Chapter 15

Autoimmunity

Inappropriate immune response against self-components
Self Ag

Self(Auto) antigen
(encoded by the host’s genome)

Humoral imm

B-cell receptors and antibodies recognize native protein antigens

pathogen

protein antigen

antibody

B cell

Self Ag

CMI: CD8 T

MHC class I

MHC class II

TCR

CD8 T cell

CD4 T cell

TCR

APC

host’s genome
1. The mechanism of self-tolerance
2. The pre-disposing factors of autoimmune diseases
3. Autoimmune diseases
Lymphocytes

Development
- Central lymphoid organs
- Activation & differentiation
- Peripheral lymphoid organs

Effector function
- Inflamed sites
In healthy individuals, the immune system is tolerant of self antigens.

<table>
<thead>
<tr>
<th>Type of tolerance</th>
<th>Mechanism</th>
<th>Site of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central tolerance</td>
<td>Deletion</td>
<td>Thymus Bone marrow</td>
</tr>
<tr>
<td></td>
<td>Editing</td>
<td></td>
</tr>
</tbody>
</table>
Central B cell tolerance

Self Ag presentation

By bone marrow stromal cells, hematopoietic cells, and macromolecules circulating in the blood plasma

Negative selection

Major epitopes

Receptor editing
Clonal deletion
Clonal anergy
Clonal ignorant

The presence of autoreactive lymphocytes in periphery
Central T cell tolerance

**Negative selection of αβ T cells by dendritic cells, macrophages, and other cells in the thymus**

- **Moderate binding**
  - Lives
- **Tight binding**
  - Dies

- **Major epitopes**
- **Self Ag presentation**
- **AIRE expression on thymic medulary cells**
- **Natural Treg**
- **Clonal deletion**
- **Clonal anergy**
- **Clonal ignorant**

**The presence of autoreactive lymphocytes in periphery**

**Figure 7.18 Negative selection of T cells in the thymus.**
The immune system is not tolerant, because these self peptides are not Normally presented by MHC molecules at sufficient levels.

Normal: without tissue injury and cell death
Self-reactive B/T cells in periphery

Affinity

Cross reactivity

High affinity to non-self Ag

Anti-nonself

Self tolerance
**In periphery (no infection)**

## Layers of self-tolerance

<table>
<thead>
<tr>
<th>Type of tolerance</th>
<th>Mechanism</th>
<th>Site of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigen segregation</td>
<td><strong>Physical barrier to self-antigen access to lymphoid system</strong></td>
<td>Peripheral organs (e.g. thyroid, pancreas)</td>
</tr>
</tbody>
</table>

**Healthy skin is not inflamed**

- **Skin**
  - Effector cell
  - Connective tissue
- **Blood capillary**

**Surface wound introduces bacteria, which activate resident effector cells to secrete cytokines**

- **bacteria**
- **dirt, grit, etc.**
- **blood clot**
- **cytokines**

**Vasodilation and increased vascular permeability allow fluid, protein, and inflammatory cells to leave blood and enter tissue**

- **fluid**
- **protein**

**The infected tissue becomes inflamed, causing redness, heat, swelling, and pain**

- **infected tissue**
Central role of CD4 T cells in tolerance

**Signal 1: Ag uptake and presentation on MHCII**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>MHC class I</th>
<th>MHC class II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoid tissues</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T cells</td>
<td>+++</td>
<td>+*</td>
</tr>
<tr>
<td>B cells</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Macrophages</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Dendritic cells</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Epithelial cells of the thymus</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>

