Autoimmunity
Self-tolerance

• Lack of immune responsiveness to an individual's own tissue antigens

Central Tolerance

Peripheral tolerance
Factors Regulating Immune Response

- Antigen availability
- Properties of the antigen
- Genetics
- Circumstances of antigen presentation
- Cytokine milieu
- Regulatory cells
- Costimulation
Susceptibility to Autoimmunity

- Environmental and genetic factors play a key role in autoimmune disease susceptibility.
- The best evidence comes from family and twin studies.
- High concordance in twins suggests shared genetic or environmental factors.
- If a disease is restricted to monozygotic twins then genetic factors are important.
- Insulin-dependent diabetes mellitus, rheumatoid arthritis, MS, SLE ~20% monozygotic twins show concordance compared with <5% dizygotic twins.
Mechanisms proposed for induction of Autoimmunity

- Release of “sequestered antigens”
These Sites Sequester Self Antigens, But Few Autoimmune Diseases Are Due to Release Of Hidden Self Antigens
Trauma to one eye results in the release of sequestered intraocular protein antigens.

Released intraocular antigen is carried to lymph nodes and activates T cells.

Effector T cells return via bloodstream and encounter antigen in both eyes.
Mechanisms proposed for induction of Autoimmunity

• Release of “sequestered antigens”

• Abnormal immunoregulation
Immunoregulatory T cells release downregulating cytokines which turn-off potential immune responses.
Autoimmunity: a question of balance

**Activating signals**
- MHC-II peptide
- Cytokines (IFN-γ)
- CD40/CD40L
- CD28/CD80,86

**Downregulating signals**
- Cytokines (IL-10, TGFβ)
- CD80,86/CTLA-4
Mechanisms proposed for induction of Autoimmunity

- Release of “sequestered antigens”
- Abnormal immunoregulation
- Bypass of helper T-cell tolerance
Induction of autoantibodies by cross-reactive antigens

<table>
<thead>
<tr>
<th>Autoantigen</th>
<th>Cross-reactive foreign antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoreactive (tolerant)</td>
<td>Non-autoreactive (non-tolerant)</td>
</tr>
</tbody>
</table>

- No help: no autoantibody production
- Help: autoantibody production
Bypass of helper T-cell tolerance

- **Modification of antigen (via drugs, microorganisms)**
  - Me-Dopa $\rightarrow$ altered synth. of Rh ag $\rightarrow$ AIHA
  - Procainamide $\equiv$ nucleosomes $\rightarrow$ $\alpha$-histone, $\alpha$-DNA $\rightarrow$ SLE

- **Cross reaction (Antigen mimicry)**
- **Shared epitopes**
- **Bystander activation**
  - Local innate immune responses and expression of second signal and costimulatory molecules on tissue APCs in site of inflammation
Cross-reacting Antigens (Molecular Mimicry)

• Viruses and bacteria possess antigenic determinants that are very similar, or even identical, to normal host cell components.

• This phenomenon, known as molecular mimicry, occurs in a wide variety of organisms.

• Molecular mimicry may be the initiating step in a variety of autoimmune diseases.
One of the most popular theories concerning autoimmunity is that cross-reactive T cell clones emerge during an immune response against an infectious agent.

Coxsackie B-induced myocarditis
Cross-reactive antigens induce autoimmune T cells

1. Microbial antigen
   - High concentration
   - 'Professional' APC
   - B7
   - CD28
   - Naïve T cell (low affinity)

2. Low concentration of autoantigen on target cell surface
   - 'Non-professional' APC
   - Maturation
   - Primed T cell (high affinity)
Mechanisms proposed for induction of Autoimmunity

- Release of "sequestered antigens"
- Abnormal immunoregulation
- Bypass of helper T-cell tolerance
- Polyclonal lymphocyte activation
Polyclonal lymphocyte activation

- Endotoxins cause such activation independent of specific antigens
- Super antigens?
- Mitogens?
Mechanisms proposed for induction of Autoimmunity

