What your autoantibodies tell us about your disease

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THE MYOSITIS ASSOCIATION

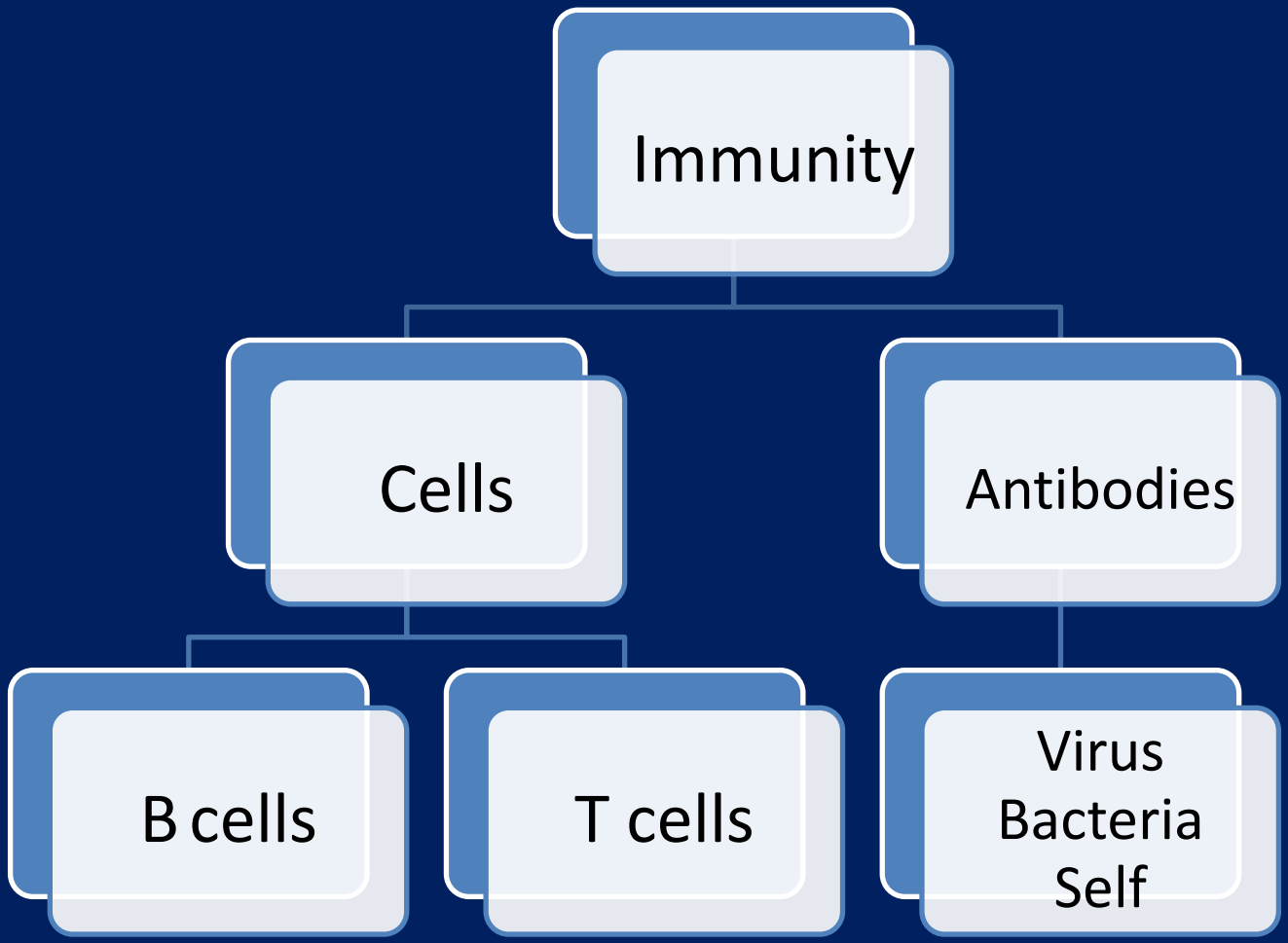
"HOW'S THE GENE-SPLICING GOING? CLONED ANY NEW HEPATITIS ANTIBODIES?"

