Body’s Defense against Infection

**IMMUNOLOGICAL MEMORY AND INFECTION:**

- **History of infection** – During primary adaptive immune response both T cells and Ab are generated that participate in protection & elimination of pathogen. Ab persists that prevents re-infection despite repeated exposures. Over time, circulating memory lymphocytes decline but upon second infection, these cells are rapidly mobilized and respond quickly to provide protection.

- **Effector and Memory lymphocytes:** Both effector B and T cells & memory B and T cells are produced during a primary immune response. Memory lymphocytes are maintained often for the lifetime of the individual and provide protection in case of re-exposure to the infectious agent.

- **Retention of Ag-specific Ab’s and T cells:** Vaccination against smallpox provides life-long protection mediated by both virus-specific Ab and T cells. Upon infection with smallpox (or reexposure to vaccine i.e. boost), circulating levels of Ag-specific Ab and T cells would increase.

- **Amount and affinity of Ab increases after each successful immunization with same Ag:** During the course of 3 immunizations with the same Ag, there is an overall increase in the amount of Ab as well as an increase in the overall affinity i.e. stronger binding to epitope. Why? Competition for binding to Ag drives selective activation of those B cells whose IgGs have the highest affinities for Ag. Following additional exposure to Ab, somatic hypermutation and isotype switching leads to affinity maturation.

- **Only memory B cells, not naïve B cells, participate in memory response.** In a primary immune response, a pathogen binding to Ag receptor of naïve B cell leads to signal to activate the cell to become an Ab-producing cell. In secondary response, IgG coating surface of pathogen delivers a negative signal via binding to FcγRIIB1 that prevents activation of the cell. In contrast, similar cross-linking of Ag receptor and FcγRIIB1 on a memory B cell activates the cell to become an Ab-producing plasma cell.

- **Influenza virus infection and generation of memory**

  Suppression of naïve B cell activation during secondary response to a pathogen good when dealing with invariant pathogen i.e. does not change antigen (measles virus). However, when confronting influenza (which is highly mutable) there are drawbacks. Every year, new flu strains emerge that escape the protective immunity of some segment of human population. In these variant strains, one or more of the epitopes targeted by the pre-existing Abs has been lost. During subsequent infections, the memory response limits Abs made to those new epitopes. With each passing year, person will be exposed to flu virus with fewer epitopes to which it can respond. This phenomenon is described as original antigenic sin.

**Kinetics of CTL antiviral response**
**Characteristic T cell response following viral infection.** CMV (cytomegalovirus) infecting elicits rapid expansion of virus-specific T cells that control/eliminate virus. Following clearance, numbers of virus-specific effector cells decline and remaining cells enter the memory pool.

**Two types of memory T cells: effector and central**

Two subsets of memory cells are generated during the course of infection. Effector memory cells reside within peripheral tissue, do not express CCR7, and rapidly respond upon re-encounter with specific Ag e.g. cytokine secretion and/or lytic activity. However functional response is realtively short lived. Central memory cells express CCR7 and reside within lymphatic tissue. These cells take longer to respond than Effector memory cells but generally are longer-lasting to help control response to re-infection.

**Maintenance of immunological memory is not dependent on Ag**

KEY POINT: Maintenance of memory lymphocytes (both T and B) does not require routine exposure to Ag. Most memory cells remain in a quiescent state with only small % undergoing turnover to maintain and renew the population. Specific cytokines/growth factors are required to maintain the memory pool. For T cells, IL-7 and IL-15 are needed to stimulate turnover. (see experiment in overheads proving this point)

**OTHER IMMUNE CELL TYPES/INTERACTIONS THAT FIGHT INFECTION**

**Gamma/Delta T cells**

-γ:δ T cells arise from same precursor cell as α:β T cells yet there is no positive/negative selection. In blood, <10% of circulating cells are γ:δ and these cells have limited TCR diversity. In general, γ:δ T cells respond to unique antigens – phosphoantigens – which are not peptides nor proteins but are intermediates and are synthesized by microbial pathogens.

- γ:δ T cells do not express CCR7 and do not percolate within the lymphatic system. However, γ:δ T cells express CCR5 and other inflammatory cytokine receptors that allow them to rapidly enter inflamed tissue early following infection. γ:δ contribute to defense via secretion of IFN-γ and TNF-α as well as secretion of granulysin.

- γ:δ T cells and host defense: γ:δ T cells aid in host defense by recognizing host response molecules e.g. MIC proteins expressed by infected cells. Through both unique γ:δ TCR as well as NKG2D, γ:δ T cells are activated to kill infected cells as well as to aid in repair.

**Natural Killer (NK) cells**

-NK cells express combinations of a variety of activating and inhibitory receptors that allow for distinguishing between healthy and infected cells. While NKG2D is expressed on every NK cell, NK cells will express different combinations of other receptors (>30 different kinds). NK cells are capable of rapidly infiltrating into infected tissue early following infection and aiding in defense through lytic activity as well as cytokine secretion.
**NK cells and detection of infection:** NK cells detect viral infection through combination of inhibitory and activating receptors. Healthy cells have normal levels of MHC class I and do not express MIC proteins, therefore NK cell receives inhibitory signals blocking killing. In contrast, viral infection increases MIC expression and can diminish MHC class I expression resulting in loss of inhibitory signal and killing through NKG2D positive signaling.

**NK cells and HLA monitoring:** NK cells aid in defense by monitoring overall levels MHC class I molecules HLA-A, -B, and –C yet is not specific for any HLA class I isotype or allotype. Monitoring is accomplished in indirect fashion through use of CD94:NKG2A (inhibitory receptor) that binds to non-polymorphic class I molecule HLA-E which has the same ubiquitous tissue distribution as HLA-A,-B, and –C but is restricted with regards to peptide binding. HLA-E only binds to peptides derived from leader sequences of HLA-A,-B, and –C heavy chains. Therefore, the amount of HLA-E on cell’s surface is a measure of the amount of HLA-A, -B, and –C made by the cell.

**NK cells and KIRs:** Killer-cell immunoglobulin-like receptors (KIRs) bind to the same face of MHC class I molecule as TCR – yet have a much smaller footprint. Polymorphisms at residues 77-83 in HLA class I a helix (particularly at position 80) determine whether a given HLA isoform can bind to a KIR. While all HLA-C allotypes are KIR ligands, only a minority of HLA-A and HLA-B allotypes are. Therefore, HLA-C are more important with regards to NK cell interactions, while HLA-A, and –B are more specialized in presenting Ag to T cells.

**Lipid antigen recognition by T cells**
Mycobacteria make unusual lipids & glycolipids not made by human cells. During immune response, these lipids serve as target Ag for effector CD4 and CD8 T cells bearing α:β TCR. The key is that Ag is presented by a group of β2-microglobulin-associated MHC class I-like glycoproteins – CD1a, CD1b, and CD1c. Expression of these molecules is restricted to DCs and activated macrophages which are the cellular targets for mycobacteria. Glycolipid Ag is then presented to T cells. T cell response results in effector T cells that secrete inflammatory cytokines that kill infected cells as well as long-lasting memory T cells.