Annals of
Reviews and Research

Juniper Publishers
key to the Researchers

Mini Review
Volume 9 Issue 3 - June 2023
DOI: 10.19080/ARR.2023.09.555761

Ann Rev Resear
Copyright © All rights are reserved by Ghalib Alkhatib

Immune Responses to the human retroviruses HIV-1 and HTLV-1

Ghalib Alkhatib*

Department of Basic Sciences, California Northstate University College of Medicine, Elk Grove, California, USA

Submission: May 29, 2023; **Published:** June 06, 2023

***Corresponding author:** Ghalib Alkhatib, Department of Basic Sciences, California Northstate University College of Medicine, Elk Grove, California, USA

Abstract

Retroviruses are viruses that integrate their reverse transcribed cDNA into the host genome. Integration into the host DNA ensures their replication and generation of new viral particles. In this minireview I will focus on the interaction of two huma retroviruses with the immune system. Both human immunodeficiency virus type 1 (HIV-1) and the human T cell leukemia virus are retroviruses that target the CD4+ T lymphocytes. The CD4 T lymphocytes play a central role in the immune system and help coordinate the immune response by stimulating other immune cells, such as macrophages, B lymphocytes, and CD8 T lymphocytes, to fight infection. HIV-1 weakens the immune system by destroying CD4 T cells resulting in acquired immunodeficiency syndrome (AIDS). In contrast, HTLV-1 infection results in the transformation of these cells causing human T cell leukemia.

Keywords: Human T cell leukemia; Immunodeficiency syndrome; IgA antibodies; Transforming growth factor; endogenous genetic elements

Abbreviations: HIV: Human immunodeficiency; AIDS: Acquired immunodeficiency syndrome; DCs: Dendritic cells; TRAIL: TNF-related apoptosis-inducing ligand; MMTS: Mouse mammary tumor virus; ATL: Adult T-cell lymphoma; TLR7: Toll-like receptor 7; CTLs: Cytotoxic T lymphocytes; NK: Natural killer; NFAT: Nuclear factor of activated T-cells; TGF-β: Transforming growth factor-β

Introduction

The immune response to these retroviruses can target the viral particles whether extracellular, intracellular, or endogenous genetic elements (Reviewed in 1). Immune cells can respond to retroviruses in these different forms by detecting specific viral proteins and through specialized cells. The incoming viral particles and infected cells induce the innate immune system to respond through germline-encoded factors. Several restrictions factors expressed by the host cells such as TRIM5, Tetherin, APOBEC3G interact with the infecting retroviruses and result in a transient increase in the expression of inflammatory cytokines. Cytokines cannot substitute for contact with pathogen components, indicating that pathogen recognition by receptors expressed by the antigen-presenting cells is essential to drive an innate immune response. Myeloid dendritic cells (DCs) are abundantly present at the mucosal sites. DC-SIGN is a cell adhesion receptor as well as a pathogen recognition receptor expressed at the surface of DCs and macrophages. As adhesion receptor, DC-SIGN mediates the contact between dendritic cells (DCs) and T lymphocytes, by binding to ICAM-3, and mediates rolling of DCs on endothelium, by interacting with ICAM-2. DC-SIGN captures HIV-1 at low titres through its high-affinity interaction with the HIV-1 envelope glycoprotein gp120. The interaction of gp120 is believed to participate in many signaling events that could have a positive or negative effect on cellular immune responses. For example, transcription of inflammatory cytokines depends on the positive activation of NF-kB in synergy with TLR4 and presentation of viral antigens to CD8 T lymphocytes [1-3].

In DCs, abortive viral RNA has been reported to activate a DDX3-MAVS signaling pathway, but HIV-1 appears to evade this pathway through an additional activity of DC-SIGN. Various responses are generated by recognition of the viral double-stranded DNA produced following reverse transcription of incoming viral RNA. The reverse-transcribed viral DNA activates the inflammasome, leading to release of the hallmark cytokine IL-1β from infected cells and induction of pyroptotic cell death. This is one of the proposed mechanisms that could contribute to the depletion of the $CD4^+$ T lymphocytes. How the HIV DNA activates the inflammasome is not well understood. Innate immune responses are induced in hosts early after transmission at the mucosal sites. For example, in a model of SIV infection, mucosal infection results in an increased

numbers of plasmacytoid DCs (pDCs), cytokines and chemokines. pDCs express the HIV receptors and respond to viral particles by producing large amounts of type I interferon. pDCs exposed to HIV-1 also upregulate the cytokine TNF-related apoptosis-inducing ligand (TRAIL), which could contribute to immunomodulation. HIV replication in mucosal $CD4^+$ T cells can lead to production of danger signals from compromised or dying infected cells. A hallmark of retroviral replication in tissues is the rapid induction of genes related to interferon or the inflammasome pathways. Experiments with the mouse mammary tumor virus (MMTV) demonstrated that the gut microbiota may participate in the mucosal immune response by retroviruses. Virus-bound bacterial lipopolysaccharide activated TLR4, leading to production of IL-6 and IL-10. While IL-6 is inflammatory, the induction of IL-10 could contribute to immune evasion by the virus.

