The immune system **learn to** discriminate between self and non-self

Immunological tolerance

- Unresponsive state that is specific for a particular Ag
- Active tolerance mechanisms are required to prevent inflammatory responses to many innocuous air-borne and food Ags.
- The most important aspect of tolerance, is **self tolerance**

Self tolerance

- Prevents the body from mounting an immune attack against **its own tissues**
- a vast diversity of antigen-specific receptors (BCR, TcR) some of which will be self reactive.
- Cells bearing these receptors must be eliminated, either functionally, physically or regulated.

Self tolerance

Tolerance to self is initially induced during embryonic life

– Tolerance occurs in both T and B cells

– Multiple mechanisms of tolerance exist

Loss of self tolerance can lead to autoimmunity

Layers of self-tolerance		
Type of tolerance	**Mechanism**	**Site of action**
Central tolerance	Deletion Editing	Thymus Bone marrow
Antigen segregation	Physical barrier to self-antigen access to lymphoid system	Peripheral organs (eg, thyroid, pancreas)
Peripheral anergy	Cellular inactivation by weak signaling without co-stimulus	Secondary lymphoid tissue
Regulatory cells	Suppression by cytokines, intercellular signals	Secondary lymphoid tissue and sites of inflammation
Cytokine deviation	Differentiation to T_H2 cells, limiting inflammatory cytokine secretion	Secondary lymphoid tissue and sites of inflammation
Clonal exhaustion	Apoptosis post-activation	Secondary lymphoid tissue and sites of inflammation

Figure 13-16 Immunobiology, 6/e. (© Garland Science 2005)

Mechanisms of Immunological Tolerance

Mechanism that eliminates most *autoreactive* T and B cells during lymphocyte development.

• ***Central Tolerance***
Negative selection (clonal deletion) is a process that establish the centranl tolerance in the thymus and bone marrow.

• ***Peripheral tolerance***
Autoreactive cells that escape central tolerance are prevented from attacking self cells by the mechanisms of ***peripheral tolerance.***

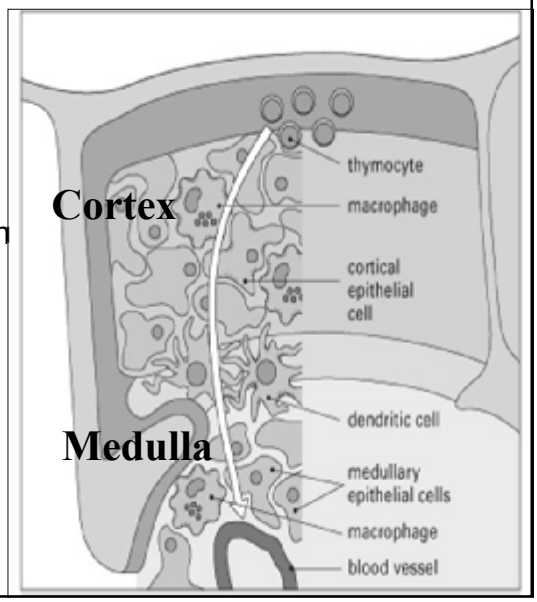
Central tolerance

T cell selection is compartmentalized in the thymus

The thymus is made up of lobes:

Subcapsular region
Immature lymphocytes
Cortex
Immature lymphocytes associated with Cortical epithelial cells

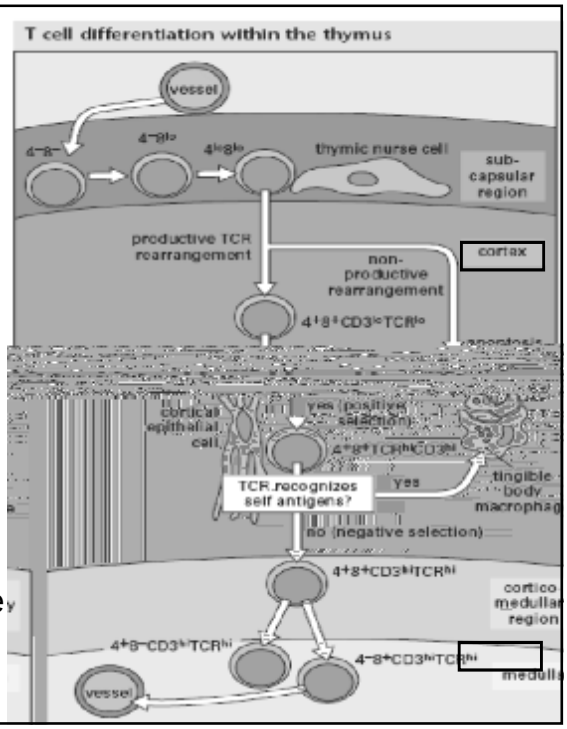
Medulla
- Mature lymphocytes
- Medullary epithelial cells
- Macrophage / dendritic cells



Central T-Cell Selection of self-tolerance

- CD4-CD8- (DN) T-cell progenitors enter the thymic cortex and rearrange their receptors to become CD4+CD8+ (DP) thymocytes.
- Positive and negative selection occurs in the thymus.

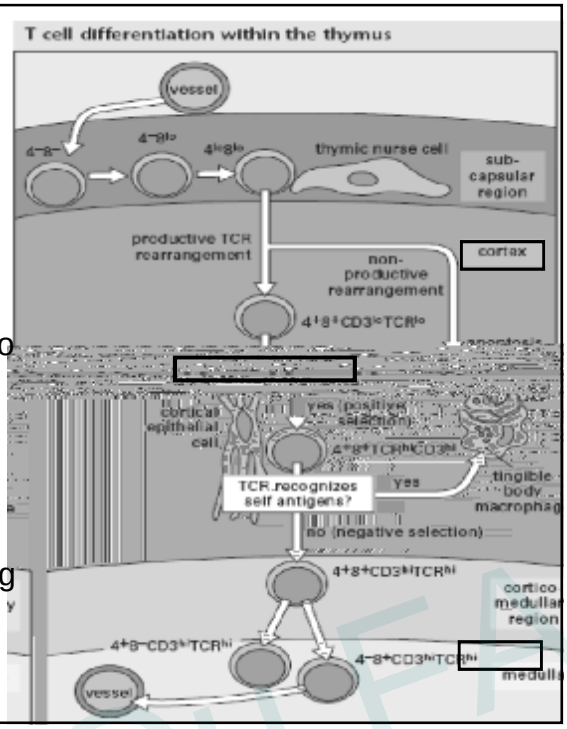
- pre-thy TCs are attracted and enter the thymic at the corticomedullary junction.
- Reach the subcapsular region: proliferate , differentiatie.
- acquire CD8 then CD4 at low density.
- Cortex: rearrangement TCR
- Maturing cells move deeper into the cortex, adhere to cortical epithelial cells (elongated, branched: provide a large surface area for contact with thymocytes



- TCRs exposed to epithelial MHC molecules: **positive selection.**
The first stage of thymic education

- only TCRs with an intermediate affinity for self MHC are allowed to develop further

- cells not selected : apoptosis
CD3, TCR, CD4, and CD8 during migration to the deeper cortex.

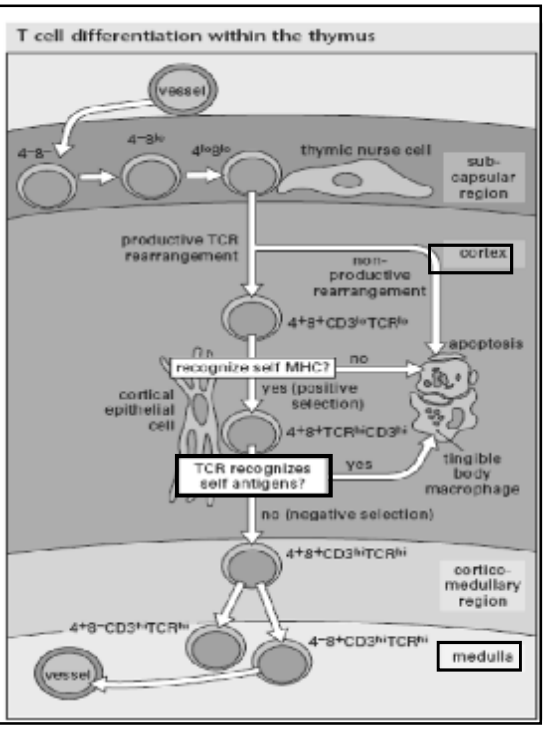


Negative selection

• TCRs self reactivity are deleted through contact with autoAgs presented by:

- medullary thymic epithelial , interdigitating cells, MQ at the corticomedullary junction.

