MAYO CLINIC

Autoantibodies in the Idiopathic Inflammatory Myopathies

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Autoantibodies in IIM

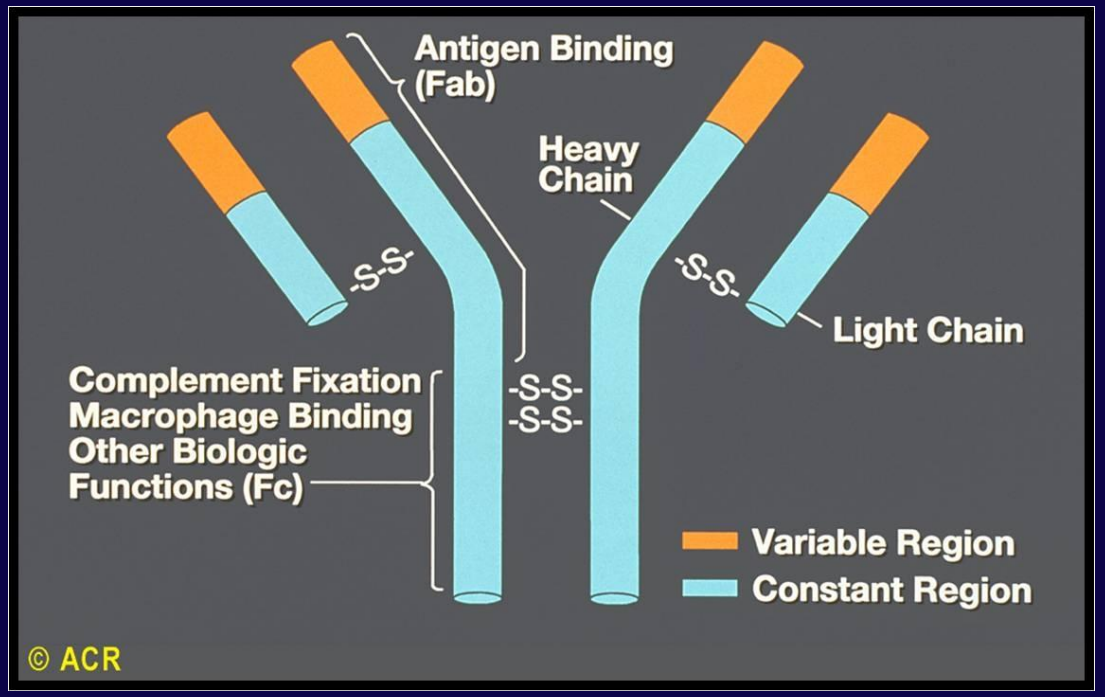
- Antibodies and autoantibodies
- Myositis specific antibodies (MSA)
- Myositis associated antibodies (MAA)
- MSA and MAA in patients with IIM
- Time for questions and discussion

Immunology Summary

- Innate immunity
- Adaptive immunity
  - Cellular
  - Humoral - antibodies

Antibodies

- Recognize and clear foreign molecules
- Isotypes
  - IgM
  - IgG
  - IgA
  - IgE
- Cleared through
  - Fc receptors
  - Complement receptors