**Professional APC**

**Signal 3 delivered by antigen-presenting cell**

- TGF-β
  - FoxP3, TGF-β, IL-10
  - T_reg cells

- IL-6
  - Bcl6, IL-21, ICOS
  - T_FH cells

- TGF-β, IL-6
  - RORγT, IL-6, IL-17
  - T_H17 cells

- IL-12, IFN-γ
  - T-bet, IL-2, IFN-γ
  - T_H1 cells

- IL-4
  - GATA3, IL-4, IL-5
  - T_H2 cells
Peripheral tolerance

When Ag exposure to immune system

<table>
<thead>
<tr>
<th>Type of tolerance</th>
<th>Mechanism</th>
<th>Site of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral anergy</td>
<td>Cellular inactivation by weak signaling without co-stimulus</td>
<td>Secondary lymphoid tissue</td>
</tr>
<tr>
<td>Regulatory T cells</td>
<td>Suppression by cytokines, intercellular signals</td>
<td>Secondary lymphoid tissue and sites of inflammation</td>
</tr>
<tr>
<td>Functional deviation</td>
<td>Differentiation of regulatory T cells that limit inflammatory cytokine secretion</td>
<td>Secondary lymphoid tissue and sites of inflammation</td>
</tr>
<tr>
<td>Activation-induced cell death</td>
<td>Apoptosis</td>
<td>Secondary lymphoid tissue and sites of inflammation</td>
</tr>
</tbody>
</table>

Figure 15.2 Janeway’s Immunobiology, 8ed. (© Garland Science 2012)
In the absence of infection

Migration of immature DC

Antigen uptake by Langerhans cells in the skin

Langerhans cells leave the skin and enter the lymphatic system

Self Ag

Epidermis

Dermis

Normal tissue

Mature dendritic cells enter the lymph node from infected tissues and can transfer some antigens to resident dendritic cells

Clonal deletion

B7-positive dendritic cells stimulate naive T cells

Specific signal alone

antigen-presenting cell

T cell becomes anergic

Naive T cell recognizes self antigen on epithelial cell

Antigen-specific signal alone induces anergy

Figure 9.13 Janeway’s Immunobiology, 8ed. (© Garland Science 2012)
Maintenance of Tolerance by Treg in the absence of infection

In the absence of infection, dendritic cells make predominantly TGF-β and little IL-6

- High TGF-β
- Low IL-6, IL-23
- Naive CD4 T cell

Adaptive Treg

T_{reg} cells

Inhibition of Th17, Th1, Th2

Cytokines: IL10, TGFβ

Cell-cell contact

Natural Treg

Adaptive Treg

Regulatory tolerance

T cell specific for self or commensal microbiota antigen recognized in presence of TGF-β becomes an induced regulatory T cell (T_{reg})

TGF-β

Figure 15.9 Janeway's Immunobiology, 8ed. © Garland Science
<table>
<thead>
<tr>
<th>Type of tolerance</th>
<th>Mechanism</th>
<th>Site of action</th>
</tr>
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<tbody>
<tr>
<td>Peripheral anergy</td>
<td>Cellular inactivation by weak signaling without co-stimulus</td>
<td>Secondary lymphoid tissue</td>
</tr>
<tr>
<td>Regulatory cells</td>
<td>Suppression by cytokines, intercellular signals</td>
<td>Secondary lymphoid tissue and sites of inflammation</td>
</tr>
<tr>
<td>Cytokine deviation</td>
<td>Differentiation to Th2 cells, limiting inflammatory cytokine secretion</td>
<td>Secondary lymphoid tissue and sites of inflammation</td>
</tr>
</tbody>
</table>

**Th2 >> Th1**
<table>
<thead>
<tr>
<th>Type of tolerance</th>
<th>Mechanism</th>
<th>Site of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activation-induced cell death</td>
<td>AICD</td>
<td>Secondary lymphoid tissue and sites of inflammation</td>
</tr>
</tbody>
</table>

**Figure 15.2 Janeway’s Immunobiology, 8ed. (© Garland Science 2012)**

**Encounter of autoreactive B cell with self antigen within germinal centers causes apoptosis**

**Figure 15.6 Janeway’s Immunobiology, 8ed. (© Garland Science)**
Maintenance of tolerance in infection

FasL/Fas: Apoptosis of effectors

Figure 11.16 Janeway's Immunobiology, 8th ed. (© Garland Science 2012)
<table>
<thead>
<tr>
<th>Immunologically privileged sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
</tr>
<tr>
<td>Eye</td>
</tr>
<tr>
<td>Testis</td>
</tr>
<tr>
<td>Uterus (fetus)</td>
</tr>
<tr>
<td>Hamster cheek pouch</td>
</tr>
</tbody>
</table>
Immune privileged sites

Immunosuppressive cytokines: TGFβ

Non-destructive response

Th2 >> Th1

CMI

Tolerance induction

FasL expression

Trimeric Fas ligand (FasL) binds to and trimerizes Fas

Figure 7.30 Janeway's Immunobiology, 6th, © Garland
1. The mechanism of self-tolerance

