Molecular Mechanisms of Autoimmunity

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Infectious Minds Presentation
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Introduction
Pick an organ, any organ . . .

Autoimmunity can affect ANY organ/organ system in the human body

- Autoimmune Uveitis
- Sjogren’s Syndrome
- Rheumatic Fever
- Autoimmune Hepatitis
- Autoimmune Oophoritis
- Rheumatoid Arthritis
- Multiple Sclerosis
- Pemphigus
- Goodpasture’s Syndrome
- Diabetes
- Addison’s Disease
- Ulcerative Colitis
- Autoimmune hemolytic Anemia
Molecular Mechanisms of Autoimmunity

How is autoimmunity induced?

What could go wrong here?
Major factors in initiation and regulation of AI disease

1. MHC Control
2. Antigen Mimicry
3. Altered Proteins
Major Histocompatibility Complex

• Human – A set of linked genes, located on chromosome 6

• Molecules encoded by the MHC:
  – Cell surface receptors
  – Bind unique antigen fragments
  – Display them for recognition by immune effectors; most importantly T – Cells
Antigen Presentation

APC to T-cell
• The **MHC** accomplishes its major role in immune recognition by satisfying two distinct molecular functions:
  
  – Binding of **peptides** (or in some cases non-peptidic molecules)
  
  – Interaction with T cells, usually via the αβ T-cell receptor (TCR).
Three MHC Class I alpha chain genes: HLA – A, B and C

Three MHC Class II alpha chain genes: HLA – DR, DP and DQ
MHC & Autoimmunity

• Regardless of the underlying cause of autoimmunity, predisposition to a given autoimmune response is associated with certain HLA allele(s)

• Involvement of the requisite HLA allele is at the level of antigen presentation by the APCs for T Cell recognition
MHC Control gone wrong? DR3, DR4

Diabetes

Normal Pancreas

Pancreas with Insulitis
### 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 I insulin-dependent diabetes mellitus</td>
<td>DR3/DR4</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>

Figure 13-20 Immunobiology, 6/e © Garland Science 2005
Major factors in initiation and regulation of AI disease

1. MHC Control
2. Antigen Mimicry
3. Altered Proteins
Molecular Mimicry

Microbe: SWA Q G A P V L

Host: VGA Q G A P A K
Molecular Mimicry

• Microbe and Host Cell:
  – Share of a linear amino acid sequence
  – Share of conformation fit

• Host immune response against the microbe reacts if the host sequence comprises a biologically important domain

• Autoimmunity may occur
Rheumatic fever is a classic example of molecular mimicry.
### Table 20.3: Molecular Mimicry Between Proteins of Infectious Organisms and Human Host Proteins

<table>
<thead>
<tr>
<th>Protein</th>
<th>Residue</th>
<th>Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human cytomegalovirus IE2</td>
<td>79</td>
<td>PDP [GRD] EED</td>
</tr>
<tr>
<td>HLA-DR molecule</td>
<td>60</td>
<td>VTE [GRD] EAE</td>
</tr>
<tr>
<td>Poliovirus VP2</td>
<td>70</td>
<td>STT KESRGTT</td>
</tr>
<tr>
<td>Acetylcholine receptor</td>
<td>176</td>
<td>TVI KESRGTK</td>
</tr>
<tr>
<td>Papilloma virus E2</td>
<td>76</td>
<td>SLHEL [QRSTK] DL</td>
</tr>
<tr>
<td>Insulin receptor</td>
<td>66</td>
<td>VYGLESLKDS</td>
</tr>
<tr>
<td>Rabies virus glycoprotein</td>
<td>147</td>
<td>TKESLVIIS</td>
</tr>
<tr>
<td>Insulin receptor</td>
<td>764</td>
<td>NKE [LVI]SE</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em> nitrogenase</td>
<td>186</td>
<td>SRQT DRED</td>
</tr>
<tr>
<td>HLA-B27 molecule</td>
<td>70</td>
<td>KAQT DREDL</td>
</tr>
<tr>
<td>Adenovirus 12 E1B</td>
<td>384</td>
<td>LRRG [MFPS] QCN</td>
</tr>
<tr>
<td>α-Gliadin</td>
<td>206</td>
<td>LGQSFRP SQQN</td>
</tr>
<tr>
<td>Human immunodeficiency virus p24</td>
<td>160</td>
<td>[GRD] EED</td>
</tr>
<tr>
<td>Human IgG constant region</td>
<td>466</td>
<td>[GRD] EED</td>
</tr>
<tr>
<td>Measles virus P3</td>
<td>13</td>
<td>LECIRALK</td>
</tr>
<tr>
<td>Corticotropin</td>
<td>18</td>
<td>LECIRACK</td>
</tr>
<tr>
<td>Measles virus P3</td>
<td>31</td>
<td>EISDNL [GRQ]E</td>
</tr>
<tr>
<td>Myelin basic protein</td>
<td>61</td>
<td>EISFKLGQE</td>
</tr>
</tbody>
</table>

*In each pair, the human protein is listed second. The proteins in each pair have been shown to exhibit immunologic cross-reactivity.