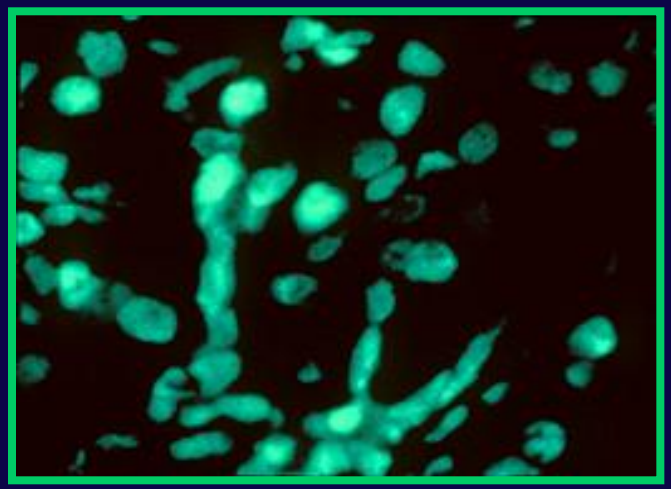


Autoantibodies

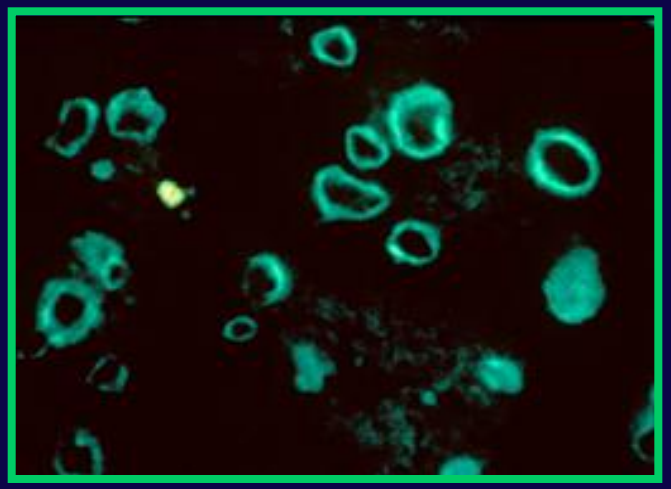
- Antibodies directed against normal cell parts

- May cause clinical features of disease
  - Systemic lupus erythematosus (ANA)
  - Wegener's granulomatosis (ANCA)
- May simply be markers of disease
  - Rheumatoid arthritis (RF)

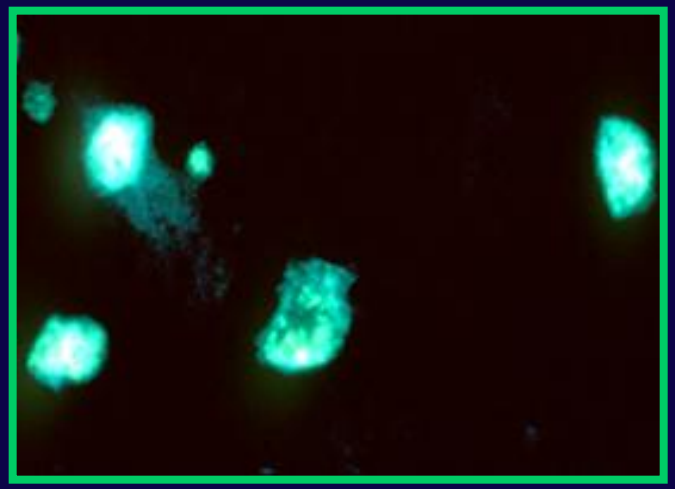
ANA IIF Patterns



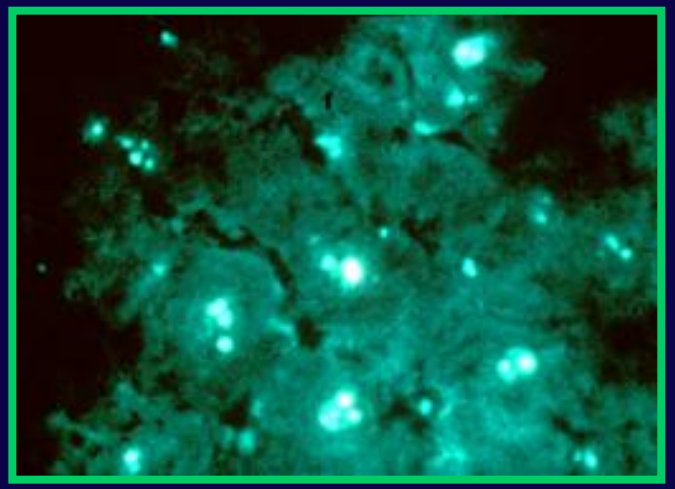
Homogenous (diffuse)



Peripheral (rim)



Speckled



Nucleolar

Ways to Define Myositis

- **Clinical**
  What is happening with the patient?
- **Serological**
  What autoantibodies are present?
- **Histological**
  What does the biopsy show?
- **Pathogenetic**
  What is causing the problem?

