What your autoantibodies tell us about your disease

Mark Gourley, MD
“How’s the gene-splicing going? Cloned any new hepatitis antibodies?”
The Importance of the Immune System

• Defends us against foreign invaders
  – Self (cancer) and Nonself (virus, bacteria, etc.)

• But, if the system doesn’t work correctly, problems can occur
  – Cancer, autoimmune diseases
What is the Immune System?
(in very simple terms)

Immunity

Cells
- B cells
- T cells

Antibodies
- Virus
- Bacteria
- Self
What Does the Cellular Immune System Do?

CELLULAR IMMUNITY

- Intracellular microbes (e.g., viruses)
- Antigen-presenting cell
- Helper T cell
- T-cell receptor
- Processed and presented antigen
- Cytokines
- Proliferation and activation of effector cells (cytotoxic T cells, natural killer cells, macrophages)
- Lysis of infected cell
What Does The Humoral Immune System Do?
What Happens When Your Tissue Cells Become Targets For The Immune System?

• Immune cells can attack the tissue and can cause injury and/or death

• Antibodies can attach tissue and cause injury and/or death
  – In autoimmune thyroiditis, the anti-thyroid antibodies can stimulate the thyroid to produce excessive thyroid hormone and make you hyperthyroid.
What Body Parts Can Be Affected?

Body Parts That Can Be Affected by Autoimmune Diseases

- Others: Glands, Muscles, Nerves
- Trachea
- Blood and Blood Vessels
- Heart
- Skin
- Esophagus
- Liver
- Kidney
- Uterus
- Ovary
- Cervix
- Brain
- Eyes
- Mouth
- Spinal Cord
- Thyroid
- Lung
- Stomach
- Joints
- Pancreas
- Large Intestine
- Small Intestine
- Bladder
- Vagina

Muscle
What is Myositis

• Inflammation of the muscle
  – Many causes for inflammation

Normal

Inflammation
Is Inflammation Harmful?

• Inflammation heals with scarring
• Scaring leads to muscle damage
• Damage causes weakness
How is Myositis Defined?

• Inflammation of the muscle that causes weakness
  – Associated with
    • Elevation in serum muscle enzyme levels
    • Abnormal electromyography (EMG) testing
    • Characteristic muscle biopsy findings
    • Rashes (dermatomyositis)
    • No mention of antibodies

• Bohan and Peter 1975
Classification Schemes

Clinical groups (Adult or Juvenile)

- Polymyositis
- Dermatomyositis
- Inclusion body
- Myositis with other CTD
- Cancer-associated
- Eosinophilic
- Granulomatous
- Focal / Nodular
- Ocular / Orbital
- Antibody define disease????
Problem Defining Myositis by Antibody

• Not all patients with myositis will have an antibody
• Antibodies are found in other diseases
• Antibodies can be sometimes found in healthy individuals
• Antibody quantity may fluctuate
  – Sometimes test positive, sometimes negative
Laboratory Studies

• Tests for autoantibodies
  – Autoimmune diseases test positive for autoantibodies
    • Thyroid disease – anti-thyroid antibodies
    • Lupus – anti-nuclear antibodies
    • Rheumatoid Arthritis – antibody to an antibody (RF)
  • Myositis Specific Autoantibodies (MSA)
  • Myositis Associated Autoantibodies (MAA)
    – MAA can be seen in myositis and commonly other autoimmune disease
      • ANAs, Ro/La, RF
Names of MSAs

- Anti-synthetase antibodies
  - Jo-1, PL-7, PL-12, EJ, OJ, KS, Ha, Zo
- PM/Scl100
- PM/Scl75
- Ku
- Ro52/TRIM21
- SRP
- Mi-2
- MDA5/CADM140
- SAE1
- HMGCR
### MSAs can be associated with syndromes