• Cells CD4 or CD8 appear and exit to the periphery via specialized vessels at the corticomedullary junction.



- TCR that bind **with moderate affinity** to self-peptide-MHC complexes on thymic epithelia receive a **survival signal (positive selection)**
- The AutoAgs are host tissue proteins expressed on thymic epithelia under regulation of the transcription **factor autoimmune regulator (AIRE).**
- Many T-cells are eliminated

Autoimmune Polyglandular syndrome type I (APS-1)

- a rare autoimmune disease results from autosomal recessive mutations of the human a autoimmune regulatory (AIRE) gene
- Characterized by at least two of the following major criteria:

- chronic mucocutaneous candidiasis,
- autoimmune adrenocortical insufficiency (Addison's disease),
- hypoparathyroidism.

Peripheral tolerance

- Occurs in the periphery after lymphocyte development
- Functional silencing or deletion of self-reactive lymphocytes that escaped elimination during the establishment of *central tolerance*.
- Established by a collection of mechanisms that act outside the thymus and bone marrow

Layers of self-tolerance

Type of tolerance	Mechanism	Site of action
Central tolerance	Deletion Editing	Thymus Bone marrow
Antigen segregation	Physical barrier to self-antigen access to lymphoid system	Peripheral organs (eg, thyroid, pancreas)
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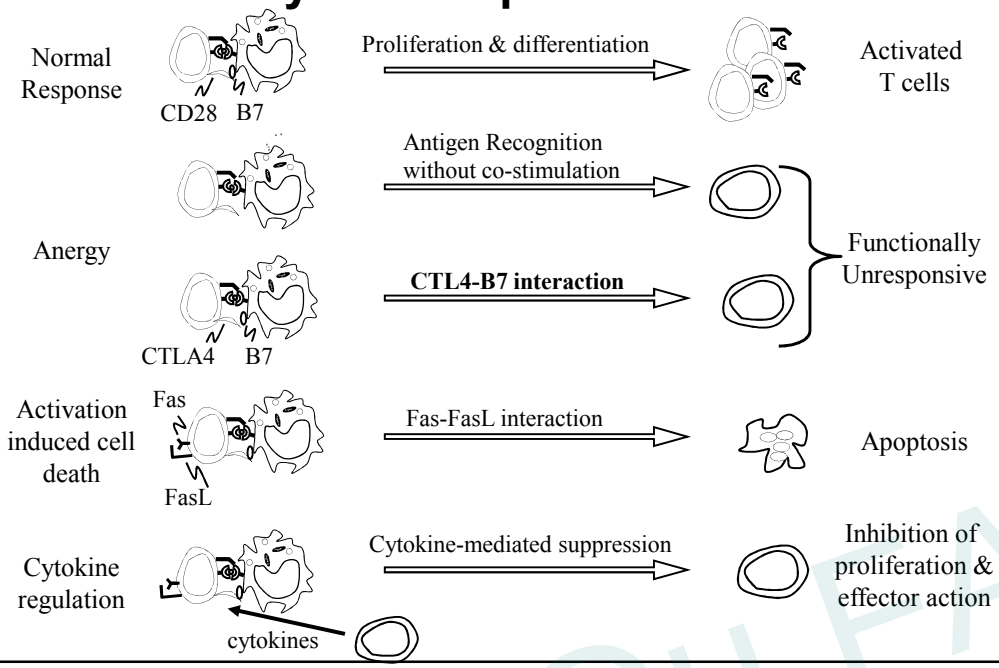
Figure 13-16 Immunobiology, 6/e. (© Garland Science 2005)

Pathways to Peripheral Tolerance



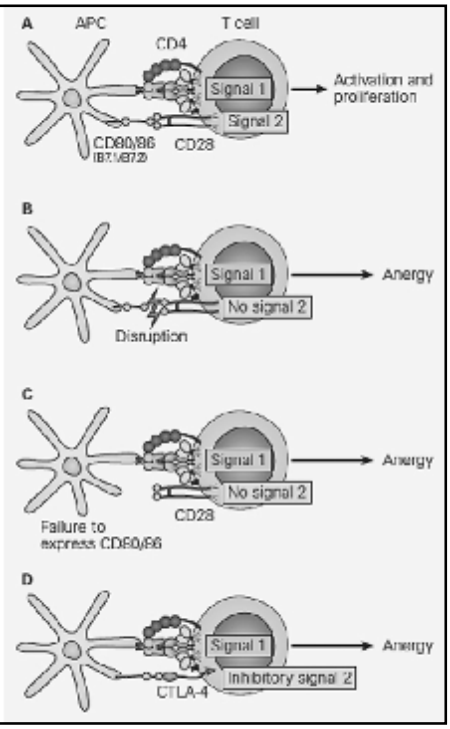
Anergy

- Major mechanism inactivating peripheral autoreactive T-cell

- Anergic T-cell cannot respond to antigenic stimuli: they do not produce IL-2 or IL-2R.

- Shortly after stimulation, T cell start displaying CTLA-4, which has a higher binding affinity than CD28 for CD80/86.

- CTLA-4 knockout mice develop profound lympho-proliferative disease



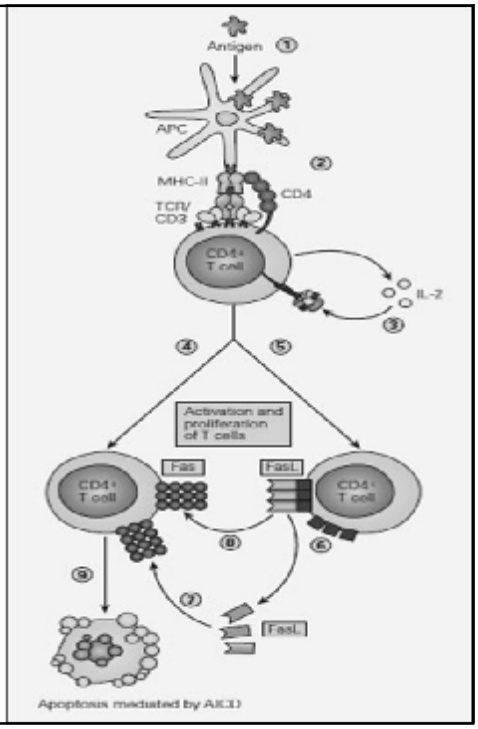
Clinical Signifificance of CTLA-4

•Rheumatoid arthritis : CTLA-4 is used as a biologic response modifier to treat patients, reducing joint inflammation.

- A fusion protein consisting of CTLA-4 and Ig (abatacept, belatacept) is used clinically in arthritis and after transplantation
- Blocking CTLA-4 using monoclonal antibodies (ipilimumab) in inhibiting tumor tolerance.

Clonal Deletion

- The best-studied mechanism eliminating activated T-cell clones is activation-induced cell death (AICD)
- Activated T-cells increase their expression of death receptors (Fas) and their ligands
- Ligation of Fas leads to T-cell apoptosis via the caspases :ending the immune response



Mutations in Clonal Deletion Pathways

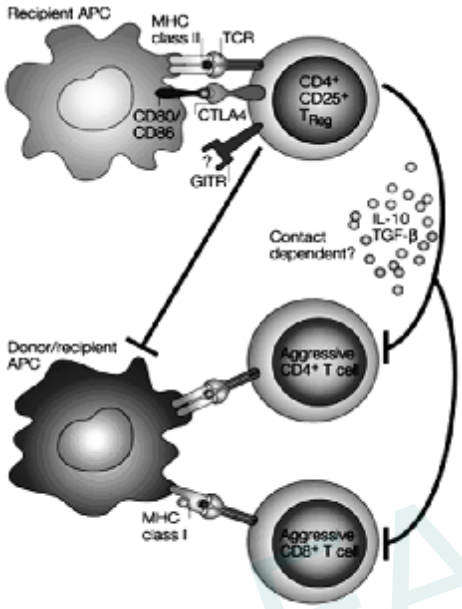
- Rare human diseases, caused by mutations in Fas or FasL. leading to lymphadenopathy and autoantibodies.
- Autoimmune lymphoproliferative syndrome (ALPS)
- IL-2 affects the Fas pathway, can lead to AICD by increasing FasL expression.
- IL-2 helps attenuate immunity by downregulating survival molecules.

