Autoimmunity and Autoimmune Diseases

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Goals

1. Define and discuss autoimmunity

2. Use autoimmune diseases to illustrate mechanisms of autoimmunity

3. Provide you with clinical correlations and applications of the basic principles of immunology
Autoimmunity

• Specific adaptive immune response mounted against a self-antigen

• Loss of Self-tolerance to self-antigens
  – Loss of central and peripheral tolerance

• Loss of central tolerance likely occurs all the time
  • May have a physiological role to clear defective or denatured molecules through the RE system
  • Normally kept in check by mechanisms of peripheral tolerance

• May be triggered by infections or aging

• May or may not cause disease
Autoimmune Disease

- Termed “horror autoxicus” by Paul Ehrlich
- Tissue response and damage triggered by autoimmunity
- Results from the dysregulation of immune processes and pathways that are involved in normal immunity
INNATE IMMUNE RESPONSE

Macrophages

Neutrophils

Mast Cells

Natural Killer Cells

Bacteria

Immature Dendritic Cell

Mature Dendritic Cell

T

B

Anti-bacterial Antibodies

Architecture of a Normal Immune Response to Bacteria

ADAPTIVE IMMUNE RESPONSE
INNATE IMMUNE RESPONSE

Autoantibodies

Citrullinated Peptides

Immature Dendritic Cell

Mature Dendritic Cell

to LN

T

B

Autoantibodies

Architecture of an Autoimmune Response

Macrophages

Mast Cells

Neutrophils

Smoking

INNATE IMMUNE RESPONSE

ADAPTIVE IMMUNE RESPONSE
INNATE IMMUNE RESPONSE → ADAPTIVE IMMUNE RESPONSE → INNATE IMMUNE RESPONSE

Smoking → Citrullinated Peptides → Mature Dendritic Cell → Immature Dendritic Cell

Macrophages → Neutrophils → Mast Cells

Autoantibodies

Cytokines, chemokines, leukotrienes, prostaglandins

Neutrophils, Mast Cells

Architecture of an Autoimmune Disease

Osteoclasts
<table>
<thead>
<tr>
<th>AUTOIMMUNE DISEASE</th>
<th>CLINICAL PHENOTYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic Lupus Erythematosus</td>
<td>Rash; inflammation of joints and serosal linings; glomerulonephritis; hemolytic anemia, systemic symptoms</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Inflammation of synovium of diarthroidal joints, systemic inflammation</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>Inflammation, dermal fibrosis, internal organ fibrosis, vasculopathy</td>
</tr>
<tr>
<td>Ankylosing Spondylitis</td>
<td>Inflammation of spine, joints, and tendon insertions; uveitis</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>Demyelination, optic neuritis, neurological deficits</td>
</tr>
<tr>
<td>Myasthenia Gravis</td>
<td>Skeletal muscle weakness, diplopia, dysarthria, dysphagia</td>
</tr>
<tr>
<td>Hashimoto's Thyroiditis</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Graves Disease</td>
<td>Hyperthyroidism, ophthalmopathy</td>
</tr>
<tr>
<td>Celiac Disease</td>
<td>Diarrhea and malabsoprtion</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>Anemia through lysis of red blood cells</td>
</tr>
<tr>
<td>Type I diabetes</td>
<td>Failure of insulin production and glycemic control</td>
</tr>
</tbody>
</table>
Autoimmune Disease

Genetic Predisposition

Initiation

Perpetuation and Progression

Clinical Disease

J Ermann et al. Nature Immunology 2001
Genetic Susceptibility to Autoimmune Diseases
## Simple Genetic Traits Associated with Autoimmune Diseases

<table>
<thead>
<tr>
<th>Gene</th>
<th>Human Autoimmune Disease</th>
<th>Mouse mutant or knockout</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AIRE</strong></td>
<td>Autoimmune polyendocrine syndrome (APS1)</td>
<td>T-cells escape thymic negative selection due to decreased expression of self antigens in thymus</td>
</tr>
<tr>
<td><strong>FOXP3</strong></td>
<td>Immune dysregulation, polyendocrinopathy, enteropathy, X-lined syndrome (IPEX)</td>
<td>Decreased generation of CD4+CD25+ regulatory T-cells</td>
</tr>
<tr>
<td><strong>FAS</strong></td>
<td>Autoimmune lymphoproliferative syndrome (ALPS)</td>
<td>Failure of apoptotic death of self-reactive T and B cells (lpr/lpr)</td>
</tr>
</tbody>
</table>
# AUTOIMMUNE DISEASES

## CONCORDANCE IN TWINS

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>MZ %</th>
<th>DZ %</th>
<th>POPULATION PREVALENCE %</th>
<th>( \lambda_s )</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>12-15</td>
<td>3-4</td>
<td>0.24-1.0</td>
<td>5-10</td>
</tr>
<tr>
<td>SLE</td>
<td>24-57</td>
<td>2-5</td>
<td>0.2</td>
<td>20-40</td>
</tr>
<tr>
<td>IDDM</td>
<td>30-50</td>
<td>0-13</td>
<td>0.4</td>
<td>15</td>
</tr>
<tr>
<td>MS</td>
<td>25</td>
<td>0-5</td>
<td>0.1</td>
<td>20</td>
</tr>
</tbody>
</table>

*WANDSTRAT AND WAKELAND: NATURE IMMUNOLOGY, 2001.*
Evidence for genetics (RA)

unrelated individuals

risk
0.5-1%

first-degree relatives

3-5%

identical twins (triplets!)