2. The pre-disposing factors of autoimmune diseases

3. Autoimmune diseases
Self tolerance

Genetic Polymorphism or defect

Clearance

Immune regulation

Autoimmunity

Genetic factors

Infection and environmental exposure

KO
Ag exposure to immune system

Tissue injury and cell death

Antigen segregation

| Physical barrier to self-antigen access to lymphoid system |

Criptic epitopes

- Necrosis:
  - Chromatin clumping
  - Swollen organelles
  - Flocculent mitochondria

- Apoptosis:
  - Mild convolution
  - Chromatin compaction and segregation
  - Condensation of cytoplasm
  - Nuclear fragmentation
  - Biebbing
  - Apoptotic bodies
  - Phagocytosis
  - Apoptotic body

Release of intracellular contents

Inflammation
Tissue injury and cell death

Self Ag exposure to immune system

Activation of autoreactive cells

Clearance mechanism
The breaking of self-tolerance

- Myocardial infarction
- Massive tissue injury and death
- Ag exposure to immune system
- Autoimmune response against cardiac antigens
- Clearance mechanism (Transient)
- Inadequate or genetically deficient
- Autoimmune disease
Self tolerance

Genetic factors

Infection and environmental exposure

Immune regulation

Autoimmunity

Clearance

Genetic Polymorphism or defect

HLA
Genetic pre-disposition

Association of HLA & autoimmune diseases
## Associations of HLA serotype with susceptibility to autoimmune disease

<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 1 (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></td>
<td></td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>DR4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hashimoto’s thyroiditis</td>
<td>DR5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Figure 15.33 Janeway's Immunobiology, 8ed. © Garland Science 2012*
Genetic pre-disposition

Figure 15.29 Janeway’s Immunobiology, 8th Ed. (© Garland Science 2012)
Signal 1
Signal 2
Signal 3
Dead cells
Bystander effect
Self Ag exposure
Activation of autoreactive cells

Genetic factors
Infection and environmental exposure

Immune regulation

Autoimmunity

Pathological B, Th1 or Th2
Infection could break self tolerance.

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Effect</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disruption of cell or tissue barrier</td>
<td>Release of sequestered self antigen; activation of nontolerized cells</td>
<td>Sympathetic ophthalmia</td>
</tr>
<tr>
<td>Molecular mimicry</td>
<td>Production of cross-reactive antibodies or T cells</td>
<td>Rheumatic fever Reactive arthritis Lyme arthritis</td>
</tr>
</tbody>
</table>

*Figure 15.39 Janeway’s Immunobiology, 8th Ed. (© Garland Science 2012)*
Self Ag
Necrosis
Infection: foreign Ag

DC-T interaction

T cells that encounter specific antigen proliferate and differentiate to effector cells

Dendritic cells bearing antigen enter the draining lymph node, where they settle in the T-cell areas

Dendritic cells take up bacterial antigens in the skin and then move to enter a draining lymphatic vessel
Infection can break tolerance

**Figure 15.40 Janeway’s Immunobiology, 8ed. (© Garland Science 2012)**
## Infection and autoimmune T cell activation

<table>
<thead>
<tr>
<th>Infection</th>
<th>HLA association</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A Streptococcus</td>
<td>Not known</td>
<td>Rheumatic fever (carditis, polyarthritis)</td>
</tr>
<tr>
<td><em>Chlamydia trachomatis</em></td>
<td>HLA-B27</td>
<td>Reiter's syndrome (arthritis)</td>
</tr>
<tr>
<td><em>Shigella flexneri, Salmonella typhimurium,</em></td>
<td>HLA-B27</td>
<td>Reactive arthritis</td>
</tr>
<tr>
<td><em>Salmonella enteritidis,</em> <em>Yersinia enterocolitica,</em> <em>Campylobacter jejuni</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Borrelia burgdorferi</em></td>
<td>HLA-DR2, DR4</td>
<td>Chronic arthritis in Lyme disease</td>
</tr>
<tr>
<td>Coxsackie A virus, Coxsackie B virus, echoviruses, rubella</td>
<td>HLA-DQ2, HLA-DQ8 DR4</td>
<td>Type 1 diabetes</td>
</tr>
</tbody>
</table>

