Autoimmunity

Robert Beatty
MCB150

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**.

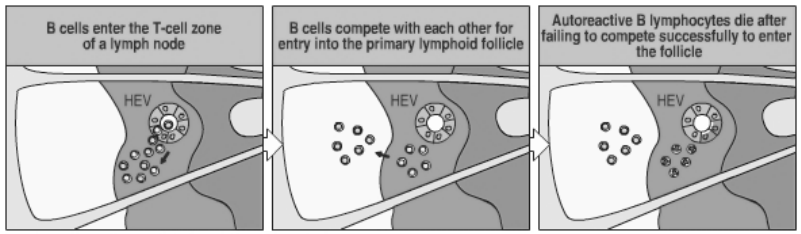
Immune Tolerance

- 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.

Inducing Autoimmunity

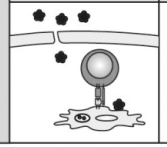
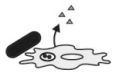
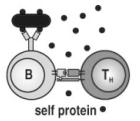
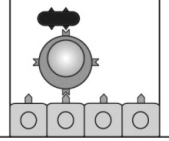
Mechanism	Disruption of cell or tissue barrier	Infection of antigen-presenting cell	Binding of pathogen to self protein	Molecular mimicry	Superantigen
Effect	Release of sequestered self antigen; activation of nontolerized cells	Release of inflammatory mediators, notably IFN-α	Pathogen acts as carrier to allow anti-self response	Production of cross-reactive antibodies or T cells	Polyclonal activation of autoreactive T cells
Example	Sympathetic ophthalmia	? SLE	? Interstitial nephritis ? SLE	Rheumatic fever ? Diabetes ? Multiple sclerosis	? Rheumatoid arthritis
					

Figure 13-26 Immunobiology, 6/e. (© Garland Science 2005)

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

TABLE 20-3 MOLECULAR MIMICRY BETWEEN PROTEINS OF INFECTIOUS ORGANISMS AND HUMAN HOST PROTEINS

Protein*	Residue†	Sequence‡
Human cytomegalovirus IE2	79	P D P L G R P D E D
HLA-DR molecule	60	V T E L G R P D A E
Poliovirus VP2	70	S T T K E S R G T T
Acetylcholine receptor	176	T V I K E S R G T K
Papilloma virus E2	76	S L H L E S L K D S
Insulin receptor	66	V Y G L E S L K D L
Rabies virus glycoprotein	147	T K E S L V I I S
Insulin receptor	764	N K E S L V I S E
Klebsiella pneumoniae nitrogenase	186	S R Q T D R E D E
HLA-B27 molecule	70	K A Q T D R E D L
Adenovirus 12 E1B	384	L R R G M F R P S Q C N
α-Gliadin	206	L G Q Q G S F R P S Q Q N
Human immunodeficiency virus p24	160	G V E T T T P S
Human IgG constant region	466	G V E T T T P S
Measles virus P3	13	L E C I R A L K
Corticotropin	18	L E C I R A C K
Measles virus P3	31	E I S D N L G Q E
Myelin basic protein	61	E I S F K L G Q E

*In each pair, the human protein is listed second. The proteins in each pair have been shown to exhibit immunologic cross-reactivity.

†Each number indicates the position in the intact protein of the amino-terminal amino acid in the listed sequence.

‡Amino acid residues are indicated by single-letter code. Identical residues are shown in blue.

SOURCE: Adapted from MBA Oldstone, 1987, *Cell* **50**:819.

