Co-infection and cancer: Viral oncogenesis in humans result in liver, blood, and brain cancer by host-pathogen interactions

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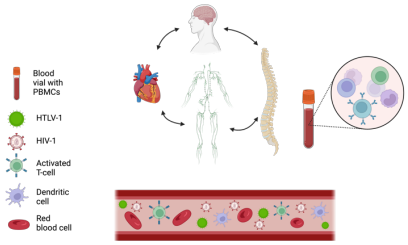
ABSTRACT

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.

SUMMARY

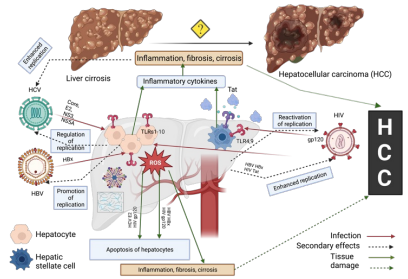
HIV-1 and HTLV Co-infection



- 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.
- HTLV-1 virions and proteins upregulate HIV-1 infection by activating CD4+ T cells
- PBMC culture with HIV-1 and HTLV-1 can activate each other
- **Tax protein of HTLV-1 stimulates HIV-1 replication by activation of HIV-1 LTR**

Cancer in HIV-1

Co-infection (HIV-1/HBV, HIV-1/HCV) increases rates of liver-related morbidity and mortality, including HCC

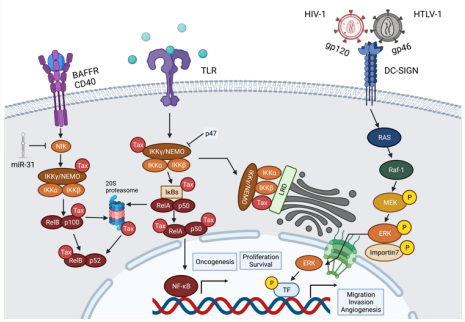


- HIV-1/HBV and HIV-1/HCV co-infected patients have decreased rates of liver-related viral clearance with HIV-1 infection; this accelerates fibrogenesis and increases the rates of liver-related morbidity and mortality, including HCC.
- High HBV and HCV viral loads are critical factors for the progression of liver cancer.
- Overexpression of viral oncoproteins induces oxidative stress and chromosomal instability and genomic damage, and promotes chronic inflammation, leading to liver damage and malignant transformation.

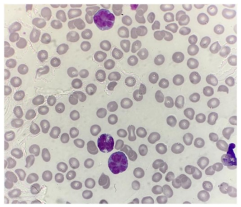
Adult T-cell leukemia/lymphoma (ATL)

- HTLV-1 infection induces ATL in about 2.5-5% of cases
- ATL is an aggressive malignancy with a short survival rate that develops more commonly in children infected with HTLV-1 compared to infected adults
- Most common symptoms of chronic ATL include a skin rash, swollen lymph nodes, hepatosplenomegaly, and lymphocytosis
- Presences of different mutations distinguishes aggressive subtypes from slowly progressing ones such as the IRF4 and MUM1 gene mutation seen in highly aggressive subtypes
- HTLV-1 Tax and HBZ are two key proteins involved in ATL oncogenesis

Peripheral T-cell Malignancy caused by HTLV-1



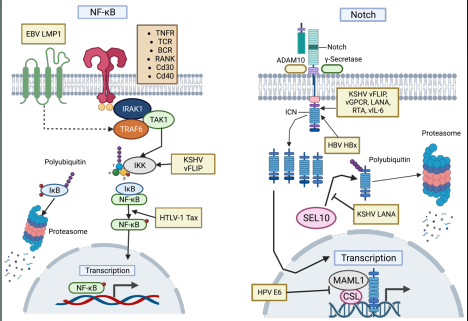
ATL is an aggressive T-cell malignancy caused by human T-cell leukemia virus type 1 (HTLV-1)



- ATL is characterized by abnormal lymphocytes, called *flower cells*, which have been cleaved and convoluted nuclei.
  - T-cell markers
  - HTLV-1 Abs in the serum
  - Monoclonal integration of HTLV-1 provirus in affected cells
- The presence of circulating "flower cells" and a low prevalence of antibody to Tax regulatory protein of HTLV-1 are characteristics of ATL.

