Lecture 22: Viruses that Infect Lymphocytes I: EBV and HTLV
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Note: I would suggest looking at the slides for this lecture. They contain a few facts which were not discussed in the lecture and are therefore not in this transcript.

This is the first of a series of two lectures about viruses that infect the immune system. The main point of this lecture is that many viruses that infect the immune system enter cells via surface molecules, and induce cellular factors that are sometimes critical to the function of immunocompetent cells. Three viruses will be discussed: HIV, HTLV-1, and EBV (HIV will be discussed again in more detail in the second lecture).

HIV

HIV is a retrovirus, and as such, it contains RNA as the genetic material, reverse transcriptase, and key proteins including the envelope (env) protein, which in the case of HIV consists of gp120 and gp41 (the transmembrane portion of env that enables the viral particle to bind and fuse with the cell membrane and enter the cell). All retroviruses have a common overall genetic structure, including a promoter-like region called LTR which allows for the transcription of other viral genes.
The main cellular component recognized by HIV is CD4, an immunoglobulin-like non-polymorphic receptor that binds MHCII (on B-cells and macrophages) through its most exterior V1 domain, and transmits signals that result in T-cell activation. T-cells then induce antibody secretion through the activation of B-cells, or a delayed type hypersensitivity response through macrophage activation. HIV interacts with CD4 through gp120.
The history of AIDS discovery is relevant: the first observations were made in the late 70s when young healthy men presented with marked immunodeficiency syndromes which made them susceptible to rare infections such as pneumocystis, as well as to tumors like Kaposi's sarcoma which had previously been seen only in older men of Jewish-Mediterranean origin. This occurred at a time when it was possible to enumerate the lymphocyte subsets, and it was found that these patients had a low CD4 T-cell count. It was later found that viral particles can bind to T-cells, and that binding can be inhibited by antibodies to CD4. The key experiment identifying CD4 as the principal cellular factor was done twenty years ago by Paul Madden, a student at P&S, who transfected a virus-resistant cell line (HeLa, an epithelial tumor line) with human CD4 cDNA and showed that the cells became susceptible to infection, while transfection with CD8 and other relevant genes had no effect. Other studies later showed that recombinant soluble CD4 could inhibit infection, a fact that biotech companies are now trying to exploit to treat AIDS.
It is worthy to note that when the CD4 transfection experiment was carried out on mouse cell lines, HIV could bind the cells but could not enter, suggesting that other factors were required for fusion and viral entry. CCR5 and CXCR4, which are chemokine receptors, were later identified as these factors. The binding of gp120 to CD4 induces conformational changes in gp120, allowing it to bind to other receptors including CCR5

and CXCR4. The type of chemokine receptors that gp120 engages can control in part the tropism, or preference of HIV for various cell types. For example, primary binding via CCR5 and CD4 enables the virus to enter macrophages as well as T-cells (M-tropism), while binding via CXCR4 and CD4 allows the virus to enter T-cells only (T-tropism).

HTLV-1

Human T-cell leukemia virus was discovered prior to the AIDS epidemic and was the first human retrovirus to be associated with a disease. The virus is of particular concern in Asia (endemic in southwestern Japan) but it also appears in other regions including the Carribean. In endemic areas, approximately 25% of healthy individuals have evidence of the virus, but most infected individuals contain it without serious problems. Similarly to HIV, HTLV enters and binds preferentially to CD4 cells, but instead of killing the cells, it causes their immortalization so that the primary clinical consequence of HTLV infection is T-cell leukemia. Patients present with splenomegaly, high white cell count, lymphadenopathy, and erythrodermic skin lesions, which are a result of the migration of T-cell tumors to the skin as part of the normal scanning function of T-cells. These patients can therefore present to the dermatologist with a marked rash. T-cell tumors can also migrate to the spinal pyramidal tract where they cause neurological problems.
The structure of the virus is similar to that of HIV. It has different env proteins, and the cellular receptors present on CD4 cells that allow the virus to bind and enter are still unknown. The important fact is that the virus has transcription activating factors which act not only on promoters of viral genes, but also on the promoters for endogenous T-cell genes, including IL2, a T-cell growth factor, IL2 receptor (CD25), as well as variety of other chemokine genes. The virus therefore enters CD4 cells, and the transcriptional elements that permit viral replication and function also affect T-cell function by inducing molecules critical for growth and activity, resulting in clonal outgrowth and leukemia, as well as immunodeficiency as a result of the uneven T-cell growth. Other molecules that are upregulated by the viral transcriptional elements include gamma-interferon, and CSF.

EBV

Epstein-Barr virus is a double-stranded DNA virus of the herpesvirus family. Greater than 90% of individuals have been exposed to it, but most never know they've had it, while others get a chronic illness and are diagnosed with mononucleosis. A small number of infected individuals have serious problems that include the development of nasopharyngeal carcinoma or B-cell lymphoma and immunodeficiency syndromes, which has become a much more common type of complication in the AIDS era.
EBV infects B-cells, not T-cells. Infectious mononucleosis is defined by fever, lymphadenopathy, and pharyngitis. These three symptoms are characteristic of many other viral infections, but they are supplemented by the transient appearance of two immunological features: the development of unusual antibodies to heterologous red cells, and a leukocytosis in blood smears exhibiting blast-like cells which makes it difficult to distinguish from leukemia in pediatric and adolescent patients.
The receptor on B-cells involved in EBV recognition and entry is CR2 (CD21), which normally functions as C3d complement receptor and triggers B-cell growth and

differentiation, as well as immunoglobulin synthesis on binding to C3d. CR2 is also expressed on epithelial cells in parts of the body including the nasopharyngeal tract. The binding of EBV to CR2 can occur without any infection, inducing these cells to proliferate and actively secrete immunoglobulin; EBV is therefore the best known mitogen for B-cells.

The first step of EBV infection involves CR2 receptor binding to the gp350/gp220 heterodimer on the EBV envelope, and receptor-mediated endocytosis. EBV then integrates its DNA into the genome, and induces B-cell growth, differentiation, and polyclonal B-cell activation independent of T-cells. If present, T-cell actually control B-cell immortalization by killing EBV-infected proliferating cell, so EBV-induced leukemia is only known to occur in immunodeficient patients, such as AIDS patients or patients under immunosuppressive therapy. The good news, however, is that if normal T-cells are reintroduced (eg by stopping immunosuppression), the B-cell tumor disappears. Another disease that is due to EBV infection is Burkitt's lymphoma, which is common among young people in some parts of Africa. The mechanism of immunosuppression in that case is unclear, but it is presumed to be due to malnutrition or infection by a variety of parasites.

Tests for EBV infection / mononucleosis include heterophile antibody testing, because patients all develop hypergammaglobulemia, as well as antibody testing for various components of EBV (eg viral capsid), and to cellular components modified by the virus. The previously-mentioned leukemia-like presentation in blood smears of mononucleosis patients is of normal CD8 lymphocytes that are proliferating in a massive defense against viral infection, leading to resolution within a couple of months.