Clonal exhaustion

An activated lymphocyte divides so quickly in the face of persistent Ag that its progeny reach the point at which they can no longer divide before memory cells have been generated.

Regulatory T Cells

- Inhibit the responses of other immune system cells.
- Inhibition is mediated by intercellular contacts and/or *immunosuppressive cytokine* secretion.
- Regulatory T cell populations may be induced or pre-existing.



immune deviation

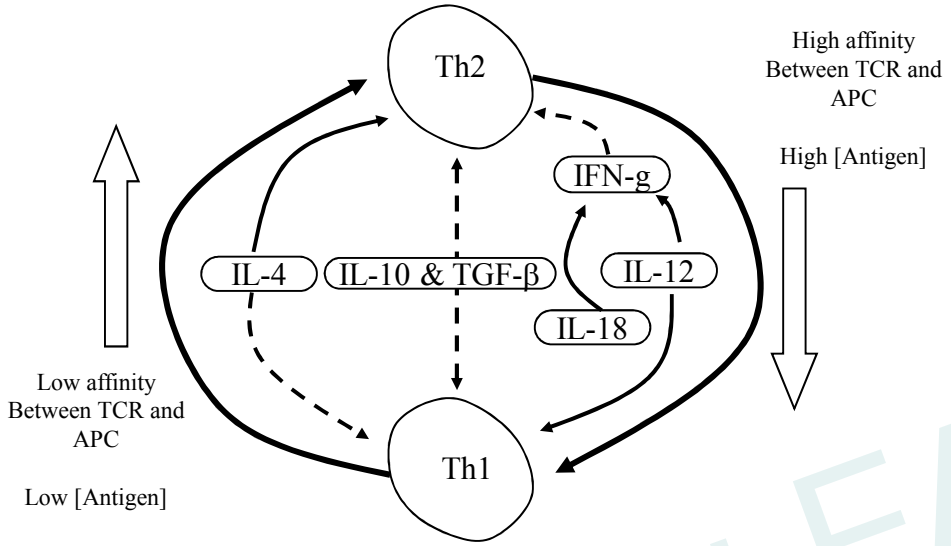
Conversion of an adaptive immune response that is harmful (autoimmunity or hypersensitivity) to a less harmful response.

Most often seen in the context of a switch from a Th1 to Th2 response, or vice versa.

Can appear to engender peripheral tolerance to an Antigen

immune deviation

$T_H1 – T_H2$ Balance



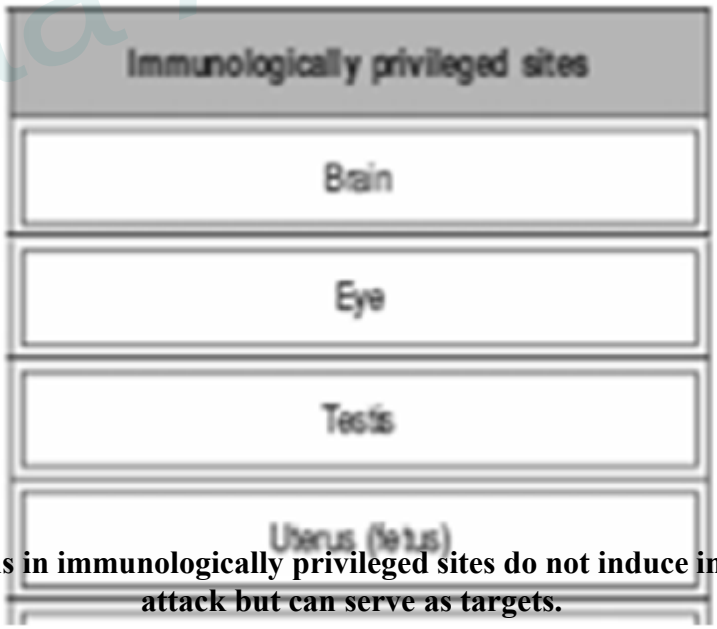
Th1 versus Th2 Balance

Disease	Th1	Th2
Experimental Leishmaniasis	**Cure**	Progression
Experimental autoimmune encephalomyelitis	Progression	**Prevention**
Tuberculosis	**Cure/Prevention**	Progression
Atopy	**Prevention?**	Progression
Type 1 Diabetes	Progression	**Prevention**

Immune privileged sites

Anatomical sites in which immune responses are actively or passively suppressed by:

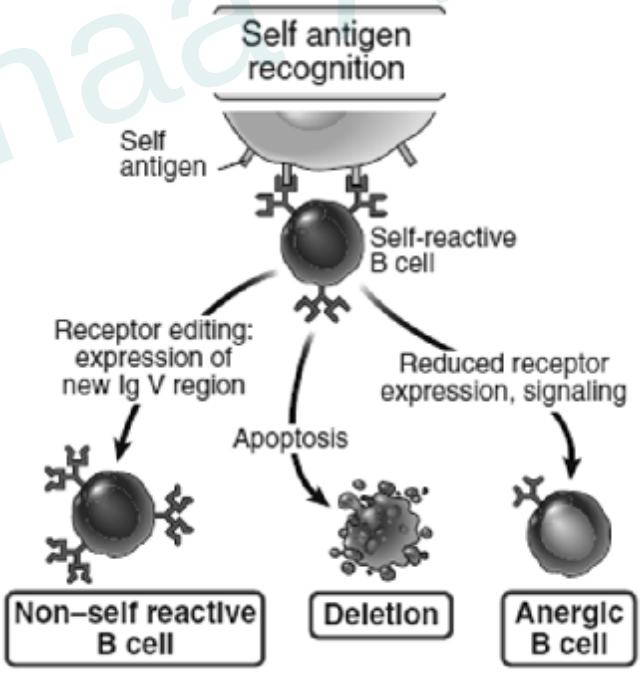
physical barriers,
hormone secretion,
low DC numbers,
immune deviation,
immunosuppressive,
cytokines, or Fas killing



Antigens in immunologically privileged sites do not induce immune attack but can serve as targets.

B-cell Tolerance

- During normal B-cell development, a set of processes help induce B-cell central tolerance
- Autoreactive B-cells are not necessarily eliminated during negative selection in the bone marrow
- B-cells that recognise autoantigens are eliminate via apoptosis or become anergic



Central tolerance in B lymphocytes

B-cell Peripheral Tolerance

exist for various reasons:

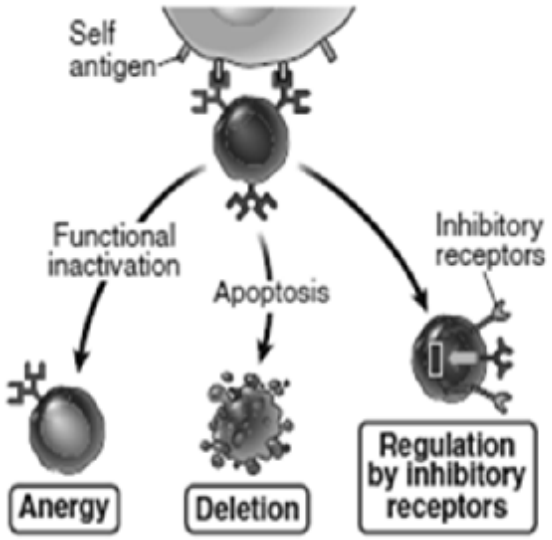
- **Imperfect T-cell tolerance**: in most autoimmune diseases, B-cells are T-cell dependent, requiring help from pre-activated cognate autoreactive T-cells.

