viruses

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Review

Co-infection and cancer: host-pathogen interactions between dendritic cells and HIV-1; HTLV-1 and other oncogenic viruses

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Abstract: Dendritic cells (DCs) function as a link between innate and adaptive immune responses. Retroviruses HIV-1 and HTLV-1 modulate DCs to their advantage and utilize them to propagate infection. Coinfection of HTLV-1 and HIV-1 has implications for cancer malignancies. Both viruses initially infect DCs and propagate the infection to CD4+ T cells through cell-to-cell transmission using mechanisms including the formation of virologic synapses, viral biofilms, and conduits. These retroviruses are both neurotrophic with neurovirulence determinants. The neuropathogenesis of HIV-1 and HTLV-1 results in neurodegenerative diseases such as HIV-associated neurocognitive disorders (HAND) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Infected DCs are known to traffic to the brain (CNS) and periphery (PNS, lymphatics) to induce neurodegeneration in HAND and HAM/TSP patients. Elevated levels of neuroinflammation have been correlated with cognitive decline and impairment of motor control performance. Current vaccinations and therapeutics for HIV-1 and HTLV-1 are assessed and can be applied to patients with HIV-1 associated cancers and adult T cell leukemia/lymphoma (ATL). These diseases caused by co-infections can result in both neurodegeneration and cancer. There are associations with cancer malignancies and HIV-1 and HTLV-1 as well as other human oncogenic viruses (EBV, HBV, HCV, HDV, and HPV). This review contains current knowledge on DC sensing of HIV-1 and HTLV-1 including DC-SIGN, Tat, Tax, and current viral therapies. An overview of DC interaction with oncogenic viruses including EBV, Hepatitis viruses, and HPV is also provided. Vaccines and therapeutics targeting host-pathogen interactions can provide a solution to co-infections, neurodegeneration, and cancer.

Keywords: Dendritic Cells; HIV-1; HTLV-1; Hepatitis viruses; EBV; Vaccines; Therapeutics; Oncogenic Viruses; Infection and Cancer

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Background

The immune system consists of two parts: innate and adaptive immunity. The innate immune system consists of physical barriers of epithelial cells, mucus secretions lining surfaces in direct contact with external pathogens, constitutively present or secreted soluble proteins and bioactive small molecules that regulate cell function, and membrane-bound receptors and cytoplasmic proteins that bind patterns expressed by invading pathogens [1]. Upon initial exposure to an antigen, the innate immune cells recognize pathogen-associated molecular patterns (PAMPs) via pattern-recognition receptors (PRRs) [2]. Recognition of a pathogen signals a specific concoction of cells including macrophages and neutrophils to the site of antigen infiltration depending on the classification of the pathogen. Soon after, the adaptive immune system is activated, allowing for proliferation of antigen-specific B and T cells [1]. The adaptive immune system creates cells and antibodies that provide the host with lasting immunity. As a result, the next time the same antigen is encountered, the body launches a much quicker and more robust immune response to the

threat. Dendritic cells (DCs) function as a link between the innate and adaptive immune responses [3].

DCs are the most potent type of antigen presenting cells (APC), expressing both self and foreign antigens on major histocompatibility complex (MHC) class I and II molecules [4]. Immature DCs reside in peripheral tissues, scavenging for any foreign pathogens. Upon recognition of an antigen, DCs endocytose the antigens via macropinocytosis and phagocytosis. These antigens are then either processed cytoplasmically or through the endosomal-lysosomal system and subsequently loaded to respective MHC receptors. MHC class I receptors present intracellular antigens (i.e. viral antigens) while MHC class II receptors present extracellular antigens (i.e. bacterial, protozoa, allergens) [5, 6]. These pathogenic antigens are presented to B and T cells within secondary lymphoid organs to trigger a full, robust adaptive immune response. The full immune response involves proliferation of the antigen-specific B and T cells to create both antibodies that bind and neutralize the pathogen as well as cytotoxic cells that can effectively recognize infected target cells and induce apoptosis in to contain the spread of the virus. DCs migrate from peripheral tissues to secondary lymphoid organs including lymph nodes, the spleen, and tonsils. Migration is accomplished through upregulation of chemokine receptors such as CCR7 [7]. Within lymphoid organs, the DCs present antigens on MHC receptors to naive T cells, stimulating precise differentiation into cytotoxic T cells (CD8+ T cells) and helper T cells (CD4+ T cells), further divided into Th1, Th2, Th17, and regulatory T cells (Tregs) types [8]. In this way, DCs can act as the key to activating the proper adaptive immune response by regulating the downstream immune response. CD8+ T cells, also known as cytotoxic T lymphocytes (CTLs), are key in defense against intracellular infections such as viruses and can directly induce apoptosis of target cells [2]. Th1 cells secrete proinflammatory cytokines like interferon g (IFN- g) and tumor necrosis factor β (TNF-β) to aid in response against intracellular infections caused by viruses and some bacteria as well as eliminating cancerous cells [8]. Th2 cells secrete interleukin (IL) -4, -5, -10, and –13 which target parasitic organisms, up-regulate antibody production, and contribute to allergic response. Th17 cells secrete IL-6, -17, -22 and TNF-α to assist in activation of neutrophils to fight extracellular bacteria. Under normal homeostatic conditions, in the absence of threat, DCs encounter self-antigens. To prevent a host response to self-antigens and thus autoimmunity, DCs must mitigate the immune response in these conditions. DCs presenting self-antigens stimulate differentiation of naive T cells into Tregs that function to suppress immunity and inhibit inflammatory response against self-antigens [9].

Within the bone marrow, DCs originate from hematopoietic precursor cells of the common myeloid progenitor (CMP) or common lymphoid progenitor (CLP) cell lines located [10]. Accordingly, the major subsets of DCs include myeloid/conventional DC1 (cDC1), myeloid/conventional DC2 (cDC2), and plasmacytoid DC (pDC) [11]. There are many versions of abbreviations for DCs. For simplicity, this paper will focus on and refer to plasmacytoid DCs as pDCs and myeloid DCs as mDCs. Growth factors necessary for DC development and differentiation include granulocyte macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (M-CSF) [10]. DCs are located all over the human body and are specialized for each organ they reside in, each type of DC expressing a unique set of CD cell markers. DCs reside in lymph nodes, the spleen, the thymus, blood, skin where they are referred to as Langerhans cells, and the gut where they are especially concentrated in Peyer's patches. Along with differing locations and CD markers, different types of DCs also have distinctive functions (Table 1). pDCs are primary pro-inflammatory Type I IFNs (IFN-α) producers in response to bacterial and viral infection [12]. IFN-α attracts inflammatory cells to the site of the imposing threat. pDCs are also activators of mDCs, helper T cells, and CTLs. mDCs are responsible for antigen presentation and mediation of T-cell responses [13, 14]. Noting differentiation of DC subtype function is vital in understanding the differential effects of viral infection towards each type of DC.

Retroviruses such as human immunodeficiency virus type 1 (HIV-1) and human T-cell leukemia virus type 1 (HTLV-1) have managed to evade the immune response by utilizing DCs to their advantage to assist with the infection of T cells. DCs are fundamental in HIV-1 and HTLV-1 retroviral infection and spread. HIV-1 and HTLV-1 initially infect mDCs as an intermediate and eventually spread infection to target CD4+ T cells. Both HIV and HTLV are thought to facilitate the propagation of the virus through cell-to-cell transmission via virological synapses to reach their target cell, CD4+ T cells [15]. Further clarity on the immune response to HIV-1 and HTLV-1 infection is needed. HIV-1 and HTLV-1 essentially hijack the host immune response and utilize mDCs to their advantage to ultimately reach their target cell. HIV-1 and HTLV-1 initially infect mDCs as an intermediate and eventually spread infection to target CD4+ T cells via mechanisms including formation of virological synapses, viral biofilms, and conduits. HIV-1 and HTLV-1 are both life-long infections that affect millions and can potentially lead to the development of detrimental diseases. Thus, expanding research to determine biochemical pathways involved in retroviral infection of DCs as well as spread from DCs to target cells is crucial.

In addition to retroviruses, DCs are also thought to be involved in sensing oncogenic viruses belonging to other families. This paper also explores the role DCs play in priming the immune system to combat viruses including Epstein-Barr virus (EBV), hepatitis B, D, and C virus (HBV, HDV, HCV), and human papillomavirus (HPV). EBV, HBV, HCV, and HPV belong to the herpesvirus, hepadnavirus, flavivirus, and papillomavirus families respectively. EBV, HBV, HDV, HCV, and HPV are all capable of contributing to detrimental viral-induced diseases and oncogenesis. As in retroviral infection, DCs are an emerging focus of research as they are involved in initial sensing and response to primary viral infection. Further research of the DC role in oncogenic viral infection will provide a better understanding of viral infection, elucidating key proteins and checkpoints of infection that could be targeted by antiviral therapies. This article provides discussion of what is currently known of DC function in retroviral HIV-1 and HTLV-1 infection as well as oncogenic viral infection.

HIV-1 and HTLV Coinfection

HTLV-1 infects CD4+ T cells and HTLV-2 infects CD8+ T cells; thus, HIV-1 disease progression could vary. HTLV-1/-2 envelope surface component (SU) has subdomains that are decisive determinants in receptor binding. ART is successful in controlling HIV disease but has little effect on HTLV-1/2 genome expression. There are direct and indirect mechanisms of these viruses that are neuropathogenic and cause neurological diseases as well as severe immune dysfunction. HIV-1/HTLV coinfection has accumulated evidence that shows coinfection may alter the natural history of general and neurological diseases through different mechanisms [16]. Coinfected individuals on ART have an increased prevalence of HTLV-1-associated neurological disease because ART has very little impact on HTLV-1 expression [17]. There are other neurological manifestations other than HAM/TSP are associated with HTLV-1 [18]. These comprise polymyositis, polyneuropathy, motor neuron disease, cognitive impairment, acute transverse myelitis, neurogenic bladder, and dysautonomia. All these disease developments are correlated with higher proviral loads [19]. HTLV-1 virions and proteins upregulate HIV-1 infection by activating CD4+ T cells [20-23]. Peripheral blood mononuclear cells (PBMC) cultures with HIV-1 and HTLV-1 can activate each other [24]. There is also an increase in antigen production and elevation of concentrations of HTLV-1 mRNA expression following coinfection with HIV-1 [25]. Interestingly, the Tax protein of HTLV-1 stimulates HIV-1 replication by activation of HIV-1 LTR [26]. The result of HIV-1/HTLV-1 coinfection leads to the excessive production of defective lymphocytes, catering to the environment's high levels of HIV-1 virion production [27]. Currently, there are no treatments that exist for acute or chronic HTLV infection. The deltaretrovirus, HTLV-2, has virions that have affinity for DC plasma membranes; however, they do not internalize or bud with DCs and this was not observed in 30 experiments [28]. This does not rule out the possibility that HTLV-2 does infect DCs.

In fact, HIV-1/HTLV-2 coinfection modulates the cellular microenvironment that favors its own viability while inhibiting HIV-1 progression [29]. HTLV-2 regulatory protein Tax exerts a protective role against HIV-1 infection. This Tax protein may promote anti-viral immune responses by activation of the canonical NF-kB pathway [30]. HTLV-2 does reduce the activation of T and NK cells and upregulates viral suppressive CCL3L1 chemokine expression. HTLV-3 surface envelope glycoprotein (gp46) binds to both activated CD4+ and CD8+ T cells, and to naïve CD4+ T cells. There is an antisense protein of HTLV-2, APH-2, that helps maintain latency by manipulating the transcription [31]. APH-2 could be regulating HIV-1 replication. For example, APH-2 overexpression inhibited HIV-1 Tat to transactivate the HIV-1 LTR-driven expression of luciferase. There is a known motif of APH-2 that down regulates the Tat-mediated transactivation. APH-2 also hampers the virus release by affecting the cellular gag expression. HTLV-3(III) was once known as the causative agent of AIDS and was the former name of HIV. In the end, HIV-1 was given to HTLV-III and HIV-1 was taxonomically separated from HTLVs.

Dendritic cells and HIV-1

HIV-1 affects approximately 40 million people of the world population and has taken over 30 million lives since the start of the pandemic in the early 1980s [32]. With such a large, affected population, it is necessary to study the mechanisms of HIV-1, to further predict potential treatment options. HIV-1 is transmitted through bodily fluids and blood and can be contracted through sharing needles and sexual intercourse [33]. HIV-1 primarily infects CD4+ immune cells [34]. There are multiple stages of infection: acute, chronic, and acquired immunodeficiency syndrome (AIDS), each with characteristic symptoms. Acute infection is characterized by a large initial loss of CD4+ cells. Normal range for CD4+ count is 500 to 1500 cell/mm^3, but CD4+ counts can decrease to 200 cells/mm^3, raising concern for AIDS. Numbers recuperate and then slowly decline again during a period of the chronic infection phase, known as the latency period. During the chronic infection phase, immune deficiency increases, increasing viral load [34]. The acute loss of adaptive immunity and latency of the HIV-1 virus, make HIV a devastating and unpredictable disease. Sequelae of HIV infection include significant weight loss, chronic weakness, increased susceptibility to coinfection by other pathogens due to immunosuppression, neurocognitive decline, and increased risk of developing cancers such as Kaposi sarcoma (KS). HIV-associated neurocognitive disorder (HAND) is characterized by chronic inflammation, neurocognitive decline, and visuomotor and perceptual alterations. HIV is known to enter the central nervous system (CNS) and infect glial cells [35]. HTLV-1 is also believed to invade the CNS, yet the mechanism of how remains uncertain [36].

Immunopathogenesis

Though DCs are less susceptible to HIV-1 infection than CD4+ T cells, they are among the first cells to encounter the virus after the infection across the mucosa and play a focal role in establishing HIV-1 infection and progression of disease [37, 38]. DCs are not only able to sense HIV-1 through both CD4 and DC-SIGN, but also able to be infected by HIV-1 to transmit the virus to CD4+ T cells, exploiting the immune response for its own advantage. This section provides an overview of HIV-1 immunopathogenesis highlighting entry and transmission, immune response to the virus, and HIV-induced pathogenesis.

Entry and Transmission

HIV-1 primarily infects CD4+ T cells and cells of the macrophage lineage but also infects DCs, B cells, NK cells, epithelial cells, eosinophils, immature bone marrow and thymic precursor cells, Langerhans cells, megakaryocytes, and CNS cells including astrocytes and oligodendrocytes [39]. Existing research heavily emphasizes the role of macrophages and CD4+ T cells in HIV-1 infections. Macrophages are among one of the first cell types to be infected by HIV-1 upon primary infection, acting as reservoirs for infection and

intermediate cells that transmit the infection to CD4+ T cells [40]. HIV-1 env protein binds to host receptors CD4 and DC-SIGN and its homolog L-SIGN [41, 42]. In early infection, HIV-1 binds to CD4 receptor and CCR5 coreceptor on macrophage cell surfaces [43]. HIV-1 binds to CD4 receptor and CXCR4 coreceptor on T cells at later stages of infection [44]. There is an emerging focus on the role that DCs play in HIV-1 infection as they are one of the first cell types to encounter HIV-1 and they contribute to the pathology of HIV-1 by assisting in viral dissemination [38, 45]. HIV-1 utilizes mDCs for infection progression by two general pathways, cis- and trans-infection (Figure 1) [46]. During cis-infection, HIV-1 binds the CD4 receptor and coreceptor on a DC as in macrophages and CD4 T cells. The virus is internalized and undergoes viral replication. Trans-infection is completely replication-independent and relies on host receptor DC-SIGN [47]. When HIV-1 binds to DC-SIGN, the pathogen is internalized, processed, and presented to CD4+ T cells on host MHC receptors [46]. Once a DC has been infected or has processed HIV-1 antigens, like macrophages, it is able to transmit the infection to CD4+ T cells through mechanisms such as formation of virological synapses [48]. Virological synapse formation induced by HIV-1 resemble immunological synapses [49]. Immunological synapses involve formation of supramolecular activation complexes (SMACs) the center (cSMAC) of which contain T cells interacting with APCs surrounded by a ring of LFA-1/ICAM-1 intaractions called peripheral SMACs (pSMACs). The distal SMAC (dSMAC) surrounds the layer of the pSMAC and is composed of dynamic F-actin. In HIV-1 infection, viral gp120 expressing APCs drive virological synapse formation to coalesce in a formation that resembles cSMAC. Formation of the virological synapse creates a controlled, contained environment to allow for effective spread of HIV-1 from gp120 presenting DCs to T cells.

