

Autoimmune Disease

- Self tolerance is lost
- Specific adaptive immune responses mounted against self antigens
- Inability to eliminate antigen leads to chronic inflammatory process
- Ehrlich termed this *horror autotoxicus*

Autoimmune diseases mediated by cytotoxic antibodies (Type II)

Syndrome	Autoantigen	Consequences
Autoimmune hemolytic anemia	Rh blood group antigens, I antigen	Destruction of red blood cells by complement and phagocytes, anemia
Autoimmune thrombocytopenic purpura	Platelet integrin GpIIb:IIIa	Abnormal bleeding
Goodpasture's syndrome	Non-collagenous domain of basement membrane collagen type IV	Glomerulonephritis, Pulmonary hemorrhage
Pemphigus vulgaris	Epidermal cadherin	Blistering of skin
Acute rheumatic fever	Streptococcal cell-wall antigens, Antibodies cross-react with cardiac muscle	Arthritis, myocarditis, late scarring of heart valves

Autoimmune diseases mediated by immune complexes (Type III)

Syndrome	Autoantigen	Consequences
Mixed essential cryoglobulinemia	Rheumatoid factor IgG complexes (with or without hepatitis C antigens)	Systemic vasculitis
Systemic lupus erythematosus	DNA, histones, ribosomes, snRNP, scRNP	Glomerulonephritis, vasculitis, arthritis

Autoimmune diseases mediated by T-cells (Type IV)

Syndrome	Autoantigen	Consequences
Insulin-dependent diabetes mellitus	Pancreatic β -cell antigen	β -cell destruction
Rheumatoid arthritis	Unknown synovial joint antigen	Joint inflammation and destruction
Experimental autoimmune encephalomyelitis (EAE), multiple sclerosis	Myelin basic protein, proteolipid protein, myelin oligodendrocyte glycoprotein	Brain invasion by CD4 T cells, paralysis

Autoimmune disease susceptibility

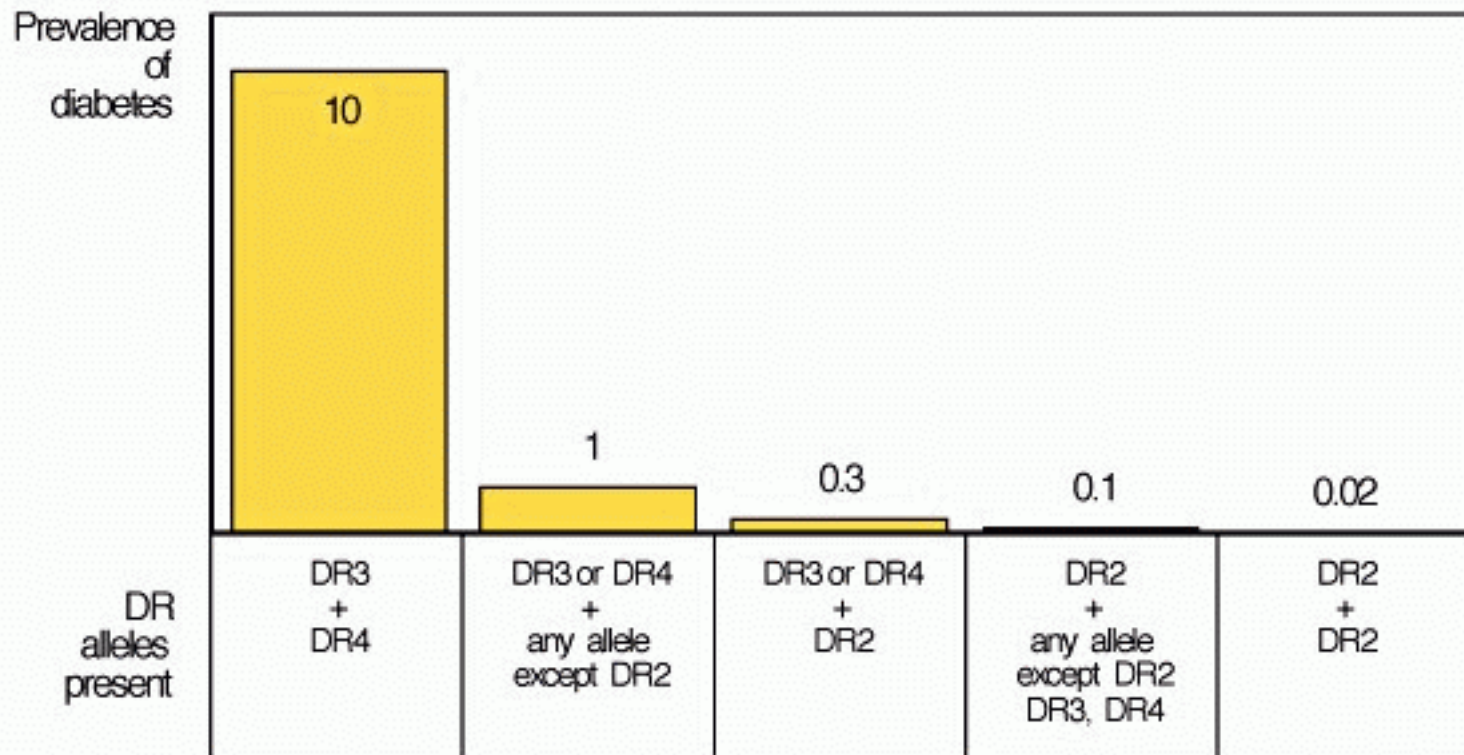
- Genetic predisposition
 - Twin studies (Diabetes: 20% monozygotic vs. 5% dizygotic)
 - Family studies
- Association with MHC genotype
 - HLA genotyping