15%

Slide courtesy of Robert Plenge MDPHD, Harvard Medical School
Common diseases : Multiple SNPs

• Single nucleotide polymorphisms (SNPs)
  – Individual bases that exist as either of two alleles in the population

• Common diseases are believed to result from a combination of susceptibility alleles at multiple loci, environmental factors and stochastic events

• Non-Mendelian Inheritance Patterns
Major Histocompatibility Complex

CD4+ T-cell
- CD28
- TCR
- CD80
- MHC II
- Antigen Presenting Cell

CD8+ T-cell
- CD28
- TCR
- CD80
- MHC I/β2M
- Antigen Presenting Cell
Major Histocompatibility Complex

- **MHC Class I**
  - HLA A: 1884 alleles
  - HLA B: 2490 alleles
  - HLA C: 1384 alleles
- **MHC class II**
  - DP: 5270 possible combinations
  - DQ: 7755 possible combinations
  - DR: 8302 possible combinations

As of June 2012
MHC Associations and Autoimmune Diseases

<table>
<thead>
<tr>
<th>Class I MHC Associations</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankylosing Spondylitis</td>
<td>HLA-B27</td>
</tr>
<tr>
<td>Grave’s Disease</td>
<td>HLA-B8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class II MHC Associations</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid Arthritis</td>
<td>HLA-DR4</td>
</tr>
<tr>
<td>Sjogren’s Syndrome</td>
<td>HLA-DR3</td>
</tr>
<tr>
<td>Systemic Lupus Erythematosus</td>
<td>HLA-DR3, DR2</td>
</tr>
<tr>
<td>Type I Diabetes</td>
<td>HLA-DR3</td>
</tr>
<tr>
<td>Celiac Disease</td>
<td>HLA-DR3</td>
</tr>
<tr>
<td>Myasthenia Gravis</td>
<td>HLA-DR3</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>HLA-DR2</td>
</tr>
</tbody>
</table>
Ankylosing Spondylitis
Ankylosing Spondylitis
# HLA-B27 and Autoimmune Disease

<table>
<thead>
<tr>
<th>Class I MHC Associated Diseases</th>
<th>% HLA-B27+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankylosing Spondylitis</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Reiter’s Syndrome</td>
<td>80%</td>
</tr>
<tr>
<td>Reactive Arthritis</td>
<td>85%</td>
</tr>
<tr>
<td>Inflammatory Bowel Disease</td>
<td>50%</td>
</tr>
<tr>
<td>Psoriatic Arthritis (with spondylitis)</td>
<td>50%</td>
</tr>
<tr>
<td>Psoriatic Arthritis (without spondylitis)</td>
<td>15%</td>
</tr>
</tbody>
</table>
Rheumatoid Arthritis
**HLA-DR4 and Rheumatoid Arthritis**

"**SHARED EPITOPE**"
QKRAA or QRRAA on DRβ chain

<table>
<thead>
<tr>
<th></th>
<th>% of RA patients</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-DRB1*0401</td>
<td>50-61%</td>
<td>5-11</td>
</tr>
<tr>
<td>HLA-DRB1*0404</td>
<td>27-37%</td>
<td>5-14</td>
</tr>
<tr>
<td>HLA-DRB1*0101</td>
<td>13-27%</td>
<td>1-2</td>
</tr>
<tr>
<td>HLA-DRB1*10</td>
<td>1.5%</td>
<td>2.3</td>
</tr>
</tbody>
</table>
Single Nucleotide Polymorphisms in Autoimmune Diseases

• Rheumatoid arthritis
  – PTPN22, PADI4, TRAF-C5 locus, STAT4, CTLA4

• Systemic Lupus Erythematosus
  – IRF5, Tyk2, STAT4, TNFSF4, ITGAM, CTLA4

• Ankylosing spondylitis
  – IL-23R, ARTS1, IL1a

• Scleroderma
  – CD247, PTPN22, IRF5, STAT4, TNFSF4, AIF, BANK1

• Inflammatory Bowel Disease
  – CARD15, IBD5, IL-23R

• Type I Diabetes Mellitus
  – CTLA4, PTPN22

• Multiple Sclerosis
  – IL2RA, IL7R
Mechanisms of Autoimmune Disease
Mechanisms of Autoimmune Disease

