Adaptive tolerance

- Central, peripheral
- T tolerance
- B tolerance
- AgR engagement – co-stimulation =>
- Apoptosis, anergy
Lymphocyte development
B cell education

Figure 7-3 Immunobiology, 7ed. (© Garland Science 2008)

Figure 7-5 Immunobiology, 7ed. (© Garland Science 2008)
Figure 7-1  Immunobiology, 7ed. (© Garland Science 2008)
### Immature B cell (bone marrow)

<table>
<thead>
<tr>
<th>Multivalent self molecule</th>
<th>Soluble self molecule</th>
<th>Low-affinity non-cross-linking self molecule</th>
<th>No self reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Cell Diagram" /></td>
<td><img src="image2" alt="Cell Diagram" /></td>
<td><img src="image3" alt="Cell Diagram" /></td>
<td><img src="image4" alt="Cell Diagram" /></td>
</tr>
<tr>
<td>Clonal deletion or receptor editing</td>
<td>Migrates to periphery</td>
<td>Migrates to periphery</td>
<td>Migrates to periphery</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>Anergic B cell</td>
<td>Mature B cell (clonally ignorant)</td>
<td>Mature B cell</td>
</tr>
</tbody>
</table>

Figure 7-12 Immunobiology, 7ed. (© Garland Science 2008)
<table>
<thead>
<tr>
<th>Stage</th>
<th>B cells</th>
<th>Heavy-chain genes</th>
<th>Light-chain genes</th>
<th>Intracellular proteins</th>
<th>Surface marker proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stemi cell</td>
<td>Germine</td>
<td>Germine</td>
<td>Germine</td>
<td>CD34, CD45, AA4.1</td>
<td></td>
</tr>
<tr>
<td>Early pro-B cell</td>
<td>D-J rearranged</td>
<td>Germine</td>
<td>RAG-1, RAG-2, TdT, λ5, VpreB</td>
<td>CD34, CD45, AA4.1, IL-7R, MHC class II</td>
<td>CD10, CD19, CD38, CD40</td>
</tr>
<tr>
<td>Late pro-B cell</td>
<td>V-D-J rearranged</td>
<td>Germine</td>
<td>TdT, λ5, VpreB</td>
<td>CD45R, AA4.1, IL-7R, MHC class II</td>
<td>CD10, CD19, CD38, CD20, CD40</td>
</tr>
<tr>
<td>Pre-B receptor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Large pro-B cell</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Small pro-B cell</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Immature B cell</td>
<td></td>
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<tr>
<td>Mature native B cell</td>
<td>IgM</td>
<td>VDJ rearranged</td>
<td>V-J rearrangement</td>
<td>CD45R, AA4.1, MHC class II IgM, IgD, IgA</td>
<td>CD19, CD20, CD40</td>
</tr>
<tr>
<td>Mature native B cell</td>
<td>IgM</td>
<td>VDJ rearranged, m. heavy chain produced in membrane form</td>
<td>V-D-J rearranged</td>
<td>CD45R, AA4.1, MHC class II IgM</td>
<td>CD19, CD20, CD40</td>
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<td>Lymphoblast</td>
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<tr>
<td>Memory B cell</td>
<td></td>
<td></td>
<td>Isotype switch to Cy, Ca, or Ct. Somatic hypermutation</td>
<td>CD45R, MHC class II IgG</td>
<td>CD19, CD20, CD40</td>
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<tr>
<td>Plasma blast and plasma cell</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CD19, CD20, CD38</td>
</tr>
</tbody>
</table>

Figure 7-45 Immunobiology, 7ed. © Garland Science 2008
T cell education
Double-negative T cells simultaneously rearrange their γδ and β TCR genes.

Signals through the γδ TCR shut off the β-chain gene and commit cell to the γδ lineage.

The γδ T cell matures and migrates to periphery.

Signals through the pre-TCR shut off the γ- and δ-chain genes and commit cell to the αβ lineage.

Rearrangement of the TCRα locus deletes entire δ locus and creates mature αβ TCR.

Figure 7-22 Immunobiology, 7th ed. (© Garland Science 2008)
**T-cell precursor rearranges its T-cell receptor genes in the thymus**

Immature T cells that recognize self MHC receive signals for survival. Those that interact strongly with self antigen are removed from the repertoire

Mature T cells encounter foreign antigens in the peripheral lymphoid organs and are activated