Breaking of self-tolerance

- 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

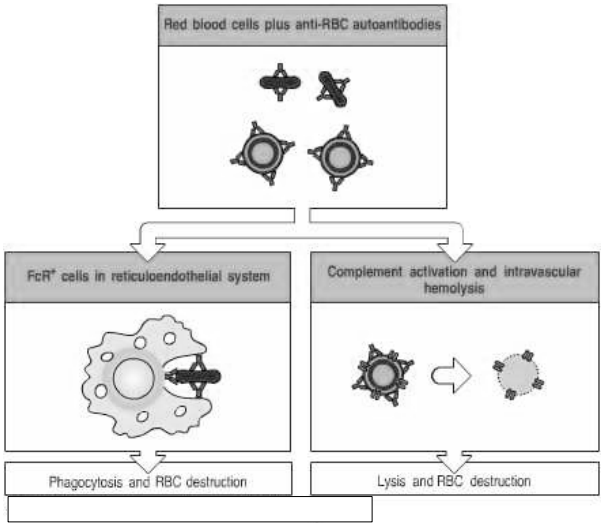
autoimmune diseases

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

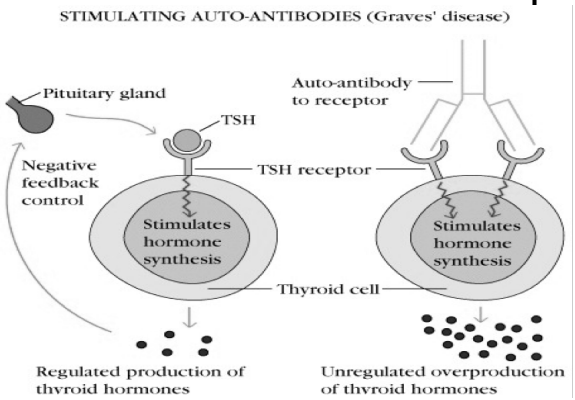
Antibodies to rbc antigens



Autoimmune hemolytic anemia

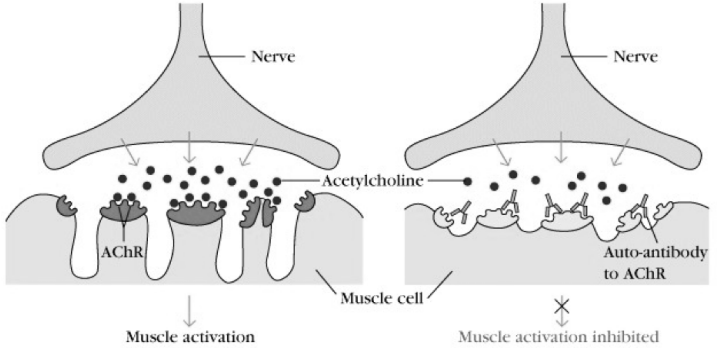
- IgM abs thought to be from infection
  - Mycoplasma or Epstein Barr virus thought to be associated.
  - Can be transient as long as you have infection.
  - Unclear how exactly triggered.

Autoantibodies to surface receptors



Graves' disease =hyperthyroid
Stimulating autoantibodies bind thyrotropin receptor for thyroid stimulating hormone.

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.

Autoantibodies to surface receptors
Blocking autoantibodies

- **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.

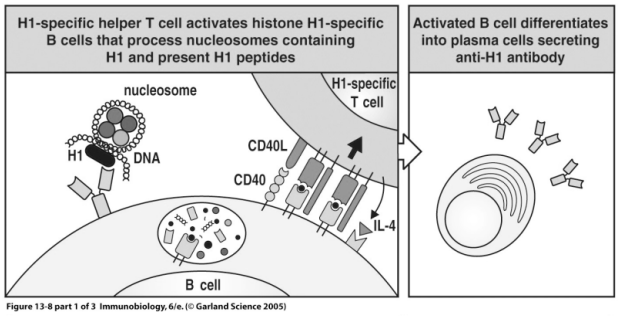
Systemic lupus erythematosus (SLE) Immune complex disease

- 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.

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 intracellula 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.

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?

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

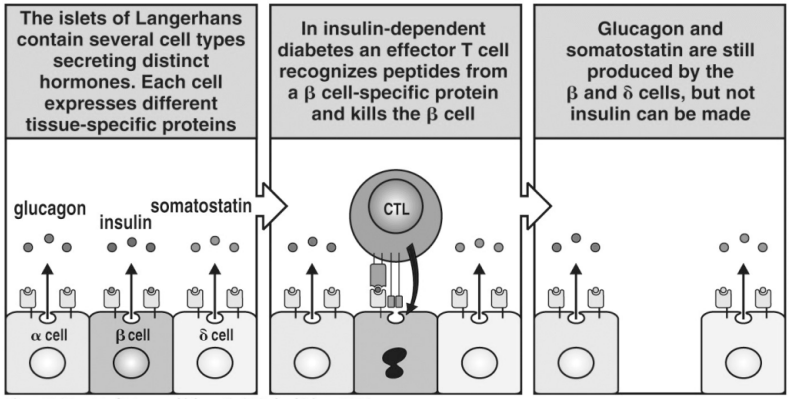


Figure 13-34 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

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.