T-J John, I Abdullah, K John. *Flower cells of HTLV-1 induced ATL. QJM.* Stellenbosch, Cape Town https://doi.org/10.1093/qjmed/hcy244. **04 Oct 2019**

Viral Oncogenesis



Viral infection is a major contributor to the global cancer burden. Oncogenic viruses promote tumorigenesis by shared host cell targets and pathways. Above are the molecular mechanisms of viral oncogenesis in humans. There is viral manipulation of host cellular signaling, DNA damage responses, immunity and microRNA targets that promote the initiation and development of cancer.

HTLV/EBV Coinfection

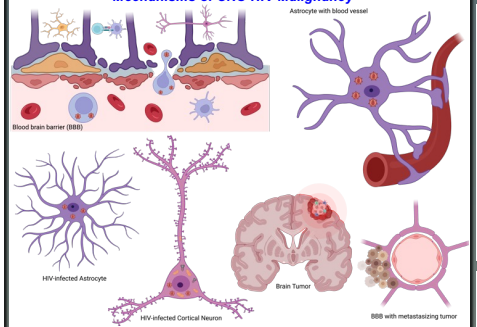
- HTLV-1 induces T cell dysfunction and B-cell proliferation.
- EBV-positive diffuse large B-cell lymphoma (EBV-DLBCL) not otherwise specified (NOS) is a classification of lymphoid neoplasms and an aggressive B-cell lymphoma associated with chronic EBV infection, and poor prognosis with standard chemotherapeutic approaches.
- The combination of EBV and HTLV-1 coinfection and immune-senescence may be transmitted by saliva, especially in PLWH
  - HTLV-1 can potentially activate an EBV promoter
  - EBV DNA, proviral DNA for HTLV-1, and Tax mRNA detected in two B-cell lines (Raji – EBV, Jurkat – HTLV-1) from peripheral blood of ATL patients
  - EBV and HTLV-1 double transfectants displayed enhanced expression of adhesion molecules and high levels of IL-4
  - EBV infection is often observed in the clinical course of ATL
- Oncovirus infection (HTLV-1, EBV) triggers EZH1/2 perturbation and H3K27me3 deposition; H3K27me3 reprogramming is a hallmark of cancer
- Structures of EZH1/2 dual inhibitors (OR-S1, (R)-OR-S2, and DS-3201, Valemotostat) effectively diminish H3K27me3 and induce gene reactivation
- **ATL-related immunodeficiency might induce EBV-associated DLBCL and associated infection complications**

HIV/EBV Coinfection

- Most HIV+ individuals also harbor EBV and HIV that augments EBV-associated malignancies and increasing in PLWH.
- EBV-related B-cell lymphomas occur frequently in AIDS patients.
- EBV infection is associated with PCNSL which occurs at a higher rate in immunocompromised individuals which validates that immune system plays a pivotal role in inhibiting EBV activities.
- Primarily, EBV latently infects B cells and nasopharyngeal epithelial cells and could interact with follicular dendritic cells (FDCs) in the germinal center (GC).
  - Transmitted by saliva, especially in PLWH
    - More frequent EBV detection in the saliva of an HIV-1-coinfected person
    - Major cause of cancer in PLWH
  - May also be shed in semen and vaginal secretions
  - Mechanisms of transactivation of an HIV LTR construct by an EBV product
  - EBV protein does transactivate the HIV LTR and appears to transactivate its own promoter (BMLF-1) by a post-transcriptional mechanism.
- EBV can also infect neurons directly or indirectly through B cell-mediated neuroinflammation and demyelination.
- **It remains to be seen if CD20, CD30, EBER interact with gp120, Nef, p17, Tat, or RT**

Brain cancer is highly prevalent in PLWH

Mechanisms of CNS-HIV Malignancy



Glioblastoma Multiforme (GBM)

