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Immunology of HIV-1 and HTLV-1 Infections

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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 human retroviruses with the immune system. Both human immunodeficiency virus type 1 (HIV-1) and the human T cell leukemia virus (HTLV-1) 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). HIV expression of certain proteins induces the apoptosis of CD4 lymphocytes leading to AIDS. After a long clinical latency period, HTLV-1 can transform lymphocytes, with subsequent uncontrolled proliferation and the manifestation of a disease called adult T-cell leukemia (ATLL). Evidence has accumulated that HTLV-1 can cause a clinically important degree of immune suppression even in the absence of malignant disease. The HTLV-host immunologic interaction plays a pivotal role in the pathogenesis of HAM/TSP. HTLV-1-infected T cells and CD8+ cytotoxic T lymphocytes (CTLs) against HTLV-1 invade the central nervous system (CNS) and release proinflammatory cytokines and chemokines, resulting in tissue damage. This mini review is based on several review articles that discussed the different aspects of the immune response to retroviral infections.

Keywords: Host genome; Cytokines; Chemokines; Endogenous retroviral elements; Cervicovaginal mucosa; IgM antibodies

Abbreviations: ADIS: Acquired immunodeficiency syndrome; ATTL: Adult T-cell leukemia; CTLs: Cytotoxic T lymphocytes; CNS: Central nervous system; HTLV: Human T-cell lymphotropic viruses; HIV: Human Immunodeficiency Virus; HAM: HTLV-I-associated myelopathy; TSP: Tropical spastic paraparesis; ERVs: Endogenous retroviruses; SIV: Simian immunodeficiency virus; MCLRs: Mannose-dependent C-type lectin receptors; DCs: Dendritic cells; TRAIL: TNF-related apoptosis-inducing ligand; ART: Antiretroviral therapy; TLR7: Toll-like receptor 7; CTLs: Cytotoxic T lymphocytes; NK: Natural killer; PBLs: Peripheral blood lymphocytes; HBZ: HTLV-1 basic zipper; PBM: PDZ binding motif

Introduction

The retrovirus life cycle involves entry into host cells, reverse transcription of viral RNA into DNA, integration of the provirus into the host genome, transcription and translation of viral genes, and finally the release of new virions through budding (Figures 1 & 2). Human T-cell lymphotropic viruses (HTLV) are horizontally transmitted retroviruses associated with rare retroviral diseases, originating from simian viruses. Human Immunodeficiency Virus (HIV), another exogenous retrovirus, causes a slowly progressing asymptomatic infection, acute symptoms, and acquired immune deficiency syndrome (AIDS), affecting CD4+ T lymphocytes. HTLVs manifest as asymptomatic infection, adult T-cell leukemia (ATL), and HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP), affecting T cells and having an incubation period of 30 to 40 years. Pathogenesis involves the expression of the trans-activator oncoprotein (tax) which causes uncontrolled proliferation of CD4+ T lymphocytes, with an unclear mechanism for tropical spastic paraparesis. The host defenses include the production of antibodies and T lymphocytes. HTLV-1 infection is prevalent in southwestern Japan, the Caribbean, and sub-Saharan Africa.

HIV shares structural similarities with HTLV, but with a larger genome; CD4 cell receptor binding initiates multiplication, and pathogenesis involves immune dysfunction due to T4 cell killing, impacting the brain in AIDS, although neurologic disease mechanisms are unclear. Host defenses include immune responses and interferon production, with HIV infection diagnosed through specific antibodies, polymerase chain reaction, and p24 antigen detection. Endogenous retroviruses (ERVs) are residual elements of previously infectious external retroviruses that have become integrated into our DNA and are now inherited through

Mendelian genetics. Although many ERVs are typically inactive, they can be triggered to become active by various stimuli, such as viral infections. HIVs have been demonstrated to stimulate the transcription and translation of endogenous retroviral elements.

