Review Article

Factors Associated with the Size of HIV DNA Reservoir

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Abstract

Objective: To review the recent literatures related to the factors associated with the size of the HIV reservoir and their clinical significance.
Data Sources: Literatures related to the size of HIV DNA was collected from PubMed published from 1999 to June 2016.
Study Selection: All relevant articles on the HIV DNA and reservoir were collected and reviewed, with no limitation of study design.
Results: The composition and development of the HIV-1 DNA reservoir in either treated or untreated patients is determined by integrated mechanism comprising viral characteristics, immune system, and treatment strategies. The HIV DNA reservoir is a combination of latency and activity. The residual viremia from the stochastic activation of the reservoir acts as the fuse, continuing to stimulate the immune system to maintain the activated microenvironment for the rebound of competent virus once treatment with antiretroviral therapy is discontinued.
Conclusion: The size of the HIV-1 DNA pool and its composition has great significance in clinical treatment and disease progression.

Key words: Antiretroviral Treatment; HIV-1 DNA; Immune Activation; Latent Reservoir; Residual Viremia

Introduction

The rapid development of novel antiretroviral treatments has increased adherence to drug regimens and reduced the related toxicity,[1-3] which has driven scientists to be interested in an HIV functional cure. Although many studies have tried to achieve functional cure, the persistence of the HIV reservoir is the main obstacle for the realization of this goal.[4] From biological aspect, HIV, as a retrovirus, has two typical steps in its viral replication cycle. The first step is reverse transcription, and the second is integration.[5] HIV DNA exists in the body in two major forms: integrated and unintegrated.[6] Precise assays to directly quantify cell-associated integrated and unintegrated HIV DNA have facilitated the close monitoring of the capacity of HIV virus proliferation even when the virus is suppressed.[7-10] The total HIV DNA level is an independent predictor of disease progression for primary HIV infection without treatment.[11,12] Accumulating research suggests that even with the efficacy of current antiretroviral medicines, it is difficult to eradicate or even efficiently reduce HIV DNA to a very low level, especially in chronically infected patients with high HIV DNA at baseline.[13] The mechanisms of HIV persistence in the reservoir during successful antiretroviral therapy (ART) have been widely reported, including residual viremia, cell-to-cell transmission, and clonal proliferation of infected CD4+ T-cells.[10,14,15]

Many factors influence the size of the HIV-1 DNA pool and its decay. The size of the HIV-1 DNA pool and its composition has great significance in clinical diagnosis and disease progression. Although there are many excellent reviews on the HIV-1 reservoir, most focus on one aspect at the basic research level.[4,16-21] Here, we described the relevant factors in a simplified way, focusing on the clinical research to make the information more intuitive to the clinician.

Viral Characteristics

The viral replicative capacity represents the virulence and predicts the speed of disease progress. The virulence of HIV variants is closely related with the viral set point and

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the decline of CD4+ T-cells.[22,23] Compared to the virus in the plasma which is more likely to represent recently produced viral particles, HIV DNA in the tissue, especially in the lymph node, often represents the sequences from the original ancestral virus.[24] However, considering the available sample resources, most quantification assays detect circular cell-associated HIV DNA in the blood.[25] In the early stage of infection, unintegrated HIV DNA represents a large proportion of the total DNA. The level of unintegrated HIV DNA is associated with the efficiency of viral replication. Thus, in most studies, the viral load is positively correlated with the quantity of HIV DNA. Just like the set point viral load, the HIV DNA tends to remain at a stable level after peak viremia without ART intervention. Although many factors influence the set point viral load, with regard to viral characteristics, the number of transmitted viruses has been a recent focus of extensive research.[26] Considering the biological characteristics of retroviruses, which undergo reverse transcription and then integration, there is no reason to rule out the possibility that the number of transmitted founder viruses has no relationship with the overall quantity of HIV DNA.[27] More studies are needed to determine the relationship between the HIV DNA baseline level and the characteristics of the virus.

Host Immune Background

In addition to virological factors, the host immune background is also associated with the clinical outcome. Sexual transmission pairs or mother–child pairs with known transmission relationships provide data about the significant role played by human leukocyte antigen (HLA) and the natural immune system in the control of disease progression.[28-35] Under a similar immune background, the ratio and the count of T-cell subsets are strongly associated with inflammation and HIV persistence.[36-38] Although there have not been many reports about the relationship between the size of HIV reservoir and HLA genotype, elite controllers with a protective HLA type tend to have a lower HIV DNA level[39] and are more likely to have powerful immune responses. The initial HIV DNA baseline can be controlled by the breadth and magnitude of HIV-1-specific CD4+ T-cells.[40-42] This is also the reason why long-term nonprogressors have very low levels of HIV DNA, outside of that from defective virus at the beginning of infection.[43,44] Antibody-dependent cell-mediated cytotoxicity is another factor that reduces or controls the quantity of cell-associated HIV DNA.[45] The association between the HLA polymorphisms and HIV reservoir is not fully understood.[46-48] More research about this field can provide information related to the mechanism of natural control and identify potential cytotoxic T-lymphocyte epitopes for vaccine design.

