

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
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

**Mechanisms**
- Destruction of cell or tissue barrier
- Infection of antigen-presenting cell
- Binding of pathogen to cell surface
- Molecular mimicry
- Superepitopes

**Effect**
- Release of accumulated cell antigen, soluble of target cells
- Induction of autoantibody synthesis on antigens present in cells
- Phagocytes can kill anti-self reactive T cells
- Protection of mesangial antibodies or T cells
- Polymerization of subboticope in T cells

**Example**
- Sympathetic encephalitis
  - Effect of adenosine in induction of AE
  - Infiltrated lymphocytes
  - Reversal of symptoms
  - Multiple sclerosis
  - P: Rheumatic arthritis

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### Organ-specific Autoimmune diseases

#### Type I antibody to cell-surface or matrix antigens
- **Autoimmune hemolytic anemia**
  - Rh blood group antigen, I antigen
  - Destruction of red blood cells by complement and antibodies
- **Autoimmune thrombocytopenic purpura**
  - Platelet antigen
  - Abnormal bleeding
- **Goodpasture's syndrome**
  - Neocollagenous domain of basement membrane collagen type IV
  - Glomerulonephritis
  - Pulmonary hemorrhage
- **Pemphigus vulgaris**
  - Epidermal cation
  - Blistering of skin
- **Acute rheumatic fever**
  - Streptococcal cell-wall antigens
  - Antibodies cross-react with cardiac muscle
  - Arthritis, myocarditis, late scarring of heart valves

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### Some common autoimmune diseases classified by immunopathogenic mechanism

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Autoantigen</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type III immune-complex disease</strong></td>
<td></td>
<td></td>
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<tr>
<td>Mixed essential</td>
<td>Rheumatoid factor IgG complexes (with or without hepatitis C antigen)</td>
<td>Systemic vasculitis</td>
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<tr>
<td>Systemic lupus</td>
<td>DNA, histones, ribosomes, SNAP, ssRNA,</td>
<td>Glomerulonephritis,</td>
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<tr>
<td>erythematosus</td>
<td></td>
<td>vasculitis, rash</td>
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<tr>
<td>Rheumatoid arthritis</td>
<td>Rheumatoid factor IgG complexes</td>
<td>Arthritis</td>
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<tr>
<td><strong>Type IV T cell-mediated disease</strong></td>
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<tr>
<td>Insulin-dependent</td>
<td>Pancreatic β-cell antigen</td>
<td>β-Cell destruction</td>
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<tr>
<td>diabetes mellitus</td>
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<tr>
<td>Rheumatoid arthritis</td>
<td>Unknown synovial or periarticular antigens</td>
<td>Joint inflammation and destruction</td>
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<td>Experimental autoimmune meningitis</td>
<td>Myelin basic protein, proteolipid protein,</td>
<td>Brain invasion by</td>
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<tr>
<td>encephalomyelitis (EAE), multiple sclerosis</td>
<td>myelin oligodendrocyte</td>
<td>CO4 T cells, weakness</td>
</tr>
</tbody>
</table>

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**Fig. 13.42**

**Fig. 13.1**

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Systemic Autoimmune Disease

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