Idiopathic Inflammatory Myopathies (IIM)

- Polymyositis (PM)
- Dermatomyositis (DM)
  - Isolated, adult
  - Juvenile
  - Malignancy
  - Overlap
- Inclusion body myositis (IBM)

Bohan & Peter, N Engl J Med 292: 344, 405, 1975
Bohan et al., Medicine 56: 255, 1977
Griggs, et al., Ann Neurol 38: 705, 1995

Clinical Features in IIM Patients: Clinical Categories

Finding	Percent of patients					
	All	PM	DM	CTM	CAM	IBM
n	181	48	70	28	12	23
Fevers	37	40	46	39	36	4
Raynaud	35	37	40	57	0	4
Myalgias	60	68	71	56	50	26
Arthritis	47	54	56	64	8	9
Distal weakness	20	15	7	4	18	91
Asymmetry	14	10	4	7	10	61
Atrophy	20	17	3	7	8	96
Falling	20	17	1	11	9	96
ILD	29	40	37	26	0	0

Love, et al., Medicine 70: 360-74, 1991

Ways to Define Myositis

- **Clinical**
  What is happening with the patient?
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  What autoantibodies are present?
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  What does the biopsy show?
- **Pathogenetic**
  What is causing the problem?

Serologic Subgroups of IIM: Myositis-Specific Antibodies

Feature	Synthetase	SRP	Mi-2
Clinical	Arthritis, ILD fever, Raynaud's	Cardiac myalgias; black women	Classic DM
Rate	Acute	Very acute	Acute
Severity	Severe	Very severe	Mild
Season	Spring	Fall	Unknown
Response	Moderate	Poor	Good
Prognosis	Poor (70%)	Terrible (25%)	Good (~100%)
Frequency	20-25%	<5%	5-10%

Antibodies to Aminoacyl-tRNA Synthetases

Name	Aminoacid
Jo-1	Histidine
PL-7	Threonine
PL-12	Alanine
EJ	Glycine
OJ	Isoleucine
KS	Asparagine
Ha	Tyrosine
Zo	Phenylalanine

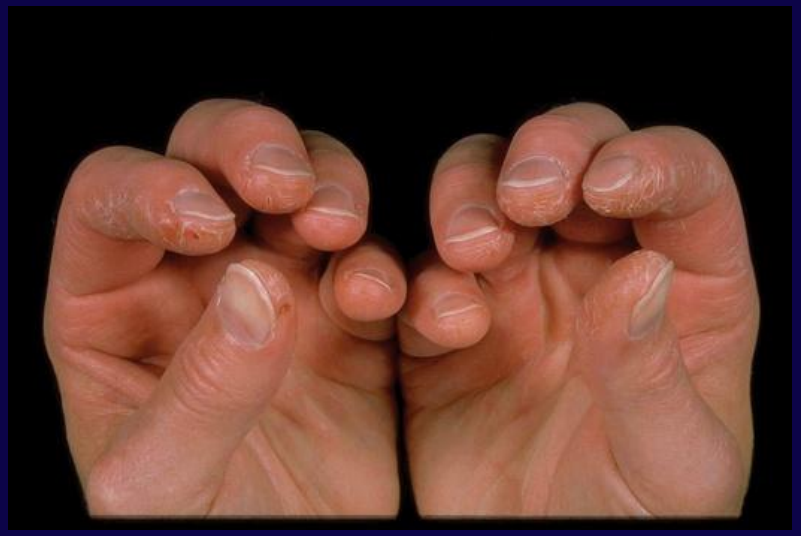
Antibodies to Aminoacyl-tRNA Synthetases (%)