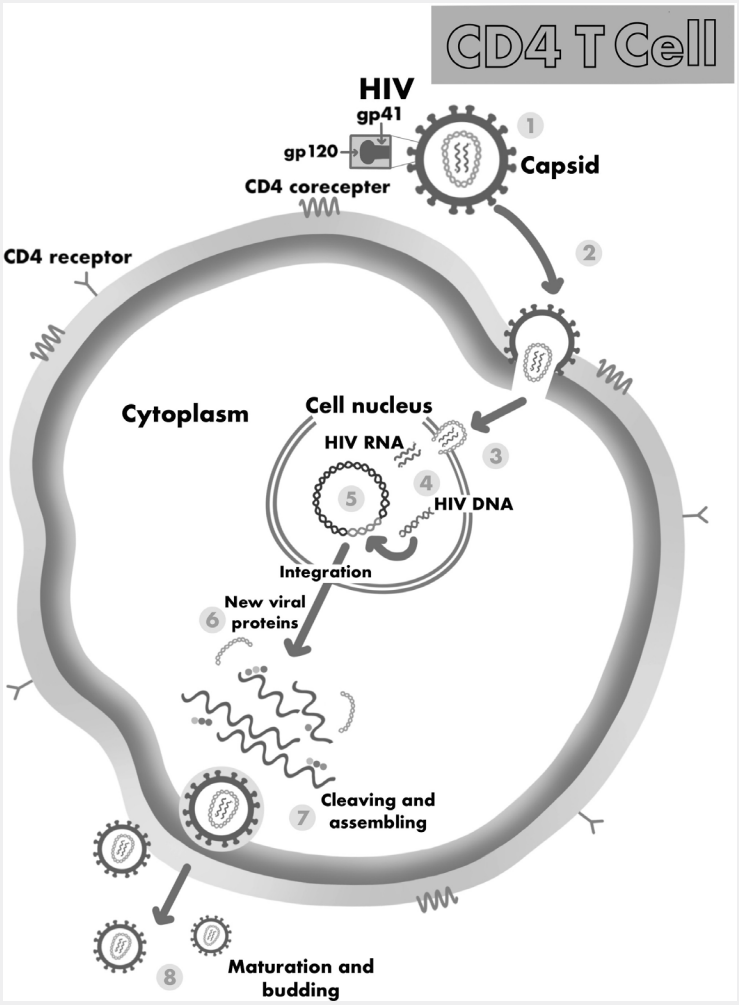

Figure 1: HIV-1 life cycle. HIV attaches to CD4+ T cells by binding to its primary receptor CD4 which results in a conformational change in gp120 exposing the V3 loop that interacts with the coreceptor, either CCR5 or CXCR4. Reverse transcription of HIV genomic RNA occurs in the cytoplasm producing double-stranded DNA transported to the nucleus. The HIV integrase enables the HIV DNA to integrate into the host cell DNA. The HIV Tat protein activates the expression of viral mRNA which is transported to the cytoplasm and translated into the different viral proteins. New HIV particles are produced and mature virions are released following capsid cleavage and rearrangement by the HIV protease. The loss of the CD4+ T cells is considered the prime feature in the dysregulation and loss of the appropriate immune response to pathogens.

HIV-1 Immunology

Immune response to HIV-1 infection

The immune response to these retroviruses can target the viral particles whether extracellular, intracellular, or endogenous genetic elements Reviewed by Xu H [1]. Immune cells can respond to retroviruses in these different forms by detecting specific viral proteins and through specialized cells. Immune responses to retroviral infection have been thoroughly reviewed by several authors Xu H [1]; SaeZ-Cirion and Manel [2]; Board, Nathan L Board [3]; Quaresma JAS [4]. The incoming viral particles and infected cells induce the innate immune system to respond through germline-encoded factors. Several restriction factors expressed by the host cells such as TRIM5, Tetherin, and 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.