The Importance of the Immune System

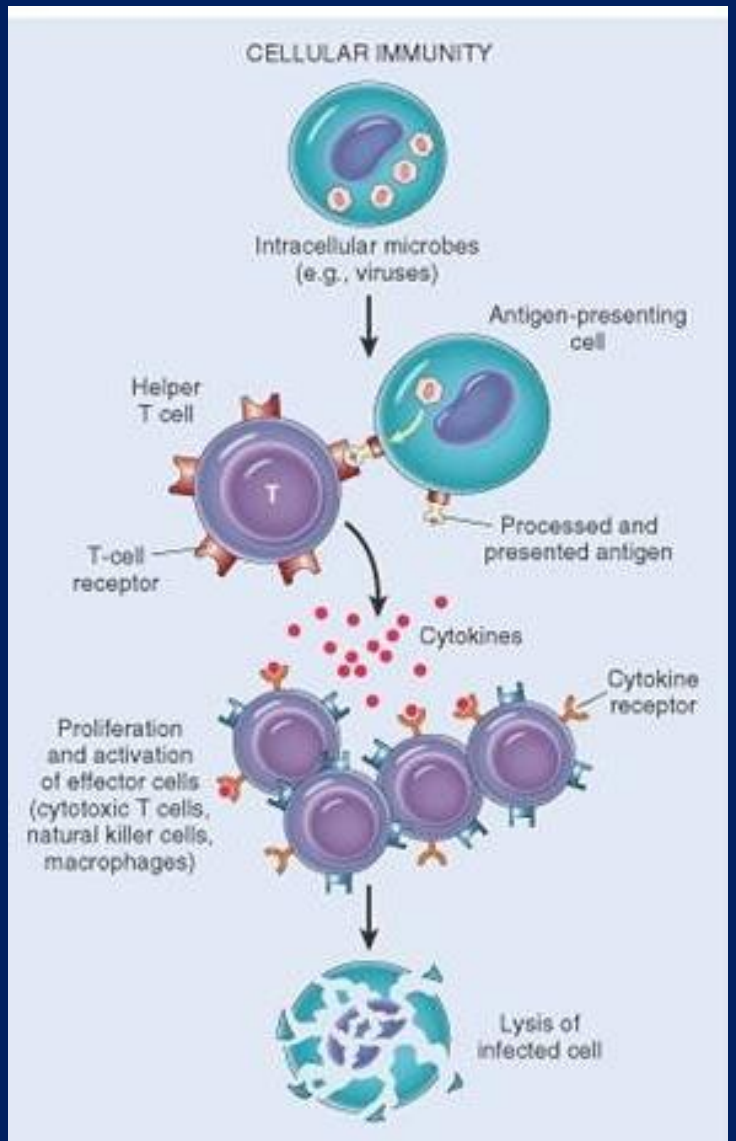
- Defends us against foreign invaders
  - Self (cancer) and Nonself (virus, bacteria, etc.)

- But, if the system doesn't work correctly, problems can occur
  - Cancer, autoimmune diseases