Activated T cells proliferate and eliminate infection

---

T-cell progenitors develop in the bone marrow and migrate to the thymus

Positive and negative selection in the thymus

Mature T cells migrate to the peripheral lymphoid organs

Activated T cells migrate to sites of infection

*Figure 7-14 Immunobiology, 7 ed. (© Garland Science 2008)*
<table>
<thead>
<tr>
<th>Process</th>
<th>Genome</th>
<th>Cell</th>
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</thead>
<tbody>
<tr>
<td>Germine gene configuration</td>
<td>β V V D J C maturing CD4⁺8⁺ thymocyte</td>
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<tr>
<td></td>
<td>α V V J C</td>
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<tr>
<td></td>
<td>8</td>
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</tr>
<tr>
<td>D₁₋J₉ rearrangement (γ- and β-chain rearrangement may also occur)</td>
<td>β V V D J C CD25⁺ CD44⁺ thymocyte rearranging β-chain genes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>α V V J C</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>V₃⁻D₃β rearrangement in frame. β-chain protein produced</td>
<td>β VDJ J C CD25⁺ CD44⁺ thymocyte cytoplasmic β⁺</td>
<td></td>
</tr>
<tr>
<td></td>
<td>α V V J C</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Surface expression of β-chain with surrogate α-chain β rearrangement stops cell proliferates CD4⁺CD8⁻ induction α transcription starts</td>
<td></td>
<td>CD4⁺8⁻→CD4⁺8⁺ surface pTαβ⁺CD3⁻ very low</td>
</tr>
<tr>
<td></td>
<td>β VDJ J C</td>
<td></td>
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<tr>
<td></td>
<td>α V V J C</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>V₃₋J₉ rearrangement surface expression of αβ·CD3 selective events begin</td>
<td></td>
<td>CD4⁺8⁺ surface αβ⁺CD3⁺</td>
</tr>
</tbody>
</table>

Figure 7-24 Immunobiology, 7ed. (©Garland Science 2008)
TCR affinity distribution

- Positive selection
- Negative selection
- Affinity selection
- Grey zones !?
Figure 7-36 Immunobiology, 7ed. (© Garland Science 2008)
Tolerance and autoimmunity

- Tolerance is not absolute
- Inflammation (costimulation, cytokines, antigens) =>
  - Risk of autoimmune reactions
- Chronic inflammation =>
  - Risk of autoimmune disease
Genetic factors

Infection and environmental exposure

Immune regulation

Autoimmunity

Figure 14-3 Immunobiology, 7th ed. (© Garland Science 2008)
Immunological feed back loops

Extracellular antigens

AuAg \rightarrow AuAb \rightarrow D/M

Au Ab

MHC II Cytokines

B

MHC II Cytokines

T_4
Immunological feed back loops

Intracellular antigens

AuAg → D/M

C ← MHC I Cytokines

MHC I Cytokines

T_8
Autoimmune diseases

- **Organ specific**
  - Only one organ involved
  - Organ specific autoantigens
  - Intracellular autoantigens

- **Systemic rheumatic**
  - Connective tissue involved
  - Several/many tissues involved
  - Common autoantigens
  - Extracellular autoantigens
  - IMPAS
  - EMPAS
AI connective tissue diseases

- Rheumatoid arthritis
- Sjögren syndrome
- Lupus erythematosus
- Phospholipid antibody syndrome
- Polymyositis/dermatomyositis
- Scleroderma
Gastrointestinal system

- Autoimmune gastritis
- Autoimmune pancreatitis
- Coeliac disease
- Inflammatory bowel disease
  - Crohn disease
  - Colitis ulcerosa
Muscle system

- Myasthenia gravis
- Autoimmune myositis
- Fibromyalgia ?
Sensory and nervous system

- Sensory system
  - Autoimmune Uveitis
- Peripheral nervous system
  - CIDP
- Central nervous system
  - Multiple sclerosis
  - Neuromyelitis optica
  - Acute lateral sclerosis
  - Guillain-Barre syndrome
  - Paraneoplastic syndromes
Prevalence of autoimmunity

- Graves' disease
- Rheumatoid arthritis
- Hashimoto's thyroiditis
- Vitiligo
- Type 1 diabetes
- Pernicious anemia
- Multiple sclerosis
- Glomerulonephritis
- Systemic Lupus E.
- Sjogren syndrome

Rate per 100,000
MHC associations and autoimmunity

- **MHC I** (HLA A, B, C)
- **MHC II**
- **Predisposition**
- **Protection**
Gene polymorphisms and autoimmunity

- MHC I, II
- Cytokines
- Cytokine receptors
- Lymphocyte signalling ligands
- Lymphocyte signalling receptors
- Predisposition, protection
T cell assay methods

- Fluorescence activated cell sorting
- Elispot
- Cytokine (release) assays
- CTL assays
T cell epitopes

- MHC I
  8 - 10 aa peptides

- MHC II
  13 - 18 aa peptides
Autoantigens and epitopes

- Proteins
- Peptides
- Phospholipids
- Glycolipids
- Glycosaminoglycans?
B cell epitopes

- Three-dimensional
- Secondary
- Linear
- Cryptic
- Modified
PTM and autoimmunity

- Carbamylation
- Citrullination
- Isopeptide cross linking
- Phosphorylation
- ?
Posttranslational modifications (PTM)

ACDEFGHIKLMNPQRSTVWY
Infection/autoimmunity

Self

* * * Immune system Activation!

