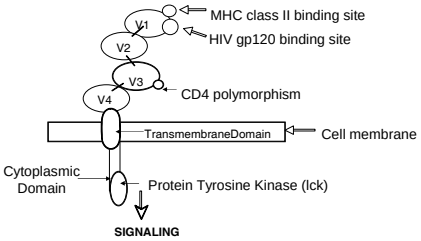
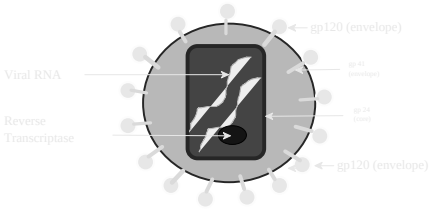
Viral Infections of the Immune System

- **HIV- infects CD4+ T cells and macrophages and enters cells via the CD4 molecule in concert with the chemokine receptors CCR5 and/or CXCR4, causes AIDS**
- **HTLV - infects CD4+ T cells, the cellular receptors are unknown, causes adult T cell leukemia**
- **EBV - infects mature B cells via the CR2 receptor, causes infectious mononucleosis, B cell lymphomas and nasopharyngeal carcinoma.**

The CD4 Receptor: Structure-Function



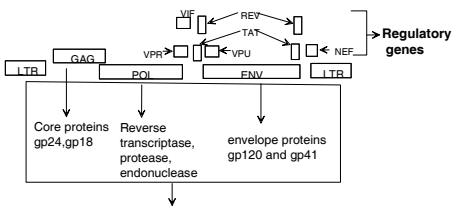
HIV Particle



Evidence that the CD4 molecule is the HIV Receptor

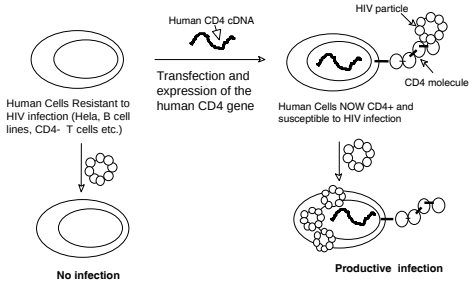
- **HIV preferentially infects CD4 cells.**
- **The HIV envelope glycoprotein gp120 binds with high affinity to the CD4 molecule.**
- **Antibodies to CD4 inhibit binding of HIV to cells and prevents infection.**
- **Transfection and expression of CD4 genes in cells renders them infectible by HIV.**
- **Recombinant soluble CD4 molecules inhibit HIV infection.**

Genomic Structure and Function of HIV-1 Genes



Long Terminal Repeats (LTR's) encode
NRE (negative response element)
TAR (transactivation response element)
NFκB (element responsive to T cell activation and lymphokines)

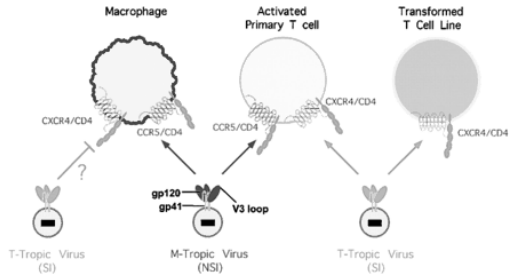
Expression of CD4 Genes in CD4- Cells Renders Cells Susceptible to HIV Infection



Evidence that Molecules other than CD4 are Important in Viral Entry

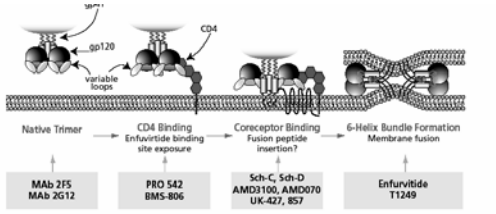
- Expression of human CD4 in murine cells permits HIV binding but not fusion, viral entry or HIV infection.
- Some cell lines which do not express CD4 can be infected by HIV.
- Some antibodies to HIV facilitate rather than inhibit viral entry by mechanisms presumably involving the Fc receptor.
- Activated normal human T cells are much more susceptible to HIV entry and infection than are resting cells.