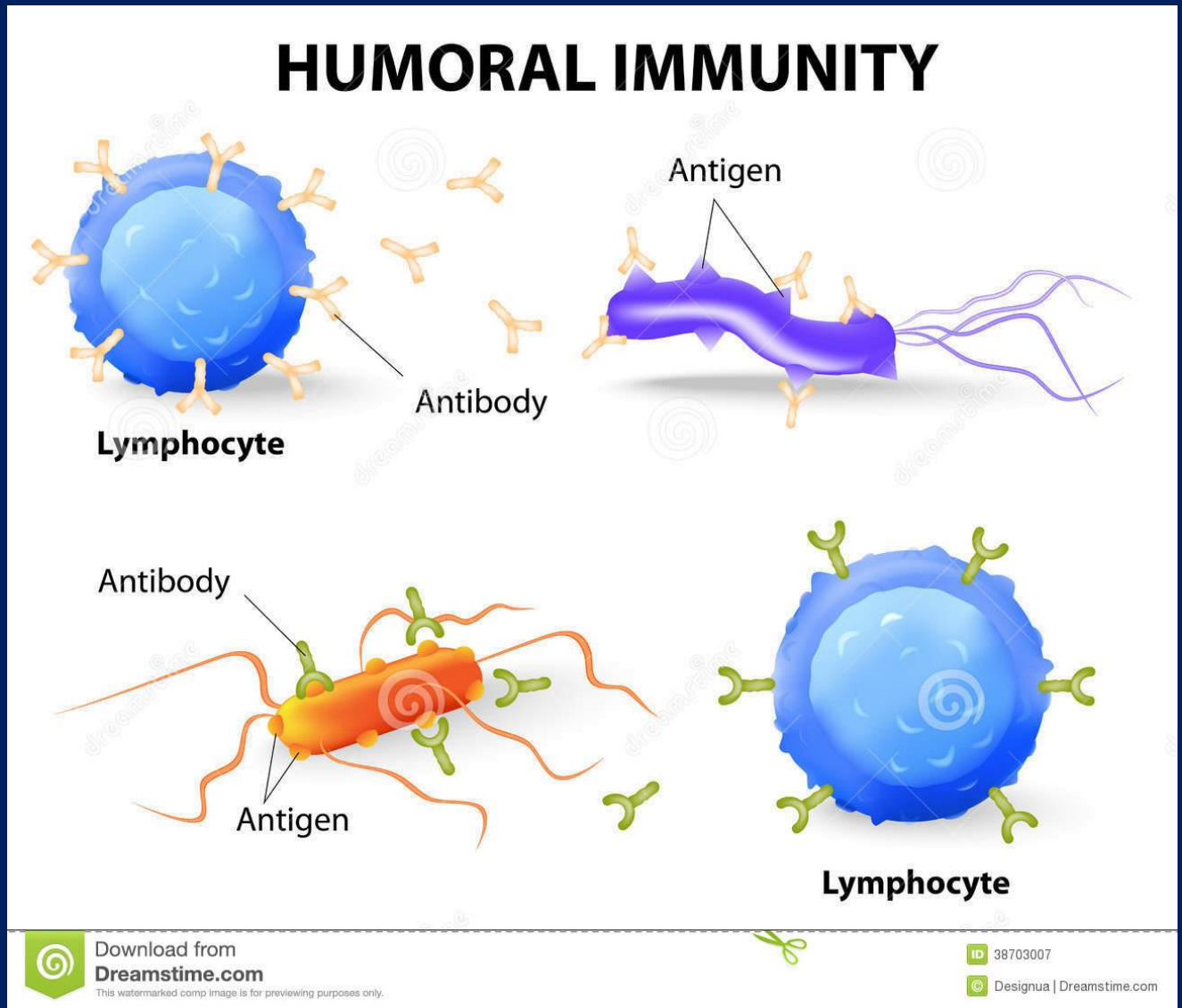
What is the Immune System? (in very simple terms)



What Does the Cellular Immune System Do?