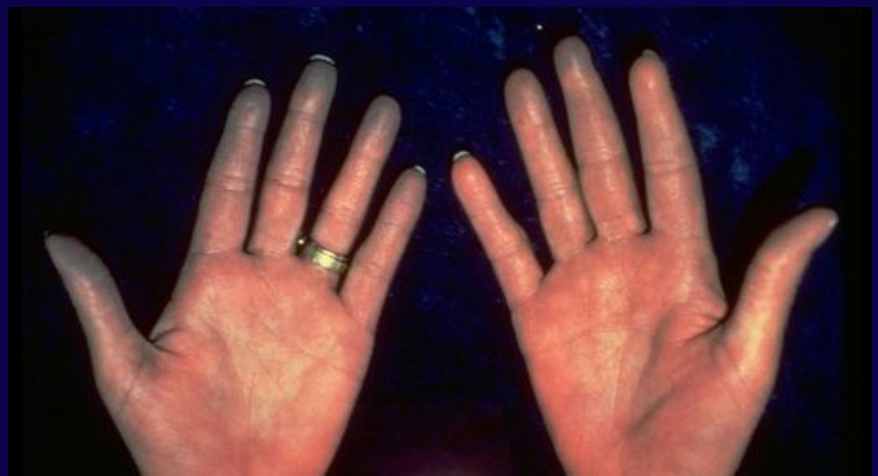
Name *n*	Aminoacid	PM *109*	DM *103*	Overlap *70*
Jo-1	Histidine	25	22	11
PL-7	Threonine	1	0	0
PL-12	Alanine	0	1	0
EJ	Glycine	0	1	0
OJ	Isoleucine	1	1	1
KS	Asparagine	1	1	0
Ha	Tyrosine			
Zo	Phenylalanine			

Chinoy et al, Ann Rheum Dis 66: 1345-9, 2007

Antisynthetase Syndrome

- Inflammatory myositis
- Interstitial lung disease
- Mechanics hands
- Arthritis
- Raynaud's phenomenon
- Fever





Anti-SRP

Antigen

- Signal recognition particle
- Regulates protein translocation through ER

Clinical features

- Acute onset necrotizing myopathy
  - Little or no inflammation
  - High CK
  - Severe weakness
  - Dysphagia
- Less ILD
- Often refractory to treatment

Anti-Mi-2

Antigen

- Helicase protein
- Nuclear transcription (forms the NuRD complex)

Clinical features

- Adult and juvenile DM
- Typically manifest as skin disease with mild muscle involvement and good response to treatment

MSA in Adult Patients (%)

Name *n*	PM *109*	DM *103*	Overlap *70*
Jo-1	25	22	11
SRP	5	2	0
Mi-2	1	16	0

Chinoy et al, Ann Rheum Dis 66: 1345-9, 2007

Clinical Features in IIM Patients: Serologic Categories

Finding	Percent of patients					
	Syn-thetase	SRP	Mi-2	MAS	Any MSA	No MSA
n	47	7	10	2	66	114
Fevers	87	0	10	0	63	23
Raynaud	62	29	30	0	52	26
Myalgias	84	100	60	50	81	49
Arthritis	94	0	20	0	70	34
Distal weakness	4	43	0	0	8	27
Asymmetry	4	0	0	0	3	21
Atrophy	4	14	0	0	5	28
Falling	4	33	0	0	6	27
ILD	89	0	0	0	64	9

