# Autoimmunity

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## Autoimmunity

- Immune recognition and injury of self tissues (autoimmunity) results from a loss of self tolerance.

## Self Tolerance

- Tolerance to self is acquired by **clonal deletion** or **inactivation of developing lymphocytes**.
  - **Clonal deletion by ubiquitous self antigens**
  - **Clonal inactivation by tissue-specific antigens presented in the absence of co-stimulatory signals**

## Peripheral T cell Tolerance Mechanisms

- **Immunological Ignorance**: Very few self proteins contain peptides that are presented by a given MHC molecule at a level sufficient for T cell activation,. Autoreactive T cells are present but not normally activated.
- **Suppressor or regulatory T cells**: mediate active suppression of autoreactive cells

## Peripheral T cell Tolerance Mechanisms

- **Immunologically privileged sites**: no lymphatic drainage or non-vascularized areas; presence of immunosuppressive factors & FasL

## Peripheral B cell Tolerance Mechanisms

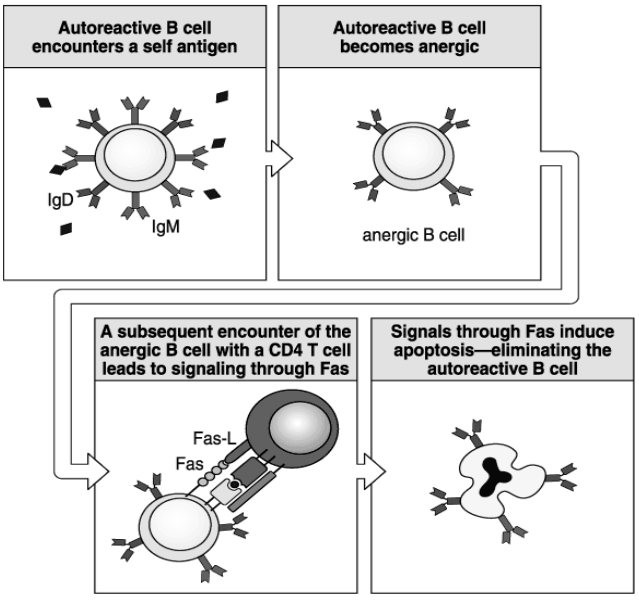
- Contact with soluble antigens:
  - downregulation of surface IgM, inhibition of signaling → anergic cells
  - **Fas-mediated apoptosis of anergic B cell following secondary encounter with CD4 T cell**

## Peripheral B cell Tolerance Mechanisms

- Contact with soluble antigens
  - **Apoptosis of autoreactive B cells generated by somatic hypermutation in germinal centers**

## Peripheral B cell Tolerance Mechanisms

- **Lack of T helper cell signals**:
  - **anergy**
  - **inhibited migration into follicles & apoptosis in T cell areas of lymph tissue**



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## Loss of Self Tolerance

- **Most self peptides are presented at <u>levels too low</u> to engage effector T cells whereas those presented at <u>high levels</u> induce clonal deletion or anergy.**
- **Autoimmunity arises most frequently to Tissue-specific antigens with only certain MHC molecules that present the peptide at an <u>intermediate level</u> recognized by T cells without inducing tolerance.**