Associations of HLA genotype with susceptibility to autoimmune disease

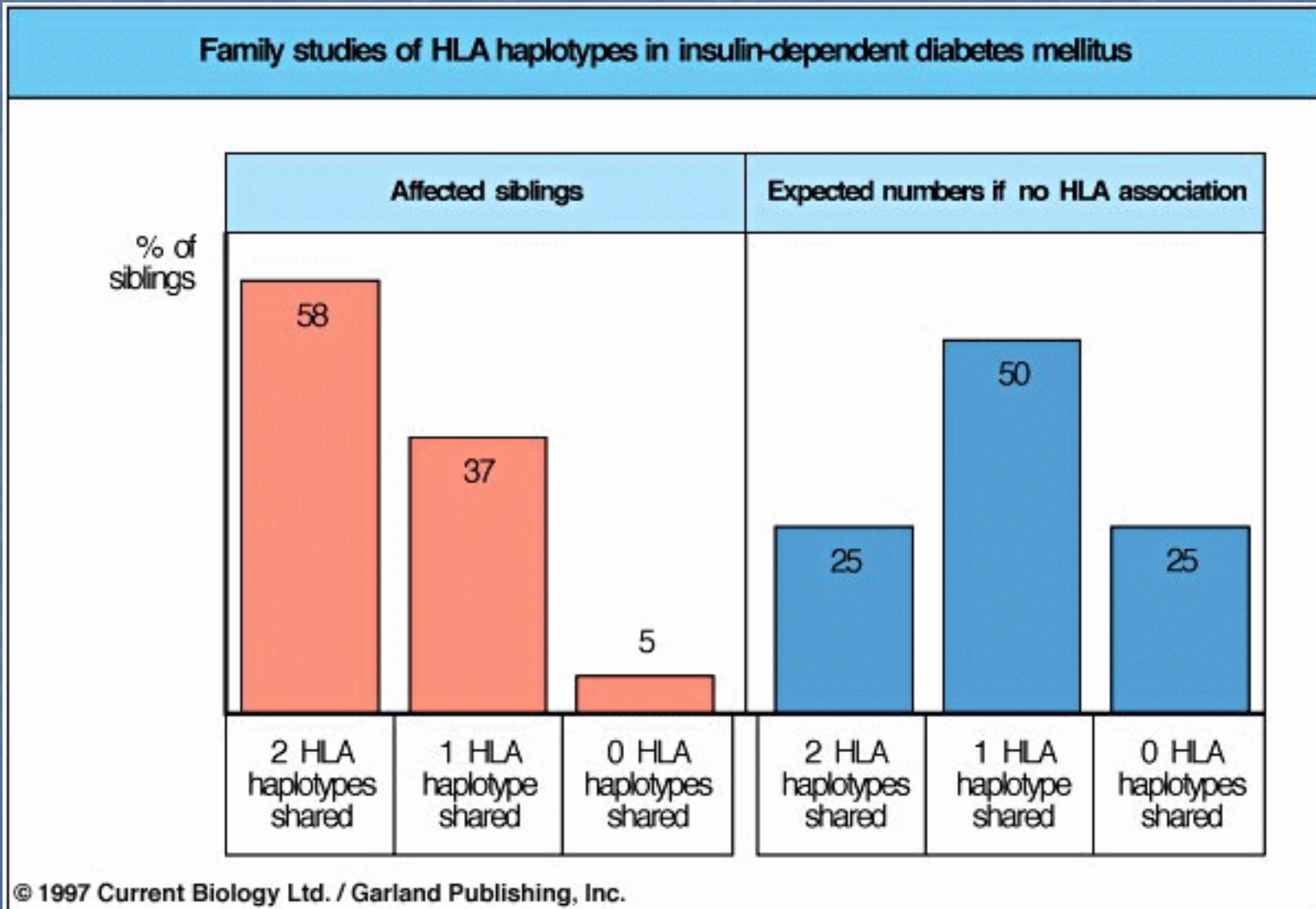
Disease	HLA allele	Relative risk	Sex ratio (♀:♂)
Ankylosing spondylitis	B27	87.4	0.3
Acute anterior uveitis	B27	10.04	<0.5
Goodpasture's syndrome	DR2	15.9	~1
Multiple sclerosis	DR2	4.8	10
Graves' disease	DR3	3.7	4-5
Myasthenia gravis	DR3	2.5	~1
Systemic lupus erythematosus	DR3	5.8	10-20
Insulin-dependent diabetes mellitus	DR3 and DR4	3.2	~1
Rheumatoid arthritis	DR4	4.2	3
Pemphigus vulgaris	DR4	14.4	~1
Hashimoto's thyroiditis	DR5	3.2	4-5

Population studies show association of susceptibility to insulin-dependent diabetes mellitus (IDDM) with HLA genotype

Population studies of HLA-DR alleles in insulin-dependent diabetes mellitus



Family studies show strong linkage of susceptibility to insulin-dependent diabetes mellitus (IDDM) with HLA genotype



Autoimmunity involves T cells

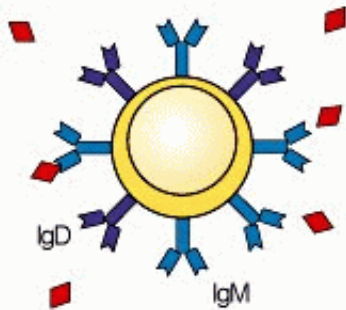
- Ability of a T cell to respond is determined by MHC genotype
- It has been hypothesized that susceptibility to an autoimmune disease is determined by differences in the ability of allelic variants of MHC molecules to present autoantigenic peptides
- Alternatively, self peptides may drive the positive selection of developing thymocytes that are specific for particular autoantigens.

