Immunology PAMM 509

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Autoimmunity and Autoimmune Disease

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Required Reading: Immunology Roitt et al Chap 20

**Learning objectives:**

1. Understand the immunological mechanisms underlying the development of autoimmunity.

2. Compare and contrast organ specific and organ non-specific autoimmune diseases.

3. What are the mechanisms for autoimmune damage?

4. How are autoimmune diseases treated?
What is an autoimmunity?

1. Demonstration of auto-reactive antibodies or lymphocytes in absence of an ongoing infection or other discernible cause

2. Breakdown of immunological tolerance and/or immune disregulation

What is autoimmune disease?

Overt disease in which self-reactivity leads to tissue pathology
1. Theories of Autoimmunity -
   Ehrlich (1910) *Horror Autoxicus*

A. McFarlane Burnet and Fenner-
   Explanation for transplant rejection of allogenic cells and tissues

   1) Organism distinguishes self from non-self:
      a) Fetal – during fetal life tolerance is established
      b) Adult – immature immune cells have a period of tolerance induction to self antigens
Burnet -
Clonal Selection theory: adaptive immunity derives from individual antigen-specific clones of T and B lymphocytes. Auto-reactive clones are eliminated on encounter with self antigen seen in early stage of life.

a) **Forbidden clones** – auto-reactive clones of lymphocytes that escape the censorship function of the thymus

b) **Auto antibodies and self reactive T cells** that develop after birth are normal components of the immune repertoire, but are kept under immunological control.
Spectrum of Autoimmune Diseases

Two types:
A) **Organ specific** – antibodies or T cells to a single organ (organ specific antigens)

Specific target organs:
Hashimoto’s Thyroiditis – thyroglobulin and thyroid peroxidase

Goodpasture’s syndrome - basement membrane collagen

Myasthenia gravis – Acetylcholine receptor

Insulin-resistant diabetes – Insulin receptor
Non organ specific autoimmune diseases:

**Common target antigens among many tissues:**

**Systemic Lupus Erythematosus (SLE)** – antibodies to intracellular nucleoproteins and formation of large amounts of immune complexes

**Rheumatoid arthritis** – production of an IgM anti-IgG antibody (rheumatoid factor) also T cells specific for an antigen present in joints
Comparison of organ specific and non-organ specific autoimmune diseases

<table>
<thead>
<tr>
<th>Organ-specific autoimmune diseases</th>
<th>Systemic autoimmune diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I diabetes mellitus</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Goodpasture's syndrome</td>
<td>Scleroderma</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Graves' disease</td>
<td>Primary Sjögren's syndrome</td>
</tr>
<tr>
<td>Hashimoto's thyroiditis</td>
<td>Polymyositis</td>
</tr>
<tr>
<td>Autoimmune pernicious anemia</td>
<td></td>
</tr>
<tr>
<td>Autoimmune Addison's disease</td>
<td></td>
</tr>
<tr>
<td>Vitiligo</td>
<td></td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td></td>
</tr>
</tbody>
</table>

Two types of autoimmune disease

<table>
<thead>
<tr>
<th>organ specific</th>
<th>non-organ specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>brain multiple sclerosis (?)</td>
<td>brain</td>
</tr>
<tr>
<td>thyroid Hashimoto's thyroiditis primary myxedema thyrotoxicosis</td>
<td>thyroid</td>
</tr>
<tr>
<td>muscle myasthenia gravis</td>
<td>muscle</td>
</tr>
<tr>
<td>stomach pernicious anemia</td>
<td>stomach</td>
</tr>
<tr>
<td>adrenal Addison's disease</td>
<td>adrenal</td>
</tr>
<tr>
<td>pancreas insulin-dependent diabetes mellitus</td>
<td>pancreas</td>
</tr>
<tr>
<td>joints rheumatoid arthritis</td>
<td>joints</td>
</tr>
</tbody>
</table>

Figure 13-1 Immunobiology, 6/e, © Garland Science 2006
Three interacting influences on the development of autoimmune diseases.

- genetic predisposition
- immune (dis-)regulation
- environmental factors
Susceptibility to autoimmune diseases is controlled by genetics and hormonal factors.