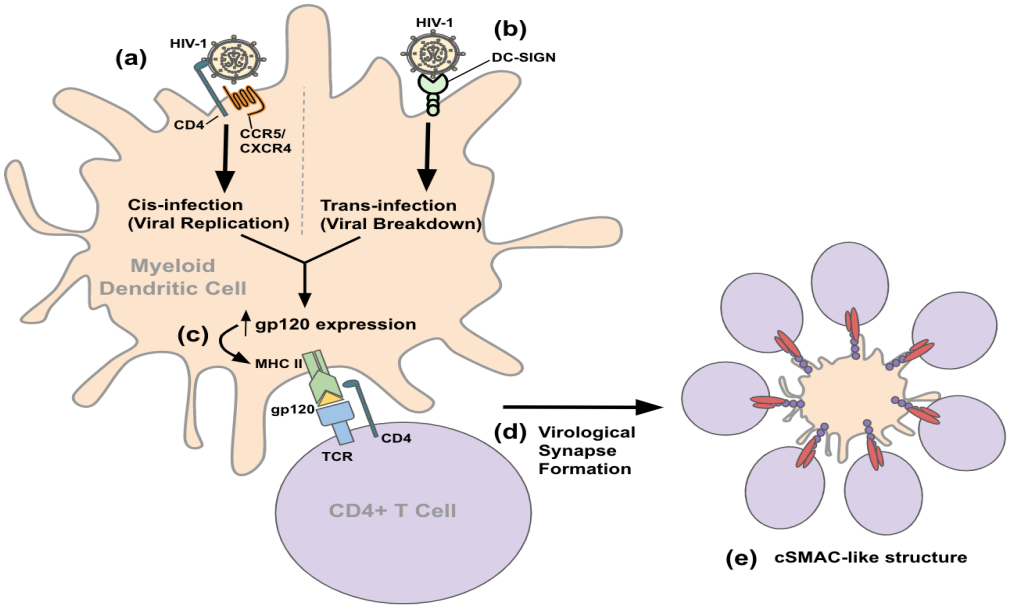

Figure 1. HIV-1 Interaction with mDC. (a) HIV-1 binds CD4 receptor and corresponding coreceptor (CCR5/CXCR4) on DC cell surface, inducing internalization of the virus, viral replication, and cis-infection where the DC itself becomes infected with HIV. (b) HIV-1 binds the DC-SIGN receptor on DC cell surface leading to viral breakdown and trans-infection where the DC merely processes HIV-1 and presents particles to other immune cells. (c) Both cis- and trans-infection lead to increased HIV-1 gp120 protein expression on MHC class II surface receptors. The DC MHC II receptor presenting gp120 binds to TCR and CD4 receptor on the T cell surface. (d) Increased gp120 expression induces virological synapse formation that resembles the cSMAC structure that is seen in immunologic synapses. (e) The cSMAC-like structure is composed of a DC that is surrounded by a ring of

CD4+ T cells. The cells are connected via ICAM-1/LFA-1 interactions where ICAM-1 is expressed on the DC and LFA-1 is expressed on the T cell.

Immune Response

Innate and adaptive immune responses are initiated to stop the spread of HIV-1 infection. In the early response to infection, HIV-1 PAMPs engage immune receptors TLR2, TLR4, TLR7, TLR8, and TLR9 and triggers cells of the innate immune system such as DCs, monocytes, macrophages, and NK cells generally secrete proinflammatory cytokines including TNF-α, IFN-α, IFN-g, IP-10, IL-15, IL-18, and IL-22 in a cytokine storm [50, 51]. The initial intense inflammatory response is thought to fuel viral replication as HIV primarily targets immune cells. HIV-1 has also evolved mechanisms to resist innate immunity through downregulation of NK cell activity and complement receptors, PAMPs modification, and RNA-mediated rapid mutations [52]. HIV-1 Nef protein induces endocytosis or retention of MHC class I molecules, decreasing MHC class I surface expression [53]. Nef protein may play a role in overcoming CD8+ T cell and NK cell-mediated recognition through selective down-regulation of TCR ligands HLA-A and -B molecules [54, 55].

As part of the innate immune response, DCs sense HIV-1 infection and are either directly infected by HIV-1 or break down the viral components to present to cells of the adaptive immune response. DC-SIGN on the DC surface acts as a PRR for the mannose patterns of the gp120 site on HIV-1 [46]. Whether an adaptive response is initiated is dependent on the structure of N-glycans in the HIV-1 pathogen [56]. The higher the mannose composition of N-glycans of HIV-1, the more efficient binding of HIV-1 to DC-SIGN for adaptative immune purposes [57]. The DC cell is trafficked to various parts of the body via chemokines and their receptors [58]. These APCs move toward the lymph nodes, including those of the CNS, as well as gut-associated lymphoid tissue (GALT) [3, 59]. In the lymph nodes, exposed DCs mature and present antigen peptides on MHC molecules, activating the adaptive immune response [60]. B and T cells are activated to produce antibodies and target infected cells respectively. Antibody is detectable within the serum after 3-4 weeks of HIV infection. Unfortunately, the adaptive immune response is not effective in curing the infection and is considered too little too late. Furthermore, HIV-1 targets CD4+ T cells resulting in CD4+ apoptosis and depletion. The markers of CD4+ T cell apoptosis including TRAIL, CCR5 microparticles, TNFR2, and soluble FAS ligand increase with HIV-1 viremia [61]. The depletion of CD4+ T cells results in host immunocompromisation and increased susceptibility to disease progression of other co-infections, oncogenesis, and viral-associated neuropathogenesis.

Cancer malignancies in HIV-1

People living with HIV (PLWH) are at an increased risk of developing cancer regardless of successful antiretroviral therapy (ART). HIV proteins such as gp120, negative factor Nef, matrix protein p17, transactivator of transcription Tat and reverse transcriptase RT are known to be oncogenic and induce oxidative stress and can be released from the infected or expressing cells [62]. Bystander epithelial cells undergo malignant transformation, and these HIV proteins can act alone or with other known oncoproteins specifically originating from other oncogenic human viruses like HCV and HBV, HPV. These cause the bulk of malignancies of PLWH on ART. HIV-1/HBV and HIV-1/HCV co-infected patients have decreased rates of spontaneous viral clearance from the liver with HIV-1 infection; this accelerates fibrogenesis and increases the rates of liver-related morbidity and mortality which includes the development of HCC [63, 64]. High HBV and HCV viral loads are critical factors for the progression to liver cancer [65]. Overexpression of viral oncoproteins induce oxidative stress and chromosomal instability, genomic damage, and promote chronic inflammation leading to liver damage and malignant transformation of liver cells [66, 67].

Brain cancer is highly prevalent in PLWH which includes primary central nervous system lymphomas (PCNSL) and glioblastomas (GBM), though the nature of the brain tumor-HIV-1 relationship is not clearly understood [68, 69]. The GBM tumors can occur near three years after HIV-1 infection [68]. HIV-1 infects several brain cell types which affect astrocytes that serve as a potential reservoir for productive infection, viral persistence, and latency [70, 71]. There are also correlations with angiogenesis factors like VEGF and VEGFRs that modulate and support tumor growth [72]. Glioma cells can link with HIV-1 envelope protein gp120. This interaction can increase glycolysis and participate in the Warburg effect that is habitual in malignancy [73]. Both Tat and gp120 induce EMT and cell migration via the TGF-β1 and MAPK signaling pathways [74]. Accessory Protein Negative Factor (Nef) inhibits the apoptotic function of p53 which affects its half-life and DNA binding activity and transcriptional activation [75]. Chronic inflammation is a characteristic of HIV-1 infection and induces a strong oxidative microenvironment. This chronic viral infection results in oxidative stress that allows virally induced cancer to evolve. This drives neoplastic transformation and develops acquired oncogenic mutations in many cells signaling cascades that drive cell growth and proliferation [76]. The deregulation of oxidative stress pathways is correlated with an escalation of ROS production and mitochondrial dysfunction [77]. HIV-associated carcinogenesis can be driven by persistent immune inflammation, dysfunction of B cells, T cells, components of the cells in the innate immune system, and potentially DCs.

Neuropathogenesis

The field of neuropathology places major emphasis on inflammation, aging, and substance use in persons living with HIV (PLWH). The HIV infected brain pathophysiology has been described in neuroimaging studies that further our knowledge of the neuroinfectious agent. Recent studies comparing levels of neuroinflammation in PLWH, and HIV-negative controls report an association between elevated neuroinflammation and poorer cognition in PLWH [78]. Neuroimaging studies beneficially provide insight into structural, functional, and molecular changes made in the brain due to HIV. HIV evokes a strong neuroimmune response and could lead to a cascade of events including chronic inflammation and cognitive decline [79]. PLWH patients continue to have the burden of health complications related to constant HIV infection, such as HAND [80]. HIV enters the CNS soon after initial infection [81]. PLWH has a continued presence of HIV RNA that is detectable in the cerebrospinal fluid (CSF) [82]. Neuroimaging enables noninvasive techniques to repeatedly measure brain changes, this makes longitudinal assessment simpler. Modern neuroimaging methods can evaluate neuroinflammation involving the injection of tagged radioisotopes using positron-emission tomography (PET) and MRI methods, specifically magnetic resonance spectroscopy (MRS). PET imaging has been used to gauge neuroinflammation due to chronic HIV infection. The radiotracer [11C]-PBR28 targets the 19kDa translocator protein (TSPO) of activated microglia. Levels of neuroinflammation are then compared with virologically well-controlled PLWH and HIV-uninfected controls.

PLWH had a significant increase of Myo-inositol within brain regions such as ventral and dorsal anterior cingulate gyrus, posterior cingulate gyrus, and intraparietal sulcus. Choline was also increased within the dorsal anterior cingulate gyrus of PLWH [79]. PLWH with increasing age has been associated with lower fractional anisotropy (FA), higher mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) along with multiple white matter tracts relative to age. This was done using diffusion tensor imaging (DTI) and interactions between HIV and aging were the strongest within fibers projecting to the temporal and frontal lobes [78, 83, 84]. This is consistent with previous literature implicating frontal-subcortical involvement due to HIV [85]. Visuomotor and perceptual systems observed have alterations in neural activity with joint effects of HIV and aging. There were disruptions in cerebral blood flow, volume, and functional connectivity discovered using functional magnetic resonance imaging (fMRI) in individuals with

HIV and frailty [86, 87]. The attention network and concentration have been investigated in HIV-positive patients [88]. The blood oxygenation level-dependent functional magnetic resonance imaging (BOLD-fMRI) was performed on 36 subjects (18 HIV and 18 seronegative [SN] controls). They were put through a set of visual attention tasks; the HIV subjects showed similar task performance as SN controls. There was decreased activation in the normal visual attention network (dorsal parietal, bilateral prefrontal, and cerebellar regions), and there was increased activation in adjacent or contralateral brain regions. It is suggested that HIV-associated brain injury leads to reduced efficiency in normal attention networks relying on neural reserves with increased usage to maintain performance during attention-requiring tasks. CCR5 is tethered to G proteins and CXCR4 binds β -arrestin, which could serve as alternative targets for co-receptor therapeutics [89]. β -arrestins can recruit the cellular machinery required for clathrin-mediated internalization which leads to either receptor being recycled [90, 91]. CCR5 and CXCR4 are both G-protein coupled, 7-transmembrane receptors (GPCR). The effectors are MAPKs, GTPases, JAK/STATs, tyrosine kinases, and more, these include p38 MAPK. Neuroinflammation is carried out by IL-1, IL-6, TNF-α, CCL2, CXCL10, MMPs, and more. This coincides with viral entry and spread which leads to neurotoxicity and neuronal dysfunction. There is a link found between synaptic compromise, metabolomics of viral reservoirs, and viral persistence with Glutamate (Glu). Glu is the most abundant excitatory neurotransmitter in the CNS [92]. In NeuroHIV, the equilibrium of Glu/GABA/Gln is altered and contributes to neuronal and glial dysfunction as well as cognitive impairment in at least half of the HIV-1 infected population, even with ART era [93-98]. The severity of brain atrophy and dementia can be detected by extracellular levels of Glu in the cerebrospinal fluid (CSF) and plasma [99-101]. Neurotoxicity in NeuroHIV pathogenesis is described by molecular mechanistic studies. HIV-1 infection and HAND have an imbalance of the Glu/GABA cycle and impaired excitatory/inhibitory state of neurons resulting in persistent stimulation of NMDARs. A small population of astrocytes become infected and carry HIV-integrated DNA [92]. These astrocytes cannot, however, produce virus. They contribute to neurotoxicity not blocked by ART which affects neighboring cells (neurons, glia).

Vaccine and Therapeutics

HIV was once considered a fatal disease, but with the implementation of combined antiretroviral therapy (cART) the life expectancy of PLWH is normal in general populations [102]. HIV-1 nanotherapeutics have gone from *in vitro* to clinical trials [103]. There are some serious side effects and complex dosing regimens with cART, thus it is limited by several factors. Nanomedicine-based anti-HIV therapeutics (HIV-1 nanotherapeutics) have been an emerging therapeutic technology in recent years, showing success at the preclinical level and/or Phase I/II clinical trials. The four common nanomaterials used in HIV-1 nanotherapeutics include dendrimers, liposomes, micelles, and nanosuspensions that have surfactants, drugs, and phospholipids. There are several advantages of nano formulated drugs vs free drugs in various applications. Nanodrugs overcome anatomical barriers such as crossing the BBB via transcytosis and/or uptake by circulating macrophages. There is active cell targeting of the nanodrug to be modified to actively target and deliver drugs to cells through the attachment of receptor targeting ligands. There are benefits of free drugs such as the extension of half-life via nano formulation. The active ingredient product of nanotechnology is VivaGel (SPL7013 Gel), a leading candidate dendrimer that was specifically designed with human safety in mind [104]. These are microbicides which are compounds that can be applied vaginally or rectally to protect the user from sexually transmitted infections (STIs).

