How human immune system controls HIV.

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Abstract

The Human Immunodeficiency Virus (HIV) targets immune cells that express the Cluster of Differentiation 4 cell surface glycoprotein ($CD4^+$ cells), which include T cells, macrophages, and dendritic cells. By integrating the double stranded DNA copy (vDNA) of its RNA genome into the target cell's chromosome, HIV creates a persistent infection. The chromosomally integrated vDNA, also known as a "provirus," survives in the host cell for its whole lifespan and produces new viruses. If untreated, the provirus continuously produces *de novo* infections and target cell death in the majority of HIV infected people (Chronic Progressors, CPs). Acquired Immunodeficiency Syndrome (AIDS) and eventually, death are the results of the immune system's increasing breakdown.

Keywords: Immunity, AIDS, Vaccine, Transmission, Infection

Introduction

The Human Immunodeficiency Virus (HIV) targets immune cells that express the Cluster of Differentiation 4 cell surface glycoprotein ($CD4^+$ cells), which include T cells, macrophages and dendritic cells [1-3]. By integrating the double stranded DNA copy (vDNA) of its RNA genome into the target cell's chromosome, HIV creates a persistent infection [4]. The chromosomally integrated vDNA, also known as a "provirus," survives in the host cell for its whole lifespan and produces new viruses. If untreated, the provirus continuously produces *de novo* infections and target cell death in the majority of HIV infected people (Chronic Progressors, CPs) [5]. Acquired Immunodeficiency Syndrome (AIDS) and eventually, death are the results of the immune system's increasing breakdown [6]. Consequently, AIDS related opportunistic infections and malignancies have caused about 35 million deaths as a result of HIV. HIV comes in two different varieties: HIV-1 and HIV-2 [7]. The continuing HIV/AIDS pandemic is caused by the HIV-1 virus, which accounts for over 95% of infections globally. West Africa is home to the relatively less harmful HIV-2 virus. Despite years of intensive study, there is still no effective HIV vaccine, which leads to millions of new HIV infections each year.

Description

People living with HIV presently have just one choice for treatment, Antiretroviral medicines (ARVs), which target and limit the action of particular HIV-1 proteins and consequently, several phases of the virus life cycle [8]. Combination Antiretroviral Therapy (cART), which combines a variety of ARVs, is considered the gold standard of care for managing pre-existing or reducing post therapy drug resistant viral strain emergence [9], which is brought on by low fidelity HIV-1 replication and/or host factor induced mutations in viral genome [10]. Since its introduction, cART has proven to be very successful at reducing the risk of transmission, inhibiting the spread of the illness, partially maintaining or restoring immunological competence and suppressing HIV-1 replication [11]. However, cART only prevents de novo infection of vulnerable cells; it has no effect on provirus production from infected cells. To make matters worse, very early in HIV-1 infection, a population of long lived resting memory $CD4^+$ T cells (rCD4s) is generated that contains a provirus that is transcriptionally quiet and therefore incapable of replicating itself (latent HIV reservoir) [12]. Any cART interruption triggers a rapid return of HIV-1 replication within days to weeks because cART does not eradicate the provirus [13,14]. cART must be continuously administered for life because it is not curative. The most important host immune response preventing HIV-1 replication *in vivo* is provided by HIV-1 specific Cytotoxic T-Lymphocytes (CTL) that expresses the CD8 cell surface glycoprotein ($CD8^+$) [15]. Human Leukocyte Antigen (HLA) class I molecules exhibit certain viral peptides on the cell surface, which the CTLs recognise and then activate to destroy HIV infected cells. However, in the case of untreated CPs, CTLs are unable to effectively stop virus replication and stop the development of AIDS. A variety of viral methods intended to anticipate or circumvent the CTL response are to blame for the failure of the CTL mediated viral control. The creation of latent HIV reservoirs, which lack the capacity to produce viral antigen and are hence resistant to CTL mediated immune responses, stands out among them [16]. The greatest obstacle to curing HIV is hence the latent HIV reservoirs [17].

Uncomfortably, despite the epidemic being 37 years old, there is presently no cure for the over 37 million people who have HIV. Consequently, AIDS related infections still cause close to

a million deaths annually. The steps of recommended medical care for PLHIV are outlined in the "HIV care continuum," a framework that includes testing and diagnosis, linking to and maintaining clinical care, starting and maintaining cART and viral suppression [18]. The majority of infected individuals, however, are either unaware of or do not have access to cART. Therefore, it is likely that the HIV/AIDS epidemic will remain a serious public health concern for the foreseeable future. Therefore, despite the related technical and logistical difficulties, it is essential that the scientific community and funding organisations continue down the road of creating therapeutic techniques to combat HIV.

Surprisingly, in a small subset of untreated (cART-naive) HIV infected people known as elite controllers/HIV Controllers (HCs), the HIV-1 replication is robustly and durably suppressed, the viral load is maintained below the clinical detection limit and the disease progression is long term prevented [19]. Strong HIV-1 specific CTL responses have been shown to play a major role in limiting HIV-1 infection in HCs, despite the observed genetic and immunologic variability across HCs. Additionally, HCs have higher levels of functional avidity (the capacity to recognise very low concentrations of HIV specific antigens) and poly functionality (the capacity to secrete multiple cytokines) in their CTLs, which help them fight off HIV infected cells. These alleles are linked to long lasting control of HIV-1 replication and long term non progression to AIDS.

Conclusion

This shows that, even in the absence of cART, the human immune response can mount a strong and durable control of HIV-1 replication and prevent the progression to AIDS. HCs have been suggested as a model for HIV cure research because they demonstrate the key characteristics of an HIV-1 "functional cure" outcome (durable suppression of viral replication, absence of transmission and non-progression to AIDS), all in the absence of cART.

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