

## Autoimmunity

K.J.Goodrum  
2005

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## Autoimmunity

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

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## 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

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### 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

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### Peripheral T cell Tolerance Mechanisms

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

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### 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**

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Peripheral B cell Tolerance Mechanisms

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

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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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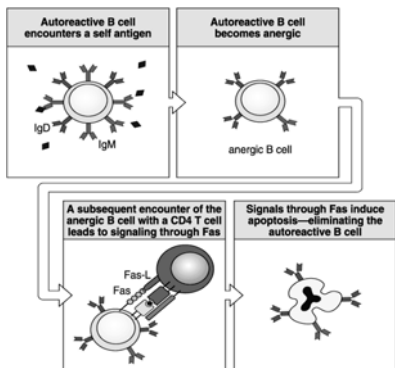


Fig 13.38 © 2001 Garland Science

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### Loss of Self Tolerance

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

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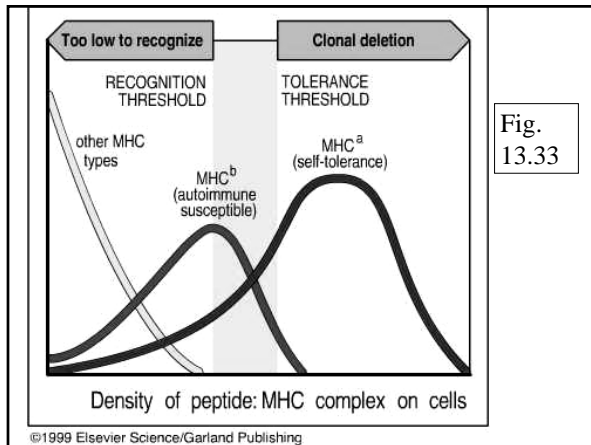


Fig. 13.33

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### 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.

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### 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.

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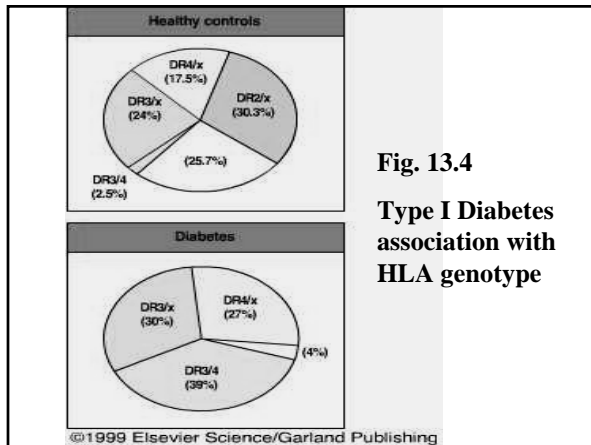
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### Mechanisms for Activation of Autoreactive Lymphocytes

- 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)

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## Mechanisms for Activation of Autoreactive Lymphocytes

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

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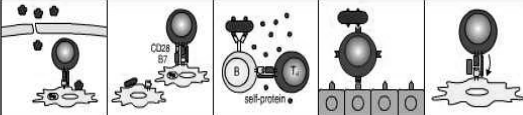
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### Infectious Mechanisms that Break Self-Tolerance

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-labeled 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	Symphathetic ophthalmia	Effect of adjuvants in induction of EAE	? Interstitial nephritis	Rheumatic fever ? Diabetes ? Multiple sclerosis	? Rheumatoid arthritis
					

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Fig. 13.42

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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 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

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Some common autoimmune diseases classified by immunopathogenic mechanism		
Syndrome	Autoantigen	Consequence
<b>Type III immune-complex disease</b>		
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
<b>Type IV T cell-mediated disease</b>		
Insulin-dependent diabetes mellitus	Pancreatic $\beta$ -cell antigen	$\beta$ -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

Fig 13.1 part 2 of 2 © 2001 Garland Science

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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