A HIV nano formulated vaccine has entered Phase II clinical trials and is named the DermaVir patch. It is a promising application of nanomedicine for HIV which is a therapeutic vaccine. The formulation of the patch involves mannosylated polyethyleneimine, glucose, and an HIV antigen-coding DNA plasmid formulated into nanoparticles [103]. The patch delivers nanoparticles to epidermal cells and is then engulfing nanoparticles

and evolving to produce an immune response. The intention is to use this as an adjuvant to conventional cART. Promising data indicate that the advancement of nanomedicine toward HIV-1 may reduce the healthcare costs of patients. This is critical to delivering these HIV-1 nanotherapeutics in the developing world, where HIV is most prevalent, in a cost-effective manner [105]. The goal of DC vaccines is mounting an HIV-1 antigen-specific T-cell response ideally clearing infection and eliminating the need for long-term ART. DC vaccine trials have been conducted utilizing autologous DCs loaded with HIV-1 antigens. This type of immunotherapy involves loading DCs with antigens *ex vivo* and then introducing the cells back into the patient [106]. DCs are critical to the recognition of HIV-1, regulation of T-cell function, and targeting of infected cells by activation of the adaptive immune system by presenting HIV-1 antigens [107, 108]. The use of autologous antigens creates a more "personalized" approach and has the benefit of allowing the extraction of HIV-1 RNA from latently infected CD4 T cells that could not be cleared by ART [109]. During infection, minimizing the emergence of HIV-1 quasispecies is recognized as an important objective of effective DC immunotherapy. The strategies currently being investigated for HIV-1 treatment include inhibiting viral protein function such as ART, Env/gp41 targeting antibodies, CCR5 antagonists, and post attachment blockers. To reverse latency there are HDAC inhibitors and PKC agonists. Immune regulation can occur with PD-1 inhibitors, BTLA/CTLA-4 targeting antibodies, and het-IL15. To enhance immune recognition and activation of CTLs the use of DC vaccines is used. With the complicated relationship between HIV-1 and DCs in mind, research focuses on locating areas in the HIV-1 infection pathway that can be used for targeted therapies. For example, inducing inhibitory compounds that may block the CD4+ binding site on gp120, preventing pDCs HIV-1 internalization [110]. This approach aims to decrease the spread of HIV-1 infection. Other vaccine approaches attempt to decrease viral load seen in chronically infected patients, for example, by inducing a Th1 response, using inactivated whole virus DC vaccination [111]. Understanding how DCs interact with HIV-1 throughout the body is the first step in teasing out vaccination efforts and treatment options. The imaging of the spatial distribution of metabolites that are orchestrated by immune events of retroviral lymphoid tissue reservoirs. There have been combined protein and nucleic acid *in situ* imaging (PANINI) that have multiplex capabilities developed to quantify simultaneously DNA, RNA, and protein levels within tissue compartments. This can also be coupled to multiplexed ion beam imaging (MIBI), there are over 30 parameters measured across archival lymphoid tissues. Multiplexed imaging with any platform (MIBI, CODEX, etc) leads to the identification of cell phenotypes and cellular neighborhoods (CNs). An antibody panel staining with >30 antibodies can be done on structural markers, lymphocytic markers, nuclear factors, macrophage markers, functional markers, and nucleic acids. Using FFPE cell pellets and lymphoid tissues PANINI-MIBI can detect single-integration events of HIV, RNA transcripts, and protein epitopes robustly on the same tissue section. Antibody-oligo based CODEX platforms and combined PANINI-MIBI captures viral events and tissue morphology [112]. Delineation of lineage-specific markers of diverse immune cells is an application of imaging platforms that can cross-validate antibody markers. The global trends in emerging nanoscale vaccines for infectious diseases include biological, experimental, and logistical problems associated with immune engineering [113]. Vaccine transport and spatial localization in lymph nodes where B-cell receptors (BCR) or surfaces of APCs like FDCs can flow interstitial fluid go localize in the LN. There are nanobodies that can inhibit CXCR4-mediated signaling and chemotaxis with 238D2 and 238D4 and the data indicates competitive antagonism for both nanobodies.

HIV researchers at the Scripps Institute have investigated a seemingly indestructible HIV-like strain, nicknamed "death star", for vaccine trials using a harmless lab-made adeno-associated virus (AAV) to combat HIV [114]. It is called eCD4-Ig and features two HIV co-receptors, CD4 and CCR5. The viral vaccine is injected into muscle and "infects" muscle cells, which causes them to produce protective eCD4-Ig. HIV is attracted to eCD4-Ig, binds, undergoes conformational change prematurely, and is no longer able to infect.

The "death star" research strain is SIVmac239 and is tough to stop. There is currently a Phase I clinical trial investigating three experimental HIV vaccines based on a messenger RNA (mRNA) platform called HVTN 302 study by NIAID-funded HIV Vaccine Trials Network (HVTN) expected to be completed by July 2023.

Dendritic Cells and HTLV-1

HTLV-1 is the first discovered retrovirus. HTLV-1 is an enveloped retrovirus with a diploid single-stranded RNA genome in the delta retrovirus group [115]. Although HTLV-1 is present throughout the world, prevalence and regional estimation remain poorly documented. HTLV-1 is estimated to impact five to ten million individuals worldwide [116]. The key known endemic regions include Japan, sub-Saharan Africa, Central America, South America, Caribbean islands, focal areas in the Middle East, and Australia-Melanesia [117]. 90% of infected individuals are estimated to be asymptomatic carriers while the remaining individuals develop HTLV-induced diseases such as adult T-cell leukemia/lymphoma (ATL), HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP), rheumatic syndromes, and HTLV-associated uveitis among other autoimmune conditions [118]. HAM/TSP is a chronic meningomyelitis of gray and white matter in the spinal cord that presents with spastic paraparesis, impairment of gait, and autonomic dysfunction of the bowel and bladder.

Immunopathogenesis

HTLV-1 hijacks the host immune system, utilizing the cells to its own benefit. HTLV-1 infects DCs and uses them to propagate infection to its target cell, CD4+ T cells. Like HIV-1, DC-SIGN plays a key role in DC sensing of HTLV-1. Some key proteins for HTLV-1 immunopathogenesis include viral Env and Tax proteins [119]. This section provides a detailed overview of HTLV-1 immunopathogenesis through entry and transmission mechanisms, interaction with the innate and adaptive immune response, and HTLV-induced disease progression.

Entry and transmission

HTLV-1 is transmitted through cell-containing body fluids and can thus be transmitted through contact with blood products, sexually, and from mother-to-child through breast milk, [117, 120]. HTLV-1 preferentially infects CD4+ T cells but has potential to infect other cell types including DCs, CD8+ T cells, B cells, and monocytes. Primary T cells are difficult to infect with HTLV-1 in vitro; they require cell-cell contact and cell-free virus transmission is inefficient [121, 122]. DCs, on the contrary, are easily infected with cell-free HTLV-1 and via viral biofilms in vitro. Evidence shows DCs exhibit a greater degree of binding to HTLV-1 virions than other cell types including T cells [123]. DCs can thus function as intermediates in propagating infection to target T cells via cell-to-cell transmission. DCs facilitate spread of infection to T cells by trans-infection in which they obtain virions and transfer them to target cells or via cis infection in which they themselves are infected and then go on to spread the infection to T cells [121].

HTLV-1 envelope glycoprotein (Env) interacts with surface receptors on host cells including DC-specific intercellular adhesion molecule-3 grabbing non-integrin (DC-SIGN), surface glucose transporter 1 (Glut-1), neuropilin-1 (NRP-1), and heparan sulfate proteoglycans (HSPG) to allow viral entry into the target cell, with DC-SIGN being the most important receptor on DCs [124, 125]. DC-SIGN facilitates HTLV-1 binding and fusion through an ICAM-dependent mechanism[125].

Cell-to-cell transmission from DCs to T cells depends on specific interactions between the cellular and viral proteins. Two types of cell-cell contacts described are tight cell-cell contacts and cellular conduits (Figure 2) [120]. The tight cell-cell contacts are proposed to involve polarized budding of HTLV-1 into synaptic clefts and cell surface transfer of viral

biofilms. Polarized budding at virological synapse requires HTLV-1 Tax protein to enhance the expression of adhesion proteins (ICAM-1) in an HTLV-1 infected cell in contact with an uninfected cell [126]. The engagement of ICAM-1 on the infected cell with LFA-1 on uninfected T cells connects the two cells creating a synapse between cells. The ICAM-1/LFA-1 interaction stimulates reorganization of the cytoskeleton in the infected cell, upon which the viral proteins are exocytosed to the virological synapse. The viral proteins concentrate within the virological synapse overtime allowing them to bind and enter the uninfected cell. The virological synapse essentially allows for directed transmission of HTLV-1 to target cells in a confined space, maximizing efficiency while minimizing recognition of viral particles by the host immune response.

Viral biofilms are another mechanism by which infections are spread cell-to-cell. Studies show mDCs contain a significantly higher proviral load compared to lymphocytes when exposed to HTLV-1 viral biofilms [122]. Thus, it is more likely for DCs to be infected by HTLV-1 biofilms and spread the virus to T cells via other mechanisms of cell-to-cell transmission, but it is possible that biofilms are still involved. In viral biofilms, HTLV-1 virions, and clusters of viral proteins like Gag and Env are concentrated in a confined, protective environment on surface of infected cells are transmitted to target cells at the virological synapses. The viral biofilms are composed of carbohydrates, collagen, agrin, linker proteins like tetherin, and O-glycosylated surface receptors CD43 and CD45 [127]. The biofilm functions as a reservoir for the viral particles to cultivate before spread of infection to neighboring cells.

Another mechanism of cell-to-cell transmission involves cellular conduits. Conduits are essentially extensions of the membrane that allow for interactions with cells over greater distances compared to adjacent cell-to-cell contact [128]. It is proposed that HTLV-1 allows for transmission over long distances by the transfer of virions through cellular conduits induced by viral protein p8 [129]. p8 induces LFA-1 clustering on T cell surface, allowing for T-cell adhesion to DCs, conjugate formation in which the HTLV-1 antigen binds to T-cells, and HTLV-1 transmission [130]. p8 overexpression in chronic HTLV-1 infection promotes polysynapse formation for viral transmission. Overexpression of p8 increases the number and length of the cellular conduits. The exact biochemical mechanism by which p8 promotes HTLV-1 transmission remains unknown.

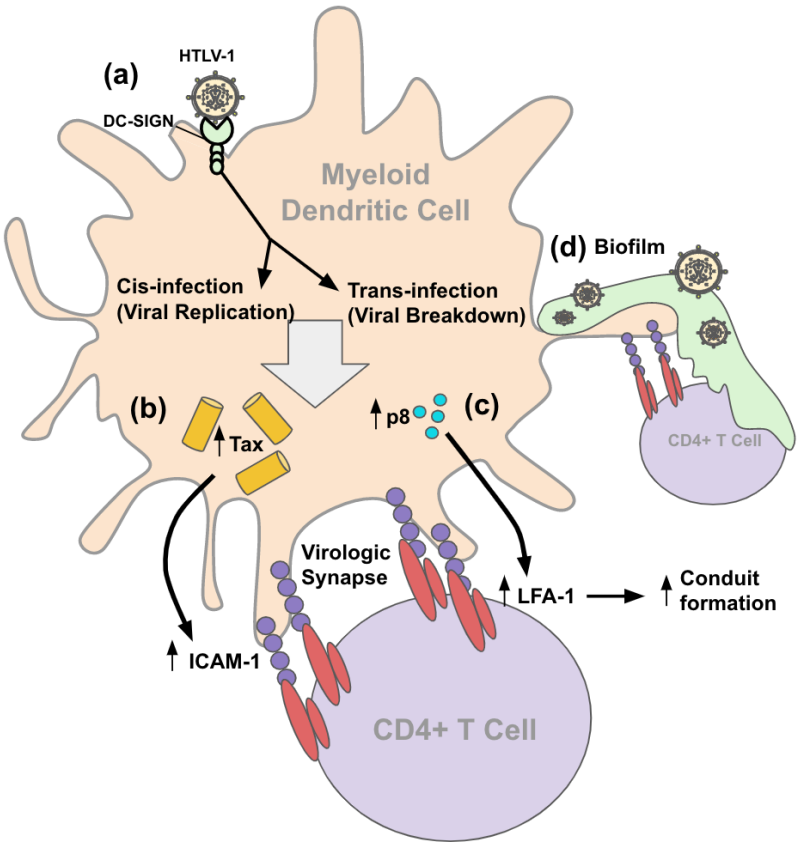

Figure 2. HTLV-1 Interaction with DC. (a) HTLV-1 binds DC-SIGN, Glut-1, NRP-1, and/or HSPG receptor on DC cell surface. DC-SIGN is the most important receptor on DCs. HTLV-1 then enters the DC and undergoes viral replication to infect the DC in a process called cis-infection. Alternatively, HTLV-1 enters the DC and undergoes viral breakdown to be processed and presented on MHC surface receptors (not pictured) in a process called trans-infection. DCs spread HTLV-1 infection to CD4+ T cells through formation of virological synapses, conduit formation, and viral biofilms. (b) HTLV-1 Tax protein accumulates in the DC and induces increased ICAM-1 expression on the surface of the DCs. Increased ICAM-1 allows for more efficient binding to CD4+ T cells via LFA-1 interaction. ICAM-1/LFA-1 interaction allows for formation of virological synapses where HTLV-1 components are exocytosed to and concentrate within to increase exposure of T cells to viral particles for infection. (c) HTLV-1 p8 protein also builds up within the DC and induces increased LFA-1 protein expression on T cells. Increased LFA-1 expression functionally allows for conduit formation between DCs and T-cells to allow for spread of infection over greater distances versus neighboring cells. (d) Viral biofilms form on the surface of the DC and act as reservoirs for viral growth to allow spread to neighboring CD4+ T cells.

Immune response

Like HIV, cell-free HTLV-1 binds and enters mDCs and pDCs peripherally. The DCs then migrate to secondary lymphoid organs where they are exposed to primary T cells to which some DCs transmit the virus through cell-to-cell cis- or trans-infection as above. As this transmission process is occurring, the rest of the host's immune system also begins launching a combative response against the viral threat from the minute that the virus enters the system. The body begins to fight the virus immediately with an innate immune response. All human host cells express membrane or cytoplasmic receptors that recognize HTLV-1 pathogen-associated patterns (PAMPs) such as HTLV RNA, non-methylated CpG DNA, and envelope glycoproteins [131]. These PAMPs are recognized by pattern recognition

receptors (PRRs) like toll-like receptors (TLRs) and RIG-I-Like Helicases (RLHs) expressed by numerous cell types including DCs, macrophages, epithelial cells, endothelial cells [132]. The PAMP/PRR interaction stimulates IFN regulatory factors IRF3 and IRF7 that promote type I interferon (IFN-I) transcription including IFN-α and IFN-β, which are effective anti-viral mediators [131]. pDCs are the major IFN-I producers. When compared to mDCs, pDCs have impaired capacity to transfer HTLV-1 to CD4+ T cells compared to mDCs, indicating they may be primarily involved in a protective response rather than transmission of the disease to cells [133]. Natural killer (NK) cells are also involved in the innate immune response against HTLV-1, though the exact mechanism of their role is not thoroughly studied. Spontaneous NK cell proliferation positively correlates with the HTLV-1 proviral load [134]. NK cell proliferation, however, is decreased in individuals that develop HAM/TSP and ATL as compared to asymptomatic carriers of HTLV-1 suggesting impaired function of NK cell proliferation and function in these conditions.

Soon after the initial innate immune response, the adaptive immune response is triggered. In the humoral immune response, B cells form antibodies against HTLV-1 core, envelope, and tax proteins [135]. These antibodies appear in the serum within 30-60 days after onset of primary infection with anti-gag antibodies predominating. A high HTLV-1 antibody titer correlates significantly with an increased proviral load, indicating that increased viral load is associated with a more robust immune response. In the cell-mediated immune response, cytotoxic T lymphocytes (CTLs) (mainly CD8+) recognize and kill infected cells by interaction with viral antigens presented on MHC class I molecules. Most of the CD8+ CTLs recognize and respond to tax protein, indicating a prime target for vaccine therapy. The CD8+ CTLs secrete proinflammatory cytokines including IL-2, IL-16, TNF-α, IFN-g, macrophage-inflammatory protein 1 α (MIP-1α) and 1 β (MIP-1β), and matrix metalloproteinase-9 (MMP-9) [136]. Although CD8+ CTL response is protective against most viruses, whether the response is protective or contributory to inflammatory and demyelinating disease process of HAM/TSP remains under investigation. The CD4+ T cells contribute to the adaptive immune response by primarily recognizing env protein [137]. The CD4+ T cells consist of effector and regulatory T cells (Tregs). The effector cells assist in activation of other immune cells and production of proinflammatory cytokines while the Tregs modulate the immune response via expression of transcription factor Foxp3 [138]. Studies suggest that HTLV-1 asymptomatic carriers and healthy controls have higher concentrations of Foxp3+ Tregs versus HAM/TSP patients, supporting that Tregs assist in mitigating the immune response. The immune response against HTLV-1 infection is a very delicate balance as there must be a strong enough response to mitigate spread of the infection yet overstimulation of the immune system also results in detrimental effects towards the host resulting in conditions such as HAM/TSP.