Levels of autoantigens may drive T cell selection

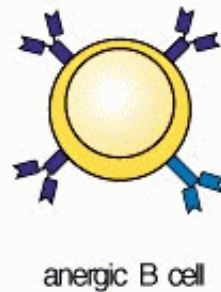
- If antigens are expressed at too low a level, they may not drive negative intrathymic selection, but sufficient to drive positive selection
- Insulin genes transcribed at high level in thymus protect against diabetes

Peripheral B-cell anergy

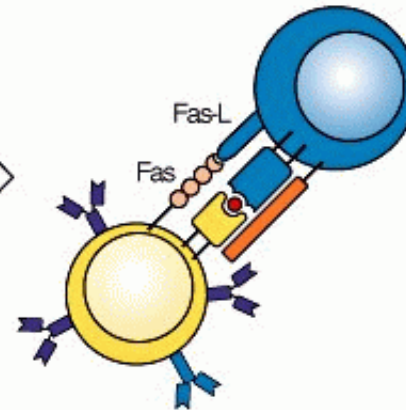
Autoreactive B cell encounters a self antigen



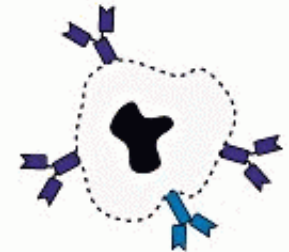
Autoreactive B cell becomes anergic



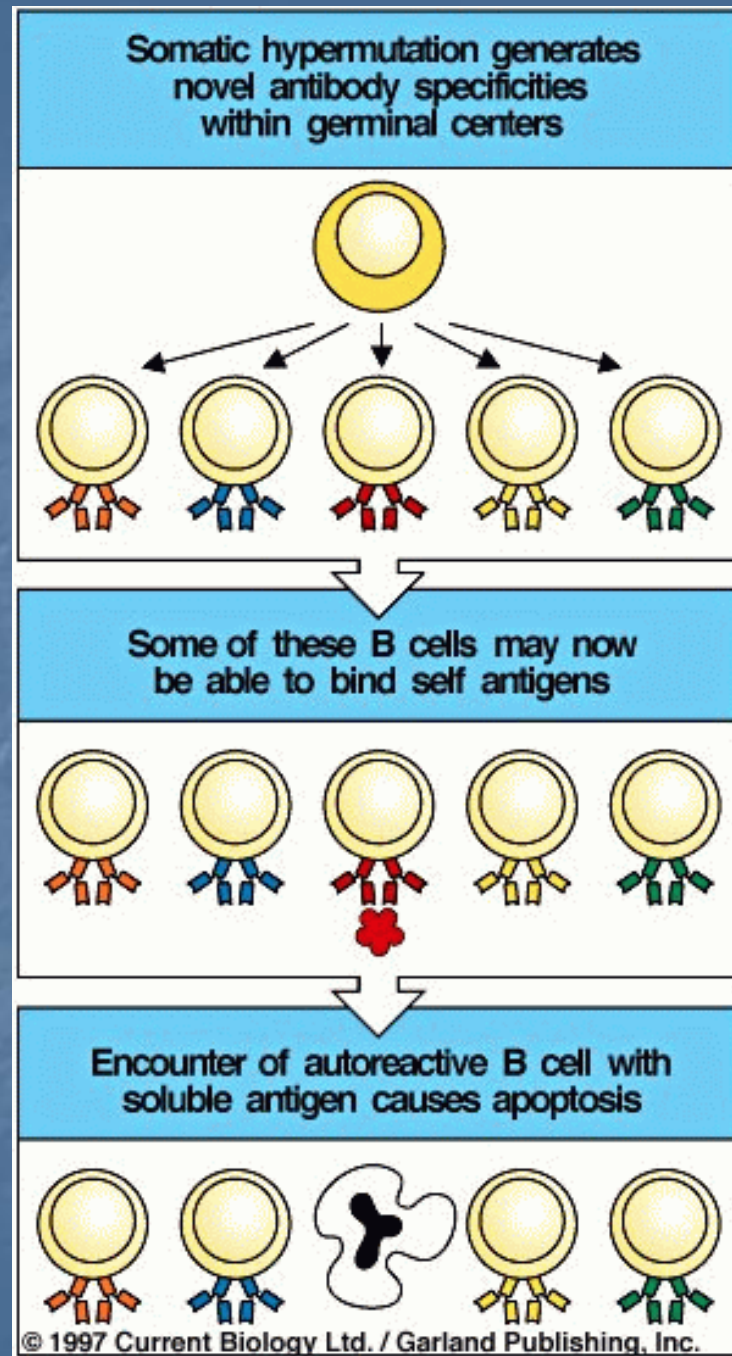
A subsequent encounter of the anergic B cell with a CD4 T cell leads to signaling through Fas