Mucosal transmission of HIV

Mucosal immunity is key to HIV transmission and spread Reviewed by Xu H [1]. The mucosal epithelium is a physical barrier that protects against HIV transmission. The oral and anogenital

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mucosae have structural characteristics that create a strong first-line defense against HIV. The oral mucosa is the first site of HIV exposure, but the risk of HIV transmission orally is low. The oral mucosa has a thick keratin layer and salivary factors that are anti-HIV. Although it is possible to contract HIV through the oral cavity, it appears that oral innate immunity plays an important role in preventing the viral infection. This may be due to the protective role of the oral mucosa and/or the anti-HIV molecules present in saliva. HIV-1 infection can impair mucosal immunity. Most HIV infections result from mucosal transmission. Vaginal and rectal transmission account for most adult infections, but pediatric HIV infections are usually the result of oral ingestion of HIV+ maternal fluids whether during delivery or breastfeeding.

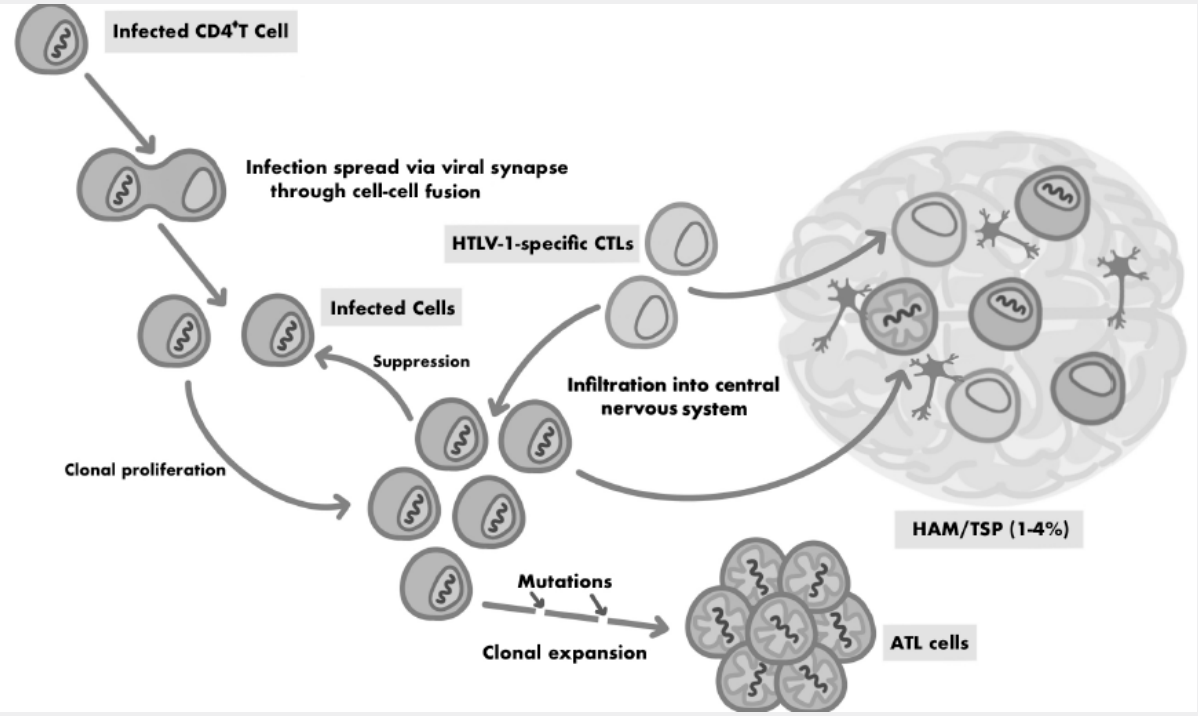

Figure 2: HTLV-1 cell infection. The HTLV life cycle begins with the interaction of viral envelope proteins with HTLV receptors resulting in the fusion of the viral membrane with the host cell membrane and uncoating of the viral core. The rest of its life cycle is similar to HIV resulting in the integration of the HTLV-1 genome into the host cell DNA. After primary infection, the clonal expansion of infected cells, rather than the novo infection of cells, represents the main route for HTLV-1 to establish persistent and chronic infection.