• Previous attempts to classify them as T-cell and B-cell mediated are outdated

• Involve Innate and Adaptive Components

• Classified based on the effector mechanisms that appear to be most responsible for organ damage:
  – Autoantibodies
  – T-cells
Autoantibodies

• Antibodies against self-antigens
• Can be found in normal, healthy individuals
• Important effectors in autoimmune disease
Autoimmune Hemolytic Anemia

- Autoantibodies against RBC antigens
  - Warm autoantibodies
    - IgG, react with Rh antigen on RBC at 37\textdegree{}C
    - Result in opsonization of RBCs and macrophage phagocytosis
  
  - Cold autoantibodies (cold agglutinins)
    - IgM, react with I or i antigen on RBC when <37\textdegree{}C
    - Activate complement and result in complement mediated lysis

- Drug induced antibodies
  - Penicillin acts as a hapten, binds to RBC and form antibodies against RBCs
Myasthenia Gravis

- Target antigen is alpha chain of the nicotinic acetylcholine receptor in the neuromuscular junction
- Autoantibodies act as antagonist
- Symptoms of muscle weakness, diplopia, dysarthria, dysphagia
- May be associated with a thymoma
- Can be transmitted to fetus through placental transmission of autoantibodies
Graves Disease

- Symptoms of hyperthyroidism
  - Heat intolerance
  - Increased metabolism, weight loss
  - Palpitations, increased HR
  - Hair loss
  - Fatigue
  - Nervousness
  - Ophthalmopathy
Graves Disease

- Autoantibodies against thyrotropin stimulating hormone receptor (TSH-receptor)
- Autoantibodies act as an agonist
- Symptoms of hyperthyroidism
- Maternal antibodies can be transmitted to fetus through the placenta resulting transient neonatal hyperthyroidism
Systemic Lupus Erythematosus

• Autoimmune disease characterized by
  – systemic autoimmunity
  – multi-organ involvement
  – production of autoantibodies against nuclear components
  – immune complexes

• Autoantibodies and immune complexes deposit in tissues including skin, joints, blood vessels, kidneys, etc.
Systemic Lupus Erythematosus: Clinical Manifestations

- General
  - Fatigue, fever, weight loss
- Musculoskeletal
  - Arthritis
  - Myositis
- Skin
  - Malar rash, discoid rash, others
  - Photosensitivity
  - Oral and nasal ulcers
  - Alopecia
- Hematologic
  - Hemolytic anemia
  - Thrombocytopenia
  - Leukopenia
  - Antiphospholipid antibody syndrome
- Renal
  - Glomerulonephritis
- Pulmonary
  - Pleurisy
  - Pleural effusions
  - Pneumonitis
  - Alveolar hemorrhage
- Cardiac
  - Pericarditis
  - Valvular thickening
  - Myocarditis
  - Atherosclerosis
- Gastrointestinal
  - Serositis
  - Pancreatitis
- Nervous system
  - Cognitive impairment
  - Seizures
  - Psychosis
  - Peripheral neuropathy
SLE: MALAR RASH
Antinuclear Antibodies

<table>
<thead>
<tr>
<th>Disease</th>
<th>% of patients</th>
</tr>
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<tbody>
<tr>
<td>Systemic Lupus Erythematosus</td>
<td>&gt;99%</td>
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<tr>
<td>Sjögren’s Syndrome</td>
<td>80%</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>80%</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>40%</td>
</tr>
<tr>
<td>Relatives of SLE patients</td>
<td>20%</td>
</tr>
<tr>
<td>Healthy normal controls</td>
<td>5%</td>
</tr>
</tbody>
</table>
## SLE : ANA Associations

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Clinical Associations</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double stranded DNA</td>
<td>Renal disease, marker for disease activity</td>
<td>40-60%</td>
</tr>
<tr>
<td>Smith Antigen (Sm)</td>
<td></td>
<td>20%</td>
</tr>
<tr>
<td>Ro/SSA</td>
<td>Subacute cutaneous lupus, photosensitivity, neonatal lupus, Sjogrens</td>
<td>40%</td>
</tr>
<tr>
<td>La/SSB</td>
<td>Low prevalence of renal disease, Sjogrens syndrome</td>
<td>10-15%</td>
</tr>
<tr>
<td>Ribonuclear protein (U1-RNP)</td>
<td>Mixed connective tissue disease</td>
<td>30-40%</td>
</tr>
<tr>
<td>Phospholipids</td>
<td>Hypercoagulable states, thrombocytopenia, miscarriages, verrucous endocarditis</td>
<td>30%</td>
</tr>
<tr>
<td>Histones</td>
<td>Drug related SLE (not specific)</td>
<td></td>
</tr>
<tr>
<td>Ribosomal P</td>
<td>Psychosis and depression</td>
<td>10-40%</td>
</tr>
</tbody>
</table>
SLE: Immunofluorescence of Skin