HTLV-1-induced cancer

HTLV-1 infection induces ATL in about 2.5-5% of cases [139]. ATL is an aggressive malignancy with a short survival rate that develops more commonly in children infected with HTLV-1 compared to infected adults [140]. The most common symptoms of chronic ATL include a skin rash, swollen lymph nodes, hepatosplenomegaly, and lymphocytosis. ATL can be divided into the aggressive acute, lymphoma, and chronic subtypes as well as the slowly progressing smoldering subtype [141]. Presence of different mutations distinguishes aggressive subtypes from slowly progressing ones such as the IRF4 (interferon regulatory factor 4) or MUM1 (multiple myeloma oncogene 1) gene mutation seen in highly aggressive subtypes. IRF4 is a transcription factor significant in B and T cell maturation believed to have a gain of function mutation and a fivefold increase in expression in aggressive ATL subtypes, making it a potential target for ATL therapies. A higher HTLV-1 proviral load correlates as a risk factor for ATL development [139].

HTLV-1 Tax and HBZ (helix-basic loop zipper protein) are two key proteins involved in ATL oncogenesis [142]. Tax expression is thought to play a role in tumor initiation, primarily through activation of the NF-kB pathway [143-145]. The NF-kB pathway

promotes lymphocyte proliferation and cell resistance to apoptosis [146]. Tax also interacts with a plethora of other proteins and pathways including NFAT, AP-1, TRAF6, cell cycle inhibitors, cyclins and cyclin-dependent kinases, and PDZ-containing proteins to further promote genetic instability and oncogenesis [146-149]. Once tumor formation occurs, Tax protein expression is repressed while HBZ continues to be ubiquitously expressed in ATL cells and HTLV-1 cells [150, 151]. HBZ promotes expression of hot genes telomerase reverse transcriptase (hTERT) and JunD, which mitigates the effect of repeated mitosis on cellular senescence, thus promoting survival of the tumor [152]. Tax and HBZ have opposite effects on several pathways. Tax activates and HBZ inhibits CREB, AP-1, NF-kB, telomerase, and Wnt; HBZ activates and Tax inhibits TGF-β [142]. Tax and HBZ coordinate function in a sophisticated manner to promote oncogenesis.

Neuropathogenesis

Most HTLV-1 infected individuals remain asymptomatic throughout life, but HTLV-1 has the potential to progress to detrimental neuro-inflammatory diseases in humans including HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP), rheumatic syndromes, polymyositis, uveitis, Sjogren's syndrome, and systemic lupus erythematosus (SLE) [118, 153]. HTLV-1 induces immune dysregulation, disrupting the balance of cytokines IFN-γ, TNF-α, TGF-β, and IL-10. These key cytokines are responsible for maintaining the balance between inflammatory and anti-inflammatory responses, so this disruption results in the loss of tolerance to host antigens, autoimmunity, and possible chronic inflammation [153]. The mechanisms of HTLV-induced autoimmunity are not completely understood. Molecular mimicry may be involved as well as an increase in pro-inflammatory cytokines IFN-γ and TNF-α with increased Th1 response and a corresponding decrease in anti-inflammatory cytokines IL-10 and TGF-β with decreased Treg cell function and decreased tolerance [154].

HAM/TSP is a chronic meningomyelitis of gray and white matter in the spinal cord presenting with progressive spastic paraparesis, impairment of gait, and autonomic dysfunction of the bowel and bladder. Biopsies of HAM/TSP patients reveal several inflammatory lesions in the brain and spinal cord from active-chronic inflammation [155, 156]. Magnetic resonance imaging (MRI) of HAM/TSP patients shows loss of spinal cord volume, suggesting degenerative pathology causing irreversible demyelination with loss of neuronal cell bodies, axons, and glial cells such as astrocytes. The anticipated risk for developing HAM/TSP is about 2% [139]. Risk factors for developing HAM/TSP include presence of HLA-DRB1*0101 and polymorphisms in genes for pro-inflammatory cytokines TNA-α and IL-15 and stromal cell-derived factor 1 (SDF-1) [157]. Studies in a HAM/TSP Jamaican cohort show decreased pDCs overall, decreased expression of HLA-DR in mDCs, and increased expression of CD86 in pDCs and mDCs [158]. HAM/TSP patients have increased levels of circulating HTLV-1 specific CD8+ CTLs which recognize viral epitopes like tax, rex, and env proteins [159]. DCs exposed to Tax can undergo activation providing constant antigen presentation and co-stimulation to T cells to evoke intense CTL response underlying the condition HAM/TSP [160, 161]. Soluble Tax protein binds immature and mature DCs to drive DC activation and maturation to elicit a Th1 phenotype. This intense proliferation of HTLV-1 specific T cells potentially cross-react with neural antigens, causing neural dysfunction seen in HAM/TSP. HAM/TSP patients also have higher titers of HTLV-1 specific IgM, IgG, and IgA antibodies both in serum and CSF as compared to asymptomatic carriers [135]. The presence of anti-HTLV-1 IgM antibodies indicates continuous active replication of the virus occurs in this subset of patients.

Vaccine and therapeutics

HTLV-1 is a lifelong infection without an existing cure; treatment is aimed at symptomatic control and slowing infection progression. Current standard treatment for HTLV-1 post-chemotherapy in Japan is allogenic hematopoietic stem cell transplantation [162]. This

process involves depleting the host's bone marrow and administrating healthy hematopoietic stem cells to augment the bone marrow function and replace the dysfunctional cells [163]. Preclinical and clinical studies for ART therapy for HTLV-1 based on success in HIV-1 therapy are ongoing[164]. Zidovudine (AZT) is a nucleoside reverse transcriptase inhibitor (NRTI) effective in treating HIV showing significant decrease in HIV gag and proviral DNA production [165]. AZT was tested against HTLV-1 infection in a rabbit model, showing decreased provirus and lymphocytic infiltration in treated animals compared to untreated controls [166]. AZT trials for HTLV-1 in cell cultures and human subjects showed variable results [164]. Cell cultures exposed to HTLV-1 and AZT simultaneously showed a protective effect on proviral DNA, RNA, and gag expression while exposure to AZT in already infected cells showed minimal effects [167]. Early studies of HAM/TSP patients showed no effect or clinical benefits of AZT monotherapy [168]. Combination therapy of AZT with epigenetic regulator valproic acid (VPA) for treating STLV-1, the simian counterpart of HTLV-1, in baboons showed a 5-12-fold decrease in proviral load in half of the animals tested, showing some promise[169]. A study of AZT and IFN-α combination therapy for ATL treatment resulted in 28% complete remission and 58% generalized major response in the 19 treated individuals, though the mechanism behind why the dual therapy was successful is unclear [170]. Lamivudine (3TC) treatment showed minimal success due to natural resistance of HTLV-1 to the drug [164]. Other NRTI-focused studies showed that tenofovir (TFV) prodrugs PMPA (9-R-(2-phosphonomethoxypropyl) adenine), tenofovir disoproxil (TDF) and tenofovir alafenamide (TAF) are more effective than TFV against HTLV-1 in cell lines. HIV antiretrovirals are limited in treating HTLV-1 because they are molecularly catered to HIV, thus further research in refining antiretroviral for HTLV-1 is needed.

The primary novel HTLV-1 therapy of interest targets Tax protein. One such therapy is a vaccine consisting of autologous DCs pulsed with Tax peptides (Tax-DC) [162, 171]. Tax-DC functions to induce HTLV-1 specific CTLs to decrease proviral load in HTLV-1 infected individuals. In test subjects, Tax-DC maintains the proviral load of HTLV-1-infected patients at a steady level around that of asymptomatic carriers. Other emerging targets for HTLV-1 therapy include DC-SIGN and apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like 3 (APOBEC3) [172, 173]. HTLV-1 transmission from DCs to T cells is shown to be primarily mediated by DC-SIGN; blocking of DC-SIGN with anti-DC-SIGN monoclonal antibodies is shown to prevent HTLV-1 transmission from DCs to T cells and decrease the number and size of HTLV-1-induced syncytial formation [125, 174]. APOBEC3 enzymes are host-antiviral restriction factors, yet the mechanism is not fully understood. Paradoxically, HTLV-1 tax expression induced increased levels of A3C, A3D, A3F, A3G, and A3H expression in humanized mouse spleen cells [175]. Targeting DC-SIGN and specific APOBEC3 factors could potentially halt viral progression.

DC Interaction with Other Human Oncogenic Viruses

EBV

EBV is a herpesvirus that primarily infects B lymphocytes where the virus establishes a latent infection and can progress to a persistent infection [176]. EBV most commonly causes mononucleosis infection but is also potentially oncogenic with associated development of lymphoid and epithelial tumors including Burkitt's lymphoma, Hodgkin's lymphoma, T cell lymphoma, B-cell lymphoproliferative syndromes, nasopharyngeal carcinoma, and gastric carcinoma [177]. EBV envelope glycoprotein gp350 binds to CD21 receptors (complement receptor 2) to bind and enter host cells, primarily B lymphocytes along with others like epithelial cells [178]. Reactivation of EBV results in lytic viral replication predominantly in plasma cells. DCs are thought to sense EBV primary infection and subsequently respond by priming host innate and adaptive immune response via cross-priming [179]. Due to the selectivity of EBV for B and epithelial cells, it is unlikely that EBV infects DCs directly as do HIV-1 and HTLV-1. DCs are proposed to sense and

respond to infection through surface TLR3 and retinoic acid-inducible gene 1 (RIG-1) binding to EBV RNA—dsRNA and EBV encoded small RNAs (EBERs). During the first 24 hours of infection, pDCs secrete high levels of type I IFNs to help limit B cell transformation by EBV via recruitment and activation of NK cells [180, 181]. DCs activate the NK cells through IL-12, IL-15, and IFN-α [182, 183]. The NK cells then go on to produce significant amounts of type II IFNs which help to restrict B cell transformation by EBV for another 3 to 4 days. The NK cells are also able to directly kill EBV infected B cells undergoing lytic replication [184]. DCs are also presumably involved in priming the adaptive immune response against EBV infection, though their exact role is under debate. While EBV-transformed B cell lines can prime T cells at low frequencies, mDCs are thought to assist with cross-presentation of EBV antigens from lytic EBV-infected B cells to premature T cells due to increased efficacy of priming with presence of autologous DCs [185]. Although alternate explanations for the immune response against EBV do exist and clarification is still needed, DCs are proposed to play a central role in activating and priming both the innate and adaptive immune responses.

HBV

Hepatitis B virus (HBV) is a human hepatotropic DNA virus (hepadnavirus) that causes a disease that is mostly spread by exposure to infected body fluids [186, 187]. HBV is the primary contributor to liver cancer globally and is ubiquitous in areas of liver cancer [188]. HBV infection is high risk and can lead to chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC). Chronic cases need medication and possibly a liver transplant. This serious liver infection is easily preventable by a vaccine. The HBV genome is a circular DNA molecule that is ~3,200 base pairs (bp) in length. HBV possesses the smallest genome of any virus known to infect man. HBV is a member of the family Hepadnaviridae and is a Class VII virus. HBV carries HBV surface antigen (HBsAg) particles, 17-22 nm in diameter these particles are filamentous particles, and 45 nm diameter virions consist of HBsAg envelope and 36 nm diameter core [189]. The infectious component of HBV is the Dane particle that can be found in HBV antigen-positive sera in patients and through routine electron and immunoelectron microscopy of liver biopsy patients (n=10) [190]. Mature HBV is enveloped, icosahedral virus packages with circular dsDNA genome with gaps in both strands. It also has a reverse transcriptase covalently bound to the 5′ end of the antisense strand; there are also host proteins included. Within the outer envelope, protein projections are spaced 60Å apart [191]. HBsAg subviral particles such as spikes have similar spacing yet are arranged in a trigonal geometry on the membrane surface, there is also an HBsAg lattice that does not align with the core's icosahedral lattice. HBV capsid has a dynamic metabolic compartment that participates in structural changes to encapsulate its genome. The interaction of the envelope capsid interaction is unsteady, and the envelope proteins have multiple structures. HBV is the lion's share of liver cancer globally and is ubiquitous in areas of liver cancer. HCC oncogenesis involves dysregulation in several cellular signaling pathways including Wnt/FZD/β-catenin, PI3K/Akt/mTOR, IRS1/IGF, Ras/Raf/MAPK, and pERK/JAK/STAT [192, 193]. HCC screen by liquid biopsy of cell-free DNA (cfDNA) is an early-stage detection of HCC. It has been developed to identify HCC from surface antigen of hepatitis B virus-positive asymptomatic individuals in the community population [194]. HBV immunization interrupts mother-to-infant transmission and is a preventative measure of cancer. DNA can be extracted from sera and peripheral blood lymphocytes on a commercially available kit (High Pure Viral Nuclei Isolation Kit, Roche Diagnostics, Canada). HBV-DNA can be tested by real-time polymerase chain reaction (PCR) using the LightCycler Real-Time PCR HBV. The WHO guidelines recommend abdominal ultrasound and alpha-fetoprotein (AFP) measurement every six months. There are several phases of clinical biomarker validation such as Phase I: preclinical exploratory to study cancer tissues to identify biomarkers. Phase II: clinical assay validation for cancer cases versus control validation. Phase III: retrospective longitudinal studies for validation in cancer subjects prior to cancer diagnosis. Phase IV: prospective

screening for prospective evaluation of stage of tumor detection. Phase V: Cancer control studies to evaluate the impact on the cancer burden in a population. There are limitations to the sensitivity of AFP alone for HCC detection and only 40-50% of HCCs do not have elevated levels of AFP. A secretory antagonist of the Wnt/B-catenin signaling pathway is Dikkopf-1 (DKK1) which is a glycoprotein. The DKK1 concentrations were significantly high in HCC patients compared to control [195]. DCs play a role in immunopathogenesis of chronic HBV infection; the DC function of patients with chronic HBV infection is impaired which may contribute to viral persistence. Laboratory efforts have conducted recombinant human granulocyte-macrophage colony stimulating factor (rhGM-CSF) combined with IL-4 which is a classic culture combination to DCs. Combining IFN-λ with rhGM-CSF and rhIL-4 can increase the expression of DC surface molecules and secretion of IL-12 and IFN-γ in patients with chronic HBV infection [64]. This could all lead to a potential DC vaccine that can induce DCs maturation to treat chronic hepatitis B. Multikinase inhibitor Sorafenib monotherapy is the standard of care for patients and is known to show survival benefits in advanced HCC [196].