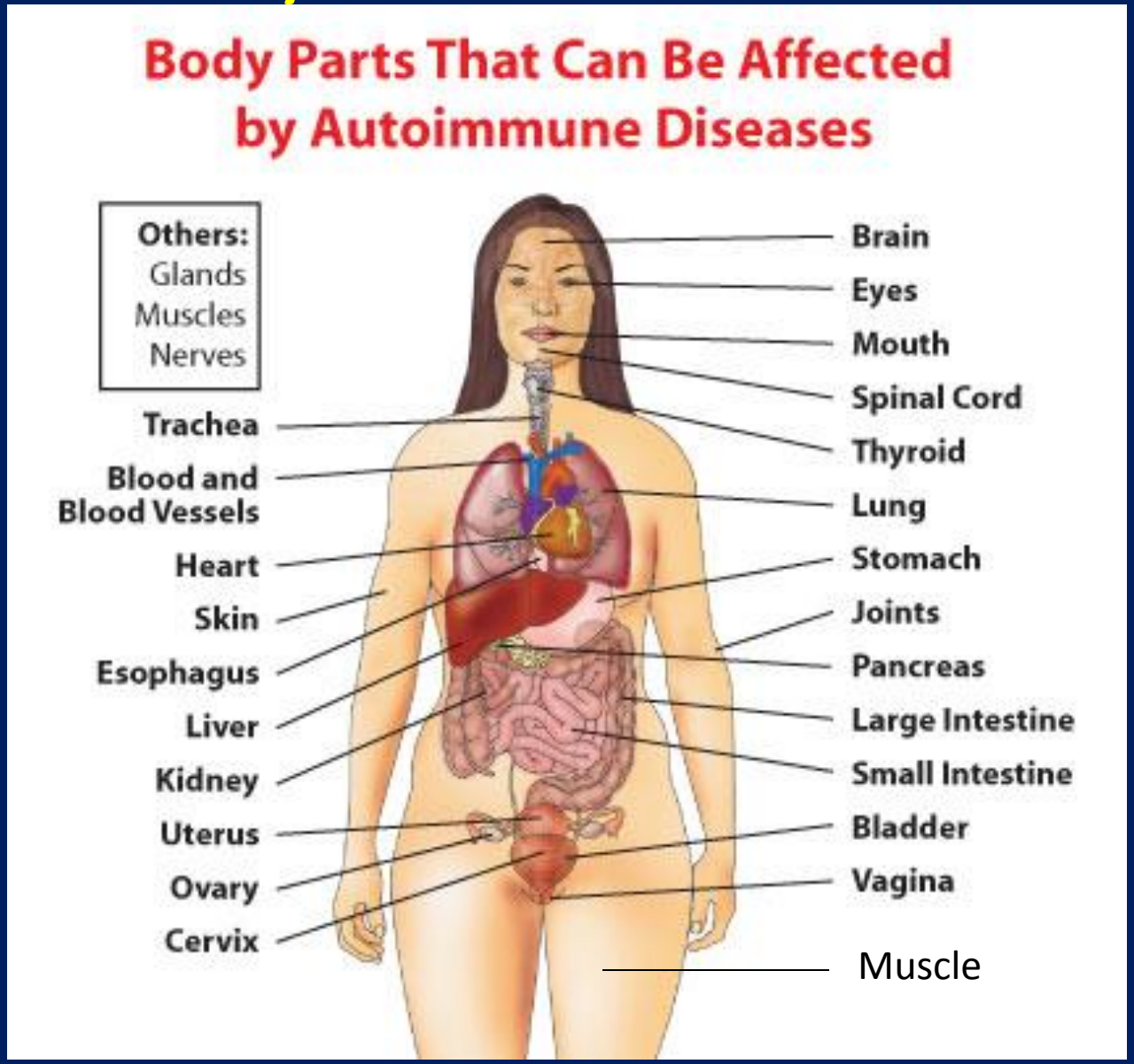
What Does The Humoral Immune System Do?



What Happens When Your Tissue Cells Become Targets For The Immune System?

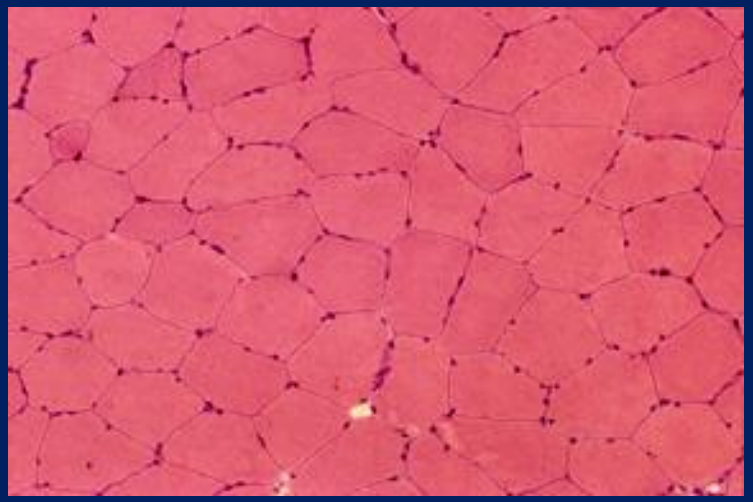
- Immune cells can attack the tissue and can cause injury and/or death
- Antibodies can attach tissue and cause injury and/or death
  - In autoimmune thyroiditis, the anti-thyroid antibodies can stimulate the thyroid to produce excessive thyroid hormone and make you hyperthyroid.

What Body Parts Can Be Affected?