- Release of “sequestered antigens”
- Abnormal immunoregulation
- Bypass of helper T-cell tolerance
- Polyclonal lymphocyte activation
- Somatic hypermutation
Somatic hypermutation generates novel antibody specificities within germinal centers

Some of these B cells may now be able to bind self antigens

Encounter of autoreactive B cell with soluble antigen causes apoptosis

Figure 13-11 Immunobiology, 6/e. (© Garland Science 2005)
Mechanisms proposed for induction of Autoimmunity

- Release of “sequestered antigens”
- Abnormal immunoregulation
- Bypass of helper T-cell tolerance
- Polyclonal lymphocyte activation
  - Somatic hypermutation

- Genetic Factors
Genetic Defects

• (a) MRL-\textit{lpr/lpr} or \textit{gld/gld} - Fas or FasL defect $\rightarrow$ SLE
• (b) Association with MHC Class II
MHC Association with Autoimmune Disease

- Many autoimmune diseases show association with specific MHC genes. The number of autoimmune patients carrying a HLA allele compared with the prevalence of that allele in the general population: Relative Risk Value
  e.g. R.A. & DR4, SLE & DR3, IDDM & DQβ - single aa at pos n. 56, Asp protects, other aas  IDDM
<table>
<thead>
<tr>
<th>Disease</th>
<th>HLA allele</th>
<th>Relative risk</th>
<th>Sex ratio (♀:♂)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankylosing spondylitis</td>
<td>B27</td>
<td>87.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Acute anterior uveitis</td>
<td>B27</td>
<td>10</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Goodpasture's syndrome</td>
<td>DR2</td>
<td>15.9</td>
<td>~1</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>DR2</td>
<td>4.8</td>
<td>10</td>
</tr>
<tr>
<td>Graves' disease</td>
<td>DR3</td>
<td>3.7</td>
<td>4–5</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>DR3</td>
<td>2.5</td>
<td>~1</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>DR3</td>
<td>5.8</td>
<td>10–20</td>
</tr>
<tr>
<td>Type I insulin-dependent diabetes mellitus</td>
<td>DR3/DR4 heterozygote</td>
<td>~25</td>
<td>~1</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>DR4</td>
<td>4.2</td>
<td>3</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>DR4</td>
<td>14.4</td>
<td>~1</td>
</tr>
<tr>
<td>Hashimoto's thyroiditis</td>
<td>DR5</td>
<td>3.2</td>
<td>4–5</td>
</tr>
</tbody>
</table>
MHC Association with Autoimmune Disease

• 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.

• The level of autoantigenic peptide presented is determined by polymorphic residues in MHC molecules that govern the affinity of peptide binding.
Self Level Sets Tolerance Degree

- Too low to recognize
  - RECOGNITION THRESHOLD
  - other MHC types
  - MHC\(b\) (autoimmune susceptible)
- Clonal deletion
  - TOLERANCE THRESHOLD
  - MHC\(a\) (self-tolerance)

Density of peptide:MHC complex on cells
Other Genetic Factors

Genetic defects in:

- Antigen clearance & presentation (C1q)
- Signaling (TCRζ)
- Co-stimulatory molecules (CTLA-4)
- Apoptosis (Fas & FasL)
- Cytokines (IL-2)
Mechanisms proposed for induction of Autoimmunity

- Release of “sequestered antigens”
  - Abnormal immunoregulation
- Cross-reactivity (molecular mimicry)
- Bypass of helper T-cell tolerance
- Polyclonal lymphocyte activation
  - Somatic hypermutation
  - Genetic Factors
- **Danger theory**
Mechanisms proposed for induction of Autoimmunity

- Proposes anti-self B & T-cells always present
- AIR is due to release of “danger signals”
- Response to tissue damage, necrosis or cell distress, e.g. infection or injury
- Inflammation response to danger signals mediated by effector mols. inc. cytokines.
- BUT can stimulate AIR without tissue damage, e.g. immunisation with self-ag
Mechanisms proposed for induction of Autoimmunity