**Differential selection:**
failure to negatively select aberrant clones

**HLA specificity:**
- B27
- DR2
- DR3
- DR3 & DR4 (DQB linked)
- DR5
- DR4
Gender difference
females >> males

The sex distribution of the major autoimmune diseases
diabetes-prone NOD mice:
Immune (dys) regulation

Overview of Controls on Self Reactivity-

A. Sequestered Antigens –
   Normally antigens in privileged sites are not seen by the immune system.

B. Absence of antigen presenting cells
   no context of presentation to the potentially auto-reactive T or B cells.
C. Lack of MHC class II expression -
Most self antigens are expressed on MHC class I
need MHC class II presentation

D. Clonal Deletion -
Auto-reactive clones are eliminated in thymus
or during development

E. Lack of cellular communication-
no co-stimulatory signal  APC : T cell  and T : B
Lymphokines and cytokines not normally activated
are kept under strict controls
Evasion of tolerance and development of self reactivity: initiation of autoimmunity

A. Sequestered Antigens
   new antigens previously hid from the immune system presented to the immune system as a result of injury, tissue breakdown, infection.

B. MHC class II - inappropriate expression
   Interferon induces MHC expression allowing better presentation of self antigens (virus infection of pancreas)
C. Polyclonal B cell activation Bypass of $T_H$ cells
   a) development of systemic autoimmune diseases
   b) probably not involved in organ specific diseases
   c) Activation due to:
      1- inherent abnormality
      2- T cell lymphokines (IL-2)
      3- Mitogenic factors (LPS, EBV)

D. Defects or inappropriate cytokine production or signaling
   a) underexpression of IL-1 receptor antagonist leads to arthritis
   b) overexpression of IL-2, -7, -10 leads to inflammatory bowel disease
Examples of defects in cytokine production or signaling can lead to autoimmunity.

<table>
<thead>
<tr>
<th>Cytokine or Protein</th>
<th>Defect</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor necrosis factor α</td>
<td>Overexpression</td>
<td>Inflammatory bowel disease, arthritis, vasculitis</td>
</tr>
<tr>
<td>Tumor necrosis factor α</td>
<td>Underexpression</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Interleukin-1–receptor antagonist</td>
<td>Underexpression</td>
<td>Arthritis</td>
</tr>
<tr>
<td>Interleukin-2</td>
<td>Overexpression</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Interleukin-7</td>
<td>Overexpression</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Interleukin-10</td>
<td>Overexpression</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Interleukin-2 receptor</td>
<td>Overexpression</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Interleukin-10 receptor</td>
<td>Overexpression</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Interleukin-3</td>
<td>Overexpression</td>
<td>Demyelinating syndrome</td>
</tr>
<tr>
<td>Interferon-γ</td>
<td>Overexpression in skin</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>STAT-3</td>
<td>Underexpression</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>STAT-4</td>
<td>Overexpression</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Transforming growth factor β</td>
<td>Underexpression</td>
<td>Systemic wasting syndrome and inflammatory bowel disease</td>
</tr>
<tr>
<td>Transforming growth factor β receptor in T cells</td>
<td>Underexpression</td>
<td>Systemic lupus erythematosus</td>
</tr>
</tbody>
</table>
Environmental factors:
Infection with microbial agents

1) disruption of cell or tissue barrier-
release of sequestered antigens and presentation
by MHC II, activation of potential auto-reactive cells
by cytokines
ie Sympathetic opthalmia
   Coxsacki B-3 virus infection of the heart
   Hepatitis B virus infection of liver
   Enterovirus infection of pancreas beta cells
2) Infection or activation of antigen-presenting cell – induces activation and presentation of antigens not normally presented (providing second signal) self proteins are made immunogenic mycobacteria, 
Experimental autoimmune encephalomyelitis adjuvants

3) Binding of pathogen to self-protein- 
T cell response to pathogen will also provide “help” to auto-reactive B cells to respond to self antigen development of immune complexes
4) Molecular mimicry/cross reactive antigens
Infectious agents can provoke autoimmunity by the induction of antibodies and T cells that react against the pathogen, but also cross-react with self antigens.
Group A streptococcus carbohydrate antigens cross-react with heart valve antigens (Rheumatic fever), Lyme disease and arthritis.
Measles virus and myelin basic protein
Epstein-Barr virus and Systemic Lupus Erythematosus
Molecular mimicry and cross reactive antigens: alternative interpretations

**Mimicry**
Cross recognition of microbial and self epitopes

**Counter-interpretations**
- Immunopathology provoked by persisting microbial epitope
- Unrelated (bystander) reactivity to self induced by infection
  - Unmasking of shielded self
  - Novel presentation of self
  - Inflammation-induced break of tolerance
5) **Superantigen activation of autoreactive T cells**
   molecules that stimulate a subset of T cells by binding MHC class II molecules and the variable domain of the T cell receptor: results in stimulating the activation of a whole subset of T cells