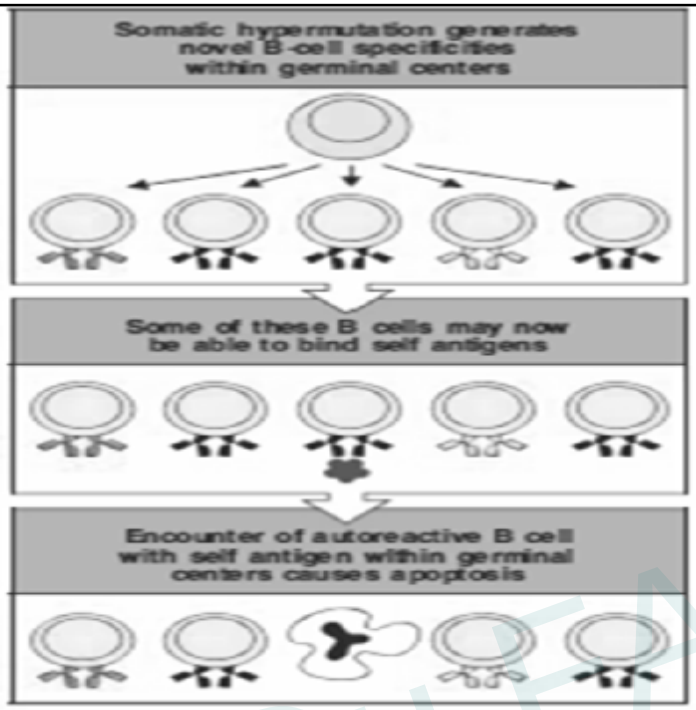
- T-independent B-cells can be activated by autoAg without T-cell help
- Microbial antigens structurally similar to autoAg can lead B-cells to produce cross-reactive Abs: **molecular mimicry**

- B-cells **hypermutate** their receptors on activation, so there is a second chance **that they may become self-reactive**

Peripheral tolerance in B lymphocyte

• Cells recognize an Ag, do not receive T cell help (helper T cells eliminated or are tolerant), the B cells become anergic



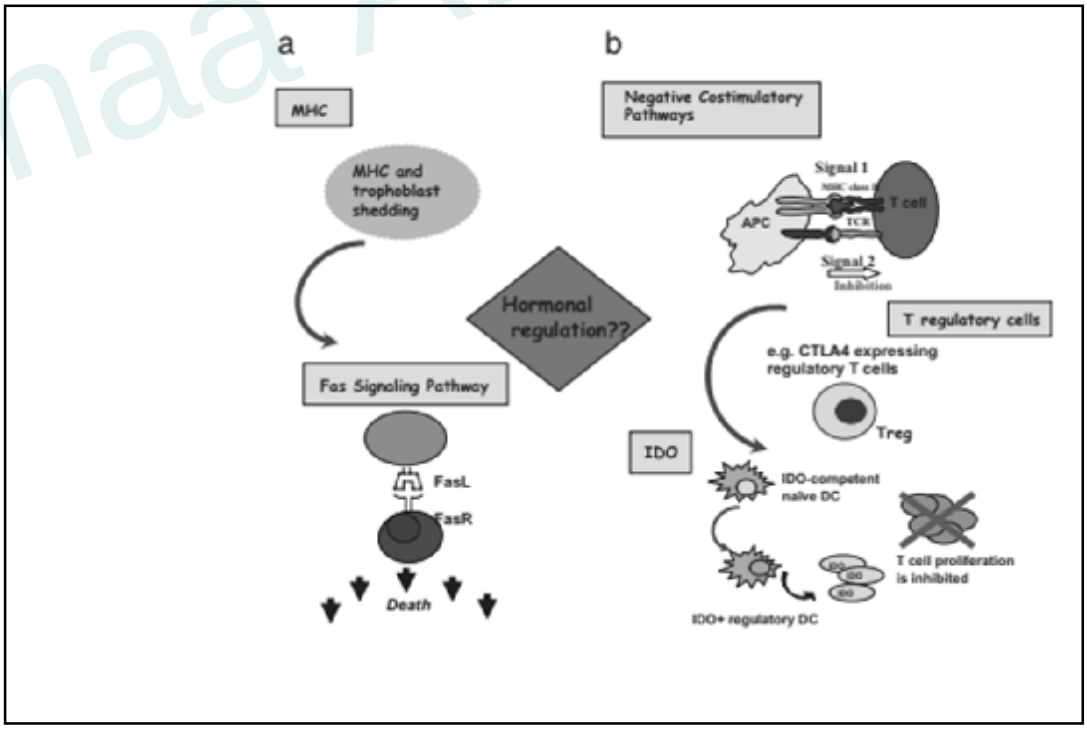


Fetal–Maternal Tolerance

- ✓ High levels of progesterone produced by placental cells suppress effector cells
- ✓ IL-10, TGF secretion by placental cells suppress effector cells
- ✓ IL-4, IL-5 secretion by placental cells induces immune deviation to Th2
- ✓ Low level of MHC class I/ class II on placental decreases antigen presentation

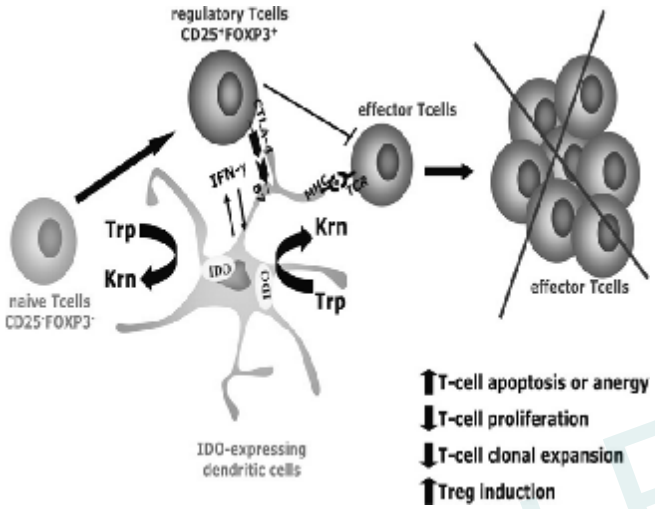
Fetal–Maternal Tolerance

- ✓ HLA-G expressed by fetal cells inactivates maternal NK cells
- ✓ Decay accelerating factor (DAF) and membrane cofactor protein **(**MCP) produced by fetal cells inhibit maternal complement activation
- ✓ FasL expressed by placental cells kills Fas-expressing activated maternal T cells
- ✓ Tryptophan deprivation via **indoleamine 2,3-dioxygenase** (IDO) production leads to decreased maternal T cell activation and increased Treg induction



IDO-mediated tryptophan degradation by DCs

tryptophan degradation along the kynurenine pathway

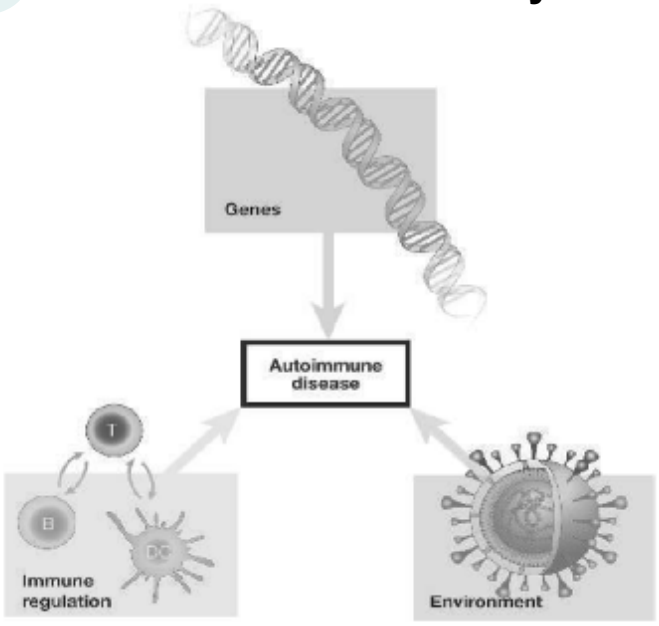


T regulatory cells

- Promoting fetal survival avoiding the recognition of semi-allogeneic tissues by maternal immune system.
- lower number of Treg cells is related to pregnancy complications.
- •Reproductive hormones act as modulators of immune reactions during pregnancy : induction of peripheral tolerance expansion of Treg cells.
- •Changes in the cytokines pattern during pregnancy can modulate the number and the function of Treg cells.

