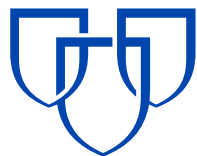


MAYO
CLINIC



Myositis 101

Steven R. Ytterberg, M.D.

Division of Rheumatology

Mayo Clinic, Rochester, MN

Myositis Association Annual Conference

Louisville, KY

Sept. 6 & 7, 2018

Disclosures

- Consulting:
 - Dynavax
 - Pfizer
- Off-label use:
 - Nothing is FDA approved other than steroids

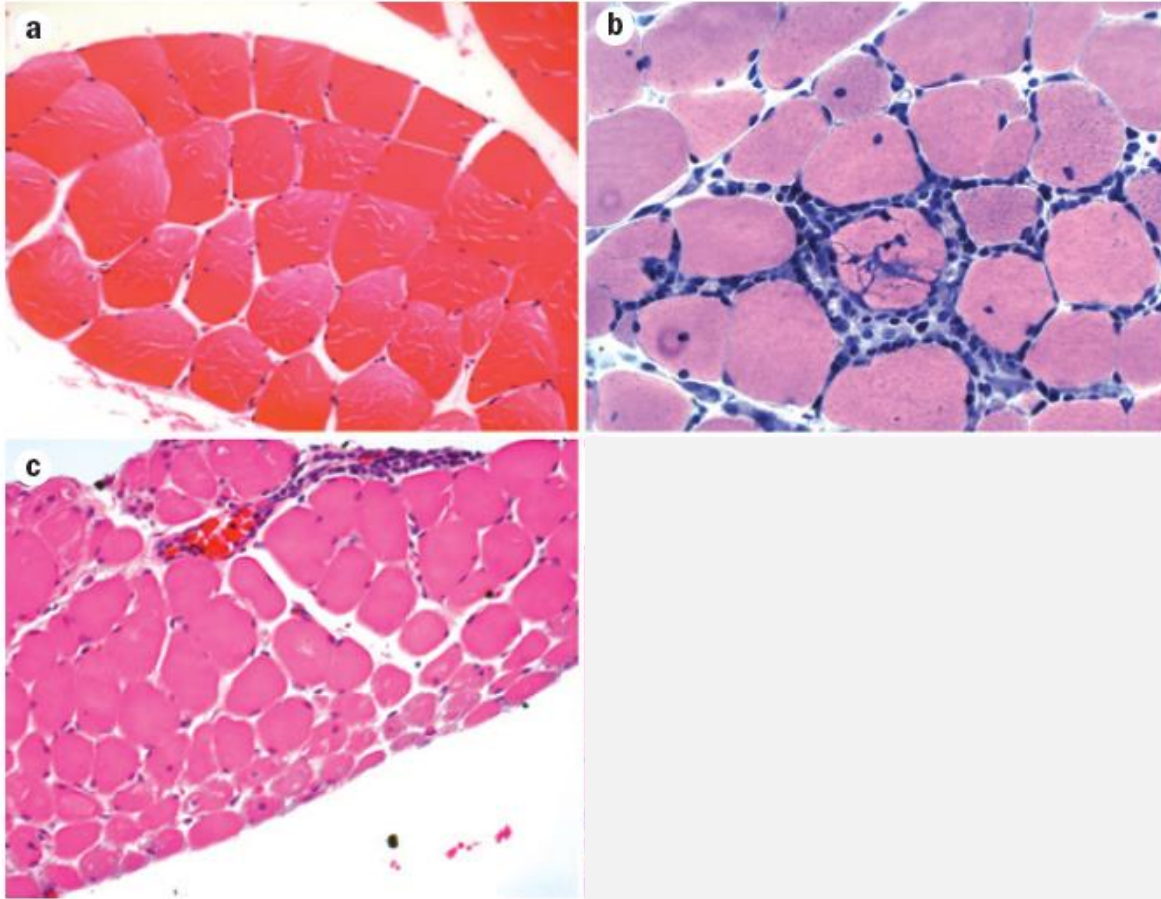
I hope to answer some common questions:

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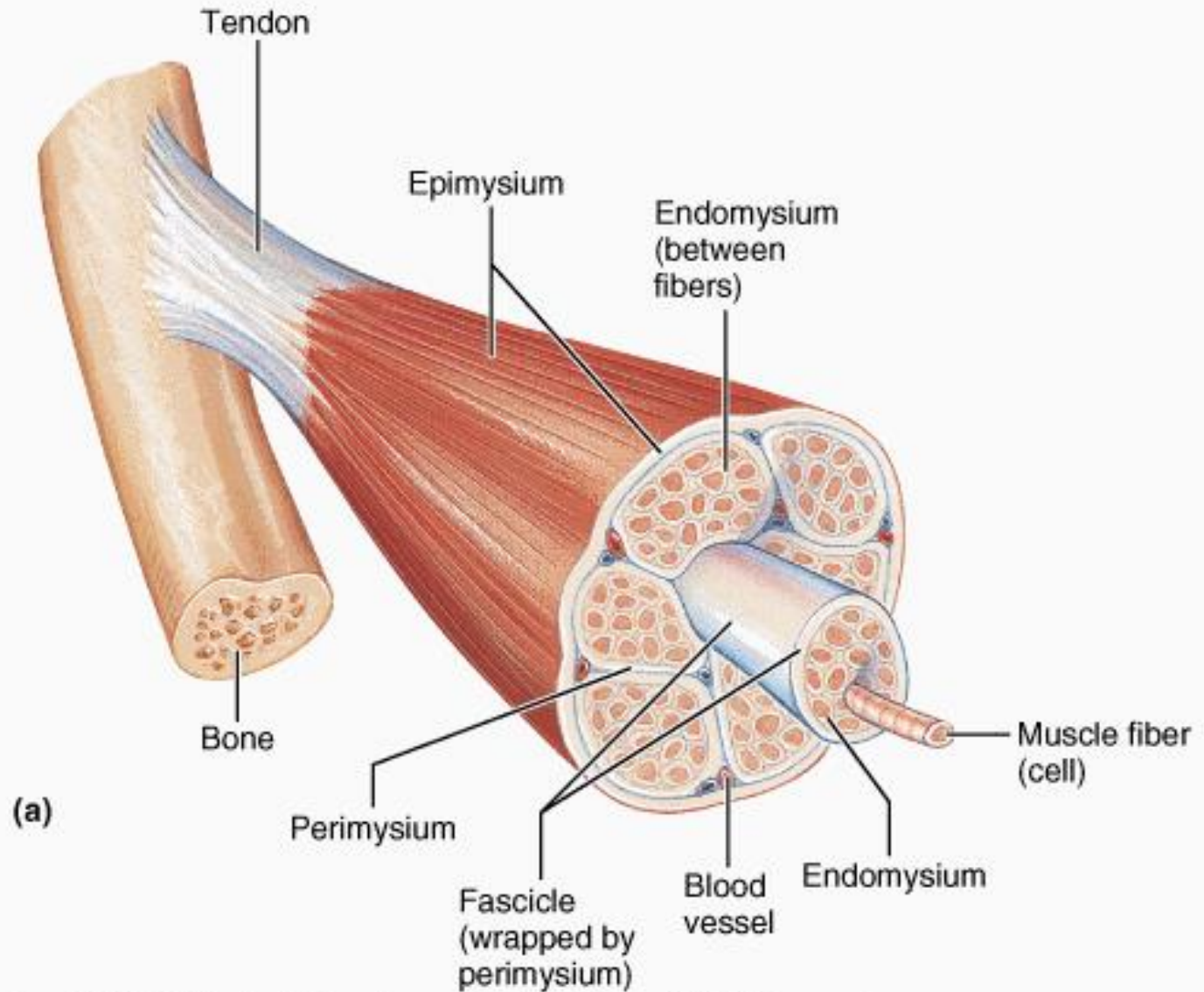
Myositis = muscle inflammation



- a) Normal muscle
- b) PM – endomysial inflammation
- c) DM – perifascicular atrophy

Mammen, Nat Rev Neurol 2011; 7:343-54

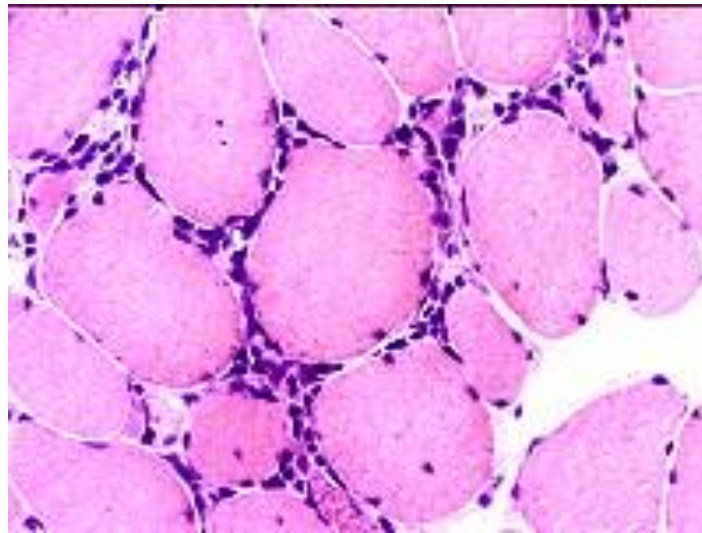
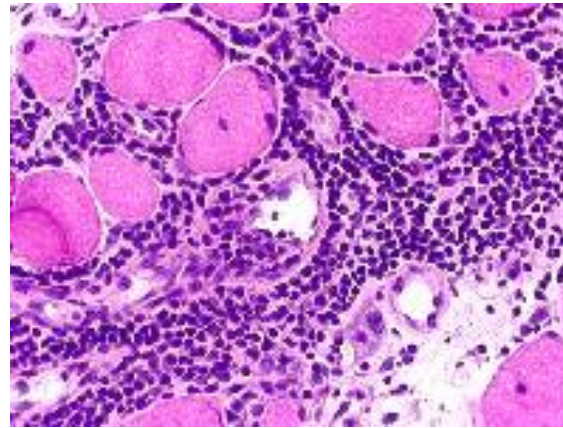
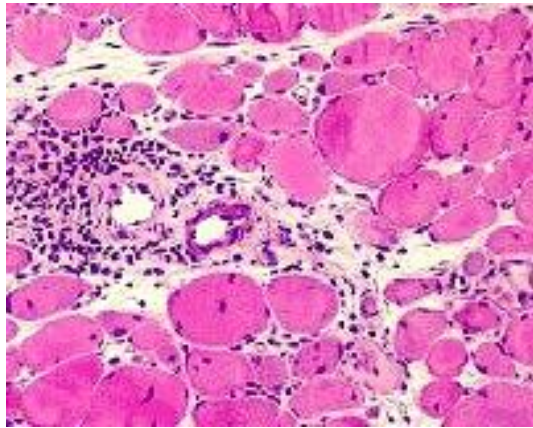
Muscle