Chemokine receptors CCR5 and CXCR4 dictate HIV cellular tropism

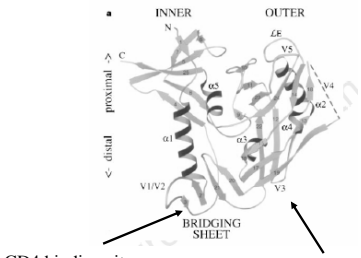


The HIV receptors: CD4 and Chemokine receptors CCR5 and CXCR4

- Binding of the gp120 envelope glycoprotein to CD4 induces conformational changes in the gp120 glycoprotein, and exposure and/or formation of a binding site for specific chemokine receptors.
- These chemokine receptors, mainly CCR5 and CXCR4, serve as obligate second receptors for viral entry. The gp120 third variable (V3) loop is the principal determinant of chemokine receptor specificity.
- The binding of chemokines to the CD4-gp120 complex enables the transmembrane coat protein of HIV, gp41, to participate directly in the fusion process and viral entry.
- Interestingly, the particular chemokine receptor used for vial entry, dictates cellular tropism. The CCR5 receptor favors entry into macrophages whereas the CXCR4 receptor favors T cell entry.



GP 120 structure



CD4 binding site

CCR5/CXCR4 binding site

HTLV-1 and Adult T Cell Leukemia

(a) common in Japan and endemic in southwestern parts of Japan, also common in the Caribbean

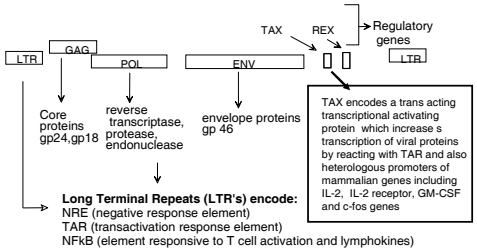
(b) associated with the retrovirus HTLV-1

(c) the leukemic cell is of mature CD3+, CD4+,CD8- helper phenotype

(d) clinically presents with hepatosplenomegaly, leukocytosis, lymphadenopathy and erythrodermic skin lesions. Some patients also have spastic paraparesis in which HTLV-1 lesions of white matter of the pyramidal tract are observed.

(e) in endemic areas 20% of healthy individuals have antibodies to HTLV-1, 90% of affected individuals have antibody

Structure and Function of HTLV-1 Genes



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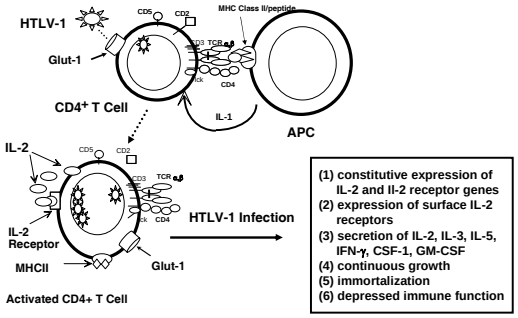
HTLV-1 Infection



(1) constitutive expression of IL-2 and Il-2 receptor genes
(2) expression of surface IL-2 receptors
(3) secretion of IL-2, IL-3, IL-5, IFN-γ, CSF-1, GM-CSF
(4) continuous growth
(5) immortalization
(6) depressed immune function

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The Ubiquitous Glucose Transporter GLUT-1 Is a Receptor for HTLV

Summary

The human T cell leukemia virus (HTLV) is associated with leukemia and neurological syndromes. The physiopathological effects of HTLV envelopes are unclear and the identity of the receptor, present on all vertebrate cell lines, has been elusive. We show that the receptor binding domains of both HTLV-1 and -2 envelope glycoproteins inhibit glucose transport by interacting with GLUT-1, the ubiquitous vertebrate glucose transporter. Receptor binding and HTLV envelope-driven infection are selectively inhibited when glucose transport or GLUT-1 expression are blocked by cytochalasin B or siRNAs, respectively. Furthermore, ectopic expression of GLUT-1, but not the related transporter GLUT-3, restores HTLV infection abrogated by either GLUT-1 siRNAs or interfering HTLV envelope glycoproteins. Therefore, GLUT-1 is a receptor for HTLV. Perturbations in glucose metabolism resulting from interactions of HTLV envelope glycoproteins with GLUT-1 are likely to contribute to HTLV-associated disorders.