HDV

HDV is an unclassified satellite virus that depends on HBV infection to infect target cells. HBV/HDV coinfection happens when a person is simultaneously infected with both HBV and HDV whereas an HDV superinfection occurs when someone is already chronically infected with HBV (CDC). HDV is known as a "satellite virus" because it can only infect people who are also infected by HBV. The patient coinfected or superinfected with HBV/HDV can result in liver cirrhosis and liver failure. HDV infection is uncommon in the United States although notably, the actual number of HDV cases in the US is unknown [197]. Significant liver disease is a result of hepatitis delta virus which is a blood-borne virus that infects hepatocytes. HDV is a single-stranded RNA virus and its propagation and replication are reliant on envelope proteins of HBV to achieve assembly and release of infectious virus particles [198]. When an individual is exposed to HDV, it is called superinfection. HDV is a small 36 nm single-stranded negative-sense RNA virus with a small RNA of about 1700 nucleotides and one with a circular conformation [199]. HDV genome replication is totally different from HBV. Delta antigens form multimers and HDV RNA wraps around such multimers. Recent experimental situations have shown that HBV envelope proteins are sufficient for the assembly of infectious HDV even in the absence of HBV replication.

Signal transduction of immune mechanisms involving DCs and CD4+ T cells and CD8+ T cells involves secreting IL-12 and presenting antigen with MHC-I pathway that activates these T cells. Intrahepatic HDV replication in HBV transgenic mice produced a positive immunohistochemical staining pattern of HDAg in HBV transgenic mice at 7 days after hydrodynamic injection. Dendritic cell-derived exosomes (Dexs) have been discovered to induce immune responses that are competent in eliminating viruses [200]. To induce a robust immune response, biological carriers deliver antigens that are used as immunomodulators from exosomes derived from mature dendritic cells exosomes (mDexs). MDexs are enriched by proinflammatory cytokines secreted by DCs. Designed exosomes loaded with ubiquitinated HDV small antigen (Ub-S-HDAg) and then treated mice bearing replicating HDV with these exosomes to investigate their antiviral effect and mechanism. There is a need to develop new therapeutic strategies to eradicate HDV in the future. HDV infection increases the risk of hepatocellular carcinoma (HCC) compared to HBV monoinfection. HDV has a ribozyme (HDV-Rz) that is around 67 nucleotides (nt) and can be used as an effective tumor gene therapy. HDV-Rz is the fastest of the known naturally occurring self-cleaving RNA and it stands out due to its stability to denaturants. The catalytic activity of HDV-Rz is required for viral replication and viral particle assembly within host cells. HDV-Rz has a self-scission property that cleaves its own sugar-phosphate backbone using a combination of metal ion and general acid-base catalysis through a cytosine nucleobase C75 that acts as a general acid and a divalent metal ion (Mg^{2+}) that

acts as a Lewis acid [201]. The HDV-Rz has the potential to be used to inhibit hepatocellular carcinoma (HCC). A previous study designed an HDV ribozyme against the RNA component of human telomerase in HCC cell lines, as normal hepatocytes and other cancers, and examined the function of HDV-Rz [188]. The total structure weight is 57.96 kDa and the crystal structure of HDV-Rz has been solved. There have yet to be cryo-EM structures of this ribozyme. There has been a comparison of secondary structures, tertiary folds, and cleavage sites of HDV and hatchet ribozyme products [202]. Gene therapy for cancer treatment focuses on efficacy and safety leading to efficient suppression of cancer cells without harming normal cells [203]. Point mutations that occur at high incidence in cancer can be used as potential targets for specific ribozyme-mediated reversal of the malignant phenotype.

HCV

HCV is a small, enveloped, plus-strand RNA virus belonging to the family Flaviviridae and the genus Hepacivirus. HCV is a liver-trophic virus that chronically infects approximately 170 million people worldwide. The HCV RNA genome encodes a single polyprotein that is post-translationally cleaved into 10 polypeptides including three structural proteins (core, E1 and E2), located at the N-terminus, and five nonstructural proteins. DC-SIGN and L-SIGN are two novel HCV envelope binding receptors, which the HCV envelope glycoprotein E2 binds through high-mannose N-glycans [204]. DC-SIGN and L-SIGN on the membrane are expressed with the highest affinity. The infected hepatocyte detects viral RNA with Toll-like receptor (TLR) 3 or TLR3 and RIG-I, and the infected hepatocyte deattenuates IFN and ISG gene expression. pDCs act as guardians in HCV-infected livers. The ability of an infiltrating pDC to secrete type I IFN typically depends on cellular sensors that can detect the presence of DNA and RNA viruses. pDCs express a subset of specialized cellular sensors named TLR8 and TLR9, that sense endosomal RNA and DNA, respectively. Direct exposure of HCV RNA to pDCs elicits an IFN response in a TLR7-dependent manner. Observations suggest that HCV RNA is transferred from infected hepatocytes to pDCs that trigger IFC response by an activation of TLR7. The mechanism of RNA transfer is unknown but could potentially occur through vesicle-mediated transfer by autophagosomes or exosomes [205-207]. DC-based vaccines against HCV have been developed. There are some being developed at the experimental level and some towards the translational level. DC-based vaccine against HCV infection includes a DC treated with the fusion protein, with challenge inoculums of anthrax toxin fusion protein containing the HCV-core epitope and was done on HCV-core specific CTLs in mice [208]. DC transduced with recombinant adenovirus with challenge inoculums recombinant adenovirus expressing HCV-core protein [209]. Another DC transfected with adenovirus encoding NS3 protein from HCV (AdNS3) was used with an outcome of a multi-epitopic CD4 T helper cell 1 (Th_1) and CD8 T-cell responses in different mouse strains [210]. DC transfected with lentiviral vectors (LV) were used, where the LV expressed HCV structural or non-structural gene clusters. There was potent stimulation of CD4 and CD8 T-cell allogenic and autologous responses [211]. DC containing microparticles of NS5 protein-coated microparticles had an antigen-specific CTL activity in mice and significantly reduced the growth of NS5-expressing tumor cells *in vivo* [212, 213]. There are also DC pulsed with HCV-LPs where the challenge inoculums were HCV-LP core, HCV-LP E2, this outcome resulted in HCV-core specific CD4 and CD8 T-cell responses [214]. There are strategies to enhance the efforts of DC-based vaccines [215]. Adjuvants include glucopyranosyl lipid A (GLA) which is a new synthetic non-toxic analog of lipopolysaccharide (LPS). Within four hours, GLA caused DC to up-regulate CD86 and CD40 and produce cytokines including IL-12p70 *in vivo* [216]. Synthetic oligodeoxynucleotides (ODNs) that contain unmethylated CpG motifs trigger cells expressing TLR9 (human pDCs, B cells) to mount an innate immune response (Th_1 production and pro-inflammatory cytokines). CpG ODNs improve the function of APCs and boost the generation of humoral and cellular vaccine-specific immune responses. Clinical trials have demonstrated CpG ODNs to

have a good safety profile and increased immunogenicity of co-administered vaccines [217]. High levels of IL-10 in chronic HCV infection have been insinuated for the poor antiviral cellular immune responses. This is an immunosuppressive effect on APCs such as DC. Diaz-Valdes' group have developed peptide inhibitors of IL-10 to restore DC functions and induce efficient antiviral immune responses. It is a cutting-edge technique to chase metal ions bound to protein to resolve ion interactions within proteins; the zinc-finger A20 is a negative regulator of the TLR and TNF receptor signaling pathways. This was found to play a pivotal role in controlling the maturation, cytokine production, and immunostimulatory potency of DC [218]. A20 has been put through mechanistic studies that tell of a regulation in DC production of retinoic acid and pro-inflammatory cytokines. These are some of the prospects of a DC-based vaccine against HCV infection. HCV infection has major implications for cancer and cancer treatment. There is an interplay between HCV-induced oncogenic signaling pathways such as the EGF pathway – HCV binding to its entry receptor complex (CLDN1/CD81) induces EGFR phosphorylation. This is encouraged by the action of NS3/4A and NS5A which negatively regulate the phosphatase TC-PTP and the process of EGFR degradation. There is also the STAT3 pathway where STAT3 activation directs the core protein and indirectly via EGFR activation and the NS5A protein that favors the production of ROS. There are also two miRNAs such as miR-135a-5p and miR-19a that decrease the expression of the negative STAT3 regulators PTPRD and SOCS3 [219]. There is also a pro-oncogenic inflammatory microenvironment induced by HCV. Viral sensors such as RIG-I and TLR3 lead to the production of type I IFNs; this occurs during HCV infection in hepatocytes. Macrophages sense the HCV-infected hepatocytes that trigger NLRP3 inflammasomes which induce secretion of IL-18 which activates NK cells. STAT3 takes part in MDSCs producing IL-10 for the expansion of regulatory T cells. This chronic liver inflammation leads to cell death, hepatocellular regeneration, and the emergence of mutated cells that may be premalignant [220].

HPV

Oncogenic HPVs are recognized to be connected to Head and neck squamous cell carcinomas (HNSCCs) that develop from mucosal epithelium in the oral cavity, pharynx, larynx, and sinonasal tract [221]. Cervical adenocarcinoma *in situ*, anal, vulvar, and vaginal intraepithelial neoplasia is caused by HPV types 16, 18, 31, 33, 45, 52, and 58. High risk HPV oncogenes have to signal pathways that include two known viral oncoproteins; E6 protein inactivates tumor suppressor p53 mediated DNA damage and apoptotic pathway. E7 protein inactivates tumor suppressor pRb mediated cell cycle regulation pathway. Cervical cancer is the fourth most common cancer among women globally, with more than 95% of cervical cancer cases attributable to human papillomavirus (HPV), a double-stranded DNA (dsDNA) virus. Cervical and other anogenital cancers are associated with infection of 'high-risk' HPVs: mainly HPV16 and HPV18. Mature DCs are essential in immune response against HPV [222]. DCs exposed to the high-risk HPV (HR-HPV) induced tumor microenvironment may attenuate effector T cell functions through programmed death receptor 1 (PD-1)/programmed death ligand 1 (PD-1/PD-L1) immune inhibitory signaling [223]. Interactions between DCs and T cells by ligation of PD-L1/PD-1 and immunoregulatory cytokine secretion may allow for immune escape during chronic HR-HPV infection. PD-1/PD-L1 axis activation causes a loss of function of CTL cells which can be restored by the administration of antibodies that blocked PD-1/PDL-1 interaction [224]. Cervical cancer cells may also favor tumor establishment by inhibiting the migration of DCs to lymph nodes (via depletion of CCR7) and inducing DC to produce Matrix metalloproteinase (MMP) 9 or MMP-9 [225].

Current HPV therapies include monoclonal antibody cetuximab with radiation, immune checkpoint inhibitors pembrolizumab and nivolumab for recurrent or metastatic HNSCC, and HPV vaccines such as Gardasil 9. HPV vaccination of all children and young

adults with HPV challenge will dramatically reduce HPV-positive HNSCC. HPV vaccines can prevent vaginal and vulvar cancer, genital warts, anal cancers, mouth, throat, head and neck cancers, and HPV-positive HNSCC in both women and men [226]. Studies reported clinical trials based on DC vaccines for cervical cancer and HNSCC [227]. DCs are very cytotoxic towards HPV16 E6 and E7 proteins expressing cells [228]. Many vaccines include adjuvants that enhance natural immunity, but their mechanisms of action are not fully understood. Adjuvant therapy targets include TLR ligands, CpG oligodeoxynucleotide (CpG ODN), LPS, and polyinosinic-polycytidylic acid (poly(I:C)) a synthetic of double-stranded RNA (dsRNA). These adjuvants aim to pulse DC activity. There is a novel HPV nanovaccine that could effectively inhibit the progression of cervical cancer by combining nanotechnology and photodynamic therapy [229]. The nanovaccine links bovine serum albumin (BSA) with the E7 antigen and then encapsulates the photosensitizer and adjuvant through disulphide bonds to form a highly biocompatible and stable structure. This nanovaccine is a targeted delivery approach to the lymph nodes that could effectively induce the maturation of DCs and stimulate T cell effects, thus enhancing antitumor immunity. This strategy can be applied to the design of a therapeutic HPV vaccine in the future for clinical use.

Conclusion and Perspectives

DCs are important mediators of innate and adaptive immunity. They are among the first cells to encounter viral infection and thus play an integral role in responding to and propagating infection in several viral infections including HIV-1, HTLV-1, EBV, HBV, HDV, HCV, and HPV. DC-SIGN is an enticing potential target for therapies aimed at stopping viral disease progression at the first step of infection. Cell-to-cell connections are influenced by ICAM-1/LFA-1 surface protein interactions which are influenced by viral proteins such as HIV-1 gp120 expression on MHC II molecules and HTLV-1 Tax protein that plays central roles in viral oncogenesis. Key mediators of HIV- and HTLV-induced neuropathogenesis include Myo-inositol and choline, Glu/GABA imbalance, NMDA receptor signaling, and Foxp3+ Tregs. Further understanding the integrative roles of these factors in viral pathogenesis is essential to developing targeted therapies. Current therapies for HIV-1 and HTLV-1 include cART, HIV-1 nanotherapeutics, and vaccine therapies. cART treatment is effective in HIV-1 treatment and has been tested in HTLV-1 as well. However, these medications including AZT, 3CT, and TFV are designed for HIV-1 and are thus not as effective for HTLV-1. Modification of these medications could optimize use for HTLV-1. HIV-1 nanotherapeutics are composed primarily of dendrimers, liposomes, micelles, and nanosuspensions that have surfactant, drugs, and phospholipids. The nanodrugs are aimed at targeting delivery to specific cells to contain viral spread. Current standard HTLV-1 therapy is hematopoietic stem cell transplantation. Novel HTLV-1 therapies are centered around Tax protein with the Tax-DC vaccine being the main one. Other potential targets for HTLV-1 therapy include DC-SIGN and APOBEC3. Viral-induced oncogenesis contributes to a significant proportion of cancer cases and can be caused by viruses in several different families as discussed. Viruses promote the development of a variety of cancers such as Burkitt's lymphoma, Hodgkin's lymphoma, T cell lymphoma, nasopharyngeal carcinoma, gastric carcinoma, Kaposi sarcoma, hepatocellular carcinoma, and cervical adenoma. Among the oncogenic viruses, DCs are important cells that intercept the virus early in infection. Overall, DCs provide a promising focus for research in retroviral infection and other oncogenic viruses.

Table 1. CD markers on Dendritic cell subtypes. Breakdown of DC populations by location including lymph nodes, spleen, thymus, blood, skin, and gut. Differential CD expression among this population of cells. The table also notes proliferative factors for select DC subtypes.