- Autoantibodies form immune complexes with autoantigens and deposit at the dermal-epidermal junction of the skin.
- IC activate the classical complement pathway components which can also be detected at the dermal-epidermal junction of the skin.
SLE: Immunofluorescence of Glomerulus

- Autoantibodies form immune complexes with autoantigens and deposit in the basement membrane of glomeruli
- IC activate the classical complement pathway components which can also be detected in the basement membrane of glomeruli
Viral Triggering of Autoantibody Production

Marshak-Rothstein. Nat Rev Imm. 2006. 6: 823-835
Autoantibodies, TLRs and Autoimmunity

[Diagram showing the interaction between DNA-specific antibodies and TLR9, and RNA-specific antibodies and TLR7 in pDC cells.

Rheumatoid-factor-positive (IgG2a-specific) B cell

DNA-specific B cell

RNA-specific B cell]
Systemic Sclerosis (Scleroderma)
## Scleroderma Associated Autoantibodies

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Clinical Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-topoisomerase I (anti-Scl70)</td>
<td>Diffuse skin involvement Pulmonary fibrosis</td>
</tr>
<tr>
<td>Anti-centromere</td>
<td>Limited scleroderma Pulmonary hypertension Digital ulcers</td>
</tr>
<tr>
<td>Anti-RNA polymerase III</td>
<td>Renal crisis Rapid progressive skin fibrosis</td>
</tr>
<tr>
<td>Anti-PM-Scl</td>
<td>Overlap myositis Young age of onset</td>
</tr>
<tr>
<td>Anti-U3RNP (fibrillarin)</td>
<td>African Americans and males</td>
</tr>
</tbody>
</table>
Multiple sclerosis

• A T-cell mediated autoimmune disease of the central nervous system characterized by
  – Demyelination in brain and spinal cord
  – inflammation and dissemination of lesions in space and time

• Symptoms: visual defects, weakness, sensory deficits, diplopia, ataxia, cognitive deficits, bowel/bladder incontinence
Pathology of MS

- An immune-mediated disease in genetically susceptible individuals

- Demyelination leads to slower nerve conduction

- Axonal injury and destruction are associated with permanent neurological dysfunction

- Lesions occur in optic nerves, periventricular white matter, cerebral cortex, brain stem, cerebellum, and spinal cord

MS Lesions on MRI

T2
BOD

T1
precontrast
black holes

T2-FLAIR

T1/Gd
postcontrast
disease activity

With permission from JW Lindsey M.D.
What Causes Demyelination and Axonal Loss in MS?

- Activation of autoreactive CD4+ T cells in peripheral immune system against myelin proteins
- Migration of autoreactive Th1 cells into CNS
- In situ reactivation by myelin autoantigens
- Activation of macrophages, B cells
- Secretion of proinflammatory cytokines, antibodies
- Inflammation, demyelination, axonal transection, and degeneration

With permission from JW Lindsey M.D.
Other Autoimmune Diseases

• Hashimotos Thyroiditis
  – Autoantibodies and autoreactive T-cells to thyroglobulin and thyroid microsomal antigens
  – Th1 cells also play a role
  – Destruction of thyroid gland leading to hypothyroidism
  – Symptoms of hypothyroidism: fatigue, goiter, dry skin, brittle hair and nails, cold intolerance, weight gain, depression

• Rheumatoid Arthritis
  – Antibodies to citrullinated peptides (anti-CCP antibodies)
  – Antibodies to Fc portion of IgG (rheumatoid factor)
  – Immune complex formation and T-cell infiltration in synovium
  – Leads to activation of innate immune system components through Fc receptors
  – Synovial inflammation, destruction of cartilage and bone erosions

• Type I Diabetes Mellitus
  – Autoreactive CD8+ T-cells to pancreatic islet cells
  – Destruction of islet cells and failure of insulin production
  – Autoantibodies to insulin and islet cell antigens (GAD) are also present, might be a result and not causative
Why learn about autoimmune diseases?

- They are fascinating diseases!
- You will see patients with autoimmune diseases.

- As our understanding of the pathogenesis increases, targeted therapeutic approaches are becoming available
  - TNF-alpha inhibitors for the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriasis, inflammatory bowel disease
  - CTLA-4 Ig for the treatment of rheumatoid arthritis
  - antiCD20 antibody (targeting B-cell) for the treatment of rheumatoid arthritis
  - Anti-IL6 receptor antibody treatment in rheumatoid arthritis
  - Beta interferon for the treatment of multiple sclerosis
  - Anti-type I interferons for the treatment of systemic lupus erythematosus (in development)
  - Many, many, many others in development