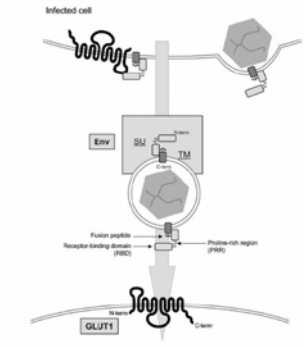
The Epstein-Barr Virus (EBV): Definitions and Clinical Syndromes

(1) Epstein-Barr virus (EBV) is a B lymphotropic human herpes virus which is worldwide in distribution. Primary infection with EBV which occurs during childhood is usually subclinical. Between 25-70 % of adolescents and usually subclinical. Between 25-70 % of adolescents and adults who undergo a primary EBV infection develop the clinical syndrome of infectious mononucleosis.

(2) Infectious mononucleosis is defined by the clinical triad of fever, lymphadenopathy, and pharyngitis combined with the transient appearance of heterophil antibodies and an atypical lymphocytosis.

(3) EBV is also associated with nasopharyngeal carcinoma, certain B cell lymphomas and immunodeficiency syndromes..

HTLV-1 Cell- Cell transmission



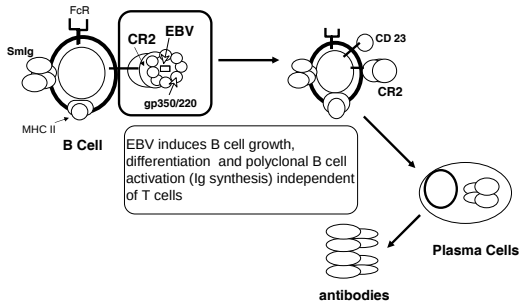
EBV Interaction with the CR2 B Cell Receptor Results in Polyclonal B Cell Activation and Differentiation

(a) The first phase of infection is binding of the EBV gp350/220 surface glycoproteins with its receptor on the B cell membrane, a 140-kd glycoprotein,designated CR2 or CD21.

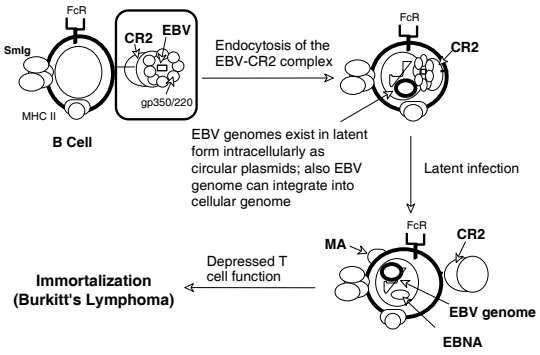
(b) The CR2 molecule normally functions as a receptor for the complement component C3d and although expressed predominately on B cells it is also expressed on some epithelial cells. The interaction of CR2 with its normal ligand, C3d, provides a signal to B cells for growth and differentiation (Ig synthesis)

(c) Binding of EBV to CR2 in the absence of other cells results in B cell activation (expression of CD23 and induction of Ig synthesis) and B cell proliferation. Thus, EBV is a potent T-independent mitogen and polyclonal activator of B cells.

EBV Interaction with the CR2/CD21 B Cell Receptor Results in Polyclonal B Cell Activation and Differentiation



EBV Latency, Immortalization and the Role of T Cells



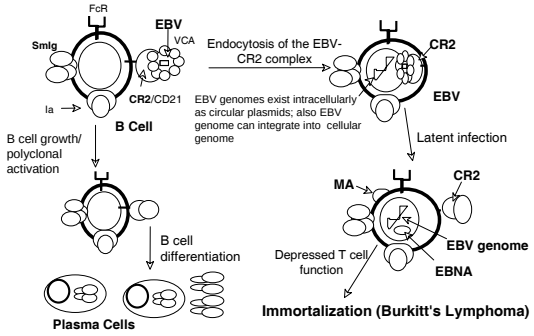
EBV Infection Results in Immortalization of B Cells and the Virus Exists in Latent Form in the Cell

(A) Following binding to the CR2 receptor, the virus enters the cell by receptor mediated endocytosis. After entry EBV genes encoding EB Nuclear Antigens (EBNA's) and latent membrane proteins (LMP's) are transcribed. These proteins as well as other gene products are essential for the virus to induce immortalization of B cells. Interestingly, LMP's bind to signaling molecules that are normally associated with CD40 and lead to the inhibition of apoptosis. This immortalization process is the principal biologic activity of EBV that underlies its role in the pathogenesis of lymphoproliferative disease.