Figure 13.32 The Immune System, 3ed. (© Garland Science 2009)
Molecular mimicry

- **Streptococcal cell wall stimulates antibody response**
- **Some antibodies cross-react with heart tissue, causing rheumatic fever**

*Figure 13.31 The Immune System, 3rd ed. (© Garland Science 2009)*
Epitope spreading

Amplification

Disease severity

Figure 15.18 Janeway's Immunobiology, 8ed. (© Garland Science 2012)
TLR signals provide co-stimulation for B cell activation

- B cells with specificity for DNA bind soluble fragments of DNA, sending a signal through the B-cell receptor
- The cross-linked B-cell receptor is internalized with the bound DNA molecule
- GC-rich fragments from the internalized DNA bind to TLR-9 in an endosomal compartment, sending a co-stimulatory signal

Figure 15.5 Janeway’s Immunobiology, 8th ed. (© Garland Science 2012)
Inflammatory bowel disease (IBD)

Multiple factors

Over responsiveness of CD4 T cells to commensal gut microbiota

Figure 15.37 Janeway's Immunobiology, 8ed. (© Garland Science 2012)
**Treg in colitis**

Inflammatory bowel disease and colitis result from autoreactive T cells in the lamina propria.

The disease can be treated by transfer of CD4 CD25 T<sub>reg</sub> cells, which home to mesenteric lymph nodes and the colon.

CD4 CD25 T<sub>reg</sub> cells proliferate and inhibit the pathogenic effector T cells.

After inflammation resolves, CD4 CD25 T<sub>reg</sub> cells remain in clusters with dendritic cell and pathogenic effector T cells.

*Figure 15.10 Janeway’s Immunobiology, 8ed. (© Garland Science 2012)*
Self-reactive B/T cells in periphery

Cross reactivity

High affinity to non-self Ag

Anti-nonself

Self tolerance

Signal 1-3
1. The mechanism of self-tolerance

2. The pre-disposing factors of autoimmune diseases

3. Autoimmune diseases
Self (auto) antigen
(encoded by the host’s genome)

Self components

Autoimmunity (B/T cells)
Abnormal infiltration of leukocytes
Inflammation
Chronic diseases

Interference or even loss of normal function

Cell/organ-specific
Systemic
Hypersensitivity & autoimmune disease

**Type II**
- IgG-Mediated Cytotoxic Hypersensitivity
- Ab directed against cell surface antigens mediates cell destruction via complement activation or ADCC

**Type III**
- Immune Complex-Mediated Hypersensitivity
- Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils

**Type IV**
- Cell-Mediated Hypersensitivity
- Sensitized $T_H1$ cells release cytokines that activate macrophages or $T_C$ cells which mediate direct cellular damage
Identification of the major immune mechanism for disease

<table>
<thead>
<tr>
<th>Autoimmune diseases involve all aspects of the immune response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease</td>
</tr>
<tr>
<td>Systemic lupus erythematosis</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
</tr>
</tbody>
</table>

Figure 15.16 Janeway’s Immunobiology, 8ed. (© Garland Science 2012)
Identification of the major immune mechanism for disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Autoantibody</th>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myasthenia gravis</td>
<td>Anti-acetylcholine receptor</td>
<td>Muscle weakness</td>
</tr>
</tbody>
</table>

![Diagram](image)

Figure 15.12 Janeway’s Immunobiology, 8ed. (© Garland Science 2012)
Experimental autoimmune encephalomyelitis (EAE)

Brain autoantigen: myelin basic protein

Inflammation

Multiple sclerosis

Mice injected with myelin basic protein and complete Freund's adjuvant develop EAE and are paralyzed.

The disease is mediated by $T_H^{17}$ and $T_H^{1}$ cells specific for myelin basic protein.

Disease can be transmitted by transfer of T cells from affected animal.

