Autoimmunity

- Factors predisposing an individual to autoimmune disease
- Mechanisms of initiation of autoimmunity
- Pathogenesis of particular autoimmune disease
- Animal models of autoimmune disease
- Treatment of autoimmune disease

Targets of Autoimmunity

- Autoimmunity can arise by both T cell and antibody mediated responses
- Some autoimmune diseases are mainly mediated by T cell mediated damage like MS or antibody mediated damage like SLE
- Traditionally grouped according to to the targets of attack
  - Organ-specific autoimmunity
  - Systemic autoimmunity

Autoimmunity

- Autoimmune diseases are pathologic conditions that result from the failure of the tolerance mechanisms to specific self antigens
- Positive Selection:
  - T cells interact with self MHC and Self peptides survive
- Negative Selection:
  - T cells interact strongly with self MHC and self peptides are killed
  - B cells that have anti-self antibodies are killed

Genetic Contributions to Autoimmunity

- Some show increased prevalence in families
- In animal models genetic predisposition is an important factor in disease susceptibility
- Multiple genes involved in autoimmune diseases
  - Example:
    - SLE at least 12 genes with low penetrance
    - No one gene marker for susceptibility
- Certain MHC class I and II genes show strong association with certain autoimmune diseases
  - Meaning, those with the disease are more likely than the rest of the population to have a certain HLA haplotype than is found in the general population
Genetic Contributions to Autoimmunity

<table>
<thead>
<tr>
<th>Disease</th>
<th>Associated HLA</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addison</td>
<td>DR3/DQ</td>
<td>6.3</td>
</tr>
<tr>
<td>AS</td>
<td>B27</td>
<td>87.4</td>
</tr>
<tr>
<td>Behçet</td>
<td>B5</td>
<td>7.4</td>
</tr>
<tr>
<td>IDDM</td>
<td>DR3</td>
<td>5.3</td>
</tr>
<tr>
<td>MG</td>
<td>DR3</td>
<td>2.5</td>
</tr>
<tr>
<td>RA</td>
<td>DR4</td>
<td>4.2</td>
</tr>
<tr>
<td>SLE</td>
<td>DR3</td>
<td>5.8</td>
</tr>
</tbody>
</table>

Environmental Contributions to Autoimmunity

- Environmental agents may provoke or exacerbate a variety of autoimmune disorders
- Infection has been implicated as a direct precipitant of autoimmune diseases
- Example MS:
  - Higher risk in N. latitudes of Europe than S. latitudes
  - Emigrants who moved from N. to S. before age 12 assumed the lower risk level of the S.
  - Emigrants who moved from N. to S. after age 12 retained the N. risk.

Systemic Autoimmunity

- Systemic Lupus Erythematosis, SLE, Lupus
  - Skin lesions, arthritis, kidney failure, cardiac problems, and neuropsychiatric issues.
  - Polyclonal B cell activation producing IgG Abs
  - Characterized by anti-nuclear antibodies (ANAs)
    - Anti-double stranded DNA abs (anti-dsDNA)
    - Anti-small nuclear ribonucleoproteins (anti-snRNP)
  - 10:1 female to male
  - Risk associations:
    - HLA-DR2 and 3
    - TNF-alpha polymorphism
    - Deficiency in complement C2,C4,C5, and C8

Systemic Autoimmunity Animal Model

- SLE mouse: BWF1
  - Clear preference for females
  - Autoantibodies to dsDNA
  - Fatal lupus nephritis
  - Castration of males makes them susceptible
  - Addition of female hormones to female mice accellerates disease
  - Addition of male hormones to females inhibits disease
  - Antibodies blocking CD4+ T cell activity inhibits disease
**Systemic Autoimmunity**

- Rheumatoid Arthritis, RA
  - Peripheral synovial joint arthritis, or degradation of cartilage
  - Antigen-antibody immune complexes lodge in the cartilage and activate complement
  - Complement activation attracts PMNs and macrophages to the joint
    - PMNs release proteases and ROIs and cause joint damage
    - Macrophages release cytokines that attract more immune cells and form a granuloma-like tissue called a pannus
    - Leukocytes in the pannus release more proteases and ROIs and cause even more damage to the joint
  - Etiology remains unknown
    - T cell initiation of disease?
    - Memory T cells in initial stages
    - Infectious or microbial agents?