<table>
<thead>
<tr>
<th>Autoantibodies</th>
<th>Target autoantigen and function</th>
<th>Clinical phenotype</th>
<th>Autoantibody frequency, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-ARS</td>
<td>ARS—intracytoplasmic protein synthesis</td>
<td>ASS</td>
<td>30–40 1–3</td>
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<tr>
<td>Anti-Jo-1</td>
<td>Histidyl</td>
<td></td>
<td></td>
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<tr>
<td>Anti-PL-7</td>
<td>Threonyl</td>
<td>Myositis, mechanic’s hands, Gottron’s papules, arthritis, fever, RP, high frequency of interstitial pneumonia</td>
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<tr>
<td>Anti-PL-12</td>
<td>Alanyl</td>
<td></td>
<td></td>
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<tr>
<td>Anti-EJ</td>
<td>Glycyl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-OJ</td>
<td>Isoleucyl</td>
<td></td>
<td></td>
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<tr>
<td>Anti-KS</td>
<td>Asparaginyl</td>
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<td></td>
</tr>
<tr>
<td>Anti-Ha</td>
<td>Tyrosyl</td>
<td></td>
<td></td>
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<tr>
<td>Anti-Zo</td>
<td>Phenylalanyl</td>
<td></td>
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<tr>
<td>Anti-SRP</td>
<td>SRP—intracytoplasmic protein translocation (six polypeptides and RNP 7SLRNA)</td>
<td>Acute onset necrotizing myopathy (severe weakness, high CK); may be refractory to treatment</td>
<td>5 &lt;1</td>
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<tr>
<td>Anti-Mi-2</td>
<td>Helicase protein—nuclear transcription (forms the NuRD complex)</td>
<td>Adult DM and JDM (hallmark cutaneous disease, milder muscle disease with good response to treatment)</td>
<td>&lt;10 &lt;10</td>
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<tr>
<td>Anti-p155/140</td>
<td>TIF1-y (p155)—nuclear transcription + cellular differentiation</td>
<td>CAM in adult DM; severe cutaneous disease in adult DM and JDM</td>
<td>13–21 23–29</td>
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<tr>
<td>Anti-p140</td>
<td>Likely to be NXP-2—nuclear transcription + RNA metabolism</td>
<td>JDM with calcinosis</td>
<td>NA 23</td>
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<tr>
<td>Anti-SAE</td>
<td>SAE—post-translational modification (targets include transcription factors)</td>
<td>Adult DM; may present with CADM first</td>
<td>5 NA</td>
</tr>
<tr>
<td>Anti-CADM-140</td>
<td>Intracytoplasmic MDA5—in innate immune responses against viral infections</td>
<td>CADM; rapidly progressive interstitial pneumonia</td>
<td>Overall—unknown NA</td>
</tr>
</tbody>
</table>

SRP: Signal recognition particle; NuRD: nucleosome remodeling histone deacetylase; TIF1-y: Transcriptional intermediary factor 1-gamma; NXP-2: Nuclear matrix protein NXP-2; SAE: Small-ubiquitin-like modifier activating enzyme; MDA5: Melanoma-differentiation associated gene 5; CAM: Cancer-associated myositis; NA: Not applicable/no data
Can MSAs Be Found in Other Disease?

• Yes
  – Then why are they called myositis specific?
  – Because finding MSA outside myositis is very uncommon

• Example:
  – Some diseases are characterized by many different autoantibodies found in the same patient
    » Systemic lupus erythematosus
    » Hepatitis C
    » Rarely, normal people
Anti-Synthetase Syndrome

• Characterized by
  – Fevers
  – Arthritis
  – Lung disease (interstitial pulmonary fibrosis)
    • severe
  – Hand rash (mechanic’s hands)
Anti-Synthetase Syndrome

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Immunoprecipitation Complex</th>
<th>Antigenic Element</th>
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<tbody>
<tr>
<td>Antisynthetases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Jo-1</td>
<td>55 kD</td>
<td>tRNA-His</td>
</tr>
<tr>
<td>Anti-PL-7</td>
<td>80 kD</td>
<td>tRNA-Thr</td>
</tr>
<tr>
<td>Anti-PL-12 (1)</td>
<td>110 kD</td>
<td>None</td>
</tr>
<tr>
<td>Anti-PL-12(2)</td>
<td>none</td>
<td>tRNA-Ala</td>
</tr>
<tr>
<td>Anti-OJ</td>
<td>&gt; 130 kD</td>
<td>tRNA-Ile</td>
</tr>
<tr>
<td>Anti-EJ</td>
<td>75 kD</td>
<td>tRNA-Gly</td>
</tr>
</tbody>
</table>
Antisynthetase Autoantibody Immunoprecipitation Patterns

(a) Total RNA

(b) Molecular marker

KDa

7.0S
5.8S
5.0S
tRNA
ELISA testing
Myositis Autoantibody Phenotypes Differ in Clinical Presentation, Genetics and Prognosis

**Anti-aminocyl-tRNA synthetases**
- Interstitial lung disease, Arthritis, Fevers, Mechanic’s hands; DR3
- 75% 5-year survival

**Anti-Signal Recognition Particle**
- Acute-onset PM, Severe weakness, Myalgias, Myocarditis; DQA1*0104
- 25% 5-year survival

**Anti-Mi-2: chromodomain helicase DNA binding protein 4**
- Classic Dermatomyositis, V-sign & shawl rashes, Cuticular overgrowth; DR7
- 90% 5-year survival
IIM — SEROLOGIC GROUPS DIFFER IN DISEASE COURSE

Strength

Normal

Mi-2/MAS

Synthetase

SRP

Therapy

Time
Value of MSAs

• Help make the diagnosis
• In some patients, need to evaluate further for specific tissue damage (ex – lungs)
• The quantity may follow the disease severity
Problems with MSAs

- Not consistently found
- False positives and false negatives
- Expensive
- Lab tests may not be the best
- Many physicians don’t know how to properly interpret the presence or absence of the antibody.
In General I find

• They are helpful
  – Diagnosis
  – Guide where disease may be more severe
  – Can sometimes follow disease severity
  – Can be predictive in how the patient will do with therapy and therefore guide treatment.
Questions????