1) **bacterial toxins and viral proteins**
   (staphlococcus: toxic shock syndrome, Epstein Barr virus)
2) T dependent antigens requiring no antigen processing
3) **Bind TCR to APC**: activation of large number of T cells (including auto-reactive T cells activated)
4) **Release of large quantities of cytokines**
Review of ways an infection could break tolerance and induce autoimmunity

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Effect</th>
<th>Example</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Disruption of cell or tissue</td>
<td>Release of sequestered self antigen; activation of nontolerized cells</td>
<td>Sympathetic ophthalmia</td>
<td></td>
</tr>
<tr>
<td>Infection of antigen-presenting cell</td>
<td>Release of inflammatory mediators, notably IFN-α</td>
<td>? SLE</td>
<td></td>
</tr>
<tr>
<td>Binding of pathogen to self</td>
<td>Pathogen acts as carrier to allow anti-self response</td>
<td>? Interstitial nephritis ? SLE</td>
<td></td>
</tr>
<tr>
<td>Molecular mimicry</td>
<td>Production of cross-reactive antibodies or T cells</td>
<td>Rheumatic fever ? Diabetes ? Multiple sclerosis</td>
<td></td>
</tr>
<tr>
<td>Superantigen</td>
<td>Polyclonal activation of autoreactive T cells</td>
<td>? Rheumatoid arthritis</td>
<td></td>
</tr>
</tbody>
</table>

Figure 13-26  Immunobiology, 6/e. (© Garland Science 2005)
Overview of factors contributing to the development of autoimmunity

Local tissue alterations: tissue injury/inflammation
release of sequestered antigens, increase costimulatory molecule expression. (Usually caused by infections)

Lymphocyte alteration: stimulation of auto-reactive lymphocytes by abnormal selection, polyclonal activation, or molecular mimicry, dysregulation of immune system

Genetic factors: inheritance of disease associated MHC and other genes, susceptibility genes, sex hormones

Environmental factors: infections
A model for the multifactorial nature of autoimmune disease

- Genetics and Epigenetic changes
- Susceptibility genes
- Environmental factors
- Exogenous or Endogenous Antigen
  - Immune Response (cytokines and effector functions)
  - Sex Hormones
  - Neuroendocrine factors

Initiating factors

Outcomes
- Tolerance
- Protection from infection
- Autoimmunity
<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>
### 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 II antibody against cell-surface or matrix antigens</strong></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 GpIb: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>
<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><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>

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**anti red cell antibodies:**

- **Red blood cells plus anti-RBC autoantibodies**
  - FcR⁺ cells in fixed mononuclear phagocytic system
  - Complement activation and intravascular hemolysis
  - Phagocytosis and RBC destruction
  - Lysis and RBC destruction

**Immune complex in kidney of SLE**

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*Figure 13-27 Immunobiology, 6/e. © Garland Science 2005*
Pancreatic β cells destroyed in Insulin dependent diabetes mellitus

The islets of Langerhans contain several cell types secreting distinct hormones. Each cell expresses different tissue-specific proteins.

In insulin-dependent diabetes an effector T cell recognizes peptides from a β cell-specific protein and kills the β cell.

Glucagon and somatostatin are still produced by the β and δ cells, but not insulin can be made.
Bone marrow transplantation: SLE and RA

cyclosporin: diabetes

anti-inflammatory: Cox-2 inhibitors

mechanical new joints, new kidney

metabolic control: thyroxine in thyroiditis, insulin in diabetes
Future Treatment of Autoimmune diseases:

**Alteration of threshold of immune activation**
- antagonize inflammatory cytokines,
- blockade of co-stimulatory factors
  (Etanercept: TNF blocking Ig, Infliximab: monoclonal antibody to TNF)

**Modulation of antigen specific autoimmune cells**
- induction of T or B cell tolerance, induction of regulatory cells
- change $T_H 1/T_H 2$ balance
  (Interferon beta 1a and copolymer I: deviation of TH1 to TH2)

**Reconstitution of the immune system**
- Bone marrow ablation and stem cell transplant

**Sparing of target organs**
- anti-inflammatory drugs
Summary

• Autoimmunity is a change from tolerance to a destruction of self antigens
• There are several mechanisms for breakdown of self tolerance and development of autoimmunity
• Factors which affect the development of autoimmunity include genetics, environmental (infections), immune disregulation.