Autoimmunity & Transplantation

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Learning Objectives

By the end of this lecture you will be able to:

① Recognize the mechanisms of tolerance and autoimmunity
② Understand the pathophysiology of some autoimmune diseases
③ Describe the scenarios of transplant immunology
Autoimmunity

• Defined as “failure of immune tolerance”

• The immune system loses the ability to discriminate between self and non-self

• Attacks and destroys healthy body tissue
Both B and T lymphocytes undergo clonal selection in primary lymphoid organs.
Peripheral tolerance

Mature lymphocytes

Foreign antigen

Immune response to foreign antigens

Self antigen

Apoptosis

Anergy

Peripheral tolerance: deletion or anergy of lymphocytes that recognize self antigens in peripheral tissues

Unresponsiveness to antigenic stimulus
Peripheral Tolerance

Also induced by T<sub>reg</sub> cells, which is a unique subgroup of CD4<sup>+</sup> T cells that recognize self-antigens on immune system cells and able to suppress the immune system and induce cell death in some immune cells.
Tolerogens

- High dosages of antigen
- Persistence of antigen in host
- IV or oral introduction
- Absence of adjuvants
- Low levels of co-stimulation molecules
<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>
<tr>
<td>Antigen segregation</td>
<td>Physical barrier to self-antigen access to lymphoid system</td>
<td>Peripheral organs (e.g. thyroid, pancreas)</td>
</tr>
<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 T_{H}2 cells, limiting inflammatory cytokine secretion</td>
<td>Secondary lymphoid tissue and sites of inflammation</td>
</tr>
<tr>
<td>Clonal deletion</td>
<td>Apoptosis post-activation</td>
<td>Secondary lymphoid tissue and sites of inflammation</td>
</tr>
</tbody>
</table>
Induction of autoimmunity

Genetic factors

Infection and environmental exposure

Strept. A (rheumatic fever)

Eye injury

HLA-B27

ankylosing spondylitis (spine inflammation)

Immune regulation

Autoimmunity

Figure 14-3 Immunobiology, 7ed. (© Garland Science 2008)
Induction of autoimmunity

- Proposed mechanisms for induction of autoimmunity (Ag recognition) include:
  - Release of sequestered antigens
  - Molecular mimicry
  - Inappropriate expression of Class II MHC
Release of sequestered antigens

• Some organs express antigens that are hidden from the immune system (immunologically privileged sites)
<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>
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<tr>
<td>Uterus (fetus)</td>
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</tbody>
</table>
Molecular mimicry

- When a pathogen expresses an antigen that is structurally close to a self antigen

Rheumatic fever is a post-streptococcal Group A disease

- Group A Strep present in throat infection; expresses large amounts of M protein
- Large amounts of IgG produced against M protein on Strep
- Antibodies against M protein can bind to molecules on cardiac cells that are very similar to M protein
- Antibody-induced injury to heart valves and sarcolemma

Figure 11-29 The Immune System, 2/e (© Garland Science 2005)
Inappropriate expression of MHC-II

- Unusual expression of MHC-II by non-APC
- Can be caused by viral infection
- May lead to self-antigen presentation to T helper cells
# Sites of autoimmune diseases

<table>
<thead>
<tr>
<th>Organ-specific autoimmune diseases</th>
<th>Systemic autoimmune diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 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 hemolytic anemia</td>
<td></td>
</tr>
<tr>
<td>Autoimmune Addison's disease</td>
<td></td>
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<tr>
<td>Vitiligo</td>
<td></td>
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<tr>
<td>Myasthenia gravis</td>
<td></td>
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</tbody>
</table>

*Figure 14-11 Immunobiology, 7ed. (© Garland Science 2008)*
AIHA (Type II hypersensitivity)

Red blood cells plus anti-RBC autoantibodies

- FcR+ cells in fixed mononuclear phagocytic system
  - Phagocytosis and RBC destruction

- Complement activation and intravascular hemolysis
  - Lysis and RBC destruction

Figure 14-20 Immunobiology, 7ed. (© Garland Science 2008)
SLE (Type III hypersensitivity)

• Typically middle-aged women
• Fever, weakness, arthritis, skin rash, kidney problems
• Produce auto-Abs to DNA, histones, platelets, leukocytes, clotting factors
• Excessive complement activation
SLE (Type III hypersensitivity)
SLE  (Type III hypersensitivity)

H1-specific helper T cell activates DNA-specific B cells that process nucleosomes and present H1 peptides

