**T cell-mediated immunity**

Acquired immune response – DOES NOT occur at site of infection (innate immune response important), but in peripheral lymphoid tissue e.g. peyer’s patches, tonsils, spleen, and lymph nodes

Secondary (2’) lymphoid tissue – architecture of tissue facilitates cell/cell interaction and aids in developing an acquired immune response

KEY POINT:
Ag needs to get to 2’ LT – Ag is taken up by Antigen Presenting Cell (APC) -> migrates to 2’ LT -> presentation to T cells -> acquired immune response -> T cells/B cells migrate out of tissue to sites of infection and eliminate foreign pathogen

All found in periphery as well as in 2’ LN tissue – location, location, location
Key in enhancing immune response

*Figure 6-1 The Immune System, 2/e (© Garland Science 2005)*
<table>
<thead>
<tr>
<th>Type of pathogen presented</th>
<th>Extracellular bacteria</th>
<th>Extracellular bacteria, soluble antigens, virus particles</th>
<th>Viruses</th>
<th>Viruses</th>
<th>Viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td>MHC molecules loaded</td>
<td>MHC class II</td>
<td>MHC class II</td>
<td>MHC class I</td>
<td>MHC class I</td>
<td>MHC class I</td>
</tr>
<tr>
<td>Type of naive T cell activated</td>
<td>CD4 T cells</td>
<td>CD4 T cells</td>
<td>CD8 T cells</td>
<td>CD8 T cells</td>
<td>CD8 T cells</td>
</tr>
</tbody>
</table>

Figure 8.3 The Immune System, 3ed. (© Garland Science 2009)
Naïve T cells need to get to secondary lymphatic tissue – how do they accomplish this?

Naïve T cells can enter the LN by crossing High Endothelial Venules (HEV) - constantly circulating from -> LN -> blood

“Homing” of T cells to secondary lymphatic tissue is determined by chemokines and cell-adhesion molecules. CCR7 (chemokine receptor) expressed on naïve T cells binds CCL19 and CCL21 which are enriched in HEV. L-selectin is also expressed on naïve T cells and binds to CD34 and GlyCam 1 on HEV surface.

Key point: $1/10^4-10^6$ T cells able to generate cognate/adaptive immune response i.e. very rare event which means constant surveillance of lymphoid tissue is required.
Lymphocytes (naïve T and B) bind to HEV in LN via interaction of L-selectin + vascular addressins. Chemokine recognition activates the integrin LFA-1 to bind tightly to ICAM-1 on the endothelial cell. Tight binding allows the lymphocyte to undergo diapedesis and enter LN tissue.
Recirculating naïve T cells can enter a LN either from blood or moving from one LN to another via connecting lymphatics. Upon encounter with cognate antigen, pathogen-specific T cells (represented in blue & green) expand and leave as effector T cells i.e. activated and ready to contribute to host defense.
T cell interaction with APCs (dendritic cells) is mediated by adhesion molecules. Upon recognition of antigen – presented within the context of MHC – intracellular signaling through the TCR induces a conformational change in LFA-1 that cause tight binding to ICAMS on the APC.
T cell activation - requires 2 signals
Signal 1 - TCR:MHC+antigen
Signal 2 - CD28:B7

Both signals required for clonal expansion of naïve cell

Figure 6-9 The Immune System, 2/e © Garland Science 2005
What regulates T cell proliferation? REMEMBER – unrestricted proliferation/cytokine production ultimately detrimental to host by damaging tissue

What controls this process?

• CD28-related proteins – CTLA-4 (CD152) is increased on T cell following CD28 stimulation and binds B7 molecules ~ 20x’s more efficiently than CD28
• CTLA-4: B7 interaction results in decreased T cell proliferation, in part, through down-regulation of IL-2
**Antigen presenting cells - APC’s**

1) “Professional” APC - DC, macrophage, and B cell
   
   Capable of expressing both MHC class I and II -> present antigen to both CD8+ and CD4+ T cells, respectively

2) Almost all other nucleated cells express MHC class I
DC: T cell interaction

DC
• B one-marow derived and migrate to blood and tissue
• Immature DC’s – decreased MHC and no B7 antigen expression; these cells are not able to stimulate naïve T cells.

How do DC’s uptake foreign antigen/pathogen?
• Share many receptors with macrophages that enable them to recognize and ingest pathogens. DEC205 is such a receptor that allows for ingestion. Also, non-specific uptake via macropinocytosis
• Once ingest pathogen -> migrate to local lymph nodes and change into

mature DC’s i.e. modulate surface antigen expression:
Increased MHC I & II, increase DC-SIGN, and increase B7 expression
Also, DC’s secrete a unique chemokine called DC-CK -> attracts naïve T cells i.e. promotes interaction with T cell with correct TCR
Macrophages – phagocytosis of bacteria and subsequent breakdown in phagolysosome releases bacterial products e.g. LPS & peptides triggers expression of MHC class II and B7.
Adjuvant - use of bacterial products to enhance antigen presentation to T cell

**Figure 6-15 The Immune System, 2/e (© Garland Science 2005)**

KEY POINT: many tissue macrophages e.g. Kupffer cells (resident macrophage of liver) often remove dead/dying cells i.e. potent source of self-Ag’s. Dangerous due to potential to stimulate autoreactive T cells. Does not happen -> WHY, diminished ability to express MCH II
B CELLS
Up-take soluble proteins via surface Ig -> peptide:MHC II – very high level expression

NOTE: B7 expression is also increased and is required for T cell activation.
Region of contact & communication between the two cells is referred to as the immunological synapse. Within the synapse, specific peptide: MHC complexes on the APC and T cell cluster together with cell-adhesion molecules forming a tight seal around the area. The signal that Ag has bound to the TCR is transmitted to the interior of the T cell resulting in activation.