Love, et al., Medicine 70: 360-74, 1991

Clinical Features in IIM Patients: Clinical Categories

Finding	Percent of patients					
	All	PM	DM	CTM	CAM	IBM
n	181	48	70	28	12	23
Fevers	37	40	46	39	36	4
Raynaud	35	37	40	57	0	4
Myalgias	60	68	71	56	50	26
Arthritis	47	54	56	64	8	9
Distal weakness	20	15	7	4	18	91
Asymmetry	14	10	4	7	10	61
Atrophy	20	17	3	7	8	96
Falling	20	17	1	11	9	96
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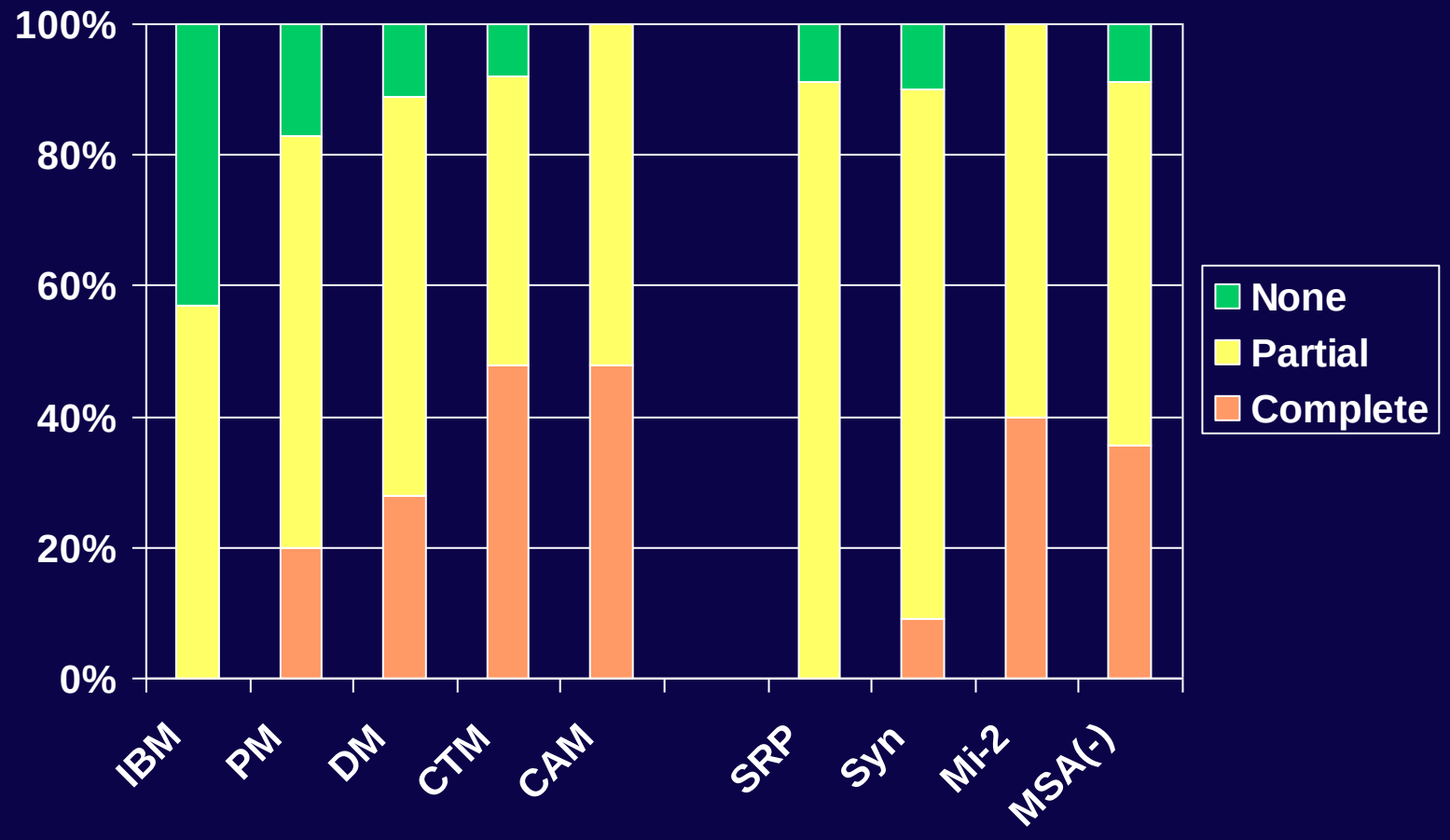
Love, et al., Medicine 70: 360-74, 1991

Response to Steroids: IIM Subgroups



Joffe et al., Am J Med 94: 379, 1993

Seasonality of IIM: Serologic Stratification

All patients:	**no seasonality**
Anti-Jo-1:	**23/31 onset Feb. - July average April**
Anti-SRP:	**7/7 onset Sept. - Feb. average Nov.**
Jo-1 (-), SRP (-):	**no seasonality in 58 patients**