DC Location	CD Molecule Expression	Cytokines and Signaling Molecules
Lymph Nodes	CD80, CD86, CD40	-
Spleen	CD8 CD11b, CD205, CD207, Clec9a	Proliferate in presence of Flt3L
Thymus	CD8, CD207	Sirpα+ dependent on CCR2 chemotaxis
Blood (pDC, cDC)	pDC: BDCA2, BDCA4 cDC: CD11	-
Skin (Langerhans)	CD207, CD45, CD11c, CD1a, CD14, CD141	Proliferate *independent* of Flt3; Dependent on CSF-1R which induces chemokines CCL2 & CCL20
Gut	CD8, CD103, CD207, CD11b	Proliferate in presence of Flt3L

List of Abbreviations

Acquired Immunodeficiency Syndrome	AIDS
Adult T-cell leukemia/lymphoma	ATLL
Alpha-fetoprotein	AFP
Antigen Presenting Cells	APC
Antiretroviral Therapy	ART
Chemokine Receptor	CCR#
Cytotoxic Lymphocytes	CTL
DC-specific Intercellular Adhesion Molecule-3 Grabbing Non-integrin	DC-SIGN
Epstein-Barr Virus	EBV
Glioblastoma	GBM
Head and Neck Squamous Cell Carcinomas	HNSCCs
Hepatitis B/C/D Virus	HBV/HCV/HDV
Hepatocellular Carcinoma	HCC
HIV-associated neurocognitive disorders	HAND
HTLV-1-associate myelopathy/tropical spastic paraparesis	HAM/TSP
Human Immunodeficiency Virus Type 1	HIV-1
Human Papillomavirus	HPV
Human T-lymphocytic virus type 1	HTLV-1
Interferon	IFN
Interleukin	IL
Long Terminal Repeat	LTR
Major Histocompatibility Complex	MHC
Myeloid Dendritic Cell and Plasmacytoid Dendritic Cell	mDC and pDC
Natural Killer Cells	NK Cells
Pathogen-Associated Molecular Patterns	PAMPs
Pattern-Recognition Receptors	PRRs
People Living with HIV	PLWH
Polymerase Chain Reaction	PCR
Protein Negative Factor	Nef
Reactive Oxygen Species	ROS
Regulatory T cells	T regs
Supramolecular Activation Complex	SMAC
Tumor Necrosis Factor	TNF

Disclosure of Potential Conflicts of Interest 989

The authors declare there is no potential conflict of interest. 990

Consent to publish 991

All authors agree to publish the content of this study as formulated. 992

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References

1. Chaplin, D.D., *Overview of the immune response.* J Allergy Clin Immunol, 2010. **125**(2 Suppl 2): p. S3-23.
2. Janeway, C.A., Jr., *How the immune system protects the host from infection.* Microbes Infect, 2001. **3**(13): p. 1167-71.
3. Martin-Gayo, E. and X.G. Yu, *Role of Dendritic Cells in Natural Immune Control of HIV-1 Infection.* Front Immunol, 2019. **10**: p. 1306.
4. Ma, J.K., et al., *MHC class II distribution in dendritic cells and B cells is determined by ubiquitin chain length.* Proc Natl Acad Sci U S A, 2012. **109**(23): p. 8820-7.
5. Hewitt, E.W., *The MHC class I antigen presentation pathway: strategies for viral immune evasion.* Immunology, 2003. **110**(2): p. 163-9.
6. Munz, C., *Antigen Processing for MHC Class II Presentation via Autophagy.* Front Immunol, 2012. **3**: p. 9.
7. Jang, M.H., et al., *CCR7 is critically important for migration of dendritic cells in intestinal lamina propria to mesenteric lymph nodes.* J Immunol, 2006. **176**(2): p. 803-10.
8. Kaiko, G.E., et al., *Immunological decision-making: how does the immune system decide to mount a helper T-cell response?* Immunology, 2008. **123**(3): p. 326-38.
9. Kondelkova, K., et al., *Regulatory T cells (TREG) and their roles in immune system with respect to immunopathological disorders.* Acta Medica (Hradec Kralove), 2010. **53**(2): p. 73-7.
10. Castell-Rodríguez, A., et al., *Dendritic cells: location, function, and clinical implications.* Biology of myelomonocytic cells, 2017: p. 21-50.
11. Collin, M. and V. Bigley, *Human dendritic cell subsets: an update.* Immunology, 2018. **154**(1): p. 3-20.
12. Chistiakov, D.A., et al., *Plasmacytoid dendritic cells: development, functions, and role in atherosclerotic inflammation.* Front Physiol, 2014. **5**: p. 279.
13. Chistiakov, D.A., et al., *Myeloid dendritic cells: Development, functions, and role in atherosclerotic inflammation.* Immunobiology, 2015. **220**(6): p. 833-44.
14. Miller, E. and N. Bhardwaj, *Dendritic cell dysregulation during HIV-1 infection.* Immunol Rev, 2013. **254**(1): p. 170-89.
15. Shimauchi, T. and V. Piguet, *DC-T cell virological synapses and the skin: novel perspectives in dermatology.* Exp Dermatol, 2015. **24**(1): p. 1-4.
16. Araujo, A.Q., *Neurological Aspects of HIV-1/HTLV-1 and HIV-1/HTLV-2 Coinfection.* Pathogens, 2020. **9**(4).
17. Ticona, E., et al., *HIV and HTLV-1 coinfection: the need to initiate antiretroviral therapy.* J Int Assoc Provid AIDS Care, 2013. **12**(6): p. 373-4.
18. Araujo, A.Q.C. and D. Wedemann, *HTLV-1 Associated Neurological Complex. What is Hidden below the Water?* AIDS Rev, 2019. **21**(4): p. 211-217.
19. Silva, M.T., et al., *Isolated bladder dysfunction in human T lymphotropic virus type 1 infection: 10 years of follow-up.* J Neurol Neurosurg Psychiatry, 2017. **88**(3): p. 278-279.
20. Zehender, G., et al., *Human T-lymphotropic virus type 2 (HTLV-2) provirus in circulating cells of the monocyte/macrophage lineage in patients dually infected with human immunodeficiency virus type 1 and HTLV-2 and having predominantly sensory polyneuropathy.* J Virol, 1998. **72**(9): p. 7664-8.
21. Moriuchi, H. and M. Moriuchi, *In vitro induction of HIV-1 replication in resting CD4(+) T cells derived from individuals with undetectable plasma viremia upon stimulation with human T-cell leukemia virus type I.* Virology, 2000. **278**(2): p. 514-9.

22. Siekevitz, M., et al., *Activation of the HIV-1 LTR by T cell mitogens and the trans-activator protein of HTLV-I.* Science, 1987. **238**(4833): p. 1575-8.
23. Zack, J.A., et al., *HIV-1 production from infected peripheral blood T cells after HTLV-I induced mitogenic stimulation.* Science, 1988. **240**(4855): p. 1026-9.
24. De Rossi, A., et al., *Reciprocal activation of human T-lymphotropic viruses in HTLV-I-transformed cells superinfected with HIV-1.* J Acquir Immune Defic Syndr (1988), 1991. **4**(4): p. 380-5.
25. Beilke, M.A., S. Japa, and D.G. Vinson, *HTLV-I and HTLV-II virus expression increase with HIV-1 coinfection.* J Acquir Immune Defic Syndr Hum Retrovirol, 1998. **17**(5): p. 391-7.
26. Bohnlein, E., et al., *Stimulation of the human immunodeficiency virus type 1 enhancer by the human T-cell leukemia virus type I tax gene product involves the action of inducible cellular proteins.* J Virol, 1989. **63**(4): p. 1578-86.
27. Rockwood, N., et al., *Immune Compromise in HIV-1/HTLV-1 Coinfection With Paradoxical Resolution of CD4 Lymphocytosis During Antiretroviral Therapy: A Case Report.* Medicine (Baltimore), 2015. **94**(50): p. e2275.
28. Zucker-Franklin, D., M. Fraig, and G. Grusky, *Interaction of human immunodeficiency virus type 1, human T-cell leukemia/lymphoma virus type I (HTLV-I), and HTLV-II with in vitro-generated dendritic cells.* Clin Diagn Lab Immunol, 1995. **2**(3): p. 343-8.
29. Pilotti, E., et al., *HTLV-1/-2 and HIV-1 co-infections: retroviral interference on host immune status.* Front Microbiol, 2013. **4**: p. 372.
30. Barrios, C.S., et al., *Human T cell leukaemia virus type 2 tax protein mediates CC-chemokine expression in peripheral blood mononuclear cells via the nuclear factor kappa B canonical pathway.* Clin Exp Immunol, 2014. **175**(1): p. 92-103.
31. Londhe, R. and S. Kulkarni, *HTLV-2 Encoded Antisense Protein APH-2 Suppresses HIV-1 Replication.* Viruses, 2021. **13**(8).
32. McLaren, P.J. and J. Fellay, *HIV-1 and human genetic variation.* Nat Rev Genet, 2021. **22**(10): p. 645-657.
33. Friedland, G.H. and R.S. Klein, *Transmission of the human immunodeficiency virus.* N Engl J Med, 1987. **317**(18): p. 1125-35.
34. Swanstrom, R. and J. Coffin, *HIV-1 pathogenesis: the virus.* Cold Spring Harb Perspect Med, 2012. **2**(12): p. a007443.
35. Lutgen, V., et al., *HIV infects astrocytes in vivo and egresses from the brain to the periphery.* PLoS Pathog, 2020. **16**(6): p. e1008381.
36. Khan, M.Y., et al., *HTLV-1 Associated Neurological Disorders.* Curr Top Med Chem, 2017. **17**(12): p. 1320-1330.
37. Smed-Sorensen, A., et al., *Differential susceptibility to human immunodeficiency virus type 1 infection of myeloid and plasmacytoid dendritic cells.* J Virol, 2005. **79**(14): p. 8861-9.
38. Manches, O., D. Frleta, and N. Bhardwaj, *Dendritic cells in progression and pathology of HIV infection.* Trends Immunol, 2014. **35**(3): p. 114-22.
39. Coffin, J.M., et al., *Proposal for naming host cell-derived inserts in retrovirus genomes.* J Virol, 1981. **40**(3): p. 953-7.
40. Groot, F., S. Welsch, and Q.J. Sattentau, *Efficient HIV-1 transmission from macrophages to T cells across transient virological synapses.* Blood, 2008. **111**(9): p. 4660-3.
41. Wilen, C.B., J.C. Tilton, and R.W. Doms, *HIV: cell binding and entry.* Cold Spring Harb Perspect Med, 2012. **2**(8).

42. da Silva, R.C., L. Segat, and S. Crovella, *Role of DC-SIGN and L-SIGN receptors in HIV-1 vertical transmission.* Hum Immunol, 2011. **72**(4): p. 305-11.
43. Bai, X., et al., *Genetic co-inactivation of macrophage- and T-tropic HIV-1 chemokine coreceptors CCR-5 and CXCR-4 by intrakines.* Gene Ther, 1998. **5**(7): p. 984-94.
44. Bleul, C.C., et al., *The HIV coreceptors CXCR4 and CCR5 are differentially expressed and regulated on human T lymphocytes.* Proc Natl Acad Sci U S A, 1997. **94**(5): p. 1925-30.
45. Sehgal, M., et al., *Dendritic Cells in HIV-1 and HCV Infection: Can They Help Win the Battle?* Virology (Auckl), 2013. **4**: p. 1-25.
46. Martín-Moreno, A. and M.A. Muñoz-Fernández, *Dendritic Cells, the Double Agent in the War Against HIV-1.* Front Immunol, 2019. **10**: p. 2485.
47. McDonald, D., *Dendritic Cells and HIV-1 Trans-Infection.* Viruses, 2010. **2**(8): p. 1704-17.
48. Kim, J.T., et al., *Dendritic cells efficiently transmit HIV to T Cells in a tenofovir and raltegravir insensitive manner.* PLoS One, 2018. **13**(1): p. e0189945.
49. Vasiliver-Shamis, G., M.L. Dustin, and C.E. Hioe, *HIV-1 Virological Synapse is not Simply a Copycat of the Immunological Synapse.* Viruses, 2010. **2**(5): p. 1239-60.
50. Carrington, M. and G. Alter, *Innate immune control of HIV.* Cold Spring Harb Perspect Med, 2012. **2**(7): p. a007070.
51. McMichael, A.J., et al., *The immune response during acute HIV-1 infection: clues for vaccine development.* Nat Rev Immunol, 2010. **10**(1): p. 11-23.
52. Murugaiah, V., et al., *Innate Immune Response Against HIV-1.* Adv Exp Med Biol, 2021. **1313**: p. 23-58.
53. Schwartz, O., et al., *Endocytosis of major histocompatibility complex class I molecules is induced by the HIV-1 Nef protein.* Nat Med, 1996. **2**(3): p. 338-42.
54. Le Gall, S., et al., *Nef interacts with the mu subunit of clathrin adaptor complexes and reveals a cryptic sorting signal in MHC I molecules.* Immunity, 1998. **8**(4): p. 483-95.
55. Cohen, G.B., et al., *The selective downregulation of class I major histocompatibility complex proteins by HIV-1 protects HIV-infected cells from NK cells.* Immunity, 1999. **10**(6): p. 661-71.
56. van Montfort, T., et al., *HIV-1 N-glycan composition governs a balance between dendritic cell-mediated viral transmission and antigen presentation.* J Immunol, 2011. **187**(9): p. 4676-85.
57. Jan, M., C. Upadhyay, and C.E. Hioe, *HIV-1 Envelope Glycan Composition as a Key Determinant of Efficient Virus Transmission via DC-SIGN and Resistance to Inhibitory Lectins.* iScience, 2019. **21**: p. 413-427.
58. Dieu, M.C., et al., *Selective recruitment of immature and mature dendritic cells by distinct chemokines expressed in different anatomic sites.* J Exp Med, 1998. **188**(2): p. 373-86.
59. Dave, R.S., P. Jain, and S.N. Byrareddy, *Follicular Dendritic Cells of Lymph Nodes as Human Immunodeficiency Virus/Simian Immunodeficiency Virus Reservoirs and Insights on Cervical Lymph Node.* Front Immunol, 2018. **9**: p. 805.
60. Coulon, P.G., et al., *HIV-Infected Dendritic Cells Present Endogenous MHC Class II-Restricted Antigens to HIV-Specific CD4+ T Cells.* J Immunol, 2016. **197**(2): p. 517-32.
61. Perreau, M., Y. Levy, and G. Pantaleo, *Immune response to HIV.* Curr Opin HIV AIDS, 2013. **8**(4): p. 333-40.
62. Isaguliants, M., et al., *Oncogenic Effects of HIV-1 Proteins, Mechanisms Behind.* Cancers (Basel), 2021. **13**(2).
63. Chew, K.W. and D. Bhattacharya, *Virologic and immunologic aspects of HIV-hepatitis C virus coinfection.* AIDS, 2016. **30**(16): p. 2395-2404.

64. Sun, H.Y., et al., *Hepatitis B virus coinfection in human immunodeficiency virus-infected patients: a review.* World J Gastroenterol, 2014. **20**(40): p. 14598-614.
65. Pinato, D.J., et al., *Hepatocellular carcinoma: an evolving challenge in viral hepatitis and HIV coinfection.* AIDS, 2017. **31**(5): p. 603-611.
66. Lemon, S.M. and D.R. McGivern, *Is hepatitis C virus carcinogenic?* Gastroenterology, 2012. **142**(6): p. 1274-8.
67. Ivanov, A.V., et al., *Oxidative stress, a trigger of hepatitis C and B virus-induced liver carcinogenesis.* Oncotarget, 2017. **8**(3): p. 3895-3932.
68. Hall, J.R. and S.C. Short, *Management of glioblastoma multiforme in HIV patients: a case series and review of published studies.* Clin Oncol (R Coll Radiol), 2009. **21**(8): p. 591-7.
69. Del Valle, L. and S. Pina-Oviedo, *HIV disorders of the brain: pathology and pathogenesis.* Front Biosci, 2006. **11**: p. 718-32.
70. Messam, C.A. and E.O. Major, *Stages of restricted HIV-1 infection in astrocyte cultures derived from human fetal brain tissue.* J Neurovirol, 2000. **6 Suppl 1**: p. S90-4.
71. Chiodi, F., et al., *Infection of brain-derived cells with the human immunodeficiency virus.* J Virol, 1987. **61**(4): p. 1244-7.
72. Dandachi, D. and F. Moron, *Effects of HIV on the Tumor Microenvironment.* Adv Exp Med Biol, 2020. **1263**: p. 45-54.
73. Warburg, O., *On the origin of cancer cells.* Science, 1956. **123**(3191): p. 309-14.
74. Lien, K., et al., *HIV-1 proteins gp120 and tat induce the epithelial-mesenchymal transition in oral and genital mucosal epithelial cells.* PLoS One, 2019. **14**(12): p. e0226343.
75. Greenway, A.L., et al., *Human immunodeficiency virus type 1 Nef binds to tumor suppressor p53 and protects cells against p53-mediated apoptosis.* J Virol, 2002. **76**(6): p. 2692-702.
76. Ivanov, A.V., B. Bartosch, and M.G. Isaguliants, *Oxidative Stress in Infection and Consequent Disease.* Oxid Med Cell Longev, 2017. **2017**: p. 3496043.
77. Bayurova, E., et al., *HIV-1 Reverse Transcriptase Promotes Tumor Growth and Metastasis Formation via ROS-Dependent Upregulation of Twist.* Oxid Med Cell Longev, 2019. **2019**: p. 6016278.
78. Luckett, P., et al., *Deep Learning Analysis of Cerebral Blood Flow to Identify Cognitive Impairment and Frailty in Persons Living With HIV.* J Acquir Immune Defic Syndr, 2019. **82**(5): p. 496-502.
79. Boerwinkle, A.H., et al., *Neuroimaging the Neuropathogenesis of HIV.* Curr HIV/AIDS Rep, 2021. **18**(3): p. 221-228.
80. Clifford, D.B., *HIV-associated neurocognitive disorder.* Curr Opin Infect Dis, 2017. **30**(1): p. 117-122.
81. Valcour, V., et al., *Central nervous system viral invasion and inflammation during acute HIV infection.* J Infect Dis, 2012. **206**(2): p. 275-82.
82. Hellmuth, J., V. Valcour, and S. Spudich, *CNS reservoirs for HIV: implications for eradication.* J Virus Erad, 2015. **1**(2): p. 67-71.
83. Kuhn, T., et al., *The joint effect of aging and HIV infection on microstructure of white matter bundles.* Hum Brain Mapp, 2019. **40**(15): p. 4370-4380.
84. Gullett, J.M., et al., *The Impact of Alcohol Use on Frontal White Matter in HIV.* Alcohol Clin Exp Res, 2018. **42**(9): p. 1640-1649.
85. Valcour, V., et al., *Pathogenesis of HIV in the central nervous system.* Curr HIV/AIDS Rep, 2011. **8**(1): p. 54-61.