Area of contact between cells is divided into 2 regions: the central-supramolecular activation complex, (c-SMAC) and the peripheral-supramolecular activation complex (pSMAC). Each region is defined by specific signaling molecules involved in cell-cell interaction/communication.
T cell stimulation requires ~ 100 specific peptide:MHC Complexes to trigger a naïve T cells
-CD3 proteins contain ITAMS - immunoreceptor tyrosine-based activation motifs which are associated with protein tyrosine kinases
-- Cytoplasmic tails of both CD4 and CD8 are associated with a protein tyrosine kinase called Lck

TCR:MHC/Ag stimulation->
1) Activation of receptor-associated kinases (ex. Fyn) results in phosphorylation of CD3 γ, δ, and ε ITAMS
2) ZAP-70 (tyrosine kinase) binds to phosphorylated ITAMS of ζ chain HOWEVER it is not activated until the co-receptor binds to MHC molecule
3) This brings the kinase Lck into the complex resulting in phosphorylation of ZAP-70
4) ZAP-70-P ultimately leads to various changes in gene expression profiles within activated cells and this occurs via activation of various txn factors ex. NFAT, NFκB, and AP-1 all of which enhance T cell proliferation, differentiation, and cytokine production
Activated T cells secrete and respond to IL-2

IL-2 produced by T cells -> Proliferation

T cell + Ag/MHC/co-stim -> G1 phase of cell cycle, increase alpha chain of IL-2 receptor

Resting T cells: β and γ chain expressed and have moderate affinity to IL-2 α, β, and γ chain -> dramatic increase in affinity for IL-2

Figure 8.17 The Immune System, 3ed. (© Garland Science 2009)
T cell activation

Tolerance – T cell activation requires correct signals to become activate i.e. Ag AND co-stimulation. Absence of either results in either no effect or anergy. This allows for tolerance to self-Ag’s and protects against autoimmunity.
Upon activation, CD4+ T cells acquire distinctive helper functions associated with specific phenotypes.

Differentiation pathway that an activated naïve T cell will take is decided early and determined by local environment within LN. Cytokines are critical in this process and participate in T cell polarization. Th1 cells are described as cell-mediated immunity while Th2 cells, dominated by Ab production, is humoral immunity.
The importance of T cell polarization is illustrated in people infected with the intracellular bacterium *Mycobacterium leprae* that is tropic for macrophages.

A Th1 response is associated with control of bacterial growth and survival of the patient.

A Th2 response results in unrestricted growth within cells (thus not accessible to Ab) and gross tissue destruction that leads to death of the patient.

<table>
<thead>
<tr>
<th>Infection with <em>Mycobacterium leprae</em> can result in different clinical forms of leprosy</th>
</tr>
</thead>
<tbody>
<tr>
<td>There are two polar forms, tuberculoid and lepromatous leprosy, but several intermediate forms also exist</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tuberculoid leprosy</th>
<th>Lepromatous leprosy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organisms present at low to undetectable levels</td>
<td>Organisms show florid growth in macrophages</td>
</tr>
<tr>
<td>Low infectivity</td>
<td>High infectivity</td>
</tr>
<tr>
<td>Granulomas and local inflammation. Peripheral nerve damage</td>
<td>Disseminated infection. Bone, cartilage, and diffuse nerve damage</td>
</tr>
<tr>
<td>Normal serum immunoglobulin levels</td>
<td>Hypergammaglobulinemia</td>
</tr>
<tr>
<td>Normal T-cell responsiveness. Specific response to <em>M. leprae</em> antigens</td>
<td>Low or absent T-cell responsiveness. No response to <em>M. leprae</em> antigens</td>
</tr>
</tbody>
</table>

Figure 8.21 The Immune System, 3ed. (© Garland Science 2009)
CD8 T cell activation is tightly controlled

Dendritic cells express high levels of B7 and can activate naïve CD8 T cells

DC readily activate naïve CD8 T cell

Activated CD8 T cell makes IL-2, driving its own proliferation and differentiation

Effector (activated) CD4 T cell secretes cytokines upon Ag recognition that increases co-stimulatory molecule expression -> CD8 T cell activation

APC stimulates effector CD4 T cell, which in turn activates the APC

Activated APC expresses B7, which co-stimulates naïve CD8 T cell

Naïve CD4 T cell, upon activation, secretes IL-2 that results in naïve CD8 T cell to express IL-2 receptor & respond to IL-2 which helps drive CD8 proliferation and differentiation.

APC activates CD4 T cell to make IL-2 and naïve CD8 T cell to express IL-2 receptors

IL-2 secreted by activated CD4 T cell is bound by CD8 T cell

Figure 8.22 The Immune System, 3rd. (© Garland Science 2009)