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.

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.

Inducing Autoimmunity
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.

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.
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.

Antibodies to rbc antigens

**Autoantibodies to surface receptors**

Graves' disease = hyperthyroid
Stimulating autoantibodies bind thyrotropin receptor for thyroid stimulating hormone.
Antibodies to acetylcholine receptors block muscle activation and trigger inflammation that causes the destruction of the nerve/muscle junctions resulting in paralysis.

**Myasthenia Gravis**

Blocking Autoantibodies

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**Hashimoto's thyroiditis** = hypothyroid

- Blocking autoantibodies inhibit thyroid function.

**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.

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

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

**Multiple sclerosis (MS)**

- 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?

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**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.

**Type I diabetes**

Specific killing of insulin producing β islet cells
Diabetes

- 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.

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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.

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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.
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

- 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.

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.

Autoantibody production in female vs male B6.Nba2 mice

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.

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??

MHC

Risk for Diabetes (IDDM)

The relative risk associated with having the DR3/DR4 combination is 25:1

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.