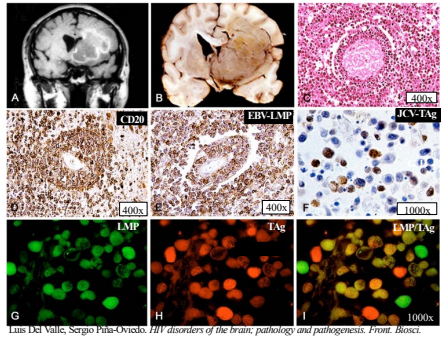
- GBM tumors can occur nearly three years after HIV-1 infection.
- HIV-1 infects several brain cell types which affect astrocytes that serve as a potential reservoir for productive infection, viral persistence, and latency.
- Astrocyte elevated gene-1 (AEG-1) implicated in malignant glioma progression and invasion
- AEG-1 enhances proliferation, angiogenesis, chemoresistance, and metastasis of malignant class
- Targeting AEG-1 could slow down progression of glioma
- **Hallmarks of malignant gliomas: tumor proliferation, invasion, angiogenesis, metastasis, and chemoresistance**
- Gliomas cells can link with HIV-1 envelope protein gp120 (increase glycolysis and Warburg effect)
- Both Tat and gp120 induce epithelial-mesenchymal-transition (EMT) and cell migration via the TGF-β and MAPK signaling pathways
- Accessory protein negative factor (Nef) inhibits the apoptotic function of p53 which affects its half-life and DNA binding activity and transcriptional activation
- **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 dendritic cells**

PCNSL

- Primary Central Nervous System Lymphoma (PCNSL) is the second most common neoplasm in HIV-1 infected individuals, and the first intracranial tumor, representing approximately 20% of all lymphomas in patients with AIDS. PCNSL is 3600-fold greater in AIDS patients than in the general populations
- PCNSL in patients living with HIV (PLWH) is a distinct entity and considered as an AIDS defining condition.
- Prognosis of HIV-related PCNSL is poor, with median survival varying from 2 to 4 months, but patients with chemotherapy do better (median survival 1.5 years)

Histopathological Features of Primary CNS Lymphomas. MRI of the brain in the case of PCNSL reveals a large necrotic mass involving the right basal ganglia and producing significant brain edema.

Brain demonstrates a large infiltrating mass that affects the basal ganglia, including the caudate nucleus, the putamen and globus pallidus. The tumor is friable, granular and exhibits areas of necrosis and focal hemorrhage.



Luis Del Valle, Sergio Piña-Oviedo. *HIV disorders of the brain; pathology and pathogenesis. Front. Biosci. (Landmark Ed)*, Temple University, Philadelphia https://doi.org/10.2741/1830. **1 Jan 2006**

EBV and JCV involves the expression of viral proteins, LMP and T-Antigen, which can bind, sequester and inactivate tumor suppressors p53 and pRb, leading to dysregulation of the cell cycle and uncontrolled proliferation.

CONCLUSIONS

- **Viral-induced oncogenesis contributes to a significant proportion of cancer cases and can be caused by viruses in several different families.**
- **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, cervical adenoma, glioblastoma/astrocytoma, and primary central nervous system lymphoma – diffuse large B cell lymphoma.**
- **Among the oncogenic viruses, DCs are important cells that intercept the virus early in infection.**

FUTURE DIRECTIONS:

- **DCs provide a promising focus for research in retroviral infection and other oncogenic viruses**
- **Target AEG-1 to slow down progression and invasion of gliomas**
- **Use structural vaccinology (SV) to design epitope-based vaccines against infectious diseases and cancer**
- **Engineering immunotherapy to target viral oncology pathways by molecular circuit reprogramming (CAR transduction, synNotch-CAR T circuits) and avoiding immunotherapy resistance**
- **Prime CNS-specific antigen myelin oligodendrocyte glycoprotein (MOG) to enable tumor cell killing by targeting antigens that are homogenous. This overcomes specificity, heterogeneity, and persistence in GBM.**
- **Target retroviral intasomes (HTLV-1, HIV-1) with allosteric inhibitors ("ALLINIs") of particle assembly during replication.**

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