Leff et al., Arthritis Rheum 34: 1391, 1991

Anti-p155/140

Antigen

- TIF 1-γ (p155)
- Nuclear transcription and cellular differentiation

Clinical features

- Cancer-associated myositis in adults
- Severe cutaneous disease in adult DM and JDM

MSA in Adult Patients (%)

Name *n*	PM *109*	DM *103*	Overlap *70*
Jo-1	25	22	11
SRP	5	2	0
Mi-2	1	16	0
155/140	0	18	0

Chinoy et al, Ann Rheum Dis 66: 1345-9, 2007

Antibodies to Aminoacyl-tRNA Synthetases

Name *n*	Non-CAM *266*	CAM *16*
Jo-1	22	0
SRP	3	0
Mi-2	6	12
155/140*	4	50

*Odds ratio 23.2 (6.1 – 84.5)

Chinoy et al, Ann Rheum Dis 66: 1345-9, 2007

Anti-p140

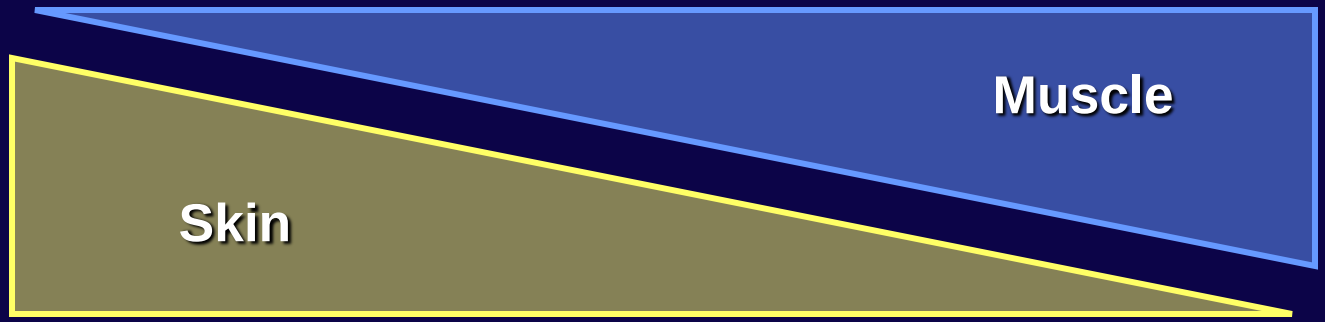
Antigen

- Likely nuclear matrix protein (NXP-2)
- Nuclear transcription and RNA metabolism

Clinical features

- JDM with calcinosis
- Found in ~20% of JDM

Spectrum of Skin Involvement in Dermatomyositis



Amyopathic dermatomyositis

Clinically amyopathic dermatomyositis (CADM)

Anti-CADM-140

Antigen

- Intracytoplasmic MDA5
- Innate immune responses against viral infections

Clinical features

- Clinically amyopathic dermatomyositis
- Rapidly progressive interstitial lung disease
- Reported in Japan

