Lecture 19
The body’s defense against infection

• T cell memory and antiviral responses
• Gamma/delta T cells
• NK cells
• Lipid Antigen Recognition by T cells
Influenza virus & immunological 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.
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.

T cells express surface markers that help distinguish between naïve, effector, and memory.

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<th></th>
<th>Naïve</th>
<th>Effector</th>
<th>Memory</th>
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<tbody>
<tr>
<td>CCR7</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
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<tr>
<td>L-selectin</td>
<td>+</td>
<td>-</td>
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<tr>
<td>CXCR3</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
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<tr>
<td>CCR5</td>
<td>-</td>
<td>+</td>
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CXCR3 & CCR5 are inflammatory chemokine receptors i.e. help direct effector T cells to sites of infection/inflammation.
Two types of memory 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 relatively 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.
Maintenance of T cell memory

Question: is Ag required for routine exposure and maintenance of T cells? NO – this is an important point that was first reported by Lau et al. (Nature, 1994)

**HOW IS MEMORY MAINTAINED?**

- life-long immunity
- presence of memory CTL’s (mCTLS’s) specific for virus

**IS PERSISTENT ANTIGEN STIMULATION REQUIRED?**

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**Expt. 1**

- Infect with virus (LCMV- attenuated form)

  - life-long immunity
  - presence of memory CTL’s (mCTLS’s) specific for virus

**Expt. 2**

- Infect with virus (LCMV-attenuated form)
- 4 weeks
- Isolate CD8+ T cells from spleen (will contain mCTL’s)
- Transfer into naïve mouse not infected/exposed to LCMV (virus)
- 1-2 years
- mCTL’s are still present as determined by in vitro anti-viral responses

**Are these cells functional in vivo?**

**Expt. 3**

- Infect with virus (LCMV)
- 4 weeks
- Transfer mCTL’s
- 1 year
- challenge with virulent strain of LCMV
- Survival accompanied by reduced viral titers within spleen
- Death accompanied by high viral titers within spleen
Bridging innate and adaptive immunity

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

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

Figure 10.30 The Immune System, 3ed. (© Garland Science 2009)
**γ:**δ T cells and host defense

γ:**δ 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.
NK cells express different receptor combinations

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 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 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 cells 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.