Copyright © 2001 Benjamin Cummings, an imprint of Addison Wesley Longman, Inc.

http://www.nooruse.ee/e-ope/opiobjektid/lihasfysiologia/lihasfysiologia_alused.html

Myositis = muscle inflammation



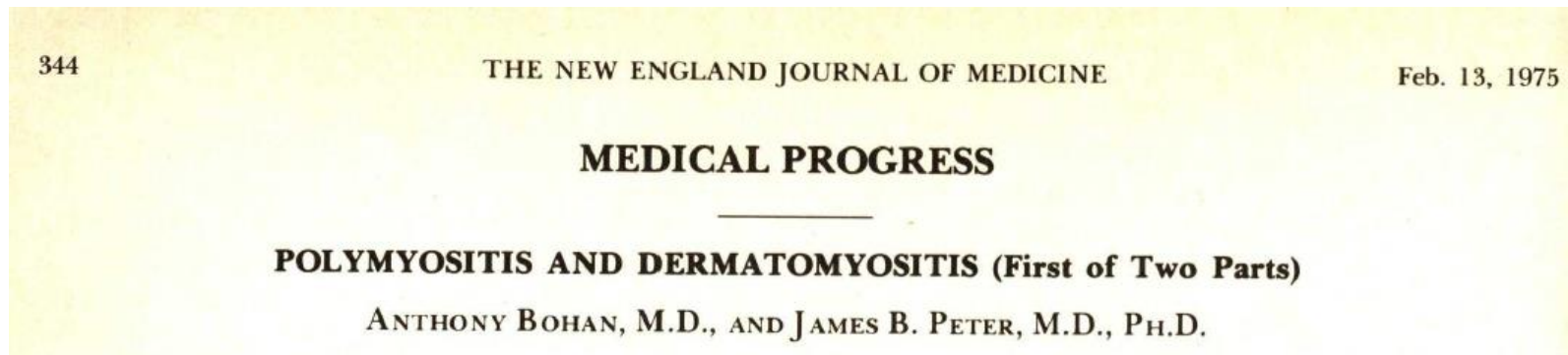
<http://www.neuro.wustl.edu/neuromuscular/pathol/inflammation.htm>

Myopathy = muscle abnormality

- Myopathy: general term for muscle abnormality
- Myositis: muscle inflammation
- Most of the muscle disorders discussed are caused by abnormality of the immune system
- Autoimmune: immune system directed toward self
- Sometimes immune system abnormality causes myopathy without inflammation

Idiopathic Inflammatory Myopathies

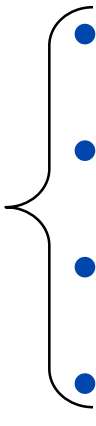
- Polymyositis (PM)
 - Dermatomyositis (DM)
- Isolated, adult
 - Juvenile
 - Malignancy
 - Overlap



Bohan & Peter, N Engl J Med 292: 344, 405, 1975

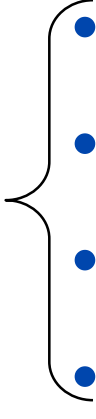
Bohan et al., Medicine 56: 255, 1977

Idiopathic Inflammatory Myopathies

- Polymyositis (PM)
 - Dermatomyositis (DM)
- 
- Isolated, adult
 - Juvenile
 - Malignancy
 - Overlap
- Inclusion body myositis (IBM)
 - Antisynthetase syndrome
 - Immune-mediated necrotizing myopathy (IMNM)