Coinfection

HIV-1-infected patients are capable of being coinfected with other viral and bacterial pathogens.[49] Strong evidence has demonstrated that asymptomatic replication of human herpesvirus can mediate immune activation and is associated with higher levels of HIV DNA during ART.[50-52] In addition, the presence of cytomegalovirus is positively correlated with the HIV DNA level in both treated and untreated individuals.[51] The probable reason for these might be as follows: The development of more activated, antigen-specific CD4+ T-cells provides new target cells for reseeding the HIV reservoir.[53] Increases in the levels of cytokines and chemokines would also stimulate inflammation and immune activation. The persistence of other viruses changes the immune environment and allows the HIV reservoir to become more diverse, which ultimately influences its decay.

Impact of Different Combination Antiretroviral Therapy Strategies and Stimulating Agents on the HIV DNA

Compared to early treatment at the acute stage, it is difficult to further reduce the reservoir of chronically infected patients with long-term treatment. Most intensified treatments have no impact on the HIV-1 reservoir compared to standard triple-drug therapy.[54-56] A switch to monotherapy from a standard regime in virally suppressed individuals has been investigated in several studies. Although there is no difference in viral control or CD4 count and even an improvement in lipometabolism with this strategy, long-term studies of the changes in the homeostasis of HIV-1 reservoir are needed.[57,58] Furthermore, new antiretroviral agents are urgently needed to act directly on the HIV-1 reservoir. Among several strategies, "shock and kill" has been an actively studied method to eradicate the reservoir. However, the results have not been optimal with either master transcription factors or interleukins as the reactivating agent's targets.[56,59,60] However, new evidence has demonstrated the persistence of activated subspecies of HIV DNA after long-term effective ART, which might suggest the use of more caution with this strategy.[61-63]

Residual Viremia

The detection limit of clinical HIV assays is 50 copies/ml of plasma.[64] With the advent of highly sensitive real-time polymerase chain reaction, which is capable of detecting single copies of HIV RNA in the plasma,[65] many studies have demonstrated the presence of residual viremia in some successfully suppressed individuals after many years of ART.[66,67] The copy number of residual viremia during the follow-up was shown in some studies to be positively associated with the baseline level of HIV DNA and RNA.[68] In one cross-sectional cohort study, 63% (80/127) of participants receiving ART for a median of 6.3 years had detectable viremia that was positively correlated with the level of HIV DNA present in the individual.[69] The mechanism of the existence of residual viremia is not clear. Drug-resistant variants might be one reason, particularly considering the low penetrance of the ART drugs in the lymphoid tissue.[18,70] In most cases, the role of residual viremia has not been completely identified.[71,72]

The persistent low level of residual viremia caused by the activated latent reservoir has a role in replenishing the pool of HIV DNA.[73] The fact that HIV-specific CD4+ T-cells are preferentially infected by HIV-1 at all stages of disease suggests the possibility that residual viremia continues to mediate the infection or stimulation of activated CD4+ T-cells even under effective ART.[74] More studies are needed to compare the productive capacity of residual viremia among patients with different reservoir sizes.

Immune Activation

Although the immune activation phenotype is diverse, the frequency of T-cells expressing HLA-DR and CD38 has often been used. Based on the recent evidence, the total HIV DNA has a closer relationship with the number of HLA-DR + CD38 - cells containing the integrated HIV DNA than with the number of CD38+ memory T-cells.[63] Like the dynamic decay of HIV DNA with ART, the level of certain immune activation biomarkers tended to be stable after 1 year of viral suppression.[75] No matter the reason for the systemic immune activation during HIV-1 infection, it is an important factor associated with the size of the HIV reservoir in a long-term plasma-suppressed cohort lacking any viral blips under ART.[76,77] A consistent positive relationship has been demonstrated between T-cell immune activation and cell-associated DNA and RNA.[78] There is a possibility that activated immune cells stimulate the proliferation of the HIV reservoir. However, Some elite controllers exhibit spontaneous viral suppression and a low level of HIV DNA but also have a high level of inflammatory markers and a high risk of clinical cardiovascular disease compared to those well-controlled on ART.[39] Based on recent evidence, immune activation tends to be a sign of the effect of the immune response on the HIV reservoir besides a direct influence. The relationship among residual viremia, cellular HIV DNA, and immune activation remains further study.[69,79,80]