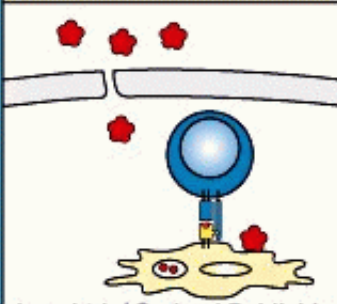
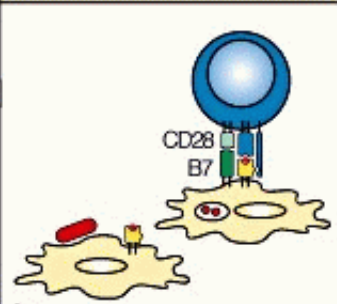
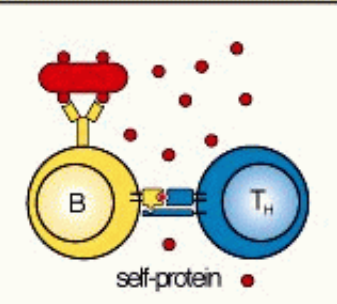
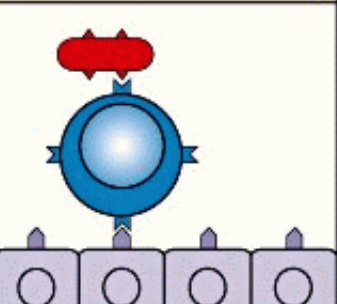
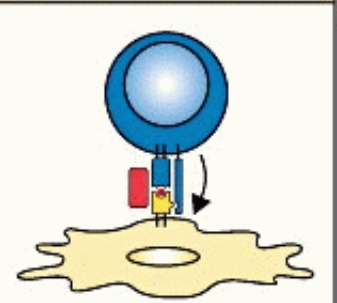
Signals through Fas induce apoptosis—eliminating the autoreactive B cell



Elimination of autoreactive B cells in germinal centers



Several ways in which infectious agents could break self tolerance

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 non-tolerized cells	Induction of co-stimulator activity	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	Effect of adjuvants: induction of EAE	? Interstitial nephritis	Rheumatic fever ? Diabetes ? Multiple sclerosis	? Rheumatoid arthritis
					

Association of infection with autoimmune disease

Associations of infection with immune-mediated tissue damage		
Infection	HLA association	Consequence
Group A <i>Streptococcus</i>	?	Rheumatic fever (carditis, polyarthritis)
<i>Chlamydia trachomatis</i>	HLA-B27	Reiter's syndrome (arthritis)
<i>Shigella flexneri</i> , <i>Salmonella typhimurium</i> , <i>Salmonella enteritidis</i> , <i>Yersinia enterocolitica</i> , <i>Campylobacter jejuni</i>	HLA-B27	Reactive arthritis
<i>Borrelia burgdorferi</i>	HLA-DR2, DR4	Chronic arthritis in Lyme disease

Some body sites are immunologically privileged

Immunologically privileged sites
Brain
Eye
Testis
Uterus (fetus)
Hamster cheek pouch

Damage to an immunologically privileged site can induce an autoimmune response

