Autoimmunity

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What is Autoimmunity?

◆ Autoimmunity is an immune response to self antigens that results in disease.

◆ The immune response to self is a result of a breakdown in immune tolerance.

Immune Tolerance

◆ Tolerance of self is a hallmark of adaptive immune response.

◆ B cell tolerance vs. T cell tolerance.

B cell Tolerance

No T cell help

Autoreactive B cells that enter lymph node should fail to get costimulation from T cells and therefore never enter primary follicles.

Maintenance of T cell tolerance

◆ Clonal deletion
  – negative selection in the thymus, deletion in the periphery.

◆ Sequestration of antigens
  – Inside nucleus
  – Inaccessible to immune system (brain, eye, testes)

◆ Immunological ignorance
  – self antigens at low density on APCs
  – or T cells do not cross barrier.

Maintenance of T cell tolerance

◆ Anergy
  – Lack of co-stimulation or second signal to T cells results in anergy.

◆ Suppression
  – T-cell cytokine mediated suppression.
  – Regulatory T cells. CD4+CD25+ CTLA4+
  T cells that produce suppressive cytokines.
Inducing Autoimmunity OR Breaking of self-tolerance

Injury (inflammation)
or
Infection

"Viral Trigger" is term for virus infection leading to autoimmune response.

Breaking of self-tolerance

◆ Release of sequestered antigens: Tissue damage by infection may allow access of T cells and B cells to sequestered antigens.

◆ Antigenic (molecular) mimicry is when similarity between foreign antigen and self protein results in cross-reactivity.

Antigenic Mimicry

◆ Inappropriate expression of Class II MHC. 
  – Abnormal expression of class II molecules can lead to presentation of self antigens that were not presented in thymus or periphery.
  – "non-APC" becomes APC with inflammation.

Classification of autoimmune diseases

Autoantibody or T cell mediated autoimmune diseases
Autoantibody mediated diseases

**Autoimmune hemolytic anemia**

Antibodies to rbc antigens

- IgM abs against CHO on rbc cell surface binds
  - causes C’ activation and lysis
  - phagocytic cell clearance

**Autoimmune hemolytic anemia**

- IgM abs thought to be from infection
  - Mycoplasma or Epstein Barr virus thought to be associated.
  - Can be transient as long as you have infection.
  - Unclear how exactly triggered.

**Myasthenia Gravis**

- Blocking autoantibodies

Antibodies to acetyl choline receptors block muscle activation and trigger inflammation that causes the destruction of the nerve/muscle junctions resulting in paralysis.

**Hashimoto’s thyroiditis**

- Blocking autoantibodies
  - Inhibit thyroid function.

**Autoantibodies to surface receptors**

- Stimulating autoantibodies

**Graves’ disease** = hyperthyroid

Stimulating autoantibodies bind thyrotropin receptor for thyroid stimulating hormone.
Goodpasture's Syndrome

- Autoantibodies to type IV collagen and non-collagenous basement membrane.
- Antibodies bind in lung and kidney causing inflammation and destruction.
- Increased risk with smoking.

Rheumatoid Arthritis

Immune Complex Disease

- Autoantibodies to ubiquitous antigens
  - IgM against IgG is called "rheumatoid factor"
  - IgG against glucose-6-phosphate isomerase.
- Primary disease manifestation
  - immune complexes get deposited in joints and trigger inflammatory response through complement activation and binding FcγRs on neutrophils and macrophages triggering degranulation.

Systemic lupus erythematosus (SLE)

Immune complex disease

- Chronic IgG production to intracellular proteins.
- Disease symptoms are widespread and varied.
  - kidney damage, lung disease, skin, eye, etc.

Systemic lupus erythematosus (SLE)

- Autoantibodies against nucleoprotein particles;
  - Nucleosome
  - Spliceosome.
  - Ribonucleoprotein complex.
- Th response to one epitope can drive auto-antibody production to many epitopes in a particle.

Lupus

One T helper epitope can provide help to multiple antibody epitopes in same particle.

Potential disease cycle for SLE

- Immune complexes form -->
  - get deposited in joints, small blood vessels -->
  - C activation, activation of phagocytes -->
  - Inflammation/damage causes more release of intracellular antigens and then
  - MORE immune complexes can form.
T cell Mediated Autoimmune Diseases

Multiple sclerosis (MS)

- T cell responses to myelin basic protein (MBP).
- The destruction of the myelin sheath results in neurological symptoms.

