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
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.

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

**Fig. 13.42**

**Type II antibody to cell-surface or matrix antigens**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Antigen 1</th>
<th>Antigen 2</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>Rh blood group antigens, I antigen</td>
<td>Destruction of red blood cells by complement and phagocytes, anemia</td>
<td></td>
</tr>
<tr>
<td>Autoimmune thrombocytopenic purpura</td>
<td>Platelet integrin GpIIb/IIIa</td>
<td>Abnormal bleeding</td>
<td></td>
</tr>
<tr>
<td>Goodpasture's syndrome</td>
<td>Non-collagenous domain of basement membrane collagen type IV</td>
<td>Glomerulonephritis Pulmonary hemorrhage</td>
<td></td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>Epidermal cadherin</td>
<td>Blistering of skin</td>
<td></td>
</tr>
<tr>
<td>Acute rheumatic fever</td>
<td>Streptococcal cell-wall antigens. Antibodies cross-react with cardiac muscle</td>
<td>Arthritis, myocarditis, late scarring of heart valves</td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 13.1**

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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’s thyroiditis
  - Myasthenia gravis
Systemic Autoimmune Disease

- Antigens and autoimmunity are distributed in many tissues (systemic)
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Scleroderma
  - Primary Sjögren’s syndrome
  - Polymyositis
Determinant spreading