Idiopathic ~~Inflammatory~~ Myopathies

Immune-mediated

- Polymyositis (PM)
 - Dermatomyositis (DM)
- 
- Isolated, adult
 - Juvenile
 - Malignancy
 - Overlap
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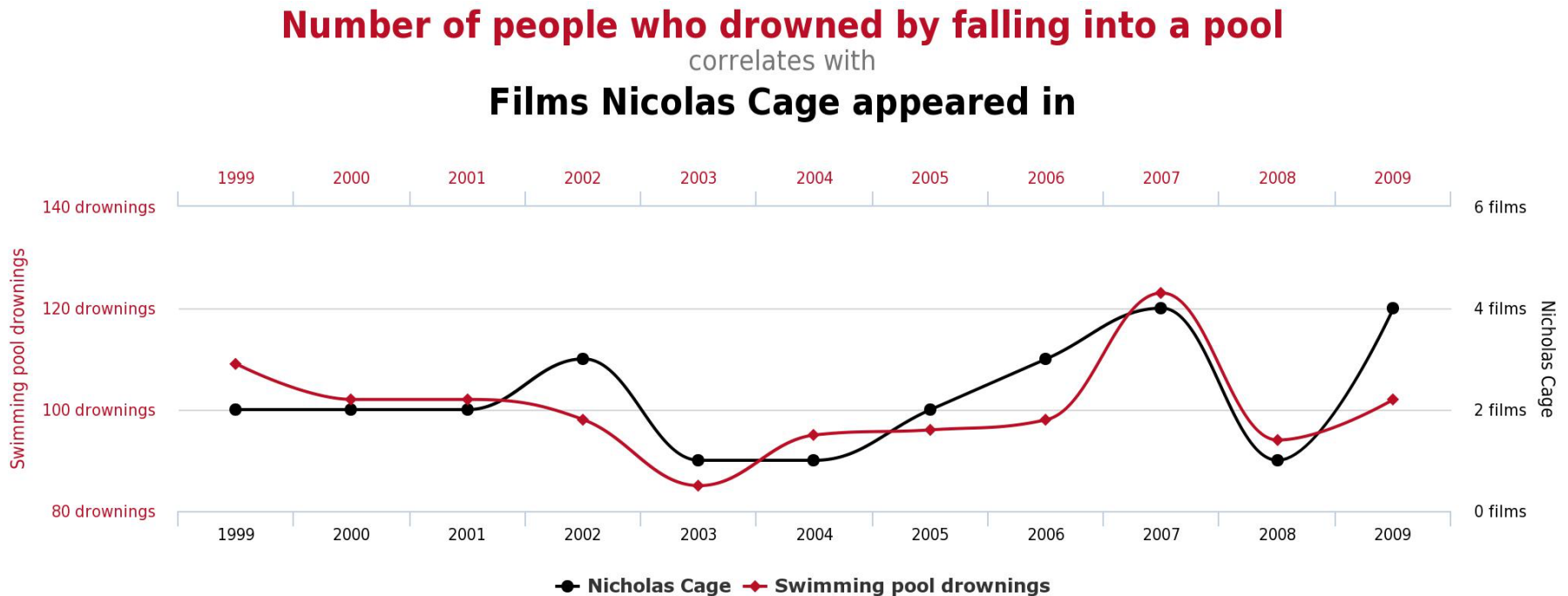
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“Cause” is a difficult term

Correlation or association \neq Causation!