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**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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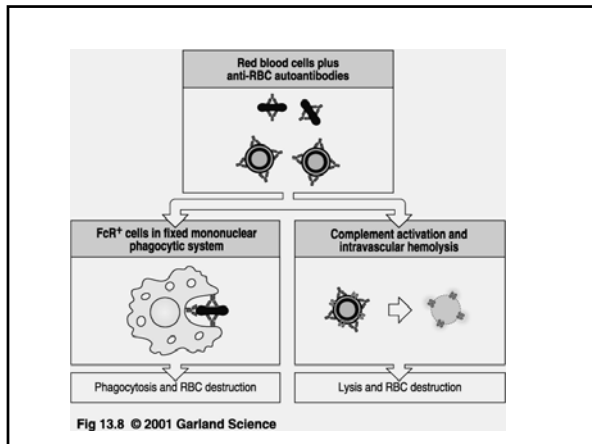
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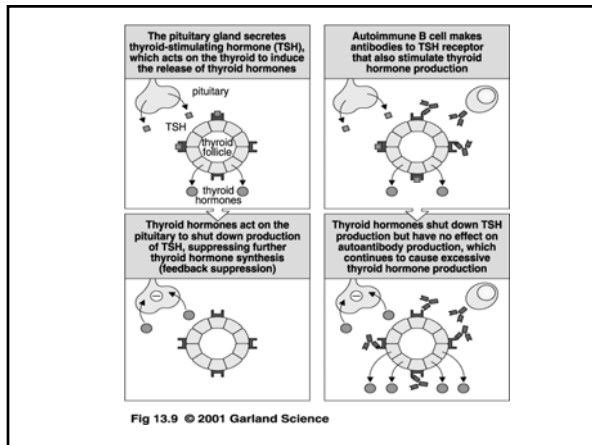
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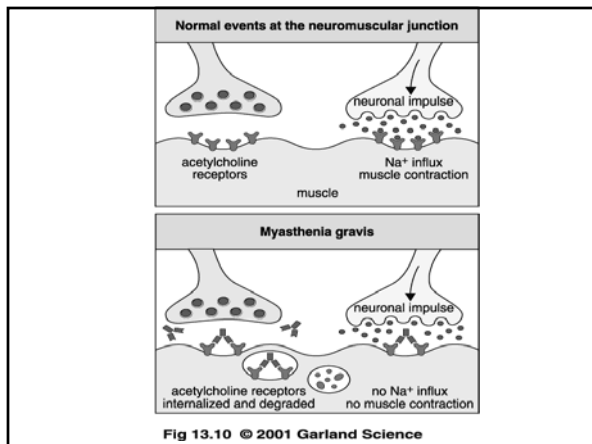
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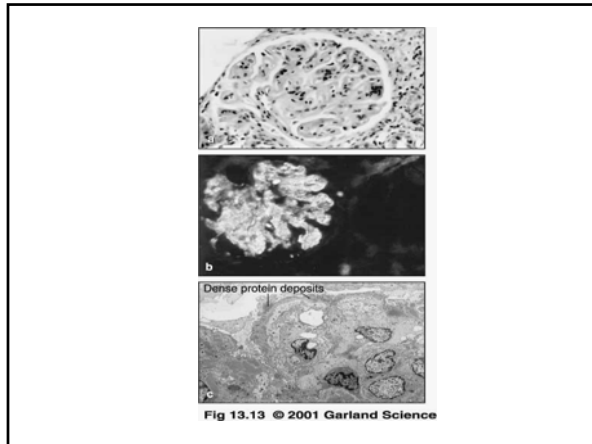
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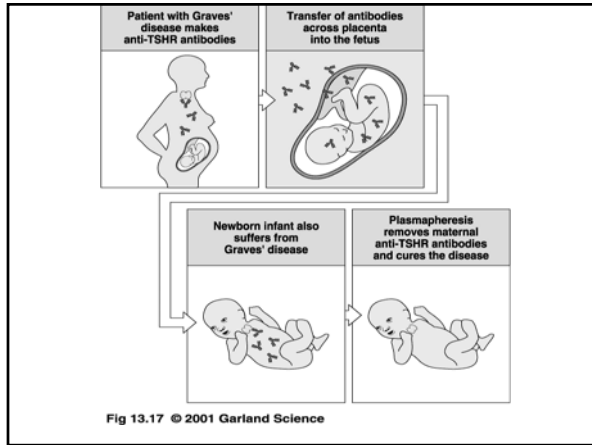
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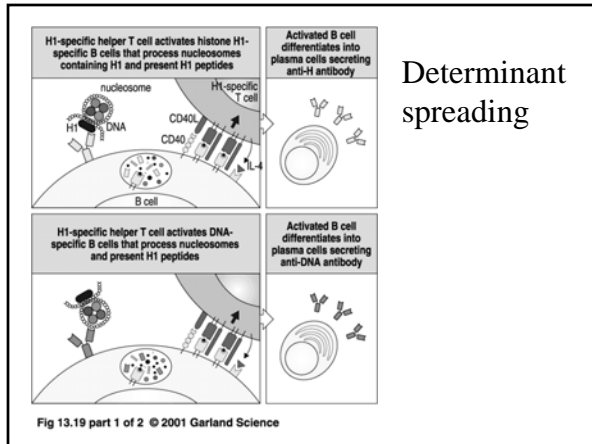
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