86. Groff, B.R., et al., *Age-related visual dynamics in HIV-infected adults with cognitive impairment.* Neurol Neuroimmunol Neuroinflamm, 2020. **7**(3).
87. Paul, R.H., et al., *Machine Learning Analysis Reveals Novel Neuroimaging and Clinical Signatures of Frailty in HIV.* J Acquir Immune Defic Syndr, 2020. **84**(4): p. 414-421.
88. Chang, L., et al., *Adaptation of the attention network in human immunodeficiency virus brain injury.* Ann Neurol, 2004. **56**(2): p. 259-72.
89. Nickoloff-Bybel, E.A., et al., *Co-receptor signaling in the pathogenesis of neuroHIV.* Retrovirology, 2021. **18**(1): p. 24.
90. Claing, A., et al., *Endocytosis of G protein-coupled receptors: roles of G protein-coupled receptor kinases and beta-arrestin proteins.* Prog Neurobiol, 2002. **66**(2): p. 61-79.
91. Zhang, J., et al., *A central role for beta-arrestins and clathrin-coated vesicle-mediated endocytosis in beta2-adrenergic receptor resensitization. Differential regulation of receptor resensitization in two distinct cell types.* J Biol Chem, 1997. **272**(43): p. 27005-14.
92. Gorska, A.M. and E.A. Eugenin, *The Glutamate System as a Crucial Regulator of CNS Toxicity and Survival of HIV Reservoirs.* Front Cell Infect Microbiol, 2020. **10**: p. 261.
93. Sailasuta, N., K. Shriner, and B. Ross, *Evidence of reduced glutamate in the frontal lobe of HIV-seropositive patients.* NMR Biomed, 2009. **22**(3): p. 326-31.
94. Cohen, R.A., et al., *Cerebral metabolite abnormalities in human immunodeficiency virus are associated with cortical and subcortical volumes.* J Neurovirol, 2010. **16**(6): p. 435-44.
95. Ernst, T., et al., *Lower brain glutamate is associated with cognitive deficits in HIV patients: a new mechanism for HIV-associated neurocognitive disorder.* J Magn Reson Imaging, 2010. **32**(5): p. 1045-53.
96. Young, A.C., et al., *Cerebral metabolite changes prior to and after antiretroviral therapy in primary HIV infection.* Neurology, 2014. **83**(18): p. 1592-600.
97. Mohamed, M., et al., *7T Brain MRS in HIV Infection: Correlation with Cognitive Impairment and Performance on Neuropsychological Tests.* AJNR Am J Neuroradiol, 2018. **39**(4): p. 704-712.
98. Cysique, L.A., et al., *HIV brain latency as measured by CSF BcL11b relates to disrupted brain cellular energy in virally suppressed HIV infection.* AIDS, 2019. **33**(3): p. 433-441.
99. Ferrarese, C., et al., *Increased glutamate in CSF and plasma of patients with HIV dementia.* Neurology, 2001. **57**(4): p. 671-5.
100. Cassol, E., et al., *Cerebrospinal fluid metabolomics reveals altered waste clearance and accelerated aging in HIV patients with neurocognitive impairment.* AIDS, 2014. **28**(11): p. 1579-91.
101. Anderson, A.M., et al., *Plasma and Cerebrospinal Fluid Biomarkers Predict Cerebral Injury in HIV-Infected Individuals on Stable Combination Antiretroviral Therapy.* J Acquir Immune Defic Syndr, 2015. **69**(1): p. 29-35.
102. Trickey, A., et al., *CD4:CD8 Ratio and CD8 Count as Prognostic Markers for Mortality in Human Immunodeficiency Virus-Infected Patients on Antiretroviral Therapy: The Antiretroviral Therapy Cohort Collaboration (ART-CC).* Clin Infect Dis, 2017. **65**(6): p. 959-966.
103. Roy, U., et al., *The potential of HIV-1 nanotherapeutics: from in vitro studies to clinical trials.* Nanomedicine (Lond), 2015. **10**(24): p. 3597-609.
104. Rupp, R., S.L. Rosenthal, and L.R. Stanberry, *VivaGel (SPL7013 Gel): a candidate dendrimer--microbicide for the prevention of HIV and HSV infection.* Int J Nanomedicine, 2007. **2**(4): p. 561-6.
105. Gulick, R., *HIV treatment 2020: what will it look like?* J Int AIDS Soc, 2014. **17**(4 Suppl 3): p. 19528.

106. Mohamed, H., et al., *The Evolution of Dendritic Cell Immunotherapy against HIV-1 Infection: Improvements and Outlook.* J Immunol Res, 2020. **2020**: p. 9470102.
107. Granucci, F., et al., *Dendritic cell regulation of immune responses: a new role for interleukin 2 at the intersection of innate and adaptive immunity.* EMBO J, 2003. **22**(11): p. 2546-51.
108. Hamimi, C., et al., *Dendritic Cells from HIV Controllers Have Low Susceptibility to HIV-1 Infection In Vitro but High Capacity to Capture HIV-1 Particles.* PLoS One, 2016. **11**(8): p. e0160251.
109. Smith, K.N., et al., *Dendritic cells restore CD8+ T cell reactivity to autologous HIV-1.* J Virol, 2014. **88**(17): p. 9976-90.
110. Herrera, C., et al., *The entry inhibitor DS003 (BMS-599793): a BMS-806 analogue, provides superior activity as a pre-exposure prophylaxis candidate.* AIDS, 2021. **35**(12): p. 1907-1917.
111. Lu, W., et al., *Therapeutic dendritic-cell vaccine for chronic HIV-1 infection.* Nat Med, 2004. **10**(12): p. 1359-65.
112. Jiang, S., et al., *Combined protein and nucleic acid imaging reveals virus-dependent B cell and macrophage immunosuppression of tissue microenvironments.* Immunity, 2022. **55**(6): p. 1118-1134 e8.
113. Singh, A., *Eliciting B cell immunity against infectious diseases using nanovaccines.* Nat Nanotechnol, 2021. **16**(1): p. 16-24.
114. Gardner, M.R., et al., *AAV-expressed eCD4-Ig provides durable protection from multiple SHIV challenges.* Nature, 2015. **519**(7541): p. 87-91.
115. Humans, I.W.G.o.t.E.o.C.R.t., *Human T-cell lymphotropic virus type 1*, in *Biological Agents*. 2012, International Agency for Research on Cancer.
116. Organization, W.H., *Human T-lymphotropic virus type 1: technical report.* 2021.
117. Gessain, A. and O. Cassar, *Epidemiological Aspects and World Distribution of HTLV-1 Infection.* Front Microbiol, 2012. **3**: p. 388.
118. Goncalves, D.U., et al., *Epidemiology, treatment, and prevention of human T-cell leukemia virus type 1-associated diseases.* Clin Microbiol Rev, 2010. **23**(3): p. 577-89.
119. Fuzii, H.T., et al., *Immunopathogenesis of HTLV-1-assoaciated myelopathy/tropical spastic paraparesis (HAM/TSP).* Life Sci, 2014. **104**(1-2): p. 9-14.
120. Gross, C. and A.K. Thoma-Kress, *Molecular Mechanisms of HTLV-1 Cell-to-Cell Transmission.* Viruses, 2016. **8**(3): p. 74.
121. Jones, K.S., et al., *Cell-free HTLV-1 infects dendritic cells leading to transmission and transformation of CD4(+) T cells.* Nat Med, 2008. **14**(4): p. 429-36.
122. Alais, S., R. Mahieux, and H. Dutartre, *Viral Source-Independent High Susceptibility of Dendritic Cells to Human T-Cell Leukemia Virus Type 1 Infection Compared to That of T Lymphocytes.* J Virol, 2015. **89**(20): p. 10580-90.
123. Kampani, K., et al., *A novel high throughput quantum dot-based fluorescence assay for quantitation of virus binding and attachment.* J Virol Methods, 2007. **141**(2): p. 125-32.
124. Martin, J.L., et al., *Molecular Studies of HTLV-1 Replication: An Update.* Viruses, 2016. **8**(2).
125. Jain, P., et al., *DC-SIGN mediates cell-free infection and transmission of human T-cell lymphotropic virus type 1 by dendritic cells.* J Virol, 2009. **83**(21): p. 10908-21.
126. Nejmeddine, M., et al., *HTLV-1-Tax and ICAM-1 act on T-cell signal pathways to polarize the microtubule-organizing center at the virological synapse.* Blood, 2009. **114**(5): p. 1016-25.
127. Pais-Correia, A.M., et al., *Biofilm-like extracellular viral assemblies mediate HTLV-1 cell-to-cell transmission at virological synapses.* Nat Med, 2010. **16**(1): p. 83-9.

128. Eusebio-Ponce, E., et al., *HTLV-1 infection: An emerging risk. Pathogenesis, epidemiology, diagnosis and associated diseases.* Rev Esp Quimioter, 2019. **32**(6): p. 485-496.
129. Van Prooyen, N., et al., *Human T-cell leukemia virus type 1 p8 protein increases cellular conduits and virus transmission.* Proc Natl Acad Sci U S A, 2010. **107**(48): p. 20738-43.
130. Malbec, M., F. Roesch, and O. Schwartz, *A new role for the HTLV-1 p8 protein: increasing intercellular conduits and viral cell-to-cell transmission.* Viruses, 2011. **3**(3): p. 254-9.
131. Journo, C. and R. Mahieux, *HTLV-1 and innate immunity.* Viruses, 2011. **3**(8): p. 1374-94.
132. Jang, J.H., et al., *An Overview of Pathogen Recognition Receptors for Innate Immunity in Dental Pulp.* Mediators Inflamm, 2015. **2015**: p. 794143.
133. Rizkallah, G., et al., *Dendritic cell maturation, but not type I interferon exposure, restricts infection by HTLV-1, and viral transmission to T-cells.* PLoS Pathog, 2017. **13**(4): p. e1006353.
134. Norris, P.J., et al., *Human T cell leukemia virus type 1 infection drives spontaneous proliferation of natural killer cells.* Virulence, 2010. **1**(1): p. 19-28.
135. Rafatpanah, H., R. Farid Hosseini, and S.H. Pourseyed, *The Impact of Immune Response on HTLV-I in HTLV-I-Associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP).* Iran J Basic Med Sci, 2013. **16**(3): p. 235-41.
136. Biddison, W.E., et al., *Human T cell leukemia virus type I (HTLV-I)-specific CD8+ CTL clones from patients with HTLV-I-associated neurologic disease secrete proinflammatory cytokines, chemokines, and matrix metalloproteinase.* J Immunol, 1997. **159**(4): p. 2018-25.
137. Goon, P.K., et al., *High frequencies of Th1-type CD4(+) T cells specific to HTLV-1 Env and Tax proteins in patients with HTLV-1-associated myelopathy/tropical spastic paraparesis.* Blood, 2002. **99**(9): p. 3335-41.
138. Satou, Y., et al., *HTLV-1 modulates the frequency and phenotype of FoxP3+CD4+ T cells in virus-infected individuals.* Retrovirology, 2012. **9**: p. 46.
139. Iwanaga, M., et al., *Human T-cell leukemia virus type I (HTLV-1) proviral load and disease progression in asymptomatic HTLV-1 carriers: a nationwide prospective study in Japan.* Blood, 2010. **116**(8): p. 1211-9.
140. Watanabe, T., *Adult T-cell leukemia: molecular basis for clonal expansion and transformation of HTLV-1-infected T cells.* Blood, 2017. **129**(9): p. 1071-1081.
141. Yoshida, N. and D.M. Weinstock, *Clinicogenetic risk modeling in ATL.* Blood, 2018. **131**(2): p. 159-160.
142. Bangham, C.R. and L. Ratner, *How does HTLV-1 cause adult T-cell leukaemia/lymphoma (ATL)?* Curr Opin Virol, 2015. **14**: p. 93-100.
143. Grossman, W.J., et al., *Development of leukemia in mice transgenic for the tax gene of human T-cell leukemia virus type I.* Proc Natl Acad Sci U S A, 1995. **92**(4): p. 1057-61.
144. Hasegawa, H., et al., *Thymus-derived leukemia-lymphoma in mice transgenic for the Tax gene of human T-lymphotropic virus type I.* Nat Med, 2006. **12**(4): p. 466-72.
145. Ohsugi, T., *A transgenic mouse model of human T cell leukemia virus type 1-associated diseases.* Front Microbiol, 2013. **4**: p. 49.
146. Matsuoka, M. and K.T. Jeang, *Human T-cell leukemia virus type 1 (HTLV-1) and leukemic transformation: viral infectivity, Tax, HBZ and therapy.* Oncogene, 2011. **30**(12): p. 1379-89.
147. Choi, Y.B. and E.W. Harhaj, *HTLV-1 tax stabilizes MCL-1 via TRAF6-dependent K63-linked polyubiquitination to promote cell survival and transformation.* PLoS Pathog, 2014. **10**(10): p. e1004458.
148. Matsuoka, M. and K.T. Jeang, *Human T-cell leukaemia virus type 1 (HTLV-1) infectivity and cellular transformation.* Nat Rev Cancer, 2007. **7**(4): p. 270-80.