Non self

* * *

Autoimmunity Chronic infection

GH
Autoimmune diseases

- Organ specific
  - Diabetes
  - Multiple sclerosis

- Systemic rheumatic (connective tissue)
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Sjögreens syndrome
  - Scleroderma
Prevalence of autoimmunity
Lupus erythematosus (LE)

- Discoid LE
- Systemic LE (SLE)
- Neonatal lupus
- Neurophychiatric lupus
- Drug induced lupus
- Mixed connective tissue disease
- Anti phospholipid syndrome
Systemic lupus erythematosus (SLE)

- Connective tissue disease
- UV sensitivity
- Skin rash
- Defective clearance of cell debris
SLE diagnosis

- Fatigue
- Rash
- Anti nuclear antibodies (ANA)
- DNA antibodies
- Histone antibodies
- Ro 60 antibodies
- Ro 52 antibodies
- La antibodies
- Sm antibodies
- RNP antibodies
- Ribosome antibodies
- Phospholipid antibodies
- Beta 2 GP I antibodies
- Complement deficiencies
SLE antigens

- IMPAS
  - DNA
  - Histone
  - Sm/RNP
  - Ro 60
  - Ro 52
  - La
  - Ribosomes
  - ........

- EMPAS
  - Collagen I
**Table 7**

**SLE Daily Activity Index: Data Collection Sheet**

<table>
<thead>
<tr>
<th>SLEDAI Score</th>
<th>Descriptor</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Seizures</td>
<td>Recent onset. Exclude metabolic, infectious or drug causes.</td>
</tr>
<tr>
<td>8</td>
<td>Psychosis</td>
<td>Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disinhibited or catatonic behavior. Exclude amnestic and drug causes.</td>
</tr>
<tr>
<td>8</td>
<td>Organic brain syndrome</td>
<td>Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus, and inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, incoherence or daytime drowsiness or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.</td>
</tr>
<tr>
<td>8</td>
<td>Visual disturbance</td>
<td>Retinal changes of SLE. Include Eidetic bodies, retinal hemorrhages, sensory/excessive or hemorrhages in the choroid or optic neuritis. Exclude hypertension, infection or drug causes.</td>
</tr>
<tr>
<td>8</td>
<td>Cranial nerve disorder</td>
<td>New onset of sensory or motor neuropathy involving cranial nerves.</td>
</tr>
<tr>
<td>8</td>
<td>Lupus headache</td>
<td>Severe, persistent headache: may be migrainous, but must be nonresponsive to narcotic analgesics.</td>
</tr>
<tr>
<td>8</td>
<td>CVA</td>
<td>New onset of cerebrovascular accident(s). Exclude arteriosclerosis.</td>
</tr>
<tr>
<td>8</td>
<td>Vasculitis</td>
<td>Ulceration, gangrene, tender finger nodules, periligual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.</td>
</tr>
<tr>
<td>4</td>
<td>Arthritis</td>
<td>More than 2 joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion).</td>
</tr>
<tr>
<td>4</td>
<td>Myositis</td>
<td>Proximal muscle pain/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.</td>
</tr>
<tr>
<td>4</td>
<td>Urinary casts</td>
<td>Hypergranular or red blood cell casts.</td>
</tr>
<tr>
<td>4</td>
<td>Hematuria</td>
<td>$&gt;5$ red blood cells/hp. Exclude stone, infection or other cause.</td>
</tr>
<tr>
<td>4</td>
<td>Pneumonia</td>
<td>$&gt;0.5$ gm/24 hours. New onset or recent increase of more than $0.5$ gm/24 hours.</td>
</tr>
<tr>
<td>4</td>
<td>Proteinuria</td>
<td>$&gt;2$ white blood cells/hp. Exclude infection.</td>
</tr>
<tr>
<td>2</td>
<td>New rash</td>
<td>New onset or recurrence of inflammatory type rash.</td>
</tr>
<tr>
<td>2</td>
<td>Alopecia</td>
<td>New onset or recurrence of abnormal hair growth or diffuse loss of hair.</td>
</tr>
<tr>
<td>2</td>
<td>Oral ulcers</td>
<td>New onset or recurrence of oral or nasal ulceration.</td>
</tr>
<tr>
<td>2</td>
<td>Pleurisy</td>
<td>Pleuritic chest pain with pleural rub or effusion, or pleural thickening.</td>
</tr>
<tr>
<td>2</td>
<td>Pericarditis</td>
<td>Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.</td>
</tr>
<tr>
<td>2</td>
<td>Low complement</td>
<td>Decrease in GM5, C3 or C4 below the lower limit of normal for testing laboratory.</td>
</tr>
<tr>
<td>2</td>
<td>Increased DNA binding</td>
<td>$&gt;23%$ binding by Farr assay or above normal range for testing laboratory.</td>
</tr>
<tr>
<td>1</td>
<td>Fever</td>
<td>$&gt;38$°C. Exclude infectious cause.</td>
</tr>
<tr>
<td>1</td>
<td>Thrombocytopenia</td>
<td>$&lt;100,000$ platelets/mm$^3$.</td>
</tr>
<tr>
<td>1</td>
<td>Leukopenia</td>
<td>$&lt;3,000$ white blood cells/mm$^3$. Exclude drug causes.</td>
</tr>
</tbody>
</table>