Diversity of the HIV-1 Reservoir

Recent developments in technology and theory have

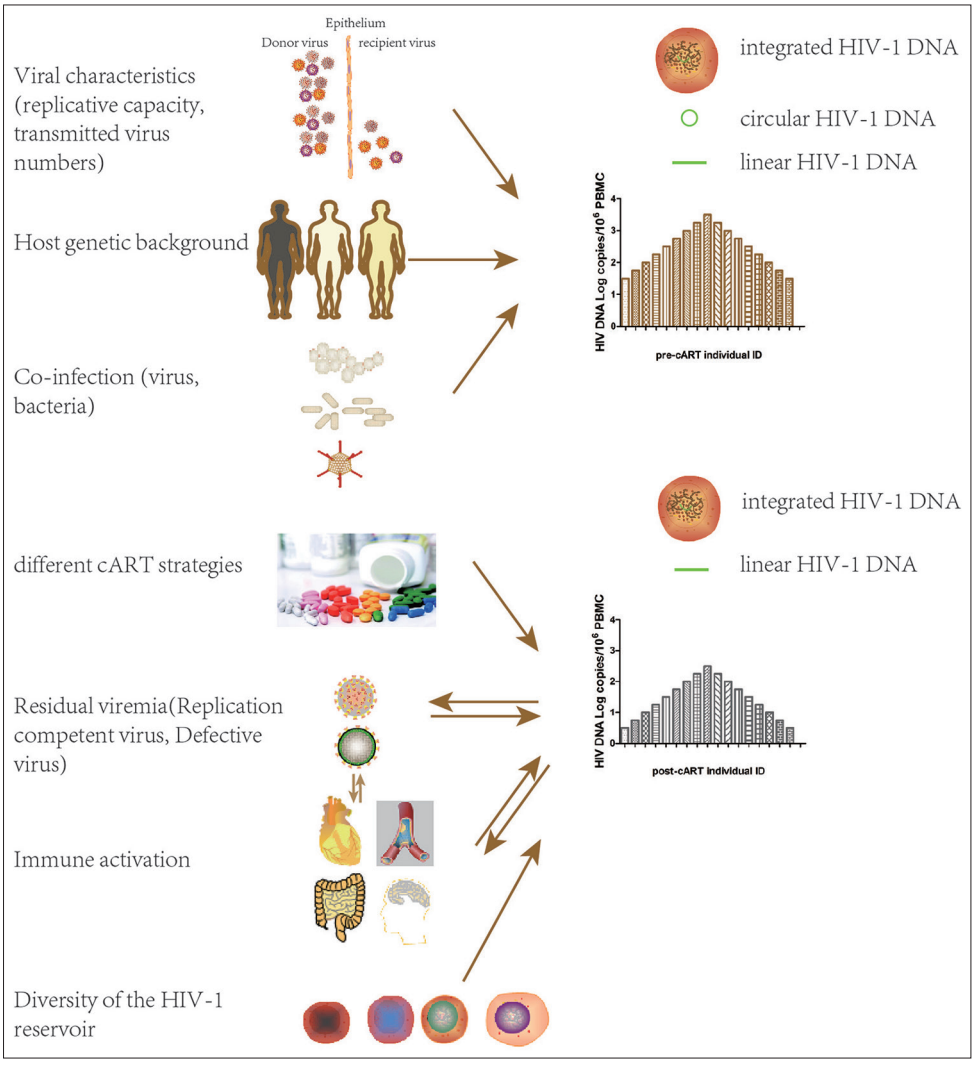

Figure 1: The composition and development of the HIV-1 DNA reservoir either in treated or untreated patients is determined by integrated mechanism comprising viral characteristics, immune system, and drugs.

increased our knowledge of the diversity of the HIV-1 reservoir.[81-83] The half-life of HIV-1 DNA in different subsets of memory T-cell populations is different; it is 277, 144, 133, and 88 months for stem-like, central-memory, transitional-memory, and effector-memory T-cells, respectively.[84,85] Some special cell subsets, such as Th17 and T follicular helper cells, play an important role in the persistence of the HIV-1 reservoir in both untreated individuals and those receiving long-term treatment.[86,87] Not only is the cell subset correlated with the rate of decay of the HIV-1 reservoir, but also the tissue compartment also influences the destiny of tissue-resident HIV-1-infected memory T-cells.[16,88] The tissues are the largest reservoir for HIV; thus, the mechanism of HIV persistence and changes in HIV DNA subspecies during ART needs to be further evaluated using nonblood samples.[89] The limitations of HIV DNA detection in peripheral blood samples are made even more clear by the continuous reduction of Th17 cells in partial gut tissue from successfully treated individuals.[90,91] More studies are needed to investigate the cell composition and interaction of the HIV-1 reservoir in long-term successfully treated individuals. The results from these studies will improve the design of strategies to control homeostatic proliferation and stability.

Conclusions

The composition and development of the HIV-1 DNA reservoir either in treated or untreated patients is determined by integrated mechanism comprising viral characteristics, immune system, and treatment strategies [Figure 1]. The immune system as a network might be altered in HIV infected patients receiving treatment compared to healthy controls.[92] A subtle balance between replication and homeostasis is required to keep the HIV reservoir at a constant level after the depletion of the actively replicating virus by ART.[93] During the period of long-term suppression of replication, a lack of a robust HIV-specific CD4+ T-cell response to eliminate the residual reservoir in circulating blood cells and tissue means that the HIV-1 reservoir remains a ticking time bomb.[42,94] The residual viremia from the stochastic activation of the reservoir acts as the fuse, continuing to stimulate the immune system to maintain the activated microenvironment for the rebound of competent virus once treatment with ART is discontinued.[15,95,96] An optimized strategy should be developed through a combination of antiretroviral medicine, specific immunity, and latent activation agents.

In summary, the size of the HIV-1 DNA pool and its composition has great significance in clinical treatment and disease progression.

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Conflicts of interest

There are no conflicts of interest.

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