Autoimmunity

Causes of Autoimmunity



Complex Disease and Genetics

Associations of HLA serotype with susceptibility to autoimmune disease			
Disease	HLA allele	Relative risk	Sex ratio (♀:♂)
Ankylosing spondylitis	B27	87.4	0.3
Acute anterior uveitis	B27	10	< 0.5
Goodpasture's syndrome	DR2	15.9	~1
Multiple sclerosis	DR2	4.8	10
Graves' disease	DR3	3.7	4–5

Figure 13-20 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Environment

Pathogens, drugs, hormones, and toxins are just a few ways that the environment can trigger autoimmunity

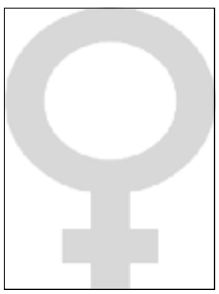
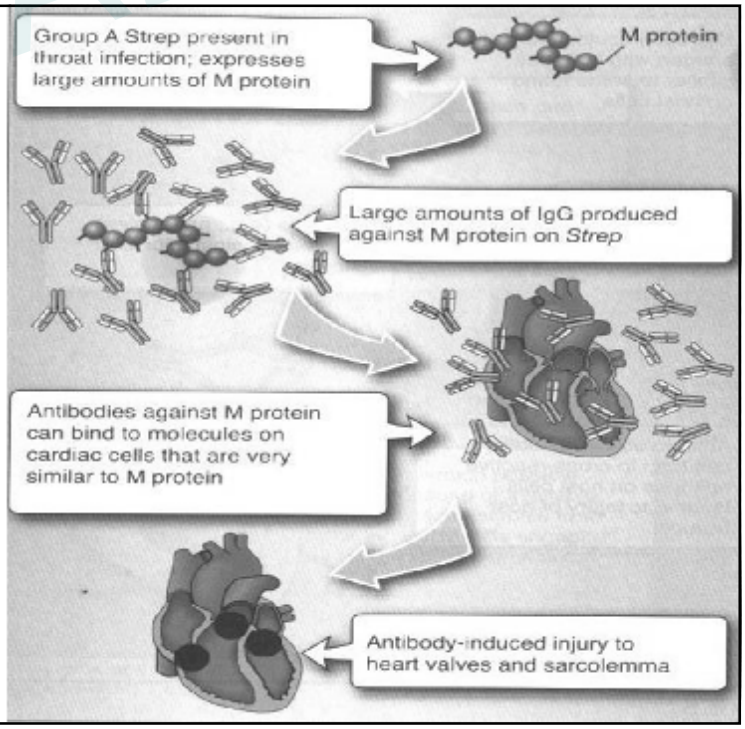


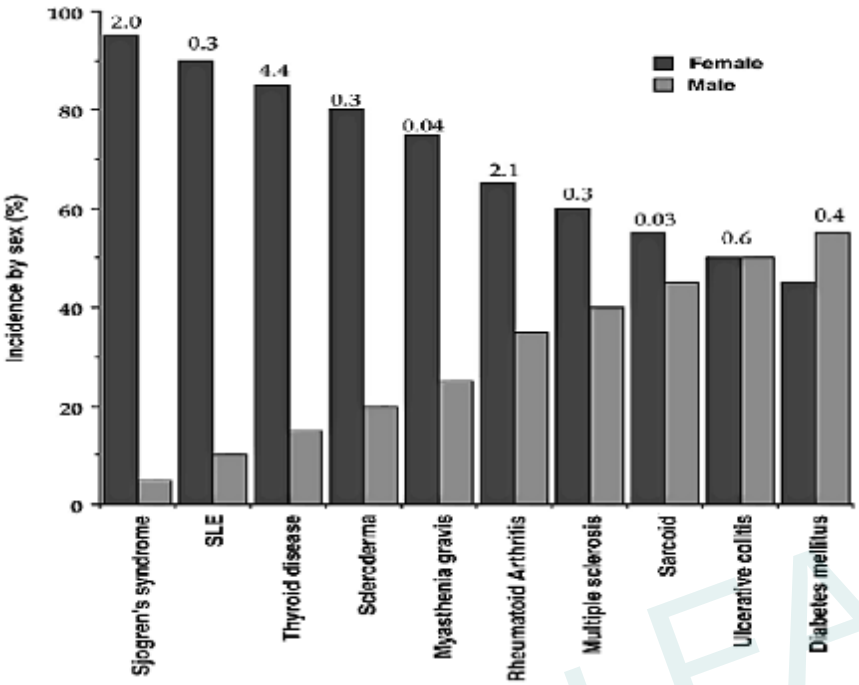
Table 1
Main Examples of Molecular Mimicry Between a Pathogen and Auto-Immune Disease

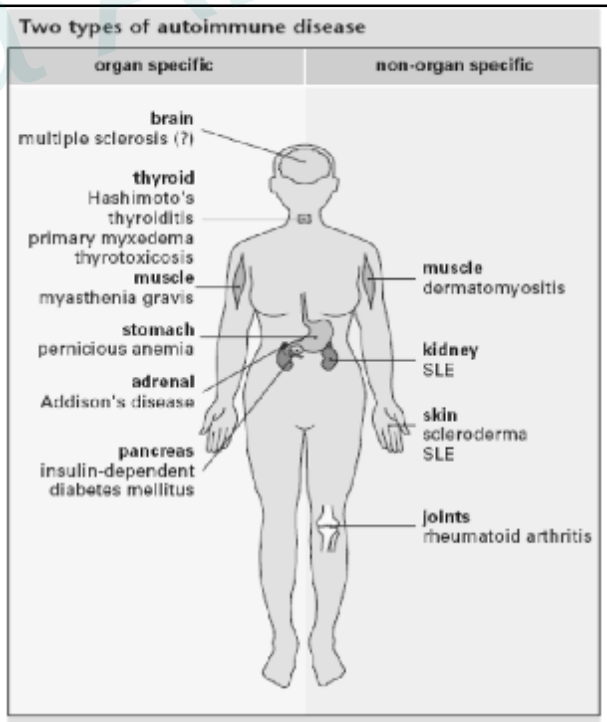
Disease	Host antigens	Pathogens
Chagas' cardiomyopathy	Ribosomal protein 23 kD, myosin, B13 protein, Cha-peptide.	*Trypanosoma cruzi*
Rheumatic fever	Cardiac myosin, tropomyosin laminin, vimentin, actin, keratin, *N*-acetyl-glucosamine	*Streptococcus pyogenes*
Myasthenia gravis	Acetylcholine receptor, neurofilaments	Herpes virus, *Hemophilus influenzae*
Multiple sclerosis	Myelin basic protein	Corona, measles, mumps, EBV, herpes
Guillain-Barré	Gangliosides, lipo-oligosaccharide	*Campylobacter jejuni*
Type 1 diabetes mellitus	Islet antigens:GAD 65, proinsulin carboxypeptidase H	Coxsackievirus B, Rotaviruses, Herpe
		hepatitis C, rhino-, hanta retroviral
Ankylosing spondylitis	HLA-B27, type I, II, IV collagen	*Klebsiella pneumoniae*, chlamydia
Antiphospholipid syndrome	β_2-glycoprotein-I	*Hemophilus influenza*, *Neisseria gonorea*, Tetanus toxin, CM
Systemic lupus erythematosus	Ro 60 kD, NMDA, dsDNA	EBVpneumococcal polysaccharide