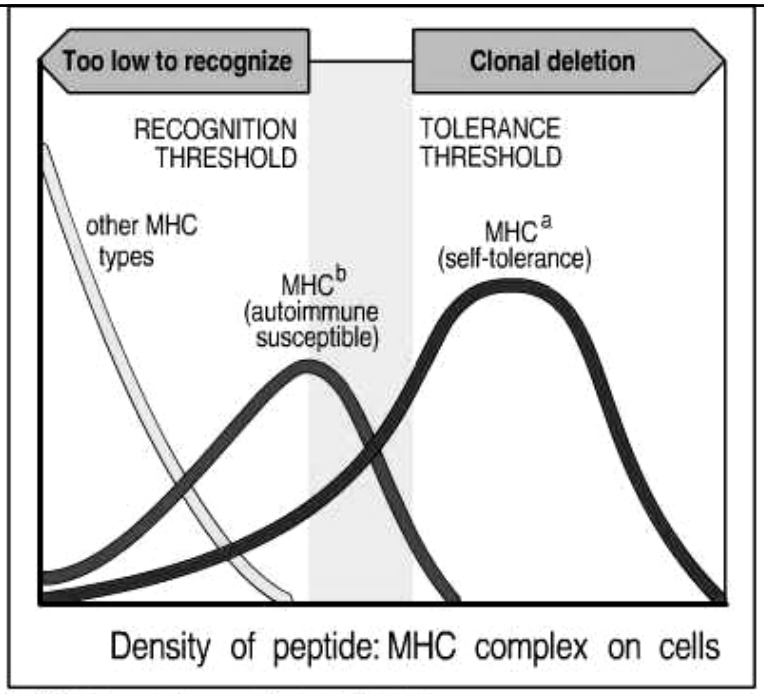



Fig. 13.33

## MHC Association with Autoimmune Disease

- **The level of autoantigenic peptide presented is determined by polymorphic residues in MHC molecules that govern the affinity of peptide binding.**
- Autoimmune diseases are associated with particular MHC genotypes.

## MHC Association with Autoimmune Disease

- **Only a few peptides can act as autoantigens so there are a relatively few autoimmune syndromes.**
- **Individuals with a particular autoimmune disease tend to recognize the same antigens with the same MHC.**

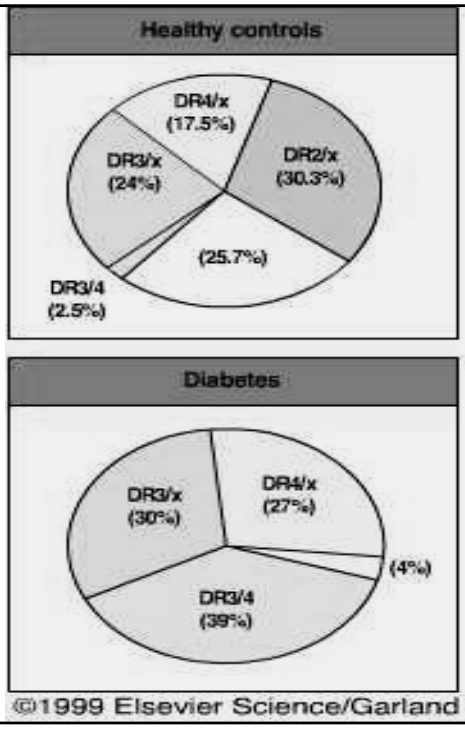


**Fig. 13.4**

**Type I Diabetes association with HLA genotype**

## Mechanisms for Activation of Autoreactive Lymphocytes

- **Infectious triggers**:
  - **stimulation of co-stimulatory signals, inappropriate MHC II expression, or cytokines**
  - **Molecular mimicry (cross-reaction)**
  - **Release of sequestered antigens**
  - **T cell bypass (pathogen binding to self protein/provision of carrier T cell epitope)**

## Mechanisms for Activation of Autoreactive Lymphocytes

- **Infectious triggers**:
  - Superantigen activity/polyclonal activation

## Infectious Mechanisms that 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-stimulatory activity on antigen-presenting cells | 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 in induction of EAE | ? Interstitial nephritis | Rheumatic fever<br>? Diabetes<br>? Multiple sclerosis | ? Rheumatoid arthritis |

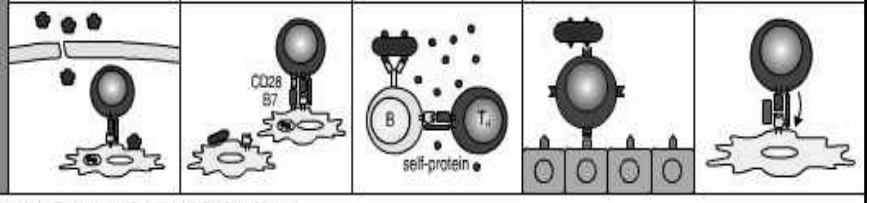




**Fig. 13.42**

| Type II antibody to cell-surface or matrix antigens | | |
|---|---|---|
| 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<br>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 |

**Fig. 13.1**

| Some common autoimmune diseases classified by immunopathogenic mechanism | | |
|---|---|---|
| **Syndrome** | **Autoantigen** | **Consequence** |
| **Type III immune-complex disease** | | |
| 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, rash |
| Rheumatoid arthritis | Rheumatoid factor IgG complexes | Arthritis |
| **Type IV T cell-mediated disease** | | |
| 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, weakness |