TABLE 20-2 EXPERIMENTAL ANIMAL MODELS OF AUTOIMMUNE DISEASES

Animal model	Possible human disease counterpart	Inducing antigen	Disease transferred by T cells
Spontaneous autoimmune disease			
Nonobese diabetic (NOD) mouse	Insulin-dependent diabetes mellitus (IDDM)	Unknown	Yes
(NZB × NZW) F_1 mouse	Systemic lupus erythematosus (SLE)	Unknown	Yes
Obese-strain chicken	Hashimoto's thyroiditis	Thyroglobulin	Yes
Experimentally induced autoimmune disease*			
Experimental autoimmune myasthenia gravis (EAMG)	Myasthenia gravis	Acetylcholine receptor	Yes
Experimental autoimmune encephalomyelitis (EAE)	Multiple sclerosis (MS)	Myelin basic protein (MBP); proteolipid protein (PLP)	Yes
Autoimmune arthritis (AA)	Rheumatoid arthritis	*M. tuberculosis* (proteoglycans)	Yes
Experimental autoimmune thyroiditis (EAT)	Hashimoto's thyroiditis	Thyroglobulin	Yes

*These diseases can be induced by injecting appropriate animals with the indicated antigen in complete Freund's adjuvant. Except for autoimmune arthritis, the antigens used correspond to the self-antigens associated with the human-disease counterpart. Rheumatoid arthritis involves reaction to proteoglycans, which are self-antigens associated with connective tissue.

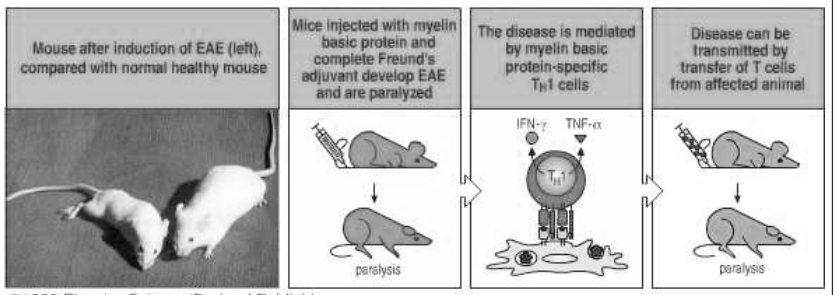
Experimental autoimmune encephalomyelitis (EAE)

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.



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

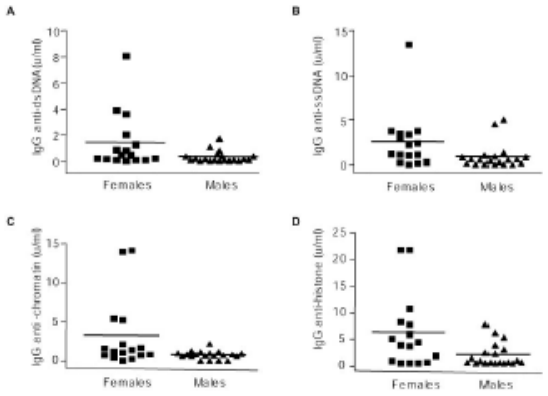
Mouse model of IDDM

- 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.

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

J 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)

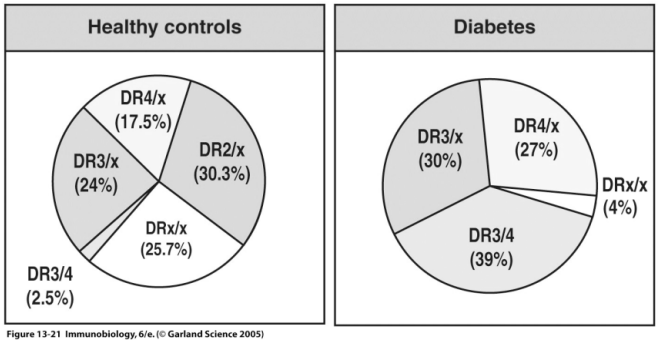


Figure 13-21 Immunobiology, 6/e. (© Garland Science 2005)

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

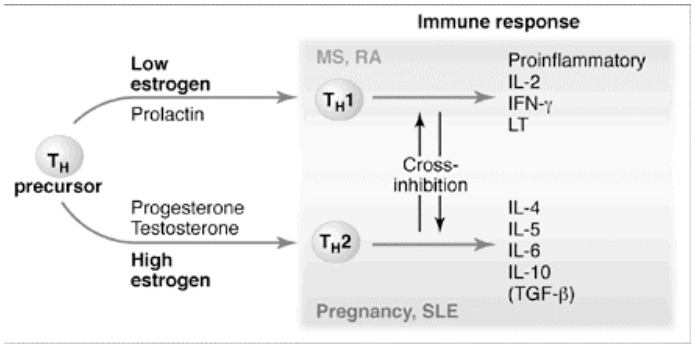
SLE (Lupus) 10:1 female:male

- 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.