Previous studies using pediatric macaques have demonstrated that oral simian immunodeficiency virus (SIV) transmission to infants is more efficient than vaginal or rectal transmission. Although oral transmission is considered rare in adults, newborn infants have a neutral gastric pH, and conceivably HIV could enter through the intestinal tract in infants. Nonetheless, studies in macaques indicated that SIV is readily transmitted across the intact rectal, vaginal, cervical, oral, and (to a lesser extent) penile mucosal surfaces. Langerhans' cells are abundant in the cervix and vaginal epithelium of humans. Although vaginal LCs do not express CD4 or CCR5, they do express HLA-DR, CD1a and a number of mannose-dependent C-type lectin receptors (MCLRs) that can function as highly efficient viral attachment factors. Further, these cells have dendritic cytoplasmic processes that extend through the epithelium to the vaginal lumen, where they are involved in sampling luminal antigens.

A plausible mechanism of mucosal HIV-1 infection involves the capture of viral particles on the vaginal luminal surface by DC processes expressing one or more MCLRs. Once the virus has been captured, the immature DCs then migrate and present the virus to the underlying lamina propria that contains abundant CD4+ and CCR5+ T cells, macrophages, and other cells that may support viral amplification. Whether CD4+ T cells are directly infected by HIV or by HIV presented by LCs in the cervicovaginal mucosa is still unclear. In some experimental models, the probability of mucosal infection is directly proportional to the availability of CD4+CCR5+ T cells in mucosal tissues.

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 an adhesion receptor, DC-SIGN mediates the contact between dendritic cells (DCs) and T lymphocytes,

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by binding to ICAM-3, and mediates the rolling of DCs on endothelium, by interacting with ICAM-2. DC-SIGN captures HIV-1 at low titers 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 positively or negatively affect cellular immune responses. For example, transcription of inflammatory cytokines depends on the positive activation of NF-kB in synergy with TLR4 and the presentation of viral antigens to CD8 T lymphocytes.

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 the 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

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 number 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 the 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.

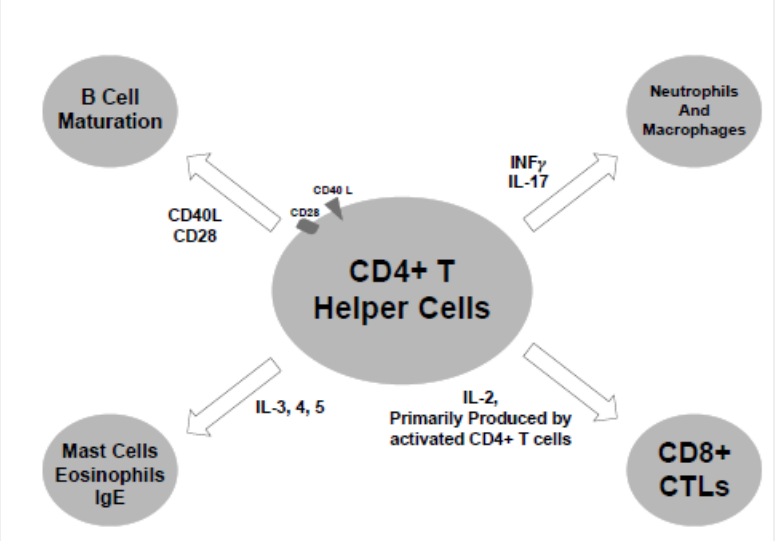

Figure 3: CD4+ T lymphocytes act as a command center for cell-mediated immunity. Upon recognizing cognate antigens binding to the TCR expressed on the cell surface, T cells become activated and develop into effector T cells. CD4+ effector T cells function as helper cells. This help is mediated by the secretion of cytokines which influence the function of surrounding cells. CD4+ T cells can be broadly divided into sub-populations defined by the pattern of secreted cytokines and surface expression of chemokine receptors that control their migration to lymphoids and other tissues. CD4+ T cells, in addition to broad classification as helper, cytotoxic or regulatory cells, can be described by their stage of maturation as naïve, effector memory, central memory, transitional memory, terminally differentiated or stem cell memory. These stages of maturation differ in longevity and in patterns of migration, which are largely defined by their surface markers including particularly chemokine receptors and β integrins.