*Each number indicates the position on the intact protein of the amino-terminal amino acid in the listed sequence.

*Amino acid residues are indicated by single-letter code. Identical residues are shown in blue.

Major factors in initiation and regulation of AI disease

1. MHC Control
2. Antigen Mimicry
3. Altered Proteins
The development of T cells:
Mature T cells encounter foreign antigens in the peripheral lymphoid organs and are activated.

Activated T cells proliferate and migrate into peripheral sites to eliminate infection.

Mature T cells migrate to the peripheral lymphoid organs.

Activated T cells migrate to sites of infection.
Protein Mutation & Altered Expression

Expression of Autoimmune Regulator Gene (AIRE) in the thymus shape the immune repertoire:

Figure 13-9 Immunobiology, 6/e. (© Garland Science 2005)
## Exceptions to the Rule – Simple Genetic Autoimmune Illnesses

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>APS-1 (Autoimmune polyglandular syndrome type 1)</td>
<td>AIRE</td>
<td>Decreased expression of self-antigens in the thymus, resulting is a defect in negative selection</td>
</tr>
<tr>
<td>IPEX (Immunodysregulation, polyendocrinopathy, enteropathy, X-linked)</td>
<td>FOXP3</td>
<td>Decreased generation of Tregs</td>
</tr>
<tr>
<td>ALPS (autoimmune lymphoproliferative syndrome)</td>
<td>FAS, FASL</td>
<td>Failure of apoptotic death of self reactive T or B cells</td>
</tr>
</tbody>
</table>
Major factors in initiation and regulation of AI disease

1. MHC Control
2. Antigen Mimicry
3. Altered Proteins
Posttranslational Modification

- **Translation**: Process of synthesizing the peptide chain of amino acids specified by the nucleotide sequence on the mRNA

- **Post-translational modification**: The chemical modification of a protein after its translation
T-CELL MEDIATED DISEASE
Autoimmunity to Sequestered Proteins
• Sequestered proteins are normally sheltered from immune recognition

• However, they can become immunogenic once exposed to recognition by immune cells and induce efficient immune responses

• A good example: Antibodies in blood can attack Myelin Basic Protein if Blood-Brain barrier is breached
Multiple Sclerosis

MS patients can have autoantibodies and/or self reactive T cells which are responsible for the demyelination.
Visual disturbances
(blurred vision, color distortions, loss of vision in one eye, eye pain)

Loss of sensation,
speech impediment, tremors, or dizziness

Mental changes
(decreased concentration, attention deficit, memory loss)

Depression
Paranoia
Uncontrollable laughter and weeping

Limb weakness,
loss of coordination and balance

Muscle spasms,
fatigue, numbness, prickling pain

Bladder and bowel dysfunction
Additional Factors!!
Pregnancy

• Antibody-mediated autoimmune diseases can appear in the infants of affected mothers as a consequence of trans-placental antibody transfer
Hormones

• Some autoimmune diseases show a significant bias in gender suggesting that sex hormones are involved in pathogenesis

• Females are much more likely to develop autoimmune illness

Hypothesis: estrogen response elements (EREs) in several genes
Estrogens and Autoimmunity

- Estrogens stimulate B cell autoimmunity
  - multiple sclerosis
  - coeliac disease
  - dermatitis herpetiformis
  - SLE
  - IgA nephropathy
  - thyroiditis
  - myasthenia gravis
  - mixed connective tissue disease

- Falling estrogens reduce B cell autoimmunity

- Estrogens inhibit T cell autoimmunity
  - pemphigus vulgaris
  - primary biliary cirrhosis
  - rheumatoid arthritis
  - Sjögren syndrome

- Falling estrogens support T cell autoimmunity

Incidence rate of autoimmune phenomena

- Childhood
- Early reproductive years: high estrogens, high progesterone
- Late reproductive years: low estrogens, low progesterone
- Early postmenopausal years: low estrogens, low progesterone
- Late postmenopausal years: low estrogens, low progesterone

B >> T cell

T > B cell
Figure 13.18 The Immune System, 3rd ed. (© Garland Science 2009)
Stress

STRESS:
• Normal Stress (Exams!)
• Chronic Stress = Disease

Stress induces change for adaptation:
• Behavioral (e.g. Moods)
• Physiological (e.g. HBP)
• Immunological (e.g. AI)
IF YOUR WORKLOAD GETS TOO MUCH...

THINK OF HOW TO BALANCE YOUR LIFE!
Future
What is an Artificial Pancreas?
Questions

WHERE DO YOU GET YOUR PROTEIN?
References