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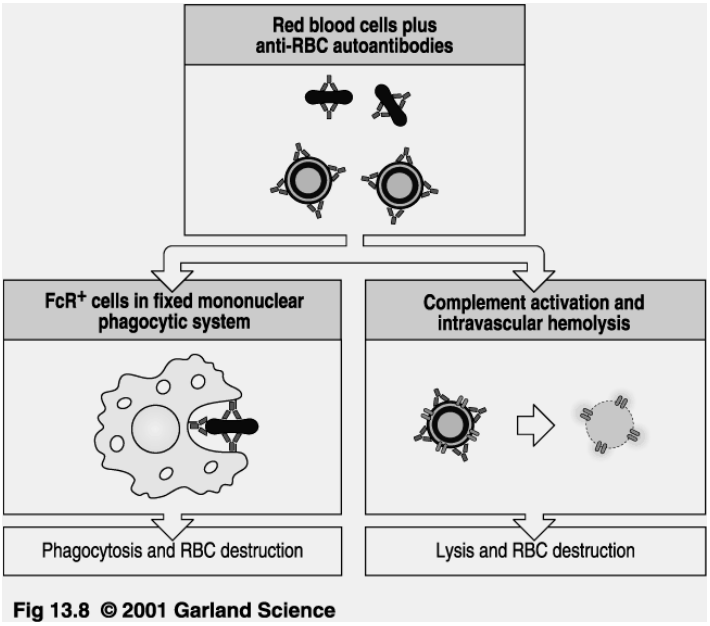
# Organ-specific Autoimmune diseases

- **Antigens and autoimmunity restricted to specific organs in the body**
  - **Type I diabetes**
  - **Goodpasture's syndrome**
  - **Multiple sclerosis**
  - **Grave's disease**
  - **Hashimoto' thyroiditis**
  - **Myasthenia gravis**

## Systemic Autoimmune Disease

- **Antigens and autoimmunity are distributed in many tissues (systemic)**
  - **Rheumatoid arthritis**
  - **Systemic lupus erythematosus**
  - **Scleroderma**
  - **Primary Sjogrens's syndrome**
  - **polymyositis**



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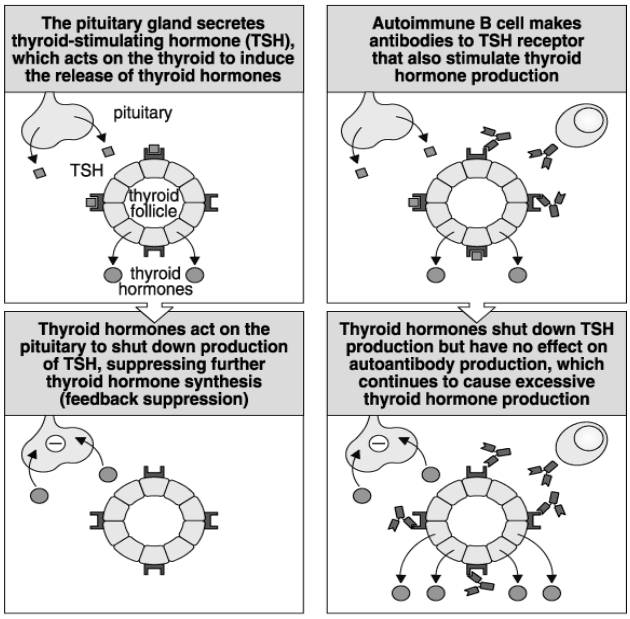