Cell-mediated Immune response

T cells characteristically possess T cell receptor (TcR) that recognize processed antigen presented by MHC molecules. Most cytotoxic T cells express cell-surface CD8 and recognize processed intracellular viral antigens, which are presented as peptides by MHC-I molecules, and kill infected cells, thereby preventing or restricting viral replication. Activated cytotoxic T

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cells secrete interferon-gamma that, together with interferon-alpha and interferon-beta produced by the infected cells, sets up a state of cellular resistance to viral infection. The helper T cells are generally positive for CD4 molecules, recognize processed extracellular antigens presented by MHC-II molecules on antigen-presenting cells, and can be divided into two major populations.

Type 1 helper (Th1) T cells secrete interferon-gamma and interleukin-2, which activate the macrophages and the CD8+ cytotoxic T cells to kill intracellular organisms (Figure 3). Type 2 helper (Th2) T cells secrete IL-4, -5, and -6, which help B cells secrete protective antibodies (Figure 4). B cells recognize antigens directly or in the form of immune complexes on follicular dendritic cells in germinal centers of lymphoid tissue. 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.

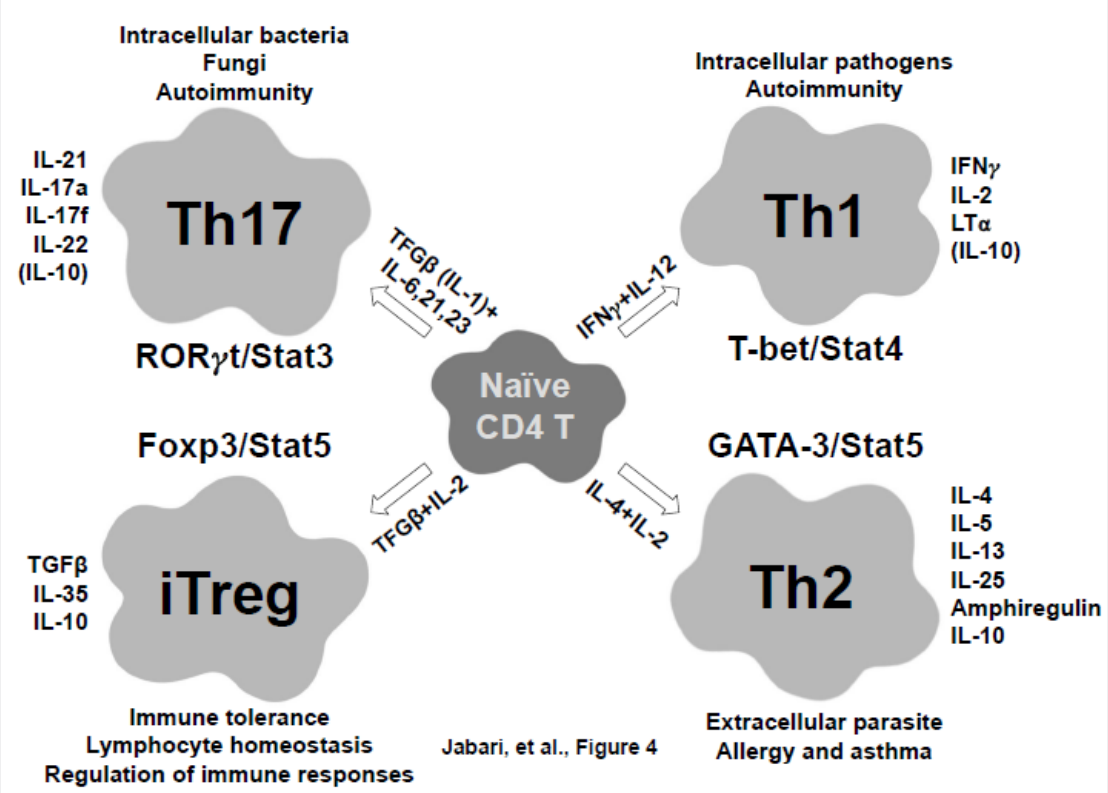

Figure 4: With cognate interactions, naïve T cells initially develop into non-polarized Th0 memory cells, and with subsequent stimulation develop into type 1 helper (Th1), type 2 helper (Th2), and type 17 helper (Th17) T cells, depending on cytokines present in the cellular micro-environment in which they develop.Th1 lymphocytes secrete interleukin (IL)-2 and interferon-gamma (IFN gamma), but not IL- 4, -5 or -6 whereas Th2 lymphocytes secrete IL-4, -5, -6 and -10, but not IL-2 or IFN gamma.

The development of the HIV-specific CD8+ T cells coincide with the decline of viremia. HIV-1-specific responses are ultimately inefficient in controlling 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 a 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

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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.

Anti-HIV antibody response

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, the 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.

Strategies to restore effective immune response

