**Immunology 2011**  
**Lecture 20**  
**Autoimmunity**  
18 October

---

**Contributors to Normal Absence of Self-Reactivity**

**A) Tolerance**
- Clonal deletion ("negative selection")
- Suppression - high T_{reg} activity
- Low T_{H} activity, [anergy]
- Receptor blockade

**B) Sequestered Antigen**
- e.g. lens protein, sperm antigens...

---

**Contributors to Autoimmunity**

**A) Breaking of Tolerance**
- Increase T_{H} activity (adjuvants...)
e.g. Lambert-Eaton Syndrome (Ca_{V} channels)
- Decrease T_{reg} activity
- Cross-reactive Ags ("molecular mimicry")
e.g. StrepA - rheumatic heart disease

**B) Release of Sequestered Antigen**
e.g. uveitis, orchitis...

---

**Some autoimmune diseases...**
- Alopecia areata
- Ankylosing spondylitis
- Arthritis
- Autoimmune hemolytic anemia
- Autoimmune hepatitis
- Behçet's disease
- Crohn's disease
- Dermatomyositis
- Diabetes mellitus, type 1
- Glomerulonephritis
- Graves' disease
- Guillain-Barré syndrome
- Inflammatory bowel disease
- Lupus nephritis
- Multiple sclerosis
- Myasthenia gravis
- Myocarditis
- Pemphigus/pemphigoid
- Pernicious anemia
- Polymyositis
- Primary biliary cirrhosis
- Psoriasis
- Rheumatic fever
- Rheumatoid arthritis
- Sarcoidosis
- Scleroderma
- Sjögren's syndrome
- Systemic lupus erythematosus
- Thyroiditis
- Ulcerative colitis
- Vitiligo
- Wegener's granulomatosis

---

**Alopecia areata**  
**Ankylosing spondylitis**  
**Arthritis**  
**Autoimmune hemolytic anemia**  
**Autoimmune hepatitis**  
**Behçet's disease**  
**Crohn's disease**  
**Dermatomyositis**  
**Diabetes mellitus, type 1**  
**Glomerulonephritis**  
**Graves' disease**  
**Guillain-Barré syndrome**  
**Inflammatory bowel disease**  
**Lupus nephritis**  
**Multiple sclerosis**  
**Myasthenia gravis**  
**Myocarditis**  
**Pemphigus/pemphigoid**  
**Pernicious anemia**  
**Polyarteritis nodosa**  
**Polymyositis**  
**Primary biliary cirrhosis**  
**Psoriasis**  
**Rheumatic fever**  
**Rheumatoid arthritis**  
**Sarcoidosis**  
**Scleroderma**  
**Sjögren's syndrome**  
**Systemic lupus erythematosus**  
**Thyroiditis**  
**Ulcerative colitis**  
**Uveitis**  
**Vitiligo**  
**Wegener's granulomatosis**
Thymic T-Cell Education: Positive & Negative Selection

**CD8 Epithelial cell**

- **Blood**
- **Thymus**
- **Immature T-cell**

**Class I-based selection for TcRs occurs in the same way as illustrated above for Class II...**

**Intrathymic T-cell maturation: Two ways to die**

1. Clonal Deletion
2. Positive Selection
3. Negative Selection

<table>
<thead>
<tr>
<th>Strength of interaction</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>Death</td>
</tr>
<tr>
<td>Weak/none</td>
<td>Death</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Death</td>
</tr>
</tbody>
</table>

**Emigration**

- **CD4**
- **CD8**

**Thymic T-Cell Education: Positive & Negative Selection**

**Initiation of Autoimmunity**

- Tissue injury may lead to:
  1) exposure of immune system to sequestered antigens
  2) “adjuvant” effect of released cell contents (“Danger” Hypothesis – innate immune recognition)
  3) tissue being rendered accessible to immune damage

**Tissue injury may result from:**

- Trauma - uveitis, orchitis
- Viral infection - (ADEM & MS? Hashimoto’s?)
- Immune complex deposition - complement deficiency (C1,4); chronic viral infections