<http://www.benchtobmore.com/wp-content/uploads/2015/09/Chart-Tiff-copy.png>

“Cause” is a difficult term

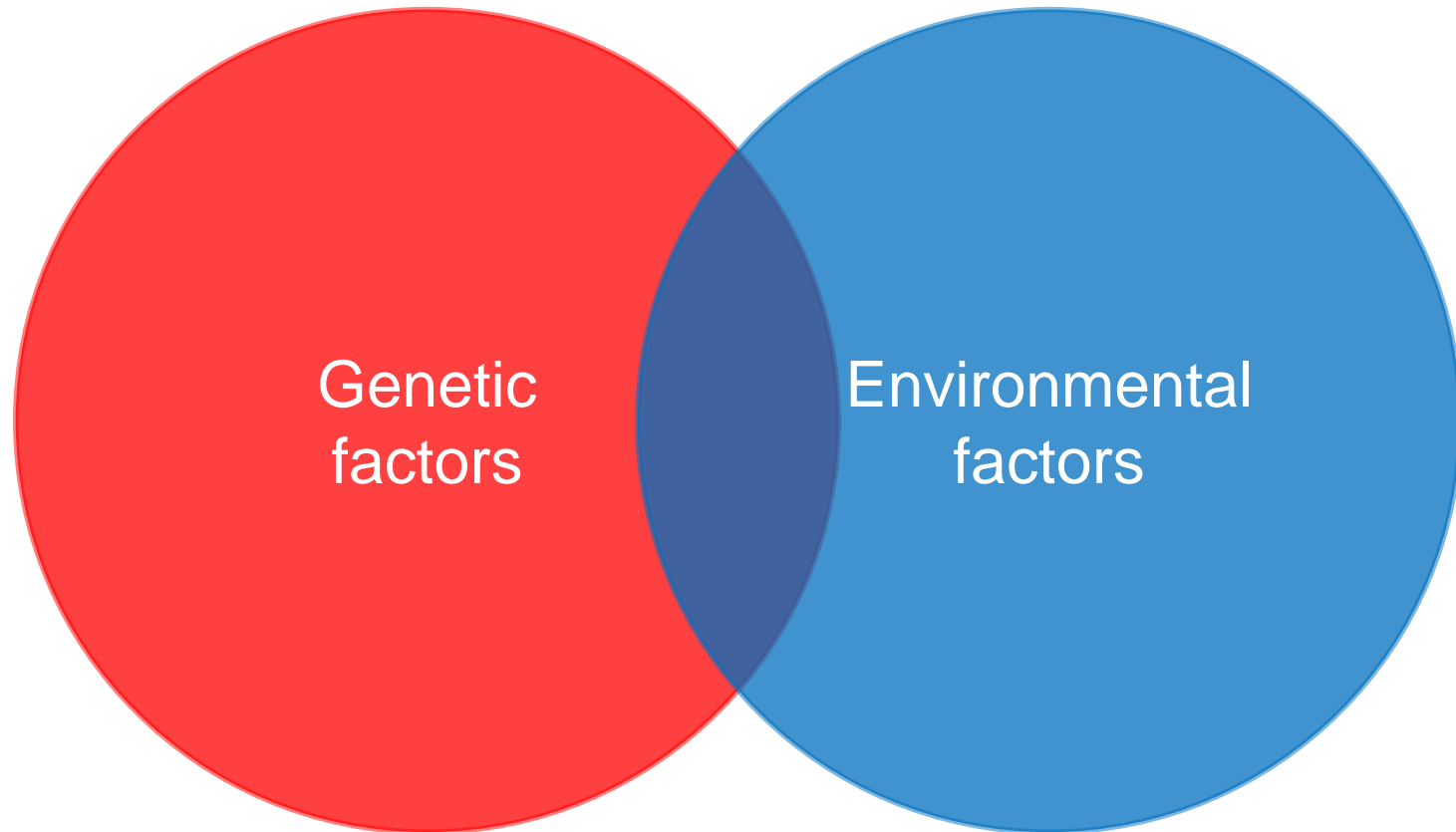
Disease triggers

- Genetic factors
- Environmental factors
- Muscle fiber change

Disease mechanisms

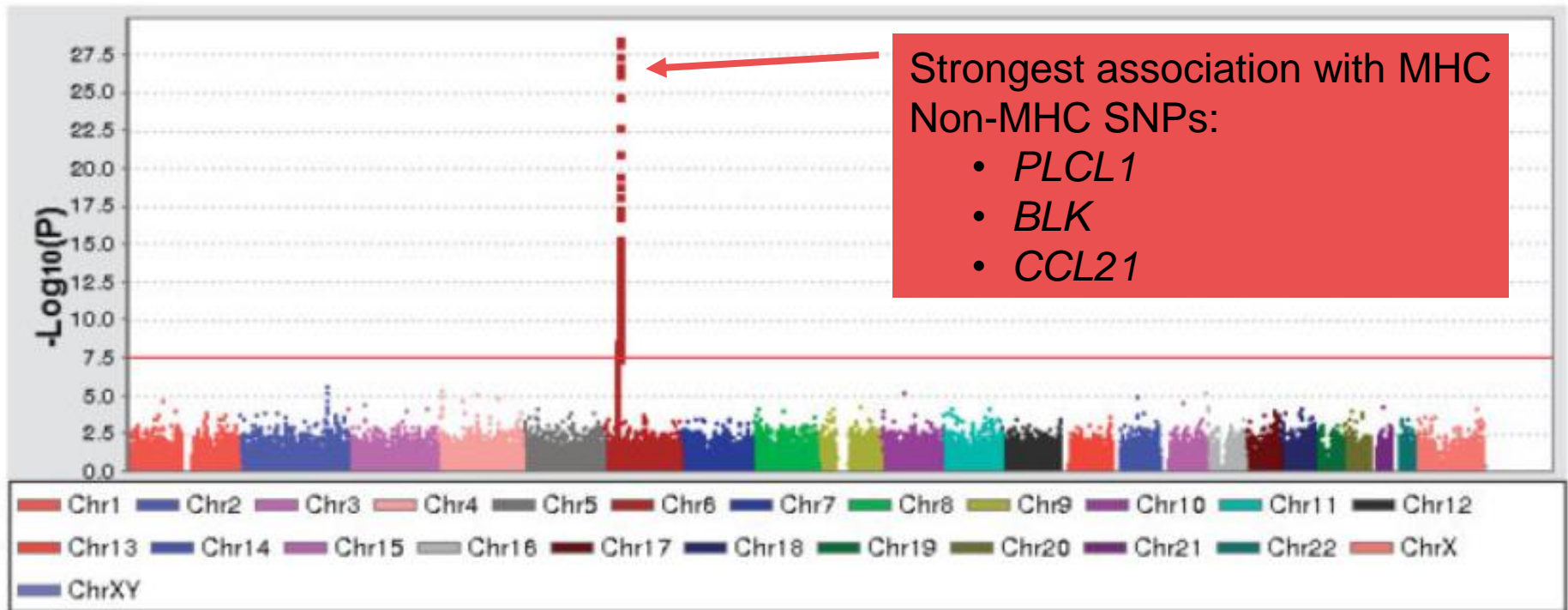
- Immune system
- Inflammation
- Muscle damage
- Others?

