

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**

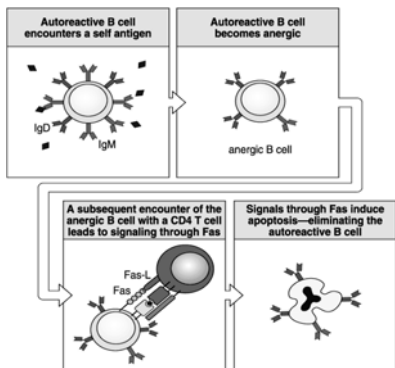
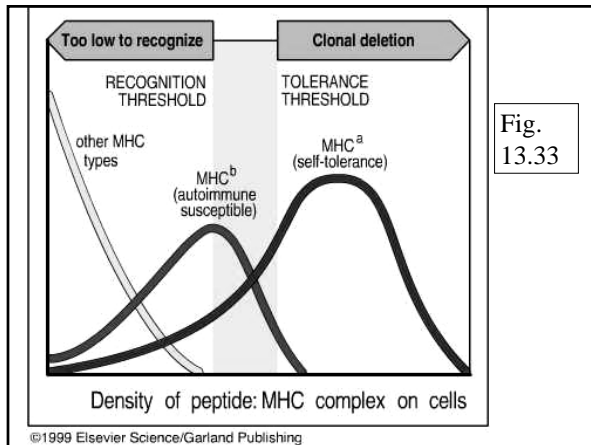


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Loss of Self Tolerance

- Most self peptides are presented at 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.

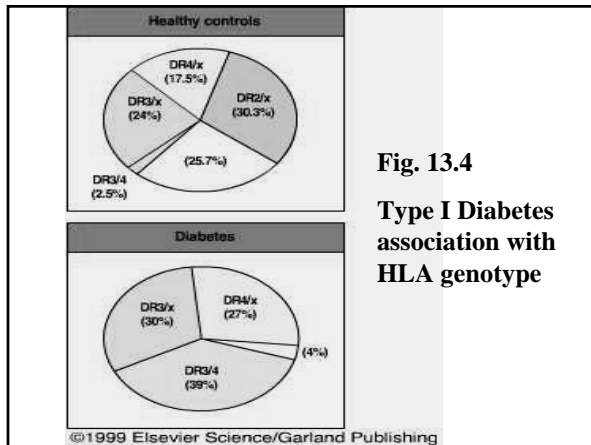


MHC Association with Autoimmune Disease

- 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.



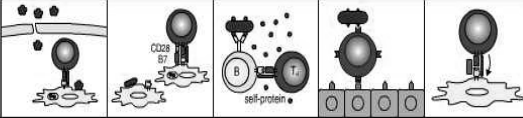
Mechanisms for Activation of Autoreactive Lymphocytes

- 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-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

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