Activated B cell differentiates into plasma cells secreting anti-DNA antibody

Figure 14-18 Immunobiology, 7ed. (© Garland Science 2008)
Type 1 DM  (Type IV hypersensitivity)

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

In type 1 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 α and δ cells, but no insulin can be made.
Treatment strategies

• Immunosuppressive drugs
• Thymectomy (e.g. with myasthenia gravis)
• Plasmaphoresis (removal of extra immune complexes)
• Treating the inflammation (corticosteroids)
• Biologicals (e.g. anti-inflammatory mAbs)
• Antigen given orally can induce tolerance
Different types of Transplants

- **Autograft**
  - Self tissue transferred from one part of body to another

- **Isograft (syngeneic graft)**
  - Tissue transferred between genetically identical individuals

- **Allograft**
  - Tissue transferred between genetically different members of same species
    - Most of our transplants

- **Xenograft**
  - Tissue transferred between different species
Recognition and Rejection

- Skin graft to syngeneic recipient
  - MHC\(^a\)
  - MHC\(^a\)
  - Graft is tolerated

- Skin graft to allogeneic recipient
  - MHC\(^a\)
  - MHC\(^b\)
  - Graft is rejected rapidly (first-set rejection)

- Second skin graft from same donor to same recipient
  - MHC\(^a\)
  - MHC\(^b\)
  - Graft shows accelerated (second-set) rejection

- T cells transfer accelerated rejection from a sensitized donor to a naive recipient
  - MHC\(^b\) sensitized to MHC\(^a\)
  - naive MHC\(^b\)
  - Graft shows accelerated (second-set) rejection

Percentage of grafts surviving

Days after grafting

Figure 14-39 Immunobiology, 7ed. (© Garland Science 2008)
Donor APCs migrate to a local lymph node and stimulate alloreactive recipient T cells

Recipient APCs process proteins and present peptides derived from the graft

Direct recognition

Indirect recognition

Figure 14-43 Immunobiology, 7ed. (© Garland Science 2008)
Recognition and Rejection

- Skin graft with Langerhans cells
- Langerhans cells migrate to local lymph node, where they activate effector cells
- Effector cells migrate to graft via blood
- Graft destroyed by effector cells

Figure 14-42 Immunobiology, 7ed. (© Garland Science 2008)
Recognition and Rejection

Skin graft to syngeneic recipient

MHC^a → Graft tolerated

Skin graft to allogeneic recipient

MHC^a → MHC^b → Graft rejected rapidly

Skin graft to minor H antigen incompatible recipient

MHC^a → Graft rejected slowly

Percentage of grafts surviving

Days after grafting

Figure 14-40 Immunobiology, 7ed. (© Garland Science 2008)
Histocompatibility

Kevin

H₁ᵇ/H₁ᵇ
H₂ᵃ/H₂ᵇ
H₃ᵃ/H₃ᵃ

Kevin’s cells

Kevin’s immune system will see □ and □ as foreign

H₁ H₂ H₃
b b a
b a a

Tom

H₁ᵃ/H₁ᵃ
H₂ᵃ/H₂ᵇ
H₃ᵃ/H₃ᵇ

Tom’s cells

Tom’s immune system will see □ as foreign

H₁ H₂ H₃
a b b
a a a
Histocompatibility

• Tissues that are antigenically similar – histocompatible

• Mismatches with Class II MHC are more likely to lead to rejection than mismatches with Class I
• Microcytotoxicity assay for MHC haplotypes

• If antigen is present on cell, complement will lyse it, and it will uptake dye (blue)

• Donor 1 has antigens in common with recipient
Polymorphic self proteins that differ in amino acid sequence between individuals give rise to minor H antigen differences between donor and recipient.

Figure 14-41 Immunobiology, 7ed. (© Garland Science 2008)
Clinical Manifestations of Graft Rejections

- **Hyperacute**
  - Within hours
- **Acute**
  - Within weeks
- **Chronic**
  - Months to years

Figure 14-44 Immunobiology, 7ed. (© Garland Science 2008)
Graft Versus Host Disease

In a hematopoietic stem-cell transplant the recipient receives some mature T cells

Alloreactive T cells are activated by recipient dendritic cells and can cause widespread tissue damage, called graft-versus-host disease (GVHD)

If recipient dendritic cells are absent, donor T cells now see only donor-derived dendritic cells and are not activated to cause GVHD

Figure 14-47 Immunobiology, 7ed. (© Garland Science 2008)
You are now able to:

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✓ Describe the scenarios of transplant immunology