149. Baydoun, H.H., et al., *HTLV-I tax increases genetic instability by inducing DNA double strand breaks during DNA replication and switching repair to NHEJ.* PLoS One, 2012. **7**(8): p. e42226.
150. Kinoshita, T., et al., *Detection of mRNA for the tax1/rex1 gene of human T-cell leukemia virus type I in fresh peripheral blood mononuclear cells of adult T-cell leukemia patients and viral carriers by using the polymerase chain reaction.* Proc Natl Acad Sci U S A, 1989. **86**(14): p. 5620-4.
151. Matsuoka, M. and P.L. Green, *The HBZ gene, a key player in HTLV-1 pathogenesis.* Retrovirology, 2009. **6**: p. 71.
152. Kuhlmann, A.S., et al., *HTLV-1 HBZ cooperates with JunD to enhance transcription of the human telomerase reverse transcriptase gene (hTERT).* Retrovirology, 2007. **4**: p. 92.
153. Abolbashari, S., et al., *The role of human T-lymphotropic virus (HTLV) in cardiovascular diseases: A review of literature.* ARYA Atheroscler, 2018. **14**(4): p. 183-187.
154. Quaresma, J.A., et al., *HTLV-1, Immune Response and Autoimmunity.* Viruses, 2015. **8**(1).
155. Izumo, S., *Neuropathology of HTLV-1-associated myelopathy (HAM/TSP): The 50th Anniversary of Japanese Society of Neuropathology.* Neuropathology, 2010. **30**(5): p. 480-5.
156. Enose-Akahata, Y. and S. Jacobson, *Immunovirological markers in HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP).* Retrovirology, 2019. **16**(1): p. 35.
157. Oh, U. and S. Jacobson, *Treatment of HTLV-I-associated myelopathy/tropical spastic paraparesis: toward rational targeted therapy.* Neurol Clin, 2008. **26**(3): p. 781-97, ix-x.
158. Manuel, S.L., et al., *An altered maturation and adhesion phenotype of dendritic cells in diseased individuals compared to asymptomatic carriers of human T cell leukemia virus type 1.* AIDS Res Hum Retroviruses, 2013. **29**(9): p. 1273-85.
159. Jacobson, S., et al., *Circulating CD8+ cytotoxic T lymphocytes specific for HTLV-I pX in patients with HTLV-I associated neurological disease.* Nature, 1990. **348**(6298): p. 245-8.
160. Manuel, S.L., et al., *Dendritic cells in autoimmune diseases and neuroinflammatory disorders.* Front Biosci, 2007. **12**: p. 4315-35.
161. Sagar, D., et al., *In vivo immunogenicity of Tax(11-19) epitope in HLA-A2/DTR transgenic mice: implication for dendritic cell-based anti-HTLV-1 vaccine.* Vaccine, 2014. **32**(26): p. 3274-84.
162. Kannagi, M., et al., *Maintenance of long remission in adult T-cell leukemia by Tax-targeted vaccine: A hope for disease-preventive therapy.* Cancer Sci, 2019. **110**(3): p. 849-857.
163. Khaddour, K., C.K. Hana, and P. Mewawalla, *Hematopoietic Stem Cell Transplantation*, in *StatPearls*. 2022: Treasure Island (FL).
164. Marino-Merlo, F., et al., *Antiretroviral Therapy in HTLV-1 Infection: An Updated Overview.* Pathogens, 2020. **9**(5).
165. Matsushita, S., et al., *Pharmacological inhibition of in vitro infectivity of human T lymphotropic virus type I.* J Clin Invest, 1987. **80**(2): p. 394-400.
166. Isono, T., K. Ogawa, and A. Seto, *Antiviral effect of zidovudine in the experimental model of adult T cell leukemia in rabbits.* Leuk Res, 1990. **14**(10): p. 841-7.
167. Macchi, B., et al., *AZT inhibits the transmission of human T cell leukaemia/lymphoma virus type I to adult peripheral blood mononuclear cells in vitro.* J Gen Virol, 1997. **78 (Pt 5)**: p. 1007-16.
168. Gout, O., et al., *The effect of zidovudine on chronic myelopathy associated with HTLV-1.* J Neurol, 1991. **238**(2): p. 108-9.

169. Afonso, P.V., et al., *Highly active antiretroviral treatment against STLV-1 infection combining reverse transcriptase and HDAC inhibitors.* Blood, 2010. **116**(19): p. 3802-8.
170. Hermine, O., et al., *Brief report: treatment of adult T-cell leukemia-lymphoma with zidovudine and interferon alfa.* N Engl J Med, 1995. **332**(26): p. 1749-51.
171. Ando, S., et al., *HTLV-1 Tax-Specific CTL Epitope-Pulsed Dendritic Cell Therapy Reduces Proviral Load in Infected Rats with Immune Tolerance against Tax.* J Immunol, 2017. **198**(3): p. 1210-1219.
172. Sasada, A., et al., *APOBEC3G targets human T-cell leukemia virus type 1.* Retrovirology, 2005. **2**: p. 32.
173. Izumi, T., K. Shirakawa, and A. Takaori-Kondo, *Cytidine deaminases as a weapon against retroviruses and a new target for antiviral therapy.* Mini Rev Med Chem, 2008. **8**(3): p. 231-8.
174. Ceccaldi, P.E., et al., *DC-SIGN facilitates fusion of dendritic cells with human T-cell leukemia virus type 1-infected cells.* J Virol, 2006. **80**(10): p. 4771-80.
175. Yao, J., et al., *Induction of APOBEC3B cytidine deaminase in HTLV-1-infected humanized mice.* Exp Ther Med, 2019. **17**(5): p. 3701-3708.
176. Young, L.S. and P.G. Murray, *Epstein-Barr virus and oncogenesis: from latent genes to tumours.* Oncogene, 2003. **22**(33): p. 5108-21.
177. Pagano, J.S., *Epstein-Barr virus: the first human tumor virus and its role in cancer.* Proc Assoc Am Physicians, 1999. **111**(6): p. 573-80.
178. Roberts, M.L., A.T. Luxembourg, and N.R. Cooper, *Epstein-Barr virus binding to CD21, the virus receptor, activates resting B cells via an intracellular pathway that is linked to B cell infection.* J Gen Virol, 1996. **77 (Pt 12)**: p. 3077-85.
179. Munz, C., *Dendritic cells during Epstein Barr virus infection.* Front Microbiol, 2014. **5**: p. 308.
180. Lotz, M., et al., *Regulation of Epstein-Barr virus infection by recombinant interferons. Selected sensitivity to interferon-gamma.* Eur J Immunol, 1985. **15**(5): p. 520-5.
181. Lim, W.H., et al., *Human plasmacytoid dendritic cells regulate immune responses to Epstein-Barr virus (EBV) infection and delay EBV-related mortality in humanized NOD-SCID mice.* Blood, 2007. **109**(3): p. 1043-50.
182. Ferlazzo, G., et al., *Distinct roles of IL-12 and IL-15 in human natural killer cell activation by dendritic cells from secondary lymphoid organs.* Proc Natl Acad Sci U S A, 2004. **101**(47): p. 16606-11.
183. Strowig, T., et al., *Tonsilar NK cells restrict B cell transformation by the Epstein-Barr virus via IFN-gamma.* PLoS Pathog, 2008. **4**(2): p. e27.
184. Pappworth, I.Y., E.C. Wang, and M. Rowe, *The switch from latent to productive infection in epstein-barr virus-infected B cells is associated with sensitization to NK cell killing.* J Virol, 2007. **81**(2): p. 474-82.
185. Bickham, K., et al., *Dendritic cells initiate immune control of epstein-barr virus transformation of B lymphocytes in vitro.* J Exp Med, 2003. **198**(11): p. 1653-63.
186. Shih, C., et al., *Hepatitis B Virus.* Trends Microbiol, 2018. **26**(4): p. 386-387.
187. Nassal, M., *HBV cccDNA: viral persistence reservoir and key obstacle for a cure of chronic hepatitis B.* Gut, 2015. **64**(12): p. 1972-84.
188. Tsuei, D.J., et al., *Male germ cell-specific RNA binding protein RBMY: a new oncogene explaining male predominance in liver cancer.* PLoS One, 2011. **6**(11): p. e26948.
189. Dane, D.S., C.H. Cameron, and M. Briggs, *Virus-like particles in serum of patients with Australia-antigen-associated hepatitis.* Lancet, 1970. **1**(7649): p. 695-8.
190. Yamada, G., et al., *Electron and immunoelectron microscopic study of Dane particle formation in chronic hepatitis B virus infection.* Gastroenterology, 1982. **83**(2): p. 348-56.

191. Venkatakrishnan, B. and A. Zlotnick, *The Structural Biology of Hepatitis B Virus: Form and Function.* Annu Rev Virol, 2016. **3**(1): p. 429-451.
192. Torresi, J., et al., *HBV-related hepatocarcinogenesis: the role of signalling pathways and innovative ex vivo research models.* BMC Cancer, 2019. **19**(1): p. 707.
193. Saxena, N.K., et al., *Concomitant activation of the JAK/STAT, PI3K/AKT, and ERK signaling is involved in leptin-mediated promotion of invasion and migration of hepatocellular carcinoma cells.* Cancer Res, 2007. **67**(6): p. 2497-507.
194. Qu, C., et al., *Detection of early-stage hepatocellular carcinoma in asymptomatic HBsAg-seropositive individuals by liquid biopsy.* Proc Natl Acad Sci U S A, 2019. **116**(13): p. 6308-6312.
195. Shen, Q., et al., *Serum DKK1 as a protein biomarker for the diagnosis of hepatocellular carcinoma: a large-scale, multicentre study.* Lancet Oncol, 2012. **13**(8): p. 817-26.
196. Wilhelm, S.M., et al., *Preclinical overview of sorafenib, a multikinase inhibitor that targets both Raf and VEGF and PDGF receptor tyrosine kinase signaling.* Mol Cancer Ther, 2008. **7**(10): p. 3129-40.
197. Patel, E.U., et al., *Prevalence of Hepatitis B and Hepatitis D Virus Infections in the United States, 2011-2016.* Clin Infect Dis, 2019. **69**(4): p. 709-712.
198. Taylor, J.M., *Infection by Hepatitis Delta Virus.* Viruses, 2020. **12**(6).
199. Chen, P.J., et al., *Structure and replication of the genome of the hepatitis delta virus.* Proc Natl Acad Sci U S A, 1986. **83**(22): p. 8774-8.
200. Yao, L., et al., *OGDHL ameliorates cognitive impairment and Alzheimer's disease-like pathology via activating Wnt/beta-catenin signaling in Alzheimer's disease mice.* Behav Brain Res, 2022. **418**: p. 113673.
201. Riccitelli, N. and A. Luptak, *HDV family of self-cleaving ribozymes.* Prog Mol Biol Transl Sci, 2013. **120**: p. 123-71.
202. Zheng, L., et al., *Hatchet ribozyme structure and implications for cleavage mechanism.* Proc Natl Acad Sci U S A, 2019. **116**(22): p. 10783-10791.
203. McCormick, F., *Cancer gene therapy: fringe or cutting edge?* Nat Rev Cancer, 2001. **1**(2): p. 130-41.
204. Lozach, P.Y., et al., *DC-SIGN and L-SIGN are high affinity binding receptors for hepatitis C virus glycoprotein E2.* J Biol Chem, 2003. **278**(22): p. 20358-66.
205. Sagan, S.M. and P. Sarnow, *Plasmacytoid dendritic cells as guardians in hepatitis C virus-infected liver.* Proc Natl Acad Sci U S A, 2010. **107**(17): p. 7625-6.
206. Wang, R.C. and B. Levine, *Autophagy in cellular growth control.* FEBS Lett, 2010. **584**(7): p. 1417-26.
207. Simons, M. and G. Raposo, *Exosomes--vesicular carriers for intercellular communication.* Curr Opin Cell Biol, 2009. **21**(4): p. 575-81.
208. Moriya, O., et al., *Induction of hepatitis C virus-specific cytotoxic T lymphocytes in mice by immunization with dendritic cells treated with an anthrax toxin fusion protein.* Vaccine, 2001. **20**(5-6): p. 789-96.
209. Matsui, M., et al., *Induction of hepatitis C virus-specific cytotoxic T lymphocytes in mice by immunization with dendritic cells transduced with replication-defective recombinant adenovirus.* Vaccine, 2002. **21**(3-4): p. 211-20.
210. Zabaleta, A., et al., *Vaccination against hepatitis C virus with dendritic cells transduced with an adenovirus encoding NS3 protein.* Mol Ther, 2008. **16**(1): p. 210-7.
211. Jirmo, A.C., et al., *Monocytes transduced with lentiviral vectors expressing hepatitis C virus non-structural proteins and differentiated into dendritic cells stimulate multi-antigenic CD8(+) T cell responses.* Vaccine, 2010. **28**(4): p. 922-33.

212. Gehring, S., et al., *Generation of immune responses against hepatitis C virus by dendritic cells containing NS5 protein-coated microparticles.* Clin Vaccine Immunol, 2009. **16**(2): p. 163-71.
213. Wintermeyer, P., et al., *Generation of cellular immune responses to HCV NS5 protein through in vivo activation of dendritic cells.* J Viral Hepat, 2010. **17**(10): p. 705-13.
214. Barth, H., et al., *Uptake and presentation of hepatitis C virus-like particles by human dendritic cells.* Blood, 2005. **105**(9): p. 3605-14.
215. Zhou, Y., et al., *Dendritic cell-based immunity and vaccination against hepatitis C virus infection.* Immunology, 2012. **136**(4): p. 385-96.
216. Pantel, A., et al., *A new synthetic TLR4 agonist, GLA, allows dendritic cells targeted with antigen to elicit Th1 T-cell immunity in vivo.* Eur J Immunol, 2012. **42**(1): p. 101-9.
217. Bode, C., et al., *CpG DNA as a vaccine adjuvant.* Expert Rev Vaccines, 2011. **10**(4): p. 499-511.
218. Song, X.T., et al., *A20 is an antigen presentation attenuator, and its inhibition overcomes regulatory T cell-mediated suppression.* Nat Med, 2008. **14**(3): p. 258-65.
219. Van Renne, N., et al., *miR-135a-5p-mediated downregulation of protein tyrosine phosphatase receptor delta is a candidate driver of HCV-associated hepatocarcinogenesis.* Gut, 2018. **67**(5): p. 953-962.
220. Kawamura, H., et al., *HCV core expression in hepatocytes protects against autoimmune liver injury and promotes liver regeneration in mice.* Hepatology, 2006. **44**(4): p. 936-44.
221. Pynnonen, M.A., et al., *Clinical Practice Guideline: Evaluation of the Neck Mass in Adults.* Otolaryngol Head Neck Surg, 2017. **157**(2_suppl): p. S1-S30.
222. Barros, M.R., Jr., et al., *Activities of stromal and immune cells in HPV-related cancers.* J Exp Clin Cancer Res, 2018. **37**(1): p. 137.
223. Yang, W., et al., *Increased expression of programmed death (PD)-1 and its ligand PD-L1 correlates with impaired cell-mediated immunity in high-risk human papillomavirus-related cervical intraepithelial neoplasia.* Immunology, 2013. **139**(4): p. 513-22.
224. Bashaw, A.A., et al., *Modulation of antigen presenting cell functions during chronic HPV infection.* Papillomavirus Res, 2017. **4**: p. 58-65.
225. Pahne-Zeppenfeld, J., et al., *Cervical cancer cell-derived interleukin-6 impairs CCR7-dependent migration of MMP-9-expressing dendritic cells.* Int J Cancer, 2014. **134**(9): p. 2061-73.
226. Johnson, D.E., et al., *Head and neck squamous cell carcinoma.* Nat Rev Dis Primers, 2020. **6**(1): p. 92.
227. Khallouf, H., A.K. Grabowska, and A.B. Riemer, *Therapeutic Vaccine Strategies against Human Papillomavirus.* Vaccines (Basel), 2014. **2**(2): p. 422-62.
228. Le Poole, I.C., et al., *Langerhans cells and dendritic cells are cytotoxic towards HPV16 E6 and E7 expressing target cells.* Cancer Immunol Immunother, 2008. **57**(6): p. 789-97.
229. Zhang, L., et al., *Photosensitizer-induced HPV16 E7 nanovaccines for cervical cancer immunotherapy.* Biomaterials, 2022. **282**: p. 121411.