- Release of “sequestered antigens”
  - Abnormal immunoregulation
- Bypass of helper T-cell tolerance
- Polyclonal lymphocyte activation
  - Genetic Factors
  - Somatic hypermutation
- Danger theory

- Hormonal status
Sex-based Differences in Autoimmunity

• Differences can be traced to sex hormones
  - hormones circulate throughout the body and alter immune response by influencing gene expression
  - (in general) estrogen can trigger autoimmunity and testosterone can protect against it

• Difference in immune response
  - ♂ produce a higher titer of antibodies and mount more vigorous immune responses than ♀
  - ♀ have higher levels of CD4+ T-cells and serum IgM
Antigen Structures in Different Type Autoimmune Diseases

**Organ specific** autoimmune disease:
Specific organ limited Ags

**Systemic** autoimmune diseases:
Ubiquitous Ags (nuclear and cytoplasmic antigens as autoantigens)
### Two types of autoimmune disease

<table>
<thead>
<tr>
<th>Organ-specific</th>
<th>Non-organ-specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>brain</td>
<td>muscle</td>
</tr>
<tr>
<td>multiple sclerosis (?)</td>
<td>dermatomyositis</td>
</tr>
<tr>
<td>thyroid</td>
<td>stomach</td>
</tr>
<tr>
<td>Hashimoto's</td>
<td>pernicious anaemia</td>
</tr>
<tr>
<td>thyroiditis</td>
<td>stomach</td>
</tr>
<tr>
<td>primary myxoedema</td>
<td>kidney</td>
</tr>
<tr>
<td>thyrotoxicosis</td>
<td>muscle</td>
</tr>
<tr>
<td></td>
<td>muscle</td>
</tr>
<tr>
<td></td>
<td>muscle</td>
</tr>
<tr>
<td>adrenal</td>
<td>muscle</td>
</tr>
<tr>
<td>Addison's disease</td>
<td>muscle</td>
</tr>
<tr>
<td>pancreas</td>
<td>muscle</td>
</tr>
<tr>
<td>insulin-dependent</td>
<td>muscle</td>
</tr>
<tr>
<td>diabetes melitus</td>
<td>muscle</td>
</tr>
</tbody>
</table>

- **Brain**: multiple sclerosis (?)
- **Thyroid**: Hashimoto's thyroiditis, primary myxoedema, thyrotoxicosis
- **Stomach**: pernicious anaemia
- **Adrenal**: Addison's disease
- **Pancreas**: insulin-dependent diabetes mellitus
- **Muscle**: dermatomyositis
- **Kidney**: SLE
- **Skin**: scleroderma, SLE
- **Joints**: rheumatoid arthritis
The spectrum of autoimmune diseases