DCs and macrophages can capture the HIV particles and transport them to the lymph nodes. In SIV models, viral replication induces a type I interferon response.

It is not known whether this unchecked type I interferon response results from either poorly controlled or uncontrolled viral replication in the lymph nodes. Live imaging studies revealed that the initial activation of $CD4^+$ T cells and $CD8^+$ T cells in lymph nodes is mediated by migrating DCs that are in distinct regions. HIV induces the activation of cytotoxic $CD8^+$ T lymphocytes that can be detected after the eclipse phase of infection. Most of the $CD8^+$ T cell expansion observed in HIV patients preceding the peak of viremia has been due to HIV-specific cells. The development of the HIV-specific $CD8^+$ T cells coincides with the decline of viremia. HIV-1-specific responses are ultimately inefficient to control infection, and exhaustion of $CD8^+$ T cells and loss of proliferation, cytotoxic potential, and capacity to produce cytokines are commonly observed during chronic HIV-1 infection. Exhaustion of $CD8^+$ T cells in HIV-1 infection may result from a specific differentiation program engaged early on during infection, and not necessarily from time-dependent decrease in functional capacities within central memory and effector cell subsets. The reasons for the failure of the immune system to develop optimal $CD8^+$ T cells against HIV is not known. Delayed maturation, and memory $CD8^+$ T cell subsets with limited cytotoxic potential or antiviral activity are predominantly observed during the earliest phases of HIV infection. Expression of the HIV Nef protein in infected cells induces MHC-I downregulation, which results in a reduced ability to stimulate $CD8^+$ T cells.

HIV-specific $CD4^+$ T lymphocytes also expand during acute infection. The presence of HIV-specific $CD4^+$ T cells with cytolytic or proliferative potential has been associated with lower levels of viremia. The levels and quality of $CD4^+$ T cell response has been linked to the efficiency of the $CD8^+$ T cell response. Like the inefficient $CD8^+$ T cell response, the functionality of HIV-specific $CD4^+$ T cell response is compromised due to the loss of proliferative capacity and production of IL-2. Interestingly, HIV-specific $CD4^+$ T cells share many of the characteristics of HIV-specific $CD8^+$ T cells in HIV-2-infected individuals and HIV-1 controllers, suggesting that the optimal development of both compartments is intertwined and necessary for the efficient control of the infection. Murine models of retroviral infection concluded that antibody responses are essential for neutralizing viral infection. IgM antibodies are detected in early stages of HIV infection, but this antibody class does not have neutralization activity. Compared to other viral infections, development of neutralizing antibodies is delayed in HIV infection. Once produced these antibodies do not control HIV-1 infection due to the presence of multiple quasi-species that can escape the neutralization effect. B cell dysfunction has been associated with the cytokine environment characteristic of HIV-1 infection and with cell exhaustion. Protective mucosal HIV-specific IgA antibodies have been reported in rare highly exposed/uninfected individuals, however, the mechanism of their development remains unknown. There are several proposed strategies for HIV-1 cure (Reviewed in 2).

These include approaches to achieve either control of viral replication without ongoing treatment or a complete elimination of infectious virus. A "Shock and kill' strategy to eliminate $CD4^+$ T cells latently infected with HIV-1 has been proposed (Reviewed in 2). Latently infected $CD4^+$ T cells contain the HIV-1 genome integrated into the host cell genome and remain undetectable by other immune cells owing to the lack of HIV-1 gene expression. Antiretroviral therapy (ART) prevents active viral replication but is unable to eliminate latently infected cells. Toll-like receptor 7 (TLR7) agonists and dendritic cells presenting cognate antigen can help to reactivate ('shock') infected cells and induce the transcription of HIV-1 genes, leading to the production of viral proteins. The infected cells can then be recognized and 'killed' by cytolytic effectors such as cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells. DCs could also contribute to the reactivation of latently infected cells during 'shock and kill' approaches through their antigen presentation function. Another HIV cure strategy that has been successfully accomplished in some patients is transplanting bone marrow cells from donors who are genetically resistant to HIV infection. This strategy, however, is limited by the number of donors who are homozygous for the CCR5Δ32 allele (Reviewed in 4). Recent studies reported resistance to HIV-1 infection in a CCR5Δ32 heterozygote [4]. The study proposed that the higher percent of resistant CCR5Δ32 heterozygotes might provide higher number of donors for stem cell transplantation.

