in elite suppressors that the level is below the detection limit of the IUPM assay. However, a particular study detected integrated DNA in 10 out of 10 elite suppressor individuals (Blankson et al., 2007; Julg et al., 2010; Graf et al., 2011). The fact that a large fraction of integrated HIV proviruses are defective and contain a large number of mutations should be brought into consideration when using an integration assay as a surrogate marker for latently infected cells.

5. How to purge latent HIV-1 reservoirs

Most strategies for purging latent HIV-1 reservoirs involve the activation of latently infected cells to induce the expression of the integrated HIV-1 DNA making it susceptible to antiretroviral therapy and immune-mediated killing. Latently infected cells can be reactivated through a number of ways. One way is to up-regulate cellular transcription to induce HIV-1 gene expression. This involves inhibiting HDACs which promote latency by regulating genome structure and transcriptional activity. A study by Archin and colleagues demonstrated that synthetic HDAC inhibitors are capable of reactivating latently HIV-infected cells in vitro (Archin et al., 2009). However, when HDAC inhibitor, HAART and valproic acid were co-administered, it gave mixed results (Lehrman et al., 2005; Blankson et al., 2007). Secondly, some interleukins have shown some promise in controlling latently infected cells. For instance, Chun and his colleagues demonstrated that patients treated with IL-2 plus HAART had fewer resting memory CD4⁺ T cells than patients who had HAART alone. The role of IL-7 in purging latently infected cells has also been tested in some studies with significant results. In addition, it is possible to purge latently infected cells by combining DNA methylation inhibitors with HAART, since DNA methylation is known to reduce intracellular transcriptional activity (Chun et al., 1999; Kauder et al., 2009). Prostratin has also been shown to up-regulate HIV-1 expression in peripheral blood mononuclear cells

from patients on HAART but down-regulates the expression of CD4 receptor; and another study has demonstrated that the transcription factor *Est1* reactivates latent HIV-1 in resting memory T cells in patients who were on HAART without resulting to general activation of T cells (Kulkosky et al., 2001; Yang et al., 2009).

Another method is to increase HIV-1 gene expression by altering the effects of non-coding cellular miRNAs. There are reports of cellular miRNAs contributing to HIV-1 latency in memory CD4⁺ T cells. When cellular miRNAs bind to the 3' end of HIV-1 messenger RNA, they inhibit viral protein translation in cells resulting to the enhancement of latency.

However, combination of the different activators may play a synergistic role in the reactivation of latent viral reservoirs as demonstrated by some studies. For instance, Reuse and colleagues have demonstrated that combining valproic acid and prostratin or suberoylanilide hydroxamic acid (SAHA)- an HDAC inhibitor- and prostratin more efficiently reactivated HIV-1 production in cell lines and cells isolated from patients receiving HAART than each compound alone (Reuse et al., 2009; Dahl et al., 2010).

6. Conclusion

Latent HIV-1 reservoirs are established early during primary infection in lymphocytes and macrophages and constitute a major barrier to eradication even in the presence of highly active antiretroviral therapy (Alcami et al., 2010). HAART reduces HIV-1 in plasma to undetectable levels, which led to the earlier idea that prolonged treatment might eradicate the infection. However, it was later discovered that HIV-1 can persist in a latent form in resting CD4⁺ T cells. In addition, both cellular and viral miRNAs could be involved in maintaining HIV-1 latency or in controlling low-ongoing viral replication. Identification of new cellular elements restricting the viral cycle provides a new paradigm on HIV-1 latency (Alcami et al., 2010). It is obvious from growing evidence that HIV-1 eradication cannot be achieved without addressing the vicious circle of HIV-1 latency and reservoirs. Latently infected cells serve as a constant source of viral rebound even in the face of antiretroviral therapy. Finally, HIV-1 reservoirs and latency present monumental challenges to the scientific community, especially those involved in therapeutic research; and at the same time offer useful clues for eradication.

7. References

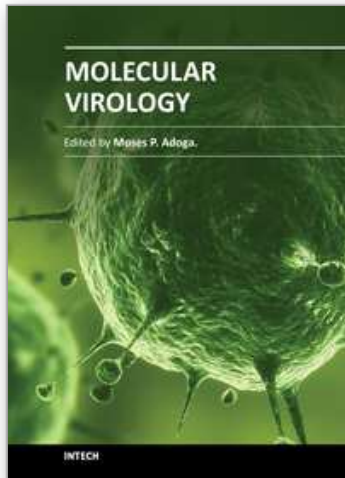
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This book covers various aspects of Molecular Virology. The first chapter discusses HIV-1 reservoirs and latency and how these twin phenomena have remained a challenge to eradication. Aspects regarding the molecular evolution of hepatitis viruses including their genetic diversities with implications for vaccine development are treated in the second chapter. Metabolic disorders that are a consequence of hepatitis C virus infection are discussed in the succeeding chapter. The following two chapters discuss influenza C virus and the applications of viral vectors in therapeutic research. Avian influenza is handled in the sixth chapter and the therapeutic potential of belladonna-200 against japanese encephalitis virus infection is discussed in the succeeding chapter. The last two chapters discuss baculoviruses and their interaction with polydnviruses. Researchers, lecturers and students will find this book an indispensable companion.

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