- The cause remains unknown, but autoimmunity possibly triggered during an inflammatory response to a viral infection is implicated.
- MBP has high sequence homology with measles protein and Hepatitis B virus protein. Antigenic mimicry?

Insulin-dependent (type I) diabetes mellitus (IDDM)

- Selective destruction of insulin-producing β cells in the islets of Langerhans of the pancreas.
- Autoantibodies and self-reactive T cells have been found in human patients with IDDM.

- CD8+ CTLs are thought to be responsible for the actual killing of the islet cells.
- Autoantibodies are present in IDDM. However, animal models of IDDM have shown that these autoantibodies alone cannot cause IDDM.
**Experimental autoimmune encephalomyelitis (EAE)**

Mouse model for multiple sclerosis

Injection of normal mice or rats with MBP in complete Freund's adjuvant can induce EAE.

**EAE Mouse Model for MS**

MBP-specific CD4+T cell clones can be isolated from mice with EAE and injection into normal animals to cause disease.

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**EAE Model for MS**

- Immunodominant epitopes of MBP have been identified.
- Different MHC haplotypes have one or two MBP peptides that are encephalitogenic, (i.e. capable of inducing disease).

**NOD (non-obese diabetic) mice**

Mouse model of IDDM

- NOD mice spontaneously develop insulitis and "diabetes-like" disease between 2 and 4 months of age.
- NOD mice injected with T_{reg} cells delay developing diabetes.
- These T_{reg} (CD4+ CD25+) cells can suppress by making--IL-10, TGF-β.

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**Mouse Model of Lupus**

- F1 cross of NZ Black X NZ White mice
  - Mice spontaneously develop immune complex disease similar to SLE. Abs to DNA, nucleoproteins.
  - Genetically complex heterozygous model of disease.
  - But used to identify lupus-associated genes e.g. Nba.2

**B6.Nba2 Mice as Model of Lupus**

B6.Nba2 mice are congenic for this lupus associated gene– but DO NOT develop full disease but have gender differences.

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Autoantibody production in female vs male B6.Nba2 mice

*Immunol. 2005 Nov 1;175(9):6190-6.*
Susceptibility Factors

MHC

◆ Relative Risk--- ratio of having a specific MHC allele increases risk for that disease.
  – E.g. Ankylosing spondylitis, an inflammatory disease of the vertebral joints, the RR with HLA-B27 is 87.

MHC

Risk for Diabetes (IDDM)

<table>
<thead>
<tr>
<th>Healthy controls</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>MHC class I</td>
<td>MHC class II</td>
</tr>
<tr>
<td>DR4 (30%)</td>
<td>DR3 (30%)</td>
</tr>
<tr>
<td>DR5 (25.7%)</td>
<td>DR2 (25.7%)</td>
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</tbody>
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The relative risk associated with having the DR3/DR4 combination is 25:1

Susceptibility Factors

Gender

◆ Increased risk associated with gender.
  – e.g. Female to male ratio for
    SLE 10:1
    MS 5:1
    Hashimoto's thyroiditis 4:1
    But IDDM is 1:1 and AS is 0.3:1.
    Why??

Susceptibility Factors

Gender

SLE (Lupus) 10:1  female:male

◆ Humans with SLE have increased estrogen
◆ Mouse/humans -lupus during pregnancy
◆ Mouse models-difference in estrogen receptors

Do increased hormones or stress exacerbate disease?

Susceptibility Factors

Gender

Does estrogen cause Th2 bias and increased lupus?

Susceptibility Factors

Immune regulation genes

◆ Increased risk associated with changes in expression of immune regulation genes.

◆ Decreased expression of Fas, FasL, assoc with SLE.

◆ Decreased amount of Complement proteins (C1, C2, C4) has been assoc with SLE.
## Susceptibility

### Environmental factors

- Smoking has been associated with Goodpasture's syndrome.
  - Potentially the damage to lung basement membrane helps trigger autoimmune response.
- Pollution, occupational exposure, etc.

## Treatment of Autoimmune Diseases

### Pharmacotherapy

- Anti-inflammatories—steroids or NSAIDS.
- Other specific drugs for symptoms e.g. insulin, thyroid hormones

### Immunotherapy

- Targeted antibodies to lyse autoreactive B cells.
- Block co-stimulation or CAMs.
- Multiple sclerosis - beta-interferon and synthetic altered peptides of MBP block T cell activation.