**Note appearance of transient autoantibodies in myocardial infarct & CCl4 hepatotoxicity.**

**Human Autoimmune Diseases and Some Animal Models**

- **Hashimoto’s Disease**
- Autoimmune thyroiditis of mice (thyroglobulin)
- Acute Disseminated Encephalomyelitis (ADEM)
- Multiple Sclerosis (MS)
  - EAE in mice and rats (myelin basic protein, et al.)
- Myasthenia Gravis (MG)
  - Rabbit anti-acetylcholine receptors (AcChR)
- Rheumatoid Arthritis (RA)
- Systemic Lupus Erythematosus (SLE)

**Genetic Defect in Negative Selection of T Cells**

- **failure of clonal deletion**

**Autoimmune Polyendocrinopathy Type I**

- Recessive Mendelian disorder, shows a spectrum of organ-specific autoimmune diseases.

Results from a mutation in AIRE, a transcription factor which promotes ectopic expression of organ-specific proteins in thymus, thus normally allowing negative selection for these antigens to occur.

**AIRE allows development of “central” tolerance to peripheral antigens.**

**Autoimmunity**

- Each can cause and exacerbate the other.

**Autoimmune Polyendocrinopathy Type I**


**Results from a mutation in AIRE, a transcription factor which promotes ectopic expression of organ-specific proteins in thymus, thus normally allowing negative selection for these antigens to occur.**


**Human Autoimmune Diseases and Some Animal Models**

- **Hashimoto’s Disease**
- Autoimmune thyroiditis of mice (thyroglobulin)
- Acute Disseminated Encephalomyelitis (ADEM)
- Multiple Sclerosis (MS)
  - EAE in mice and rats (myelin basic protein, et al.)
- Myasthenia Gravis (MG)
  - Rabbit anti-acetylcholine receptors (AcChR)
- Rheumatoid Arthritis (RA)
- Systemic Lupus Erythematosus (SLE)

**Intrathymic Germinal Centers in Myasthenia Gravis**

- **Inflammation**
- **Autoimmunity**

- **Initiation of Autoimmunity**
- **Tissue injury may lead to:**
  1) exposure of immune system to sequestered antigens
  2) “adjuvant” effect of released cell contents (“Danger” Hypothesis – innate immune recognition)
  3) tissue being rendered accessible to immune damage

**Tissue injury may result from:**

- Trauma - uveitis, orchitis
- Viral infection - (ADEM & MS? Hashimoto’s?)
- Immune complex deposition - complement deficiency (C1,4); chronic viral infections

**Note appearance of transient autoantibodies in myocardial infarct & CCl4 hepatotoxicity.**

**Human Autoimmune Diseases and Some Animal Models**

- **Hashimoto’s Disease**
- Autoimmune thyroiditis of mice (thyroglobulin)
- Acute Disseminated Encephalomyelitis (ADEM)
- Multiple Sclerosis (MS)
  - EAE in mice and rats (myelin basic protein, et al.)
- Myasthenia Gravis (MG)
  - Rabbit anti-acetylcholine receptors (AcChR)
- Rheumatoid Arthritis (RA)
- Systemic Lupus Erythematosus (SLE)

**Intrathymic Germinal Centers in Myasthenia Gravis**

- **G.C. in thymus**
  - (T-cells labeled red)
- **Cells producing anti-AChR within a G.C.**

**“Tertiary” lymphoid tissue...**

**Rheumatoid Factor**
- IgM autoantibodies against IgG
- Important in differential diagnosis of autoimmune diseases (e.g., ~80% positive in RA, ~25% positive in SLE)

  Many other auto-antibodies can be found in RA, e.g., anti-nuclear & anti-cyclic citrulline peptide

**HLA Association with Autoimmunity**

<table>
<thead>
<tr>
<th>Disease</th>
<th>HLA</th>
<th>Relative Risk</th>
<th>Sex ratio F/M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankylosing spondylitis</td>
<td>B27*</td>
<td>~85</td>
<td>~0.3</td>
</tr>
<tr>
<td>Birdshot retinopathy</td>
<td>A29*</td>
<td>~170</td>
<td>~1</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>DR4*</td>
<td>~4</td>
<td>~0.3</td>
</tr>
<tr>
<td></td>
<td>DR3*</td>
<td>~6</td>
<td>~15</td>
</tr>
</tbody>
</table>

**Will be discussed further in Clinical Correlate and in “Genetic Control”**

(Note presence of “shared epitope” in β-chains of all HLA-associated DR4 alleles...)