There are several proposed strategies for HIV-1 cure Reviewed by Seez-Cirion and Manel [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 accomplished in some patients is transplanting bone marrow cells from donors who are genetically resistant to HIV infection. The in vivo use of cord blood stem cells isolated from individuals who are homozygous for a 32-base pair deletion (Δ32) in the CCR5 gene as a potential therapy for AIDS. The overall goal of this transplantation strategy is to generate CD4+ T lymphocytes that resist HIV-1 infection and restore the immune system in HIV patients. This strategy, however, is limited by the number of donors who are homozygous for the CCR5Δ32 allele Reviewed in Alkhatib G [5].

While the idea of generating resistance to HIV is very intriguing, there are several scientific findings to consider Alkhatib B [6]. The defective CCR5 gene containing the deletion encodes a prematurely terminated protein that is not detected at the cell surface. We have demonstrated that this truncated mutant protein is indeed expressed in CCR5-/- subjects. Recent studies suggest that expression and stability of the CCR5Δ32 protein are critical for developing the observed resistance. It has been proposed that resistance to HIV-1 in CCR5Δ32 homozygotes may result from both genetic loss of CCR5 on the cell surface as well as active downregulation of CXCR4 expression by the mutant CCR5Δ32 protein.

Therefore, it will be critical to test whether the donor cord blood sample expresses this HIV suppressive factor, the CCR5Δ32 protein. There is also concern about the availability of cord blood samples that are homozygous for the deleted CCR5 allele. While one copy of the mutant allele occurs at high frequency in certain human populations the reported frequency of the homozygous genotype is much lower. CCR5Δ32 generally is found in populations of European descent, with allelic frequencies ranging from 0 to 0.29 (~3% of Caucasians). Additionally, it was previously determined that the mutant CCR5Δ32 allele is present at a frequency of ~0.10 (1%) in the Caucasian population of the United States. The finding that HIV-1 infection has been reported in some individuals who are homozygous for the mutant CCR5 allele lowers the enthusiasm for the cord blood stem cell transplantation approach reviewed by Alkhatib G [5].

HIV+ individuals have been identified in some hemophiliac CCR5-/- patients and several CCR5-/- homosexuals indicating that the protective effect of the CCR5Δ32 mutation is not absolute. However, it could be argued that these finding should not lower our enthusiasm to transplant cord blood stem cells carrying the CCR5Δ32 homozygous genotype. First, these HIV+ CCR5-/- subjects are very rare and do not represent a significant number compared to the majority of CCR5-/- subjects who are HIV-. Second, the mechanism of the loss of the protective effect in the HIV+CCR5-/- subjects is still unclear and requires further investigation. Our data demonstrated that some of these subjects do not express the CCR5Δ32 protein.