Myositis is likely triggered by genetic and environmental factors



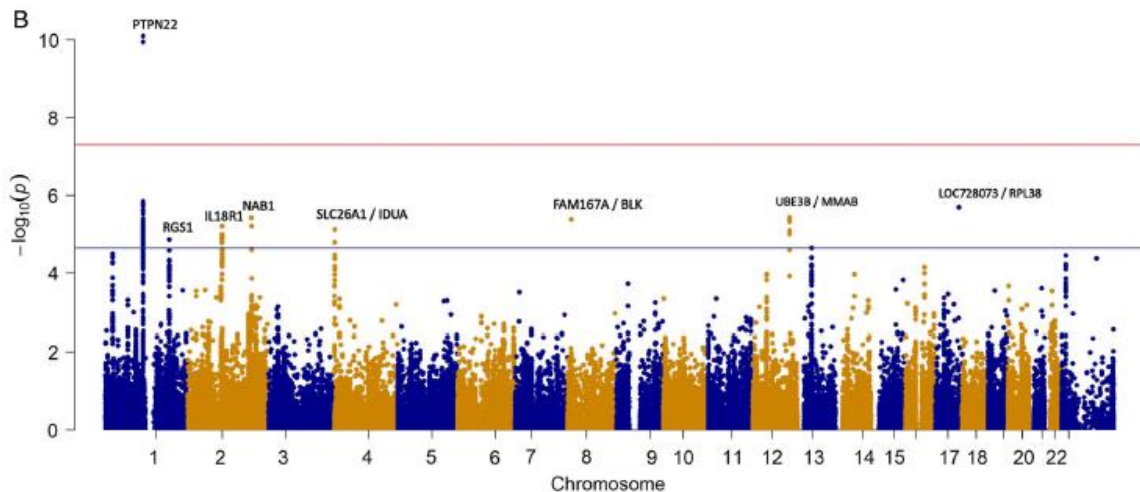
Genome-wide association study (GWAS) in DM/JDM

Genes related to the immune system's recognition of foreign proteins are most highly associated with DM/JDM