<table>
<thead>
<tr>
<th>Organ-Specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hashimoto's thyroiditis</td>
</tr>
<tr>
<td>primary myxoedema</td>
</tr>
<tr>
<td>thyrotoxicosis</td>
</tr>
<tr>
<td>pernicious anaemia</td>
</tr>
<tr>
<td>autoimmune atrophic gastritis</td>
</tr>
<tr>
<td>Addison's disease</td>
</tr>
<tr>
<td>premature menopause (few cases)</td>
</tr>
<tr>
<td>insulin-dependent diabetes mellitus</td>
</tr>
<tr>
<td>stiff-man syndrome</td>
</tr>
<tr>
<td>Goodpasture's syndrome</td>
</tr>
<tr>
<td>myasthenia gravis</td>
</tr>
<tr>
<td>male infertility (few cases)</td>
</tr>
<tr>
<td>pemphigus vulgaris</td>
</tr>
<tr>
<td>pemphigoid</td>
</tr>
<tr>
<td>sympathetic ophthalmia</td>
</tr>
<tr>
<td>phacogenic uveitis</td>
</tr>
<tr>
<td>multiple sclerosis (?)</td>
</tr>
<tr>
<td>autoimmune haemolytic anaemia</td>
</tr>
<tr>
<td>idiopathic thrombocytopenic purpura</td>
</tr>
<tr>
<td>idiopathic leucopenia</td>
</tr>
<tr>
<td>primary biliary cirrhosis</td>
</tr>
<tr>
<td>active chronic hepatitis (HBsAg negative)</td>
</tr>
<tr>
<td>cryptogenic cirrhosis (some cases)</td>
</tr>
<tr>
<td>ulcerative colitis</td>
</tr>
<tr>
<td>atherosclerosis (?)</td>
</tr>
<tr>
<td>Sjögren's syndrome</td>
</tr>
<tr>
<td>rheumatoid arthritis</td>
</tr>
<tr>
<td>dermatomyositis</td>
</tr>
<tr>
<td>scleroderma</td>
</tr>
<tr>
<td>mixed connective tissue disease</td>
</tr>
<tr>
<td>anti-phospholipid syndrome</td>
</tr>
<tr>
<td>discoid lupus erythematosus</td>
</tr>
<tr>
<td>systemic lupus erythematosus (SLE)</td>
</tr>
</tbody>
</table>
Mechanisms of Autoimmune Damage
Mechanisms of Autoimmune Damage

- Autoimmunity is initiated in the same way as adaptive immune responses

- **Clinical outcome** is determined by
  - self Ag(s)
  - the mechanism of tissue damage

- The mechanism of tissue damage is classified by the scheme adopted for *hypersensitivity reactions*.

- More than one type of hypersensitivity may be involved
Mechanisms of Autoimmune Damage

• Tissue injury is caused by a response to self Ag ➔ Chronic diseases
• The Ag cannot be removed so the response persists
• Epitope spreading ➔ Progressive diseases
• Tissue damage can be mediated by the effector mechanisms of both T cells and B cells (antibodies)
Epitope spreading

Circulating B cell binds self antigens released from injured cells

B cell is activated by a T cell specific for self peptide

B cells differentiate into plasma cells, secreting large amounts of self-antigen specific antibody

At sites of injury, self-antigen specific antibody initiates an inflammatory response, causing more cell injury

More B cells bind self antigens, amplifying the cycle of tissue damage

Figure 13-7 Immunobiology, 6/e. (© Garland Science 2005)
Autoimmune responses resemble hypersensitivity reactions

- **Type II**: Antibodies (Abs) against cell surfaces/extracellular matrix
- **Type III**: Soluble immune complexes deposited in tissues
- **Type IV**: Effector T cells
Injury caused by antitissue antibody

Mechanism of antibody deposition

- Antibody deposition
- Antigen in extracellular matrix

Complement- and Fc receptor-mediated recruitment and activation of inflammatory cells

Effector mechanisms of tissue injury

- Neutrophils and macrophages
- Enzymes, reactive oxygen intermediates

Tissue injury
### Some common autoimmune diseases classified by immunopathogenetic mechanism

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Autoantigen</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type II antibody against cell-surface or matrix antigens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>Rh blood group antigens, I antigen</td>
<td>Destruction of red blood cells by complement and FcR⁺ phagocytes, anemia</td>
</tr>
<tr>
<td>Autoimmune thrombocytopenic purpura</td>
<td>Platelet integrin GpIIb:IIIa</td>
<td>Abnormal bleeding</td>
</tr>
<tr>
<td>Goodpasture's syndrome</td>
<td>Noncollagenous 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, myocarditis, late scarring of heart valves</td>
</tr>
</tbody>
</table>
Failure of vitamin $B_{12}$ absorption in pernicious anaemia