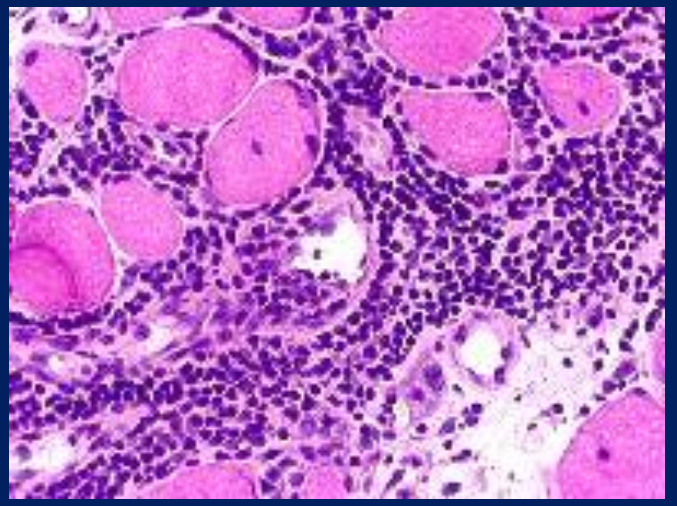


What is Myositis

- Inflammation of the muscle
  - Many causes for inflammation



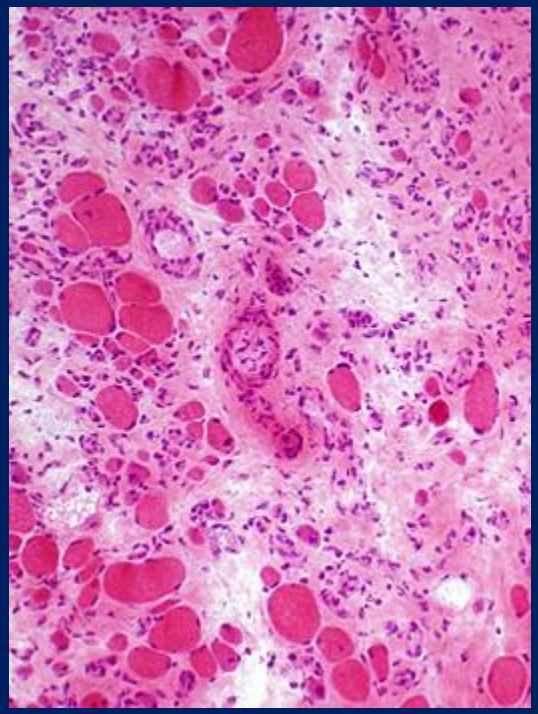
Normal



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

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

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 specfic?
  - 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