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**Rheumatoid Arthritis, RA**

- SLE mouse
  - NZB × NZW
  - Mild autoimmune hemolytic anemia
  - BWF1 Lupus-like disease

<table>
<thead>
<tr>
<th>Symptom</th>
<th>% Positive BWF1 mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antinuclear antibodies</td>
<td>46</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>80</td>
</tr>
<tr>
<td>Lupus nephropathy</td>
<td>75</td>
</tr>
<tr>
<td>Severe nephropathy</td>
<td>38</td>
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</table>

Animal Models of Rheumatoid Arthritis, RA

- Collagen-induced arthritis (CIA)
- Adjuvant-induce arthritis (AIA)
- Pristane-induced arthritis (PIA) (paraffin oil)
- CIA = intense joint destruction similar to RA
  - T cell mediated and antibody response to collagen; subsequent complement activation

Systemic Autoimmunity

- Multiple Sclerosis, MS
  - Tissue-specific etiology but systemic effects
    - Demyelination of neuronal axons in the brain and spinal cord
    - Myelin sheath damage interferes with nerve signal impulse transmission
    - Systemic loss of motor and sensory function
  - Two major forms clinically:
    - Remitting/relapsing and progressive
  - Infiltration of T, B and macrophages into the CNS during disease process
    - Inflammatory cytokines and chemokines
    - Unknown what actually causes the damage to the myelin sheath of the axons
      - Anti MBP T cells and antibodies are found in patients with MS
  - North Americans and European Whites.
    - Prevalence increases with distance from the equator
    - Possible Infectious agents include HBV6, EBV, and Chlamydia pneumoniae

Collagen-induced arthritis (CIA)

<table>
<thead>
<tr>
<th>Group</th>
<th>No. with arthritis/ total no. of mice</th>
<th>Mean day of onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental</td>
<td>2/10</td>
<td>80</td>
</tr>
<tr>
<td>Control</td>
<td>9/10</td>
<td>44</td>
</tr>
</tbody>
</table>

Multiple Sclerosis, MS

- Schwann cells (oligodendrocytes) form the myelin sheath of the axons they grow around
EAE as a model for MS

- Experimental Allergic Encephalomyelitis mouse
  - Immunize certain strains of mice with myelin proteins
  - Develop acute disease with spontaneous remission and relapse cycles
  - TH1 cytokines are associated with disease
  - TH2 cytokines are effective at downregulating EAE symptoms

EAE as a model for MS

- T cells home to the brain where they mediate destruction of the myelin sheath
- T cells in brain correlates with disease symptoms

Organ-specific Autoimmune Disease

- Myasthenia Gravis, MG
  - Muscle weakness and fatigue are caused by autoantibodies against nicotinic acetylcholine receptors (AChR) at the neuromuscular junction
    - They block binding of ACh to AChR and prevent nerve-signal propagation
    - Complement activation may cause additional damage
  - Young women (20s 30s) and Older men (50s 60s)
  - Molecular mimicry to infectious peptides?

Organ-specific Autoimmune Disease

- Insulin Dependent Diabetes Mellitus, IDDM, Type I Diabetes
  - Cell mediated damage to the pancreatic Beta cells of the islets of langerhans
    - Preclinical insulitis:
      - Infiltration of lymphocytes (CD4+, CD8+ T cells and B cells) and presence of autoantibodies in the islets of langerhans
      - Macrophage are activated by T cells and increase damage
      - T cells specific for insulin, heat shock proteins, islet cell antigens, glutamic acid decarboxylase (GAD)
  - Autoantibodies against cytoplasmic islet cell antigens are found in 80% of patients; can also be found in preclinical patients
  - Effects are systemic
    - Lack of insulin production by beta cells results in hyperglycemia, weight loss, and ketoacidosis
    - Produce chronic metabolic derangements that lead to decreased bloodflow to the extremities
  - Viral infection as a cause?
    - Possible sequence homology between a cytoplasmic islet antigen and coxsackievirus and nucleoprotein in influenza virus
    - Congenital rubella infection has also been correlated

Insulin Dependent Diabetes Mellitus, IDDM, Type I Diabetes

A. Normal Islets of Langerhans
With Beta cells producing insulin

B. Infiltration of Islets of Langerhans
with lymphocytes and Destruction of Beta cells
Insulin Dependent Diabetes Mellitus, IDDM, Type I Diabetes Animal Model

- Nonobese diabetic mouse, NOD mouse
  - Insulitis in almost 100% of the mice
  - 80% females progress to diabetes
  - 30% males progress to diabetes

Organ-specific Autoimmune Disease

- Chronic autoimmune thyroiditis: HT and GD
  - Hashimotos thyroiditis, HT
    - Inflammatory thyroid characterized by a goiter with or without hypothyroidism
    - Cellular infiltration and autoantibodies in thyroid
    - Loss of thyroid function probably due to autoantibodies against TSHR
    - 2:1 female to male
  - Graves Disease, GD
    - Hyperthyroidism and goiter
    - Stimulatory autoantibodies against TSHR causing thyroid growth and increase in thyroid hormones
    - 10:1 female to male
  - Viral infections?

Hashimotos thyroiditis, HT

- A.
  - Normal thyroid tissue
- B.
  - Intense lymphocyte infiltration
**Hashimotos thyroiditis, HT**

- Normal regulation of thyroid hormone production

**Graves Disease, GD**

- Anti-TSHR antibody stimulates TSHR signal transduction and causes thyroid to produce even more products
- Subverts feedback inhibition

**Animal models of autoimmune thyroiditis**

- Obese chicken
  - Resembles HT
  - Hypothyroidism, cellular infiltration into thyroid
- NOD mice and BB rats also have a low incidence of thyroiditis along with diabetes