Anti-SAE

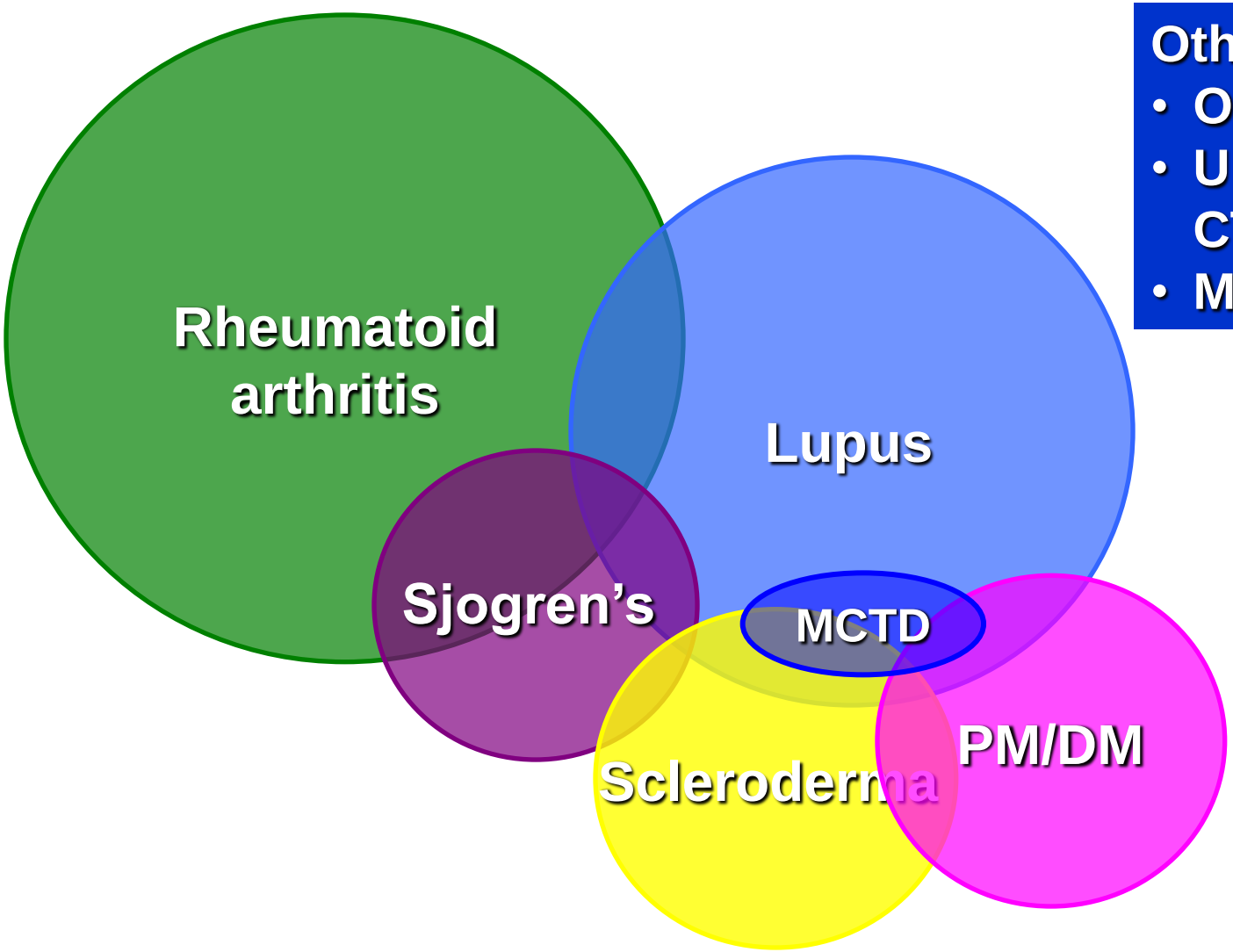
Antigen

- Small ubiquitin-like modifier activating enzyme
- Post-translational modification of proteins

Clinical features

- Adult DM, ~ 8%
- Present first with skin and then progressive muscle disease
- Little lung involvement

Connective Tissue Diseases



Other terms:

- **Overlap CTD**
- **Undifferentiated CTD**
- **Mixed CTD**

ENA Antibodies

Extractable nuclear antigens (ENA) – RNA/protein complexes

Classic ENAs	
• SSA/Ro	Sjögren's, SLE
• SSB/La	Sjögren's, SLE
• Sm	SLE
• U1-RNP	MCTD, SLE
2 additional antigens	
• Jo-1	Myositis with ILD
• Scl-70	Scleroderma
Other MAA	
• U3-RNP	
• Ku	
• PM-Scl	

Why do MSA matter?

- Understand the cause of disease and/or mechanisms leading to specific clinical features
- Prognostication – do they predict:
  - Need for more or less treatment
  - Need for more or less evaluation
- If they cause disease they might be a target for treatment

Time for questions