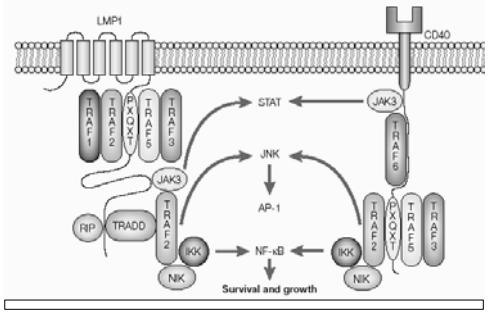
(B) Immortalization can be abrogated by T cells. Congenital, acquired or iatrogenically induced T cell deficiency can lead to outgrowth of EBV immortalized B cell tumors.

(C) EBV exists intracellularly as multiple copies of double stranded circular plasmids which replicate in early S phase using cellular DNA polymerases. In addition, the EBV genome can also integrate into cellular DNA. As circular plasmids or integrated DNA the virus enters a latent phase which is the hallmark of the EBV-cell relationship. T cell deficiency can induce a switch from latency to active replication.

Biology of EBV Infection of B cells



LMP's bind to signaling molecules that are normally associated with CD40 and lead to the inhibition of apoptosis



Diseases Associated with the Epstein-Barr Virus (EBV)

(1) Infectious Mononucleosis

(2) Burkitt's Lymphoma

(3) Nasopharyngeal Carcinoma

(4) x-linked lymphoproliferative syndrome

(5) Lymphoma in immunosuppressed host

The Clinical Syndrome of Infectious Mononucleosis

(1) After an incubation period of 4-8 weeks, prodromal symptoms of malaise, anorexia and chills frequently precede the onset of pharyngitis, fever and lymphadenopathy by several days. Pharyngitis is the symptom which most frequently brings the patient to medical attention. Most patients complain of severe headache. Abdominal pain is rare in the absence of splenic rupture. The disease is self-limited in the vast majority of patients and resolves within weeks to months.

(2) Physical findings include: fever, exudative and petechial pharyngitis (90%), posterior and/or anterior adenopathy (90%), splenomegaly (50%), and macular erythematous rash (10%).

(3) Laboratory findings: heterophil antibody, atypical lymphocytes, polyclonal hypergammaglobulinemia, EBV-specific antibodies-IgM antibodies to the VCA are diagnostic of primary EBV infection. IgG antibodies to VCA is present in the majority of patients at presentation.

EBV-Specific Antibodies

(1) Antibodies to Viral Capsid Antigens (VCA)

IgM present at clinical presentation and persists for 1-2 months. IgG present at clinical presentation and persists lifelong-"standard EBV titre"

(2) Antibodies to Early antigens (EA)

Peaks at 3-4 weeks; presence correlates with more severe disease; present in high titre in African Burkitt's Lymphoma

(3) Antibodies to EB Nuclear Antigens (EBNA's)

present 3-6 weeks after onset; lasts lifelong

Immunologic Features of Infectious Mononucleosis

(1) B lymphocytes are infected

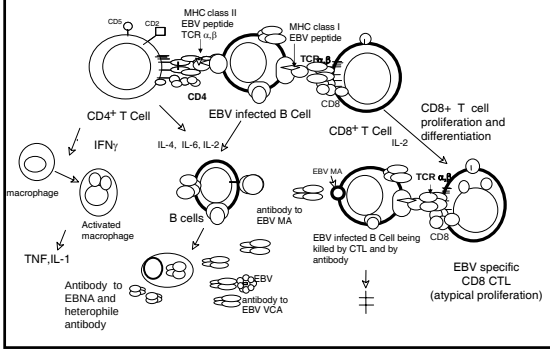
(2) B cells are polyclonally activated to secrete Ig, including the secretion of heterophile antibodies

(3) CD8+ cells proliferate as the atypical lymphocytes which function as killer cells of EBV infected B cells

(4) Because CD8+ cell proliferate the CD4/CD8 ratio is decreased

(5) The immune response to EBV includes the CD8+ killer cells and antibody production to the EBV antigens (VCA, MA and EBNA)

The Immune Response to EBV



Proliferation of CD8+ Killer T cells in EBV Infection