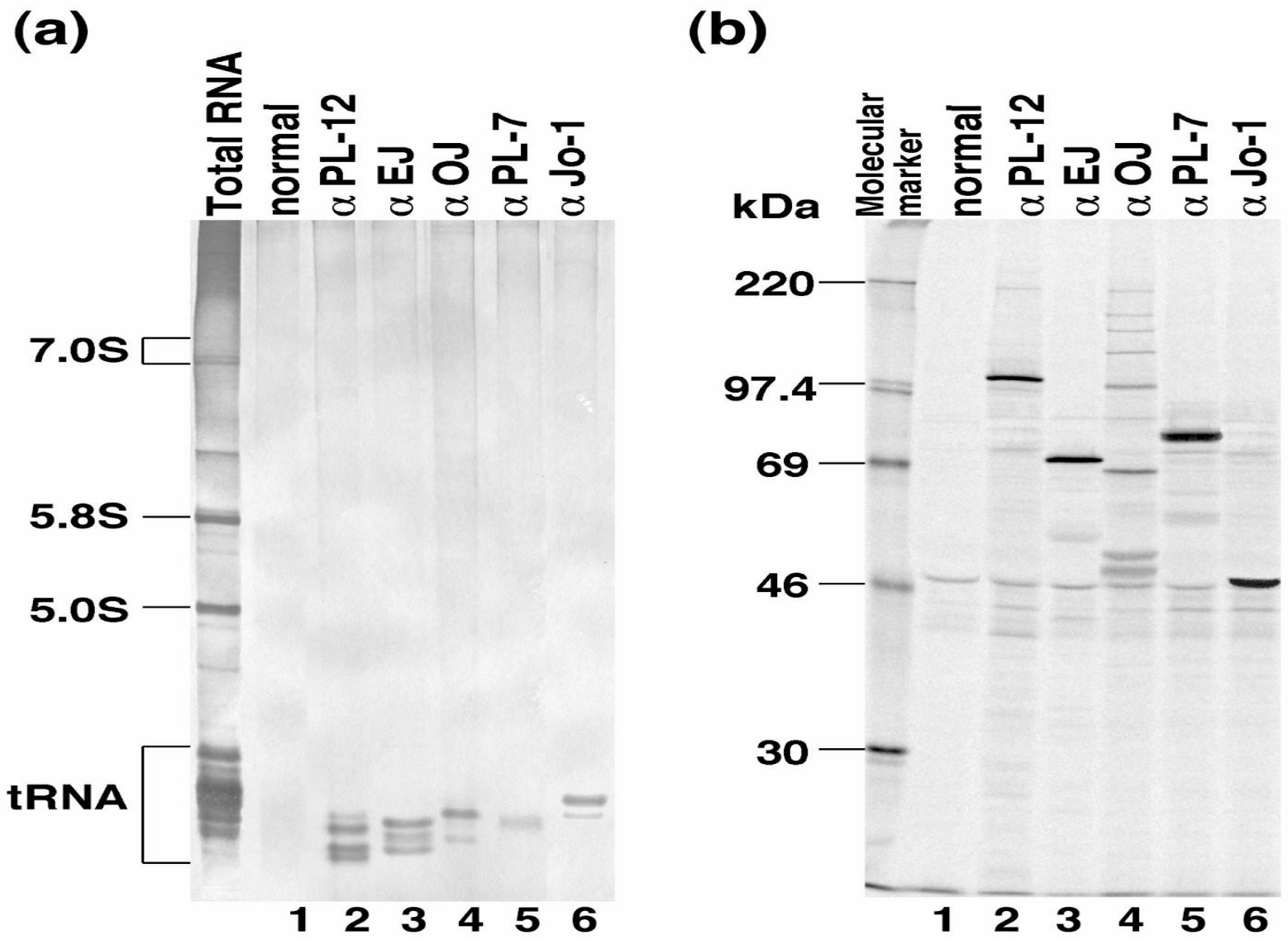
Anti-Synthetase Syndrome

- Characterized by
  - Fevers
  - Arthritis
  - Lung disease (interstitial pulmonary fibrosis)
    - severe
  - Hand rash (mechanic's hands)

Anti-Synthetase Syndrome

Autoantibody	Immunoprecipitation Complex: Protein	Immunoprecipitation Complex: RNA	Antigenic Element
Antisynthetases			
• Anti-Jo-1	55 kD	tRNA-His	HisRS tRNA-His
• Anti-PL-7	80 kD	tRNA-Thr	ThrRS
• Anti-PL-12 (1) Anti-PL-12(2)	110 kD none	None tRNA-Ala	AlaRS tRNA-Ala
• Anti-OJ	> 130 kD	tRNA-Ile	IleRS
• Anti-EJ	75 kD	tRNA-Gly	GlyRS

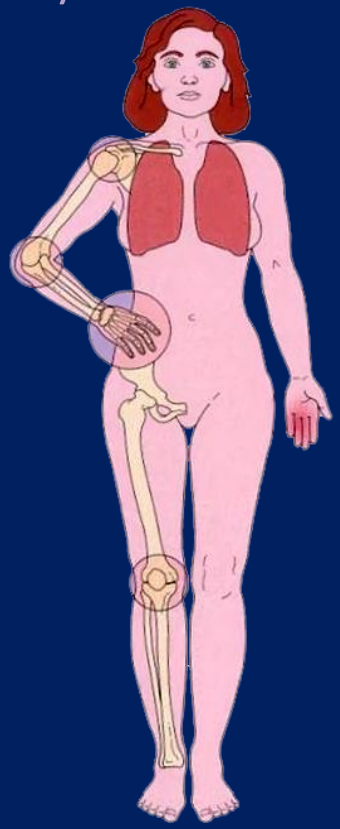
Antisynthetase Autoantibody Immunoprecipitation Patterns



ELISA testing

Myositis Autoantibody Phenotypes Differ in Clinical Presentation, Genetics and Prognosis