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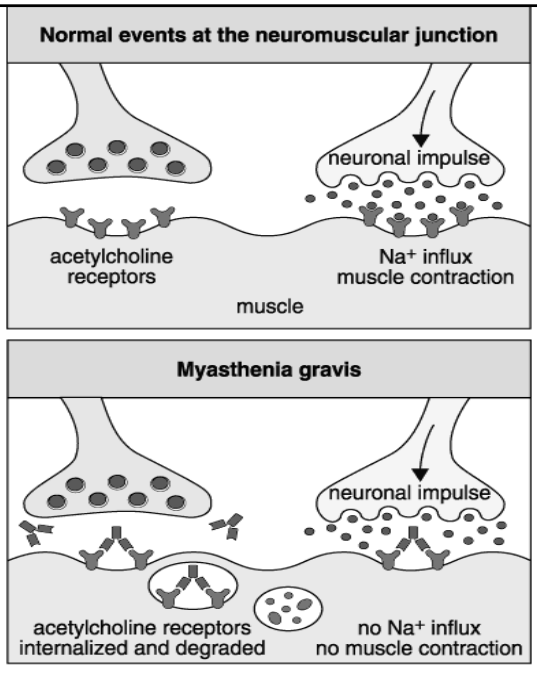


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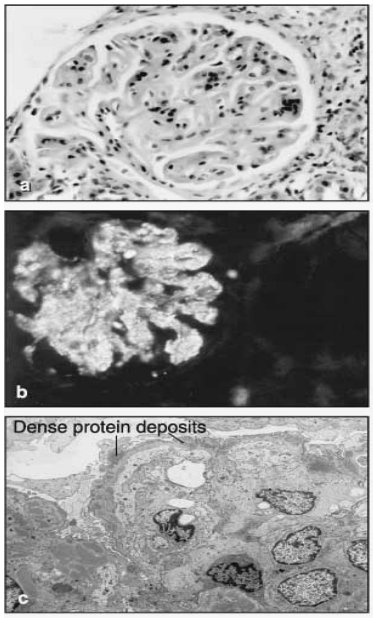


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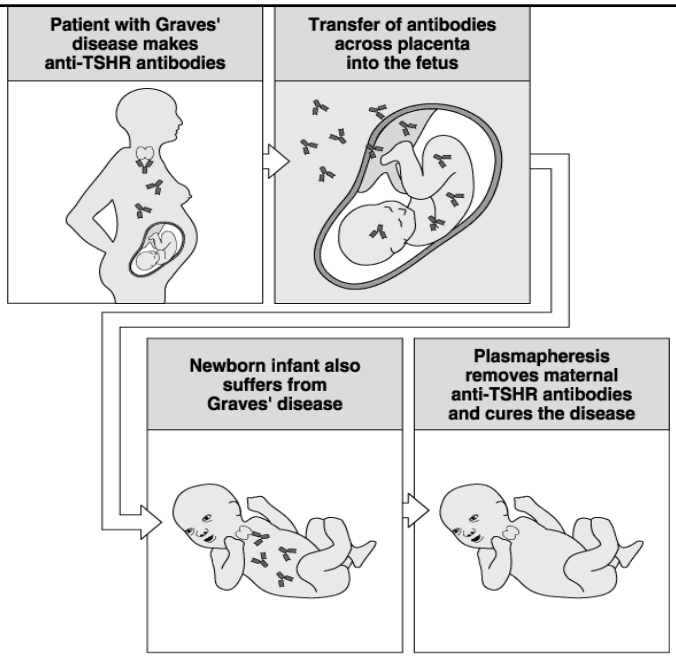


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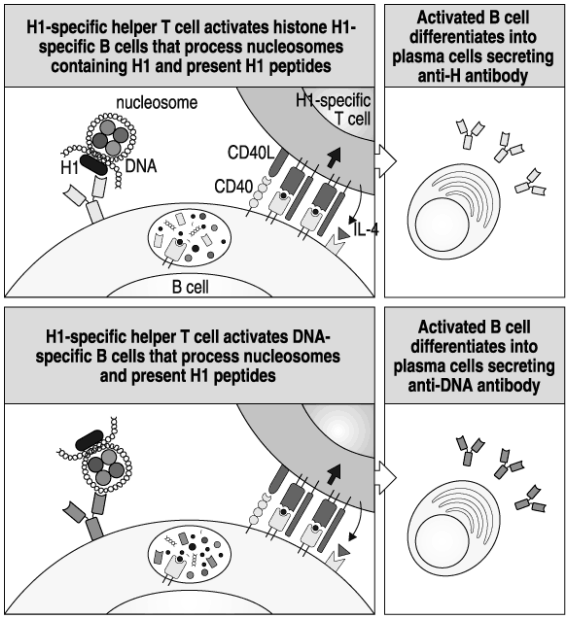


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# Determinant spreading