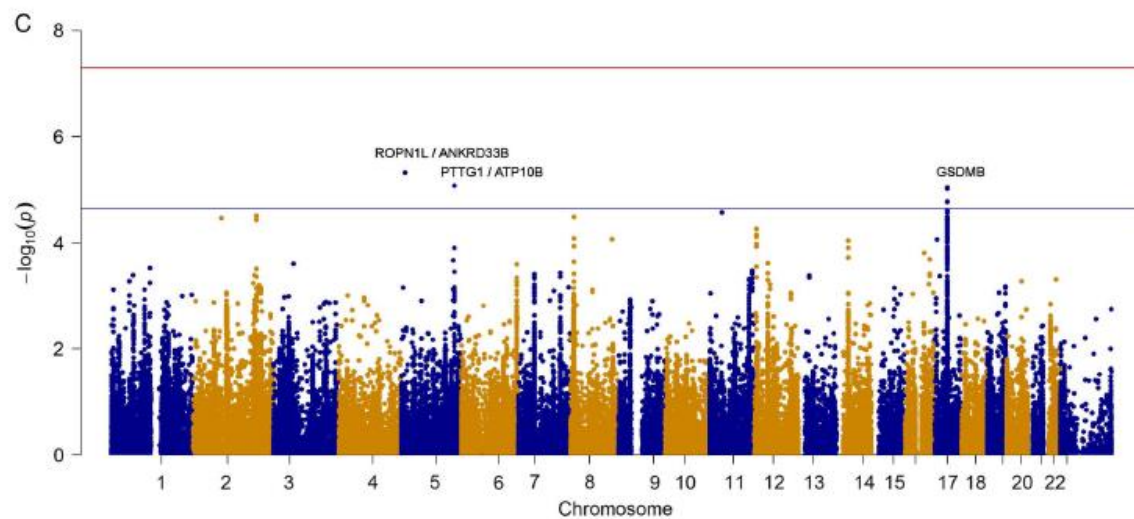


Miller et al., *Arthritis Rheum* 2013; 65: 3239-47

GWAS in PM and DM



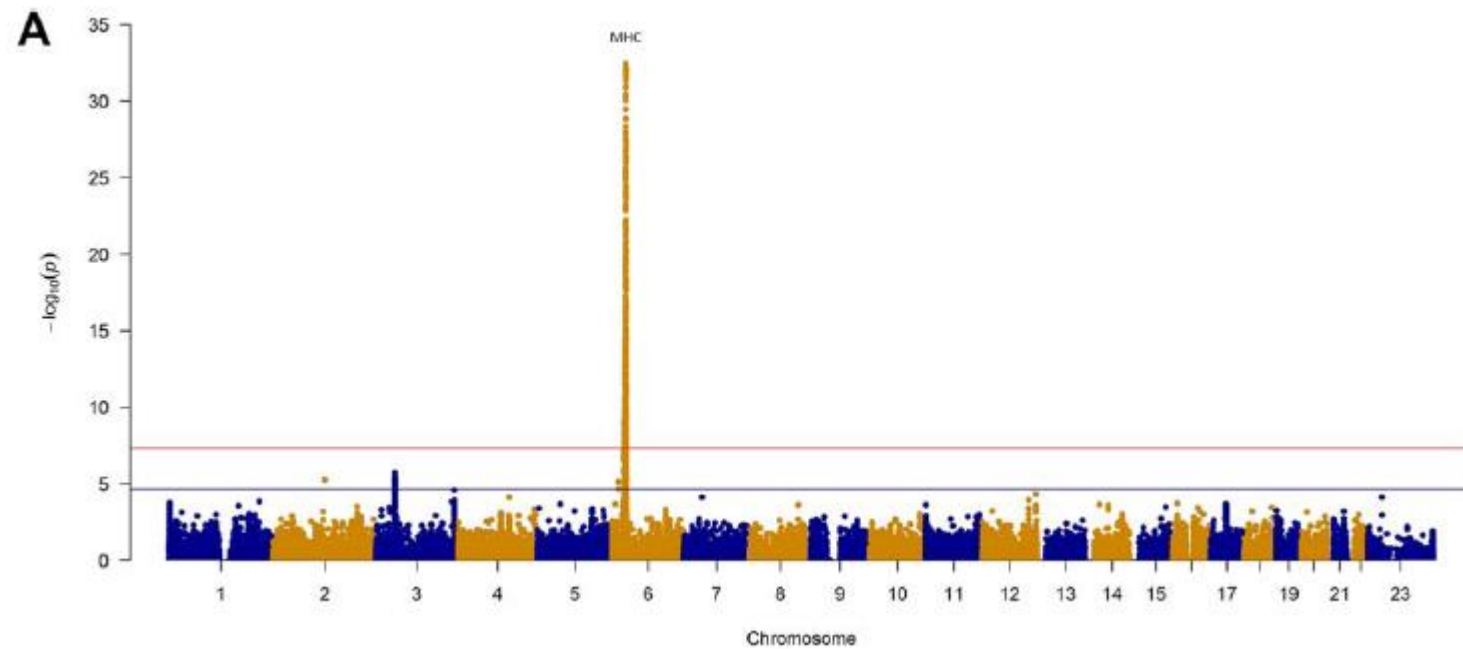
Adult PM



Adult and
juvenile DM

Rothwell et al., Ann Rheum Dis 2016; 75: 1558-66

HLA-DRB1 in IBM



Rothwell et al., Arthritis Rheumatol 2017; 69: 1090-9

Classes of environmental exposures

- **Chemical factors**

- Silica
- Asbestos
- Metals
- Pesticides
- Industrial chemicals and solvents
- Air pollution
- Smoking
- Personal care products

- **Physical factors**

- Ionizing radiation
- UV radiation
- Electric and magnetic fields

- **Biologic factors**

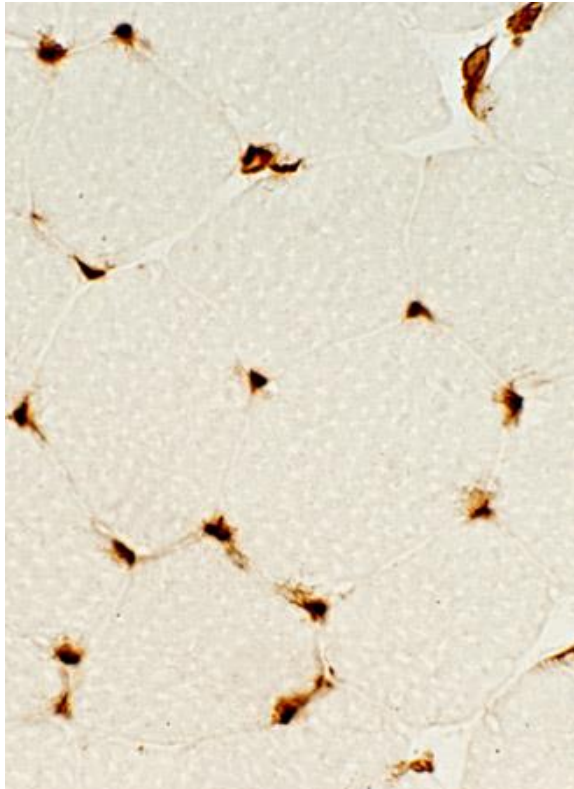
- Infectious agents
- Foods and dietary contaminants
- Molds
- Mycotoxins
- Other toxins