Rheumatic fever



Sex differences in autoimmunity

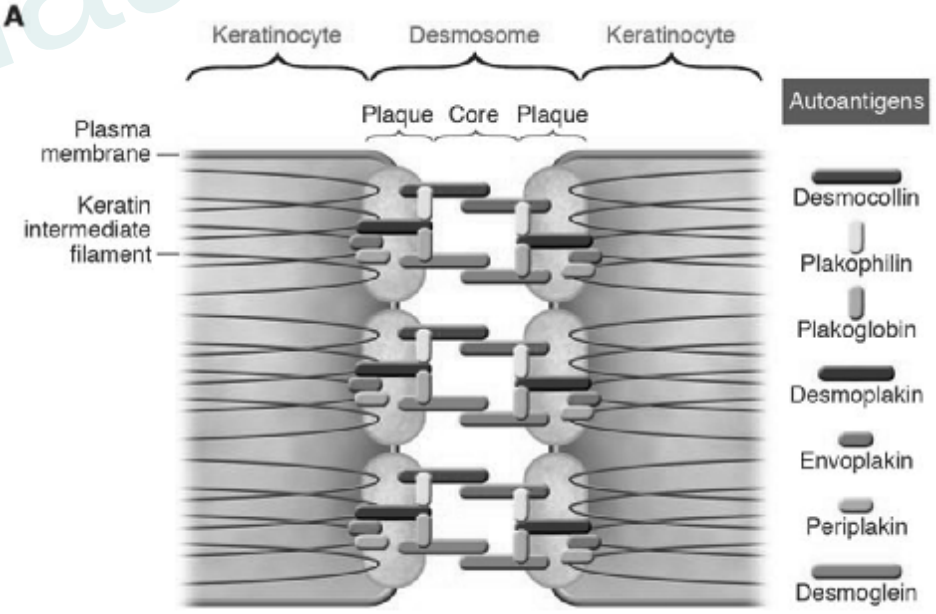


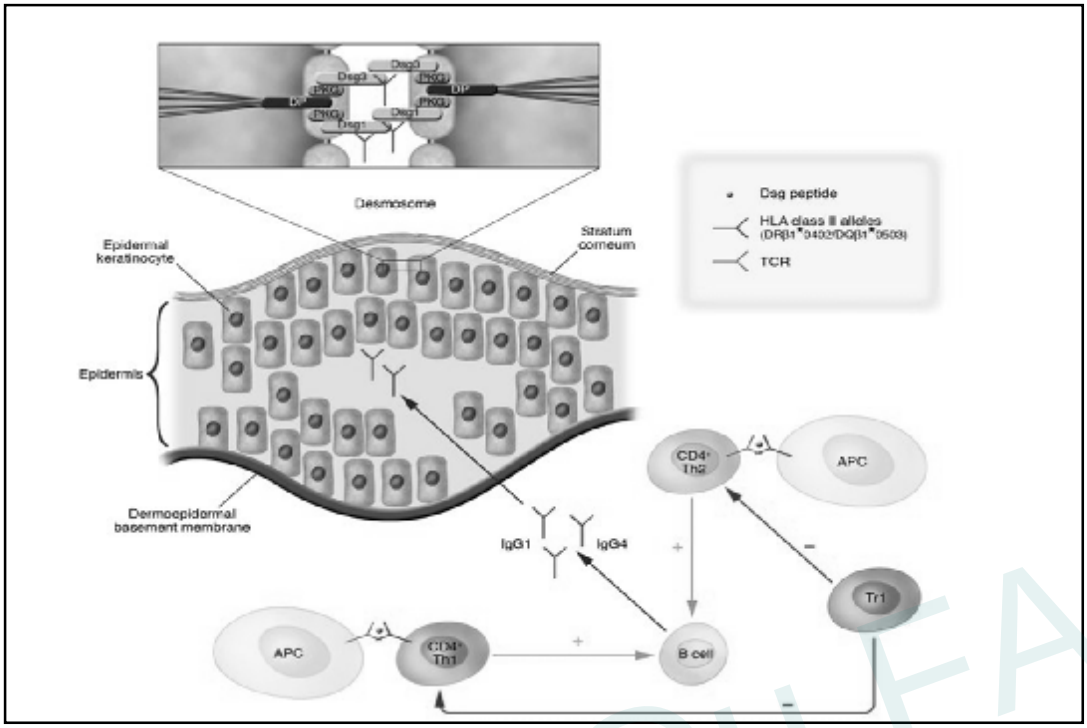


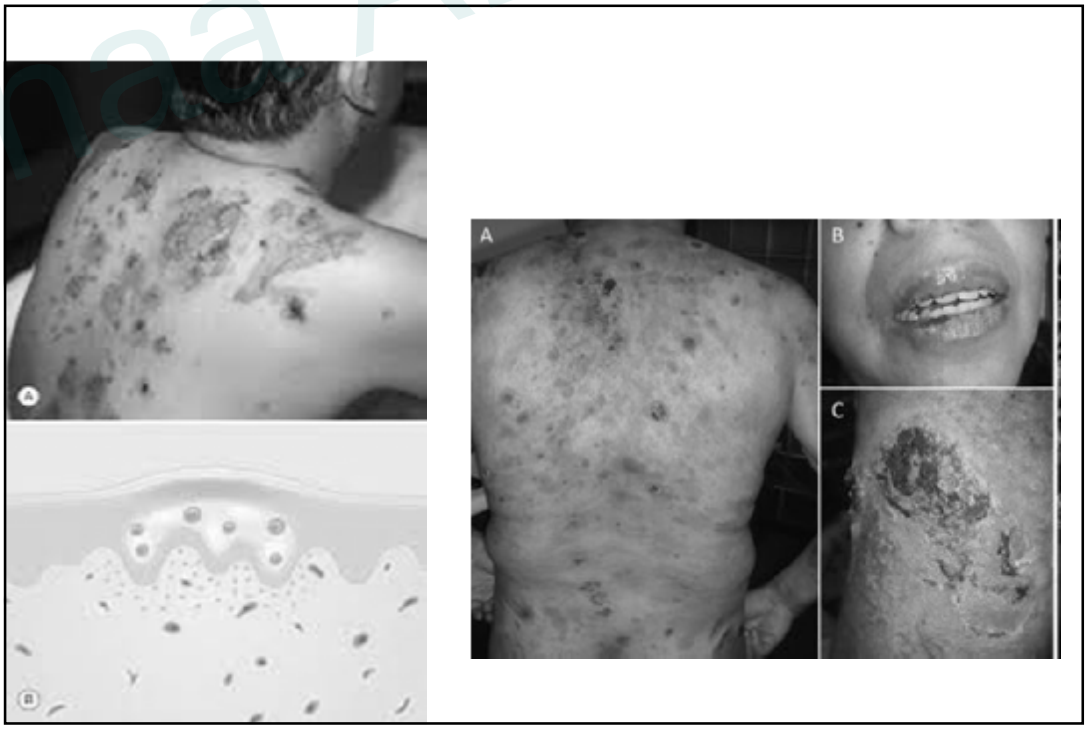
B or T? That is the question

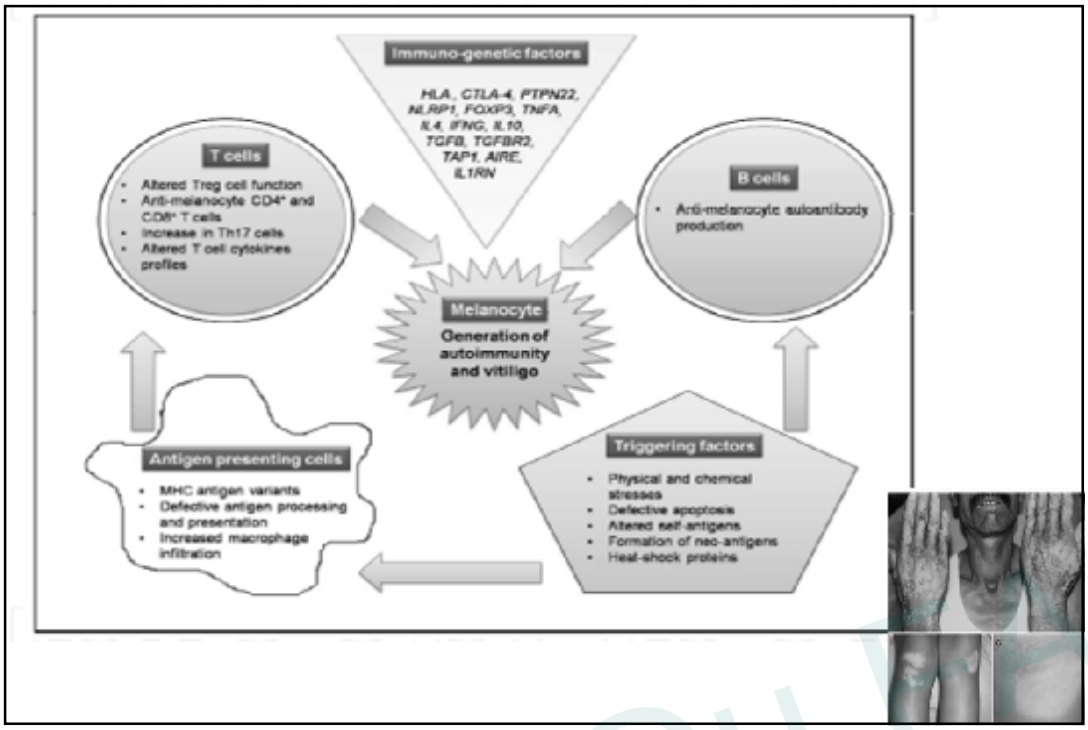
Autoimmunity is hard to classify as strictly a B cell or T cell mediated disease as multiple arms of the immune system are involved

Autoantigens of human autoimmune bullous skin disorders and their role in epidermal and dermoepidermal adhesion.