**TOTAL SLEDAI SCORE:**

Reprinted, with permission, from Remiarczuk (1972)
SLE

Table 1. Systemic lupus erythematosus characteristics [2] and predisposing immunodeficiencies [1,3,4]

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SLEDAI score weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic disorders</td>
<td>8-56</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>8</td>
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<tr>
<td>Arthritis</td>
<td>4</td>
</tr>
<tr>
<td>Myositis</td>
<td>4</td>
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<tr>
<td>Renal disorders</td>
<td>4-16</td>
</tr>
<tr>
<td>Rash</td>
<td>2</td>
</tr>
<tr>
<td>Alopecia</td>
<td>2</td>
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<tr>
<td>Mucosal ulcers</td>
<td>2</td>
</tr>
<tr>
<td>Serositis</td>
<td>2-4</td>
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<tr>
<td>Hematologic disorders</td>
<td>1-2</td>
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<tr>
<td>Low complement</td>
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<tr>
<td>ANAs</td>
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<tr>
<td>Fever</td>
<td>1</td>
</tr>
</tbody>
</table>

Immunodeficiencies

- Complement (C1q, C2, C3, C4, CRP, etc.)
- Inflammatory response
- Immunoglobulin binding/function
- Immunoglobulin receptor function
- Costimulatory/coinhibitory signals (PD1, CTLA4, etc.)
- Cytokine/chemokine signaling (IRF5, STAT4, IL-10, etc.)
- T-cell function and signaling
- B-cell function and signaling
- Dendritic cell function
- Apoptosis
- Chromosome X-linked (XX and XXY)
Complement deficiencies in SLE

- Partial deficiency a potential risk factor for SLE
- Defects not associated with SLE

MBL
- C1q: 93%
- C1r/s: 57%
- C4: 75%
- C2: ~10%
- C3: 13%

Sporadic reports only

Percentage of patients with homozygous deficiency affected by lupus-like illness
SLE immuno-deficiencies
Eppstein-Barr virus

**Characteristics**
- Enveloped virus (Fig. 1)
- HHV4
- Infects epithelial cells, B-cells and other cell types
- Can shift between latent and lytic states
- Infects 95–100% of the world’s population
- 172 kbp double-stranded DNA genome coding for 87 proteins and two EBERs
- Currently, more than 100 complete EBV genomes and more than 10,000 EBV sequences are recorded

**Associated diseases**
- Infectious mononucleosis
- Lymphomas (Burkitt’s, Hodgkin’s, and others)
- Nasopharyngeal carcinoma and other HNCs
- Gastric cancers
- SLE
- SS
- RA
- MS
Eppstein-Barr virus
EBV and SLE
EBV and SLE

**Figure A**
- Total CD69-expressing T-cells
- CD8+ CD69-expressing T-cells
- CD4+ CD69-expressing T-cells

Healthy controls vs. SLE patients

**Figure B**
- Total CD69-expressing T-cells
- CD8+ CD69-expressing T-cells
- CD4+ CD69-expressing T-cells

EBNA1-specific T-cells vs. EBV-EA/D-specific T-cells

Significance levels: *** p < 0.001, ** p < 0.01, * p < 0.05.
**EBV and SLE**

<table>
<thead>
<tr>
<th>EBV-specific (CD69+) T-cells</th>
<th>EBV Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>EBNA1</td>
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<td>Total CD8+</td>
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</tbody>
</table>
EBV and SLE
Apoptosis/clearance
SLE etiology

Triggers:
- Hormones
- Viruses
- UV-light
- Drugs

Pre-clinical SLE

Clinical SLE

Symptoms

Disease

Normal immunity

Benign Autoimmunity

Pathogenic Autoimmunity

Organ damage

Genetic susceptibility
SLE etiology

Genetics: immuno-profile

EBV-infected cells

Abs(EBV)

AutoAbs

SLE symptoms

SLE

EBV-infected cells

EBV

CMV

Reactivations

Reinfections

Birth

EBV

CMV

Infection(s)
medication(s)
UV light, radiation
chemicals

Environment:
Infections and immuno-modulation

Time