HTLV-1 infection of $CD4^+$ T lymphocytes can modify the cell function. $CD4^+$ T lymphocytes are the central acquired immune response regulators (Reviewed in 3). Changes in their behavior can trigger inflammatory reactions that can break immune system tolerance, leading to autoimmunity. HTLV-1 infection is primarily associated with adult T-cell lymphoma (ATL) and HAM/TSP. HAM/TSP patients present a series of immunological dysfunctions, including spontaneous proliferation of HTLV-infected T $CD4^+$

How to cite this article: Ghalib A. Immune Responses to the human retroviruses HIV-1 and HTLV-1. Ann Rev Resear. 2023; 9(3): 555761. DOI:10.19080/ARR.2023.09.555761

lymphocytes, an increase in the migratory capacity of circulating leukocytes, and increased production of inflammatory cytokines, particularly neurotoxic cytokines such as IFN-γ and TNF-α in the affected regions along the spinal cord. Tax, the HTLV-1 oncoprotein, is an important factor of pathogenicity, and it is the causative agent for initiating transformation of infected $CD4^+$ T lymphocytes leading to HTLV-1 associated diseases. Several theories have been proposed to explain the development of HAM/TSP. One theory state that HTLV-1 induces a cytotoxic and demyelinating inflammatory process of a progressive nature. The lymphocytes are activated during spastic paraparesis; when they cross the blood–brain barrier, the inflammatory process initiates in the CNS, resulting in lesions. Direct cytotoxicity is another theory that proposes HTLV-1-cytotoxic $CD8^+$ T lymphocytes crossing the blood-brain barrier and destroying the infected glial cells by cytotoxicity or cytokine production. The cytotoxicity theory suggests an autoimmunity mechanism causing lesions by molecular mimicry. A host-encoded neuronal protein that is like the HTLV-1-encoded Tax protein can cause immune cross-reaction, leading to CNS inflammation.

Conclusion

Several studies reported that the HTLV-1 Tax protein affects several transcription factors including CREB/ATF, NF-κB, AP-1, SRF, and nuclear factor of activated T-cells (NFAT), as well as a number of signaling cascades involving PDZ domain-containing proteins such as Rho-GTPases and JAK and STAT signal transducers, thus altering the transforming growth factor-β (TGF-β) cascades. These factors are involved in cell proliferation and activation, including expression of cytokines and activation of viral proteins. Additionally, expression of FOXP3, an important transcription factor for the differentiation, function, and homeostasis of regulatory T lymphocytes (Tregs) has also been reported to be altered in HTLV-1-infected patients. Irregularities in the expression of FOXP3 may lead to loss of immune tolerance and the probable development of autoimmune diseases. The mechanisms underlying the previously proposed association of HTLV-1 infection and autoimmunity are not yet fully understood.

References

1. SaeZ-Cirion A, Manel N (2018) Immune Responses to Retroviruses. Annual Review of Immunology 36: 193-220.
2. Board NL (2022) Engaging innate immunity in HIV-1 cure strategies. Nature Reviews Immunology 22: 499-512.
3. Quaresma JAS (2016) HTLV-1, Immune Response and Autoimmunity. Viruses 8(1): 5.
4. Alkhatib B (2023) Resistance to Human Immunodeficiency Virus 1 Infection Conferred by a Compound CCR5Δ32 and CCR5 C20S Heterozygote. The Journal of Infectious Diseases.

This work is licensed under Creative Commons Attribution 4.0 License
DOI:10.19080/ARR.2023.09.555761

Your next submission with Juniper Publishers will reach you the below assets

- Quality Editorial service
- Swift Peer Review
- Reprints availability
- E-prints Service
- Manuscript Podcast for convenient understanding
- Global attainment for your research
- Manuscript accessibility in different formats
  (Pdf, E-pub, Full Text, Audio)
- Unceasing customer service

Track the below URL for one-step submission
https://juniperpublishers.com/online-submission.php

How to cite this article: Ghalib A. Immune Responses to the human retroviruses HIV-1 and HTLV-1. Ann Rev Resear. 2023; 9(3): 555761. DOI:10.19080/ARR.2023.09.555761