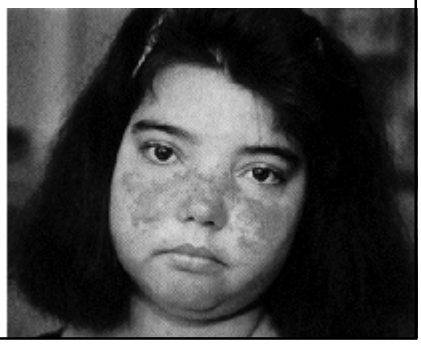
systemic lupus erythematosus (SLE)

- systemic autoimmune disease

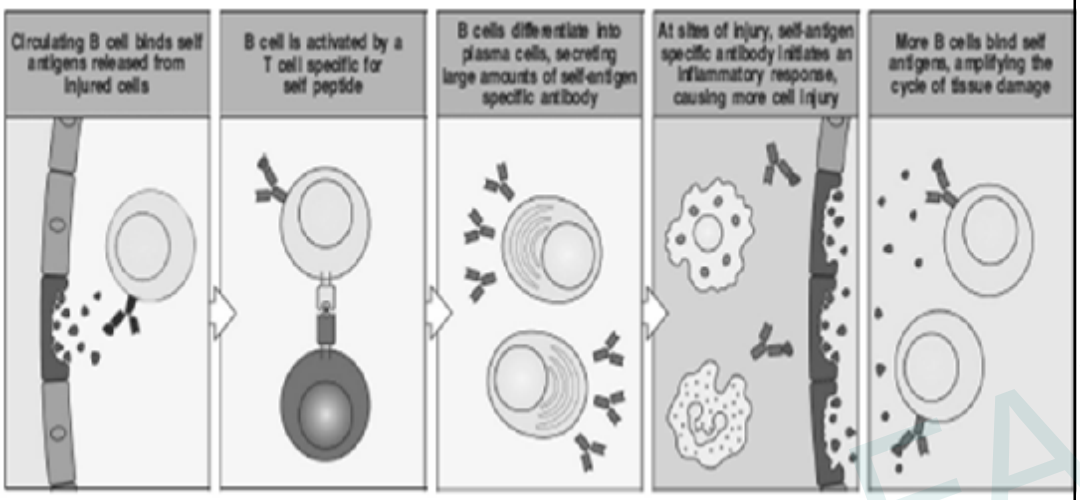
- Females 10-times more susceptible than males

- Characterized by a systemic production of anti self antibodies (most commonly associated with anti-DNA antibodies)

- Classical complement pathway deficiencies



systemic lupus erythematosus (SLE)



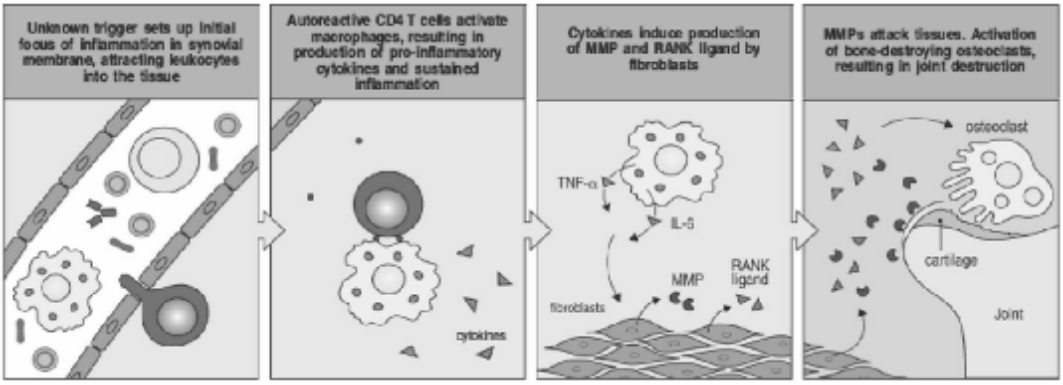
Rheumatoid Arthritis :RA

- Chronic disease, inflammation of the synovium, damages the cartilage, erosion of the bone.

- RA was considered an autoimmune disease driven mainly by B cells producing anti-IgG autABs (RF)

- Association with particular class II HLA-DR genes suggested that T cells were involved in the pathogenesis of this disease.

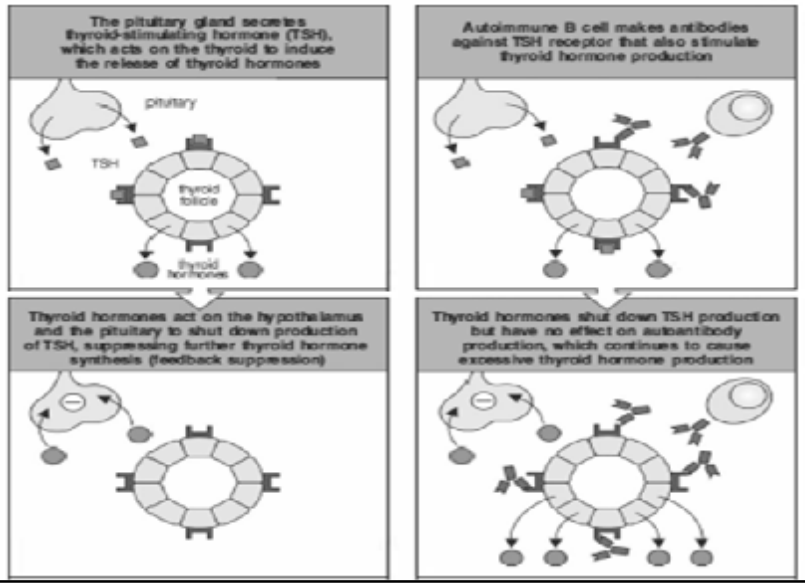
RA : pathogenesis



Matrix metalloproteinases (MMPs

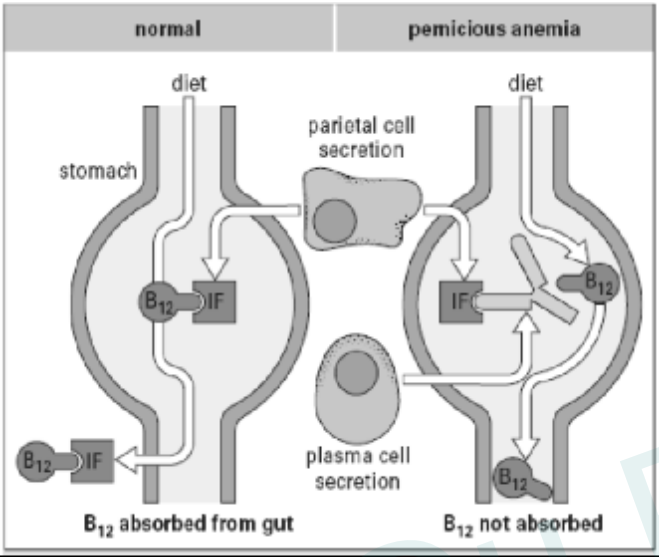
The TNF family cytokine RANK ligand, expressed by T cells and fibroblasts in the inflamed joint, is the primary activator of bone-destroying osteoclasts

Feedback regulation of thyroid hormone production is disrupted in Graves' disease

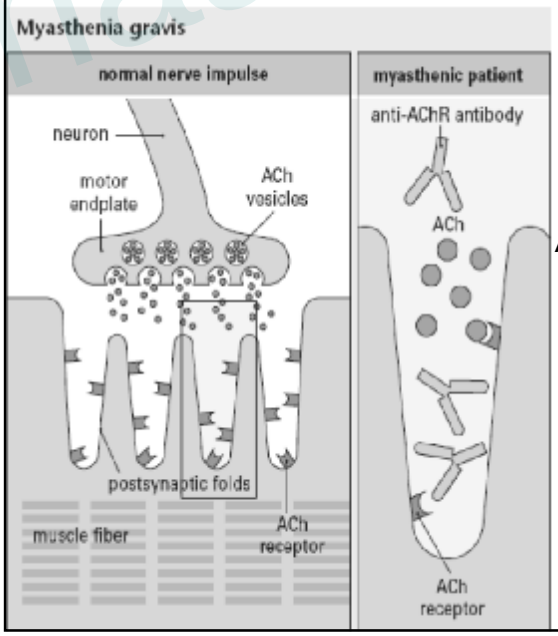


In pernicious anemia an autoantibody interferes with the normal uptake of vitamin B_{12}