Alteration of tissue barriers

Figure 15.13 part 2 of 2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)
Ab:
Cell destruction

Figure 15.20 Janeway’s Immunobiology, 8ed. (© Garland Science 2012)
### Diseases mediated by antibodies against cell-surface receptors

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Antigen</th>
<th>Antibody</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graves’ disease</td>
<td>Thyroid-stimulating hormone receptor</td>
<td>Agonist</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Acetylcholine receptor</td>
<td>Antagonist</td>
<td>Progressive muscle weakness</td>
</tr>
<tr>
<td>Insulin-resistant diabetes</td>
<td>Insulin receptor</td>
<td>Antagonist</td>
<td>Hyperglycemia, ketoacidosis</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Insulin receptor</td>
<td>Agonist</td>
<td>Hypoglycemia</td>
</tr>
</tbody>
</table>

**Figure 13.17** Diseases mediated by antibodies against cell-surface receptors. Antibodies act as agonists when they stimulate a receptor on binding it, and as antagonists when they block a receptor’s function on binding it.
Myasthenia gravis

Function-blocking antibody

Normal events at the neuromuscular junction:
- acetylcholine receptors
- neuronal impulse
- Na⁺ influx
- muscle contraction

Myasthenia gravis:
- acetylcholine receptors internalized and degraded
- no Na⁺ influx
- no muscle contraction

Muscle weakness

Figure 15.22 Janeway's Immunobiology, 8th ed. (© Garland Science 2012)
The need to increase cell metabolism

Stimulating antibody

Thyroid hormones shut down TSH production but have no effect on autoantibody production, which continues to cause excessive thyroid hormone production

Graves’ disease

Hyperthyroid
Autoimmune diseases transferred across the placenta to the fetus and newborn infant

- Patient with Graves' disease makes anti-TSHR antibodies
- Transfer of antibodies across placenta into the fetus
- Newborn infant also suffers from Graves' disease
- Plasmapheresis removes maternal anti-TSHR antibodies and cures the disease

Figure 15.15 Janeway's Immunobiology, 8ed. (© Garland Science 2012)
Autoantibodies against common components of human cells can cause systemic autoimmune disease.

Cell death

AutoAg exposure

dsDNA
Nucleoprotein

Circulation

Deposition
Deposition of immune complex

Figure 13.11 The characteristic facial rash of systemic lupus erythematosus. Although this butterfly-shaped rash was first used to recognize the disease, it is seen in only a proportion of patients who have the disease when defined immunologically. Photograph courtesy of M. Walport.

Figure 15.25 Janeway's Immunobiology, 8th. (© Garland Science 2012)
Figure 13.9 Comparison of histological sections of a pancreas from a healthy person and a patient with type 1 diabetes. Panel a shows a micrograph of a tissue section through a healthy human pancreas, showing a single islet. The islet is the discrete light-staining area in the center of the photograph. It is composed of hormone-producing cells, including the β cells that produce insulin. Panel b shows a micrograph of an islet from the pancreas of a patient with type 1 diabetes with acute onset of disease. The islet shows insulitis, an infiltration of lymphocytes from the islet periphery towards the center. The lymphocytes are the clusters of cells with darkly staining nuclei. Both tissue sections are stained with hematoxylin and eosin; magnification × 250. Photographs courtesy of G. Klöppel.
**Hashimoto’s thyroiditis**

**Chronic inflammation**

**Intense leukocyte infiltration**

**Tissue damage**

**Hypothyroid**

*Figure 13.7 Hashimoto’s thyroiditis.* In a healthy thyroid gland the epithelial cells form spherical follicles containing thyroglobulin (panel a). In patients with Hashimoto’s thyroiditis the thyroid gland becomes infiltrated with lymphocytes, which destroy the normal architecture of the thyroid gland and can become organized into structures resembling secondary lymphoid tissue (panel b), as shown in the schematic diagram at the right. Courtesy of Yasodha Natkunam.
Figure 13.34 Induction of HLA class II expression on tissue cells facilitates autoimmunity. Thyroid epithelial cells do not normally express HLA class II molecules (top panel). They are induced to do so by IFN-γ (center panel). They are then able to present thyroid peptides to activated antigen-specific T cells, which induces autoimmune thyroid disease (bottom panel). IFN-γ produced by activated T cells feeds back to amplify HLA expression and antigen presentation.
1. The mechanism of self-tolerance

2. The pre-disposing factors of autoimmune diseases

3. Autoimmune diseases
Homework

1. The mechanism of self-tolerance
2. The pre-disposing factors of autoimmune diseases
3. Autoimmune diseases

Analyze the biological significance of the survival of auto-reactive clones in the central lymphoid organs.