Autoimmunity and Autoimmune Diseases

With Great Appreciation and Thanks to:
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Department of Internal Medicine
Division of Rheumatology and Clinical Immunogenetics
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
Central Tolerance – induced during early stages of development
Peripheral Tolerance – induced in mature lymphocytes
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

ADAPTIVE IMMUNE RESPONSE

- Immature Dendritic Cell
- Mature Dendritic Cell
- T Cell
- B Cell
- Anti-bacterial Antibodies

Architecture of a Normal Immune Response to Bacteria
INNATE IMMUNE RESPONSE

Smoking

Citrullinated Peptides

Mast Cells

Macrophages

Immature Dendritic Cell

ADAPTIVE IMMUNE RESPONSE

Mature Dendritic Cell

to LN

T

B

Autoantibodies

Architecture of an Autoimmune Response
INNATE IMMUNE RESPONSE → ADAPTIVE IMMUNE RESPONSE → INNATE IMMUNE RESPONSE

Smoking → Citrullinated Peptides to LN

Mast Cells, Neutrophils, Macrophages

Mature Dendritic Cell

Immature Dendritic Cell

T → B → Autoantibodies

Neutrophils, Mast Cells

Cytokines, chemokines, leukotrienes, prostaglandins

Architecture of an Autoimmune Disease

Osteoclasts

MLS
<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 malabsorption</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>
<tr>
<td>Autoimmune Disease</td>
<td>Mechanism</td>
</tr>
<tr>
<td>---------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>Autoantibodies to RBC antigens</td>
</tr>
<tr>
<td>Autoimmune thrombocytopenia purpura</td>
<td>Autoantibodies to platelet integrin</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Autoantibodies to acetylcholine receptor in neuromuscular junction</td>
</tr>
<tr>
<td>Graves' disease</td>
<td>Autoantibodies to receptor for thyroid-stimulating hormone (TSH)</td>
</tr>
<tr>
<td>Hashimoto's thyroiditis</td>
<td>Autoantibodies and autoreactive T cells to thyroglobulin and thyroid microsomal antigens</td>
</tr>
<tr>
<td>Type I diabetes (insulin-dependent diabetes mellitus; IDDM)</td>
<td>Autoantibodies and autoreactive T cells to pancreatic islet cells</td>
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<tr>
<td>Goodpasture's syndrome</td>
<td>Autoantibodies to type IV collagen</td>
</tr>
<tr>
<td>Rheumatic fever</td>
<td>Autoantibodies to cardiac myosin (cross-reactive to streptococcal cell wall component)</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>Autoantibodies to epidermal components (cadherin, desmoglein)</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>T-cell response against myelin basic protein</td>
</tr>
<tr>
<td>Systemic lupus erythematosus (SLE)</td>
<td>Circulating immunocomplexes deposited in skin, kidneys, etc, formed by autoantibodies to nuclear antigens (antinuclear antibodies, or ANA), including anti-DNA</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Autoantibodies to IgG (rheumatoid factors); deposition of immunocomplexes in synovium of joints and elsewhere; infiltrating autoreactive T cells in synovium</td>
</tr>
</tbody>
</table>
Genetic Susceptibility to Autoimmune Diseases
Autoimmune Disease

Genetic Predisposition
  ↓
Initiation
  ↓
Perpetuation and Progression
  ↓
Clinical Disease

J Ermann et al.  Nature Immunology 2001
# 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>

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: 767 alleles
  - HLA B: 1178 alleles
  - HLA C: 439 alleles
- **MHC class II**
  - DP: 3591 possible combinations
  - DQ: 3264 possible combinations
  - DR: 2121 possible combinations

As of January 2009.

Chromosome 6 in humans
# 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
<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>
Common diseases: Multiple SNPs

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

- Non-Mendelian Inheritance Patterns

- Single nucleotide polymorphisms (SNPs)
  - Individual bases that exist as either of two alleles in the population.
Single Nucleotide Polymorphisms in Autoimmune Diseases

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

- Systemic Lupus Erythematosus
  - IRF5, Tyk2, STAT4, TNFSF4, ITGAM, CTLA4, BLK-C8orf

- Scleroderma
  - CD247 (CD3 zeta chain), PTPN22, IRF5, STAT4, TNFSF4, TBX21, AIF, BLK-C8orf

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

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

- Type I Diabetes Mellitus
  - CTLA4, PTPN22

- Multiple Sclerosis
  - IL2RA, IL7R
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 37degC
    • Result in opsonization of RBCs and macrophage phagocytosis

  – Cold autoantibodies (cold agglutinins)
    • IgM, react with I or i antigen on RBC when <37degC
    • 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
- 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


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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
<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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<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>
<tr>
<td>Antigen</td>
<td>Clinical Associations</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>Double stranded DNA</td>
<td>Renal disease, marker for disease activity</td>
</tr>
<tr>
<td>Smith Antigen (Sm)</td>
<td></td>
</tr>
<tr>
<td>Ro/SSA</td>
<td>Subacute cutaneous lupus, photosensitivity, neonatal lupus, Sjogrens</td>
</tr>
<tr>
<td>La/SSB</td>
<td>Low prevalence of renal disease, Sjogrens syndrome</td>
</tr>
<tr>
<td>Ribonuclear protein (U1-RNP)</td>
<td>Mixed connective tissue disease</td>
</tr>
<tr>
<td>Phospholipids</td>
<td>Hypercoagulable states, thrombocytopenia, miscarriages, verrucous endocarditis</td>
</tr>
<tr>
<td>Histones</td>
<td>Drug related SLE (not specific)</td>
</tr>
<tr>
<td>Ribosomal P</td>
<td>Psychosis and depression</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
Viral Triggering of Autoantibody Production

Marshak-Rothstein. Nat Rev Imm. 2006. 6 : 823-835
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&lt;br&gt;Pulmonary fibrosis</td>
</tr>
<tr>
<td>Anti-centromere</td>
<td>Limited scleroderma&lt;br&gt;Pulmonary hypertension&lt;br&gt;Digital ulcers</td>
</tr>
<tr>
<td>Anti-RNA polymerase III</td>
<td>Renal crisis&lt;br&gt;Rapid progressive skin fibrosis</td>
</tr>
<tr>
<td>Anti-PM-Scl</td>
<td>Overlap myositis&lt;br&gt;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!
- Some of 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 of 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