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.

**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)

Fig. 13.4

Type I Diabetes association with HLA genotype

**Mechanisms for Activation of Autoreactive Lymphocytes**

- **Infectious triggers:**
  - Superantigen activity/polyclonal activation
Infectious Mechanisms that Break Self-Tolerance

### Example
- **Sympathetic ophthalmia**
- **Effect of adjuvants in infectious disease**
  - Induction of thymus-independent antigens
  - Production of antibodies to self antigens
  - Polyclonal activation of B cells

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

<table>
<thead>
<tr>
<th>Autoimmune hemolytic anemia</th>
<th>Rh blood group antigens, T antigen</th>
<th>Destruction of red blood cells by complement and phagocytes, anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune thrombocytopenic purpura</td>
<td>Platelet integrin Glycoprotein</td>
<td>Abnormal bleeding</td>
</tr>
<tr>
<td>Goodpasture’s syndrome</td>
<td>Non-collagenous domain of basement membrane collagen type IV</td>
<td>Glomerulonephritis, Pulmonary hemorrhage</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>Epidermal cadherin</td>
<td>Blistering of skin</td>
</tr>
<tr>
<td>Acute rheumatic fever</td>
<td>Streptococcal cell-wall antigens, Antibodies cross-react with cardiac muscle</td>
<td>Arthritis, myositis, late scarring of heart valves</td>
</tr>
</tbody>
</table>

### 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>Mixed essential cryoglobulinemia</td>
<td>Rheumatoid factor IgG complexes (with or without hepatitis C antigens)</td>
<td>Systemic vasculitis</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>DNA, histones, ribosomes, snRNPs, RNP</td>
<td>Glomerulonephritis, vasculitis, rash</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Rheumatoid factor IgG complexes</td>
<td>Arthritis</td>
</tr>
<tr>
<td>Type IV T cell-mediated disease</td>
<td></td>
<td></td>
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<tr>
<td>Insulin-dependent diabetes mellitus</td>
<td>Pancreatic β-cell antigen</td>
<td>β-Cell destruction</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Unknown synovial joint antigen</td>
<td>Joint inflammation and destruction</td>
</tr>
<tr>
<td>Experimental autoimmune encephalomyelitis (EAE), multiple sclerosis</td>
<td>Myelin basic protein, proteolipid protein, myelin oligodendrocyte glycoprotein</td>
<td>Brain invasion by CD4+ T cells, weakness</td>
</tr>
</tbody>
</table>

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 Sjogren’s syndrome
  - Polymyositis
Determinant spreading