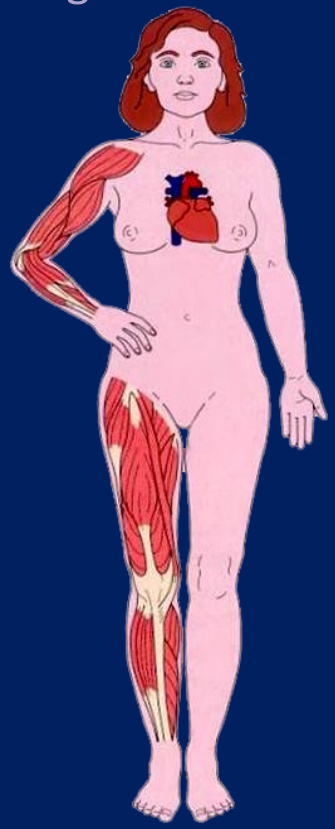
Anti-aminoacyl-tRNA synthetases



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

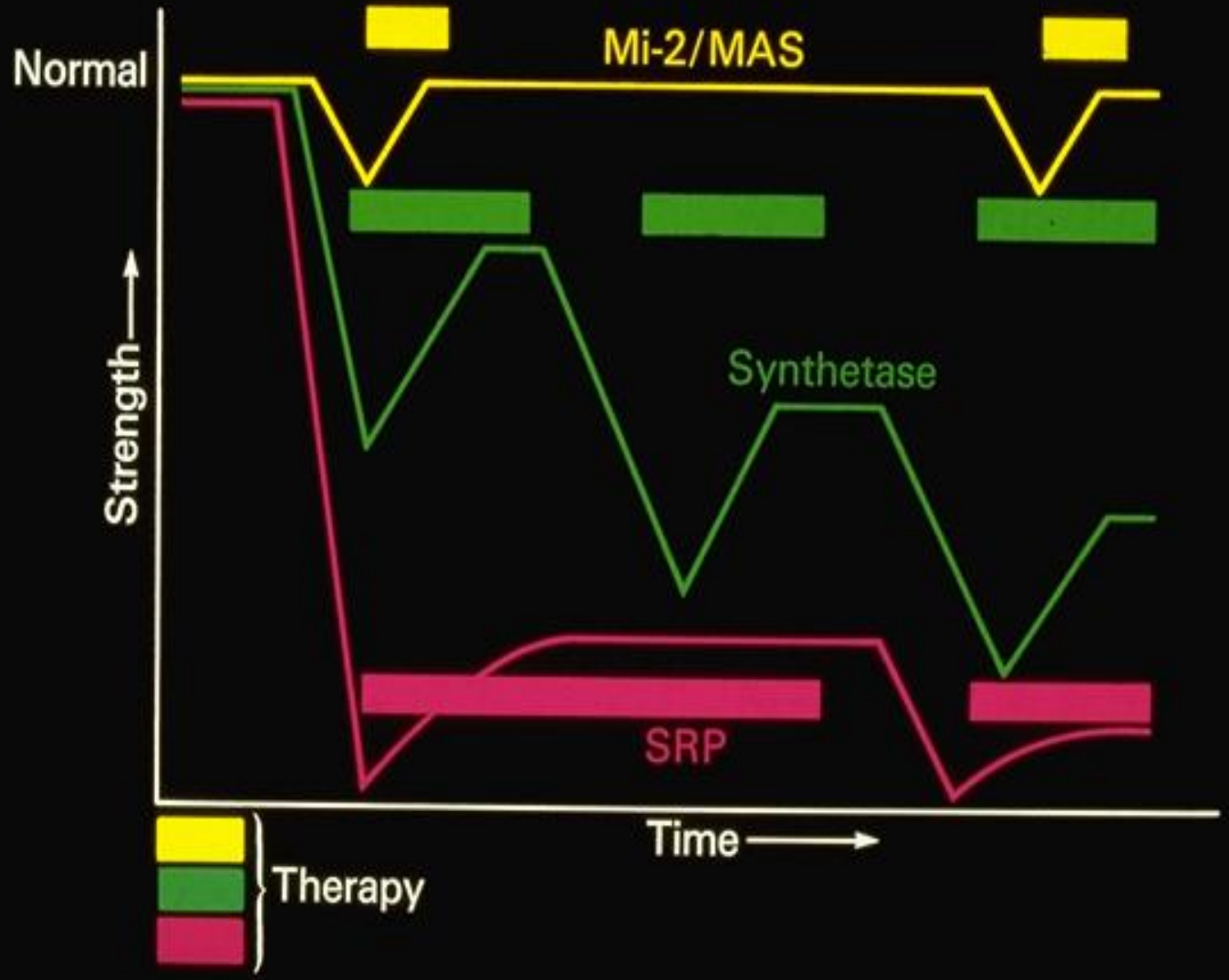
25% 5-year survival

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



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 severve
  - Can sometimes follow disease severity
  - Can be predictive in how the patient will do with therapy and therefore guide treatment.

Questions????