---

**Gender Differences in Prevalence of Autoimmune Diseases**

<table>
<thead>
<tr>
<th>Disease</th>
<th>HLA Risk</th>
<th>Sex ratio F/M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hashimoto’s thyroiditis/hypothyroidism</td>
<td>50:1</td>
<td>9:1</td>
</tr>
<tr>
<td>SLE</td>
<td>9:1</td>
<td></td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>9:1</td>
<td></td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td>9:1</td>
<td></td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>9:1</td>
<td></td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>8:1</td>
<td></td>
</tr>
<tr>
<td>Chronic active hepatitis</td>
<td>8:1</td>
<td></td>
</tr>
<tr>
<td>Grave’s disease/hyperthyroidism</td>
<td>7:1</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>3:1–4:1</td>
<td></td>
</tr>
<tr>
<td>Scleroderma</td>
<td>3:1–4:1</td>
<td></td>
</tr>
<tr>
<td>Myelodysplasia</td>
<td>2:1–3:1</td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>2:1</td>
<td></td>
</tr>
<tr>
<td>Autoimmune thrombotic purpura</td>
<td>1:1–2:1</td>
<td></td>
</tr>
<tr>
<td>Type 1 Diabetes mellitus</td>
<td>1:1</td>
<td></td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>1:1</td>
<td></td>
</tr>
<tr>
<td>Autoimmune myocarditis</td>
<td>1:1.2</td>
<td></td>
</tr>
</tbody>
</table>

* Modified from Fairweather and Rose [55] and McCarthy [4]

---

**Estrogen Effects in Autoimmune Diseases**

- Low estrogen: MS, RA
- High estrogen (e.g., pregnancy): TH2

  - proinflammatory: IL-2, IFNγ...
  - TH1
  - IL-4, IL-10, TGFβ...

  1) Choice between TH1 and TH2
  2) TH1 vs. TH2 antagonism
  3) Differential disease associations

---

**Two forms of autoantibody-mediated tissue damage in kidney**

1) anti-basement membrane Ab, “smooth” distribution
2) immune complex deposition, “lumpy-bumpy” distribution

---

**Glomerulus in Goodpasture’s Syndrome**

Antibodies directed against basement membrane “smooth” distribution.
Glomerulus in Immune Complex Disease
Immune complexes trapped from serum, “lumpy-bumpy” distribution.

Autoantibodies Affecting Cell Signalling Mechanisms

Myasthenia Gravis: anti-ACh receptor, antagonist
Grave’s Disease: anti-TSH receptor Ab, acts as agonist; hyperthyroidism (distinguish this from Hashimoto’s thyroiditis [anti-thyroglobulin])
Lambert-Eaton Syndrome: Ab to CaV channels, blockers; presynaptic defect resulting in muscle weakness, vision problems, etc. (associated with small-cell carcinoma of the lung, which expresses Cav)

[anti-receptor Ab, proposed new category of “Gell & Coombs Type V…”]

Paraneoplastic Syndromes
...are caused indirectly by the presence of benign or malignant neoplasms and include many autoimmune conditions.
Autoantibodies:
Lambert-Eaton Syndrome: Ab to CaV channels (often associated with small cell lung cancer)
Stiff-Man Syndrome: Ab to the synaptic protein amphiphysin (associated with breast cancer).
[Also non-paraneoplastic form with auto-Ab to glutamic acid decarboxylase (GAD)].

[Not all paraneoplastic conditions are autoimmune: Eosinophil Cushing’s Syndrome: ACTH produced by a tumor stimulates the adrenal to overproduce glucocorticoids.]

Transplacental transfer of maternal auto-antibodies...

...transfers disease.

See also Myasthenia gravis, thrombocytopenia purpura, etc.

WEDNESDAY
Genetic Control of Immune Responses
POPS 2, Transplantation, 1:00-3:00

THURSDAY
CC#1: Rheumatoid Arthritis, 8:30 AM
Dr. Pamela Prete