Previous studies described certain strains of mice lacking genes critical for the development of lymphocytes have been given human stem cells at birth, which differentiate into all of the known human lymphocyte subpopulations. The "humanized" mice appear to have a normal immune system with normal systemic distribution of the human lymphocytes. Using human cord blood stem cells that are homozygous for the CCR5Δ32 will probably determine whether it is possible to generate a human immune system that is resistant to HIV infection. I think developing

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this system will be necessary to understand the mechanism of resistance in vivo. It will be critical to determine whether the transplanted cord blood stem cells will differentiate and give rise to lymphoid cells that are resistant to X4 and R5 HIV-1 infection.

Previous data in the literature provided optimism that resistance to HIV can be modeled in a humanized mouse model by reconstituting the animals with peripheral blood lymphocytes (PBLs) derived from CCR5Δ32 homozygous and heterozygous subjects. These studies reported resistance of the transplanted cells to R5 but not to X4 strains. It was found that the extent of T-cell dysfunctions induced by an X4 strain of HIV-1 in SCID mice reconstituted with human PBLs was related to the in vivo state of activation of the human lymphocytes. It will be interesting to test whether humanized mice reconstituted with CCR5-/- cord blood stem cells would be resistant to both X4 and R5 strains of HIV-1.

Interestingly, the first successful allogeneic stem cell transplantation in an HIV-positive patient has recently been reported at the 15th Conference on Retroviruses and Opportunistic Infections in Boston, Massachusetts Reviewed in Alkhatib G [5]. The donor stem cells originated from a healthy HIV-negative CCR5-/- individual. The patient managed transplantation without any remarkable irregularities and developed a functional reconstitution of his T-cell immunity. The transplanted patient showed no detectable HIV during a 22-month follow-up period. Although this case provided the proof of principle experiment, it remains a single case, and the long-term effects of such treatment are still unknown. Recent studies reported resistance to HIV-1 infection in a CCR5Δ32 heterozygote Alkhatib B [6]. The study proposed that the higher percent of resistant CCR5Δ32 heterozygotes might provide a higher number of donors for stem cell transplantation.

Immunology of HTLV-1 infection

The human T-lymphotropic virus type 1 (HTLV-1) infects the CD4+ T-cells. HTLV-1 infection of CD4+ T lymphocytes can modify the cell function (Figure 2). CD4+ T lymphocytes are the central regulators of the acquired immune response Reviewed by Xu H [1]; Board NL [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+ 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 the 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 stated 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.

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 several 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 the expression of cytokines and activation of viral proteins. Additionally, the 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. In conclusion, there is increasing evidence that subjects chronically infected with HTLV-1, even in the absence of malignant disease, have a degree of immunomodulation that has significant effects on infection with several different pathogens. HTLV-1 infection appears to affect the immune system in a multitude of complex pathways which are just beginning to be discovered: these effects differ according to the pathogens encountered by the host.

The antisense viral transcript encodes HTLV-1 basic zipper protein (HBZ) and the viral transactivator Tax. Tax and HBZ are thought to play key roles in HTLV-1 infection and oncogenesis. Transgenic mice expressing Tax or HBZ develop neoplastic diseases, indicating that they function as oncogenes Cavallari I [7]; D'Agostino DM [8]; Grossman WJ [9]; Satou Y [10]. HTLV-1 enters and dysregulates the host immune system, resulting in chronic inflammation or transformation of infected cells. Tax protein expression is associated with the increase in CIITA levels. CIITA induces expression of HLA-II-related genes, leading to upregulation of HLA-II molecules on the cell surface of HTLV-1-infected and ATL cells. This confers an immunosuppressive phenotype to these cells. CTL response against immunogenic

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viral proteins, particularly Tax, is the predominant immune response against HTLV-1, especially during the initial stages of infection. Tax is a potent activator of viral transcription and exerts pleiotropic effects on cell signaling deregulating different cellular pathways thus mainly contributing to HTLV-1-induced neoplastic transformation.

