Lecture 15. Viruses That Infect Lymphocytes: EBV & HIV

LEARNING OBJECTIVES:

1. Understand the different clinical syndromes that result from infection by these viruses, the routes the immune system uses to control the infection and the immune responses that are diagnostically important.

2. Coordinate knowledge about the viral genome from your lectures on virology with the immune response to the virus

3. Understand viral tropism in terms of the properties of the virus to bind to specific cellular receptors and infect certain cells

4. Understand the different elements involved in the host-pathogen relationship and the factors and viral strategies that foster microbial persistence, avoid surveillance and engender viral co-evolution with the human host

5. Understand the detailed nature of the T cell response that controls infection with these viruses and the reasons it fails to do so completely

6. Appreciate what is meant by T cell immunodominant epitopes and what events at the level of MHC and TCR repertoire underlie successful recognition of a viral peptide

7. Understand the events that occur within the individual as the HIV-1 infection evolves, how the virus evades recognition of immunodominant epitopes and that the strains that are most pathogenic in terms of effect on CD4 T cells are usually not the sexually transmitted strain

8. Appreciate the elements of the “epitope war” that is played out during the clinical asymptomatic period of HIV-1 infection and what distinguishes rapidly progressing from slow progressing infection

9. See that the hierarchy of different infections that appear during the progression to AIDS reflect the different stages of progressive loss of immune funtion

10. Appreciate the problems in developing a vaccine for HIV-1

SUMMARY:

1. Host immune defense consistently fails to clear certain viral infections.

   Two contrasting viruses: EBV and HIV. Viruses use various mechanisms of avoiding immune surveillance. Only a relatively few virus peptides are recognized by the CD8 T cell clones: termed immunodominant epitopes.

2. EBV infection is normally controlled by a cytotoxic T cell response, which can be defective in certain clinical scenarios.

   Syndromes resulting from EBV infection depend on age at infection and ability of CD8 T cell immune response to control the virus. Atypical lymphocytes seen in EBV infection are activated, proliferating CD8 T cell clones responding to EBV peptides.
   Viruses often infect cells of the immune system through receptors that are immunologically

important. In the case of EBV it is CD21, in the case of HIV-1 it is a complex of CD4 and a chemokine receptor.

The EBV infection begins as a productive lytic infection, but the CD8 T cell response forces the virus to go “under cover” as a latent infection and express a different set of viral genes.

CTL responses are Class I-restricted and are mainly directed against a few immunodominant epitopes on peptides from EBV nuclear antigens of the EBNA- 3 family, and the latent membrane protein LMP 2.

An example of thwarting immunosurveillance is the EBNA1 molecule that contains a gly-ala repeat region that inhibits the ATP motor of the proteasome, impeding further insertion of EBNA1 into the proteasome, thus halting its degradation and preventing development of an immune response against this peptide.

T cells play a crucial role in enforcing the maintenance of latency and thwart proliferation of EBV infected B cells by killing these cells; failure of continued T cell suppression may lead to emergence of polyclonally proliferating B cells and subsequently a monoclonal immunoblastic B cell lymphoma. The *in vitro* model for this is the ability to derive B cell lymphoblastoid line from most people by culturing their lymphocytes in the presence of a T cell-inhibiting drug like cyclosporine. The lymphoblastoid line and the immunoblastic B cell lymphoma express all the latency genes and a distinctive set of genes that governs their behavior. Burkitt’s lymphoma results from a different pattern of EBV latency.

The HLA-A11 molecule usually presents peptides encoded by the EBNA3B gene. In parts of Asia the prevalence of the HLA-A11 allele is high and EBV strains in these regions have mutated an anchor residue to prevent presentation by HLA-A11.

3. HIV infection is typically asymptomatic or “flu-like” at first, followed by a variable period of sub-clinical viral replication and eventual symptomatic AIDS.

HIV-1 infects cells by binding to a membrane receptor complex consisting of CD4 and a chemokine receptor, the nature of the latter determines tropism of the virus for different populations of CD4
T cells and monocytes.

First (acute) phase: “Flu-like” infection by R5-tropic virus triggers CD8 T cell response that controls viral replication but does not eliminate latent infectious virus primarily located in monocytes and memory CD4 T cells. Antibodies to HIV-1 are formed but these neither clear the infection nor are protective.

Clinically symptomatic phase: 2-12 or more years. Ability of immune system to control viral proliferation depends on host’s HLA class I alleles, etc. and relies on a few CD8 T cell clones that recognize immunodominant epitopes. HIV-1 mutates because of the lack of proofreading by reverse transcriptase, and variants escape the CD8 T cell response. Other mutations in the viral envelope change to R4 tropism that favors infection and destruction of CD4 T cells.

Symptomatic phase: acquired immune deficiency (AIDS) appears upon depletion of critical CD4 T cell subsets.

Vaccination efforts have been unsuccessful to date, and the most sophisticated current recombinant vaccines do not appear to protect and might hasten progression to AIDS.