Intrinsic Factor
IF



Myasthenia Gravis

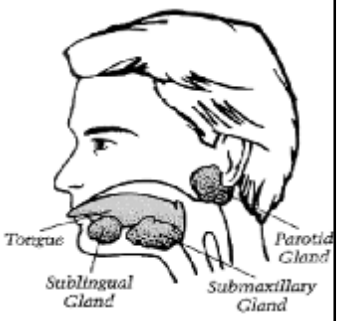


Disease marked by progressive weakness and loss of muscle control
Classified as a "B cell" Disease
Autoantibodies against acetylcholine receptors

Sjogren's Syndrome

- Autoantibodies and autoreactive T cells
- against ribonucleoprotein antigens
- Lymphocyte infiltration of exocrine glands, leading to dry eyes and/or dry mouth

other organs, leading to systemic disease



Diabetes

Disease in which the body does not produce or properly use insulin

"T cell" Disease

T cells attack and destroy pancreatic beta cells

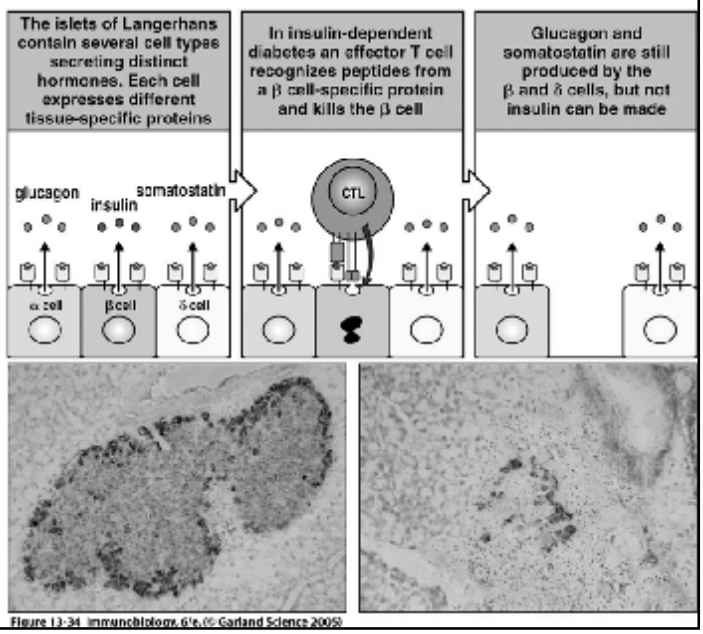
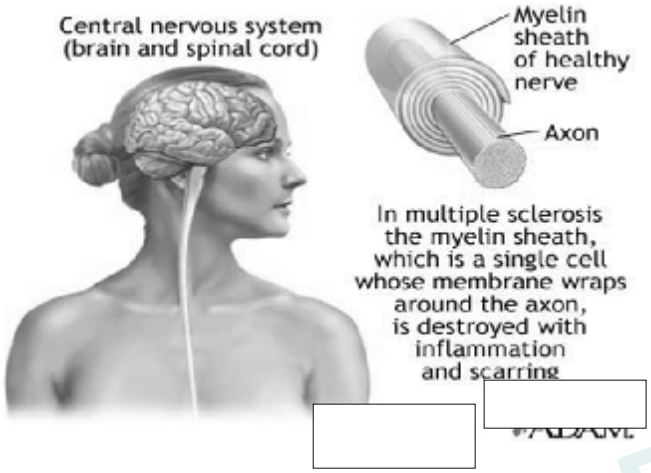


Figure 13-34 Immunobiology, 6'e.© Garland Science 2005)

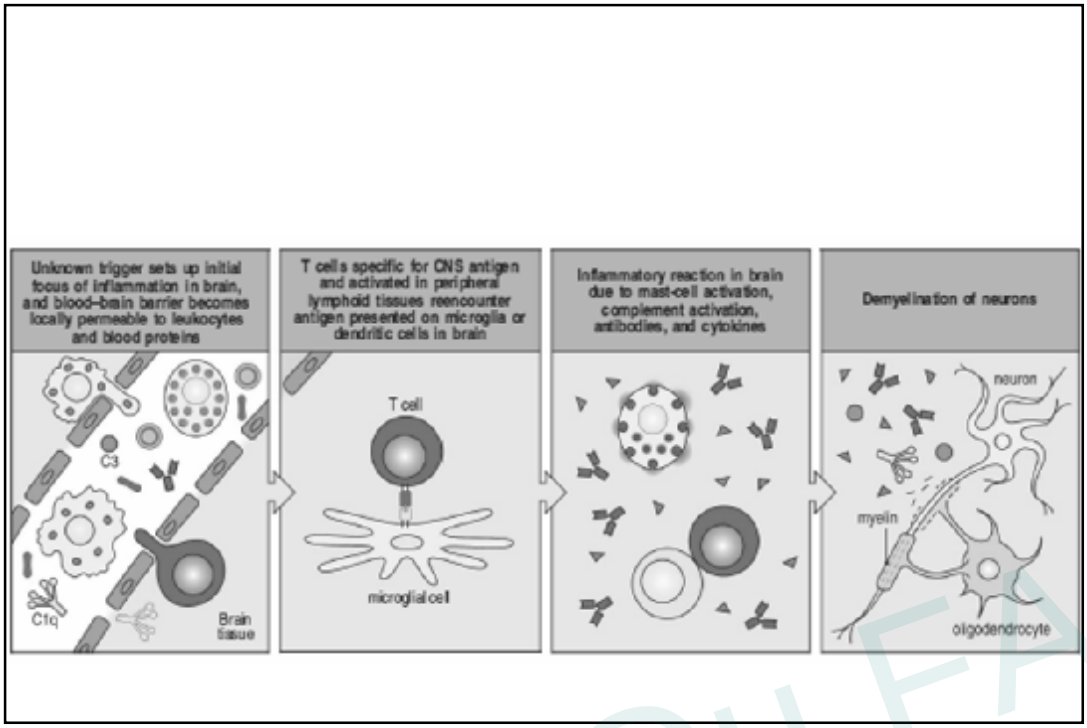
Multiple Sclerosis



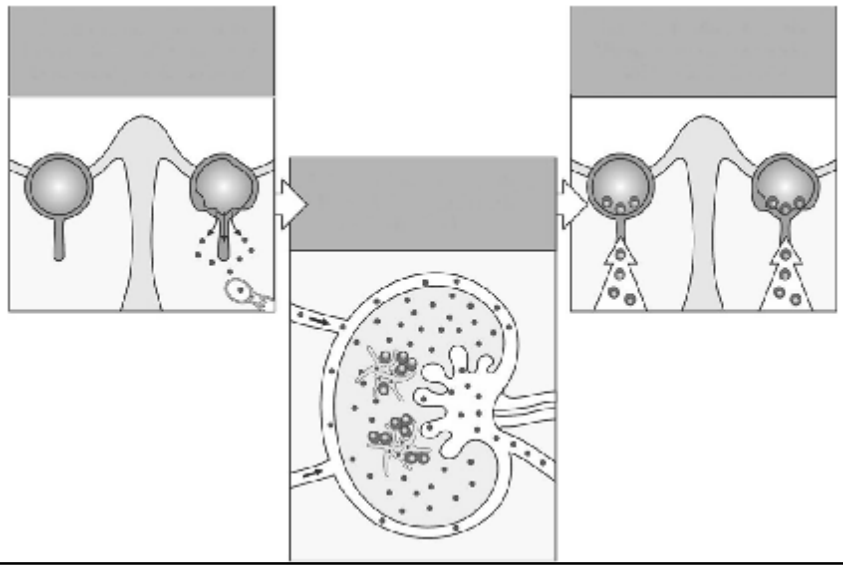
Multiple Sclerosis

- Symptoms my range from numbness in extremeties, through blindness, paralysis, death.

- There are both environmental and genetic components to the disease



sympathetic ophthalmia



Autoimmune diseases transferred across the placenta to the fetus and newborn infant		
Disease	**Autoantibody**	**Symptom**
Myasthenia gravis	Anti-acetylcholine receptor	Muscle weakness
Graves' disease	Anti-thyroid-stimulating-hormone (TSH) receptor	Hyperthyroidism
Thrombocytopenic purpura	Anti-platelet antibodies	Bruising and hemorrhage
Neonatal lupus rash and/or congenital heart block	Anti-Ro antibodies Anti-La antibodies	Photosensitive rash and/or bradycardia
Pemphigus vulgaris	Anti-desmoglein-3	Blistering rash