<table>
<thead>
<tr>
<th>normal</th>
<th>pernicious anaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>diet</td>
<td>diet</td>
</tr>
<tr>
<td>stomach</td>
<td>stomach</td>
</tr>
<tr>
<td>parietal cell secretion</td>
<td>parietal cell secretion</td>
</tr>
<tr>
<td>$B_{12}$ absorbed from gut</td>
<td>$B_{12}$ not absorbed</td>
</tr>
</tbody>
</table>

$B_{12}$ absorbed from gut

$B_{12}$ not absorbed
Type III Hypersensitivity
Autoimmunity

Immune complex–mediated tissue injury

Mechanism of antibody deposition

Effector mechanisms of tissue injury

Circulating immune complexes

Complement- and Fc receptor–mediated recruitment and activation of inflammatory cells

Blood vessel

Site of deposition of immune complexes

Neutrophils

Neutrophil granule enzymes, reactive oxygen intermediates

Vasculitis
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>
</tr>
<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, snRNP, scRNP</td>
<td>Glomerulonephritis, vasculitis, rash</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Rheumatoid factor IgG complexes</td>
<td>Arthritis</td>
</tr>
<tr>
<td>Syndrome</td>
<td>Autoantigen</td>
<td>Consequence</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>--------------------------------------------------</td>
<td>--------------------------------------------</td>
</tr>
<tr>
<td><strong>Type IV T cell-mediated disease</strong></td>
<td></td>
<td></td>
</tr>
<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>

Figure 13-27 part 3 of Immunobiology, 6/e. (© Garland Science 2005)
Type IV Hypersensitivity

**Delayed-type hypersensitivity**

- APC or tissue antigen
- CD4+ T cell
- CD8+ T cell
- Inflammation
- Cytokines
- Normal cellular tissue
- Tissue injury

**T cell–mediated cytolysis**

- CD8+ CTLs
- Cell lysis and tissue injury
<table>
<thead>
<tr>
<th>Disease</th>
<th>T cells</th>
<th>B cells</th>
<th>Antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Pathogenic Help for antibody</td>
<td>Present antigen to T cells</td>
<td>Pathogenic</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Pathogenic</td>
<td>Present antigen to T cells</td>
<td>–</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Help for antibody</td>
<td>Antibody secretion</td>
<td>Pathogenic</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Pathogenic</td>
<td>Present antigen to T cells</td>
<td>Present, but role unclear</td>
</tr>
</tbody>
</table>
Graves' Disease

- Abs against the TSH receptor mimic the natural ligand
- leads to chronic overproduction of $T_3$/$T_4$ insensitive to regulation
- Results in hyperthyroidism
- Individuals suffer from heat intolerance, nervousness, weight loss, outwardly bulging eyes

Figure 11-5 The Immune System, 2/e (© Garland Science 2005)
Myasthenia Gravis

Abs bind to the Ach receptor on muscle cells, resulting in their endocytosis and degradation. This results in a loss of muscle sensitivity to neuronal stimulation, leading to progressive muscle weakness. Often characterized by droopy eyelids and double vision.
Systemic Lupus Erythematosus (SLE)

- **Multisystem** autoimmune disease
- Abs against DNA, histones, ribosomes form immune complexes with Ags released from damaged cells
- **B-cell hyperreactivity** is a feature of LE, caused by excess T-helper activity
- Affects skin, kidneys, serosal surfaces, joints, CNS and heart *(deposition of Immune complex)*
Rheumatoid arthritis

• Non-suppurative proliferative synovitis which leads to destruction of articular cartilage and progressive disabling arthritis

• 3-5X more common in women than in men

• Initiated by activation of T-helper cells which produce cytokines and activate B cells to produce antibodies

• 80% of patients with rheumatoid factors (antibodies against Fc portion of IgG)

• Precise trigger which initiates destructive immune response is not known
Insulin-dependent diabetes mellitus (IDDM)

Selective destruction of insulin-producing β cells located within the islets of Langerhans by T cells

Several autoantigens are recognized by both Abs and T cells, including insulin and glutamic acid decarboxylase (GAD)