The in vivo role of HBZ has been studied in HBZ transgenic mice. HBZ is the only regulatory/accessory gene encoded by HTLV-1 to be expressed in all ATL patients and necessary for the proliferation of ATL cells Satou Y [11]. Mice expressing HBZ under the Granzyme B promoter developed lymphoproliferative disease and hypercalcemia Esser [12]. HBZ transgenic models in which HBZ expression is restricted to CD4+ are preferentially used to study the inflammatory process correlated with HTLV-1–mediated pathogenesis. These HBZ transgenic mice develop systemic inflammation and T-cell lymphoma Mitagami [13] and show higher levels of the immunosuppressive cytokine IL-10 and dysfunctional Treg cells Satou Y 2011; Yasuma K [14]. In an interesting HBZ-transgenic-based model, it was recently demonstrated that HBZ plays a pivotal role in dysregulating the cytokine signaling modulating the IL-10/JAK/STAT signaling pathway. As expected, in HBZ-transgenic model the loss of IL-6 and expression of IL-10 accelerates inflammation and lymphomagenesis Higuchi Y [15].

HBZ-transgenic-derived T-cell lymphoma has also been used to establish an HBZ-induced T-cell line, named Ht48, which has been used to test an HBZ-targeted HTLV-1 vaccine. This model identified a candidate peptide (HBZ157-176) for vaccine development by using recombinant vaccinia virus-vaccinated mice Sugata K [16]. In addition to the numerous studies aimed at dissecting the molecular function of the Tax and HBZ viral protein in in vitro cellular models provided interesting contributions towards interpreting their role in vivo in the lymphoproliferative process have also been derived using humanized mouse models. Recently, the contribution of the Tax PDZ binding motif (PBM) to T-cell proliferation was analyzed in humanized mice carrying a human hemato-lymphoid system. It was shown that Tax-PBM enhanced HTLV-1-mediated T-cell proliferation compared to a PBM-deleted mutant, and that this domain is required for T-cell proliferation. Furthermore, comparative transcriptome analyses of T cells derived by humanized mice infected with wt and mutant Tax showed that the absence of PBM is associated with the deregulation of genes involved in T-cell signaling and proliferation, apoptosis induction, and cytoskeletal organization Peres E [17].

Despite recent advances in ATL treatment, including multiagent chemotherapy, allogeneic hematopoietic stem cell transplantation, anti-CCR4 monoclonal antibody, and antiviral therapy, the ATL prognosis remains poor. Cell and animal models, although they suffered limitations concerning replicating HTLV-1 human infection and related diseases, have been and remain extremely useful models for identifying new key host and viral factors required for HTVL replication and pathogenesis. It is expected that these models will be improved following the recent advancement in cell-based technologies. Genome editing by CRISPR/Cas9 system targeting HTLV integrated genomes, single-cell analyses, immunogenic peptide design, RNA-based therapy, and improvement in drug delivery are all expected to contribute to the future development of novel and more effective therapies for HTLV-1-related diseases.

References

1. Kumar P (2019) Numerical quantification of current status quo and future prediction of water quality in eight Asian megacities: Challenges and opportunities for sustainable water management. Environ Monit Assess 191(6): 319.
2. Maja MM, Ayano SF (2021) The Impact of Population Growth on Natural Resources and Farmers' Capacity to Adapt to Climate Change in Low-Income Countries. Earth Syst Environ p. 1-13.
3. Pandey CL, Maskey G, Devkota K, Ojha H (2019) Investigating the Institutional Landscape for Urban Water Security in Nepal. Sustain J Rec 12: 173-181.
4. Good Governance (2013) What is Water Security? unwater_poster.
5. United Nations (2018) Sustainable Development Goal 6 Synthesis Report on Water and Sanitation 2018 2018 Sustainable Development Goal 6 Synthesis Report on Water and Sanitation.
6. Fida M, Li P, Wang Y, Alam SMK, Nsabimana A (2022) Water Contamination and Human Health Risks in Pakistan: A Review. Exposure and Health 15: 619-639.
7. Flooded yet thirsty: Climate disaster and water access in Pakistan during 2022-2023 (n.d.) Displacement Tracking Matrix.
8. Safe drinking water remains unavailable to nearly half of the people living in Pakistan (2024) United Nation Pakistan.

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