Miller, et al., J Autoimmun 2012; 39: 259-71

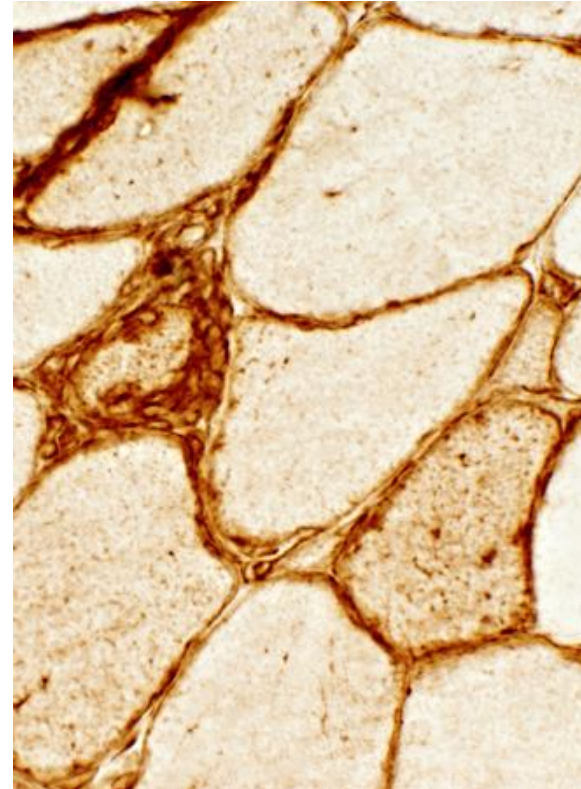
Pathogenesis of IIM

Feature	DM	PM	IBM
Increased MHC I	+	+	+
B-cell mechanisms	+	-	-
T-cell mechanisms	+	+	+
Inclusions	-	-	+
Autoantibodies (Myositis specific antibodies)	+	+	+

MHC I expression in muscle



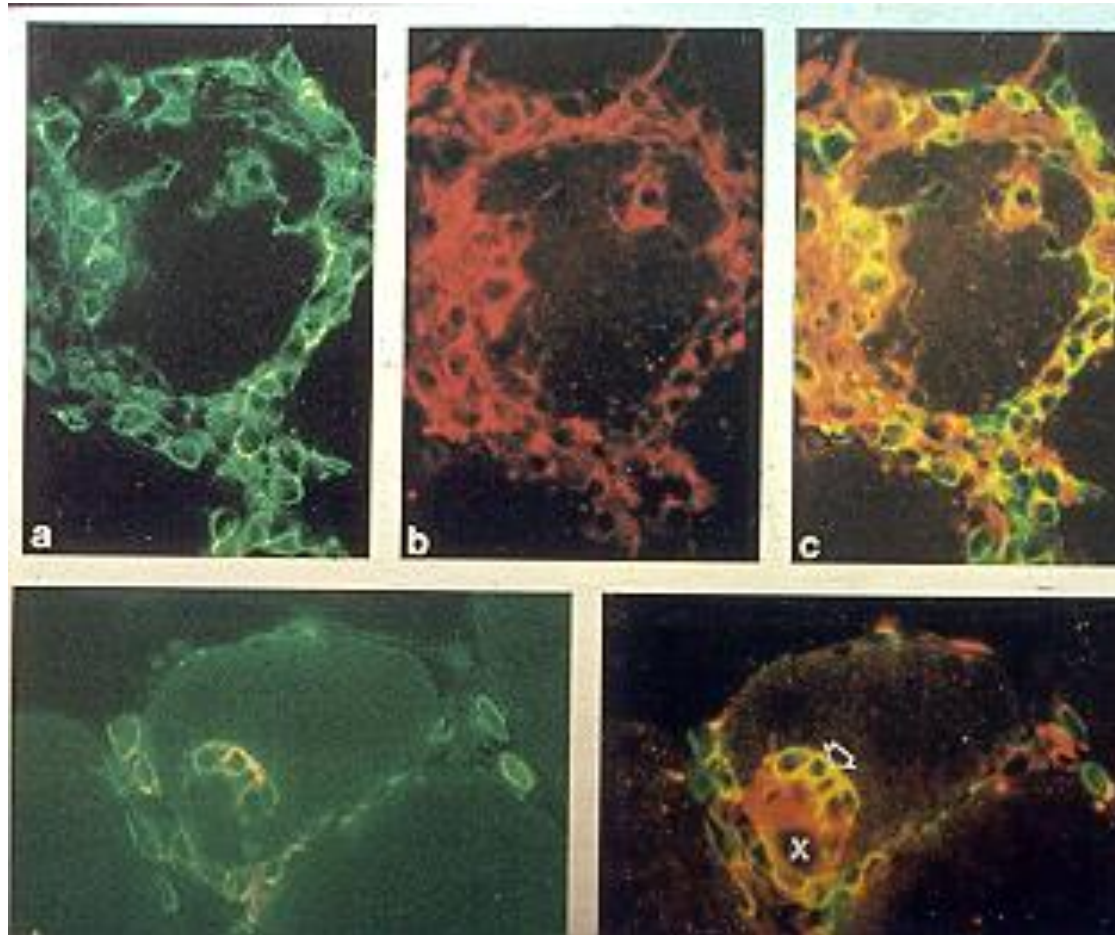
Normal



IBM

<http://neuromuscular.wustl.edu/pathol/ibm.htm>

Activated T cells (T lymphocytes) invade and damage muscle in IBM and PM



Arahata & Engel, Ann Neurol 1984; 16:193

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What does myositis do to patients?

- It depends
 - On the specific disorder
 - On the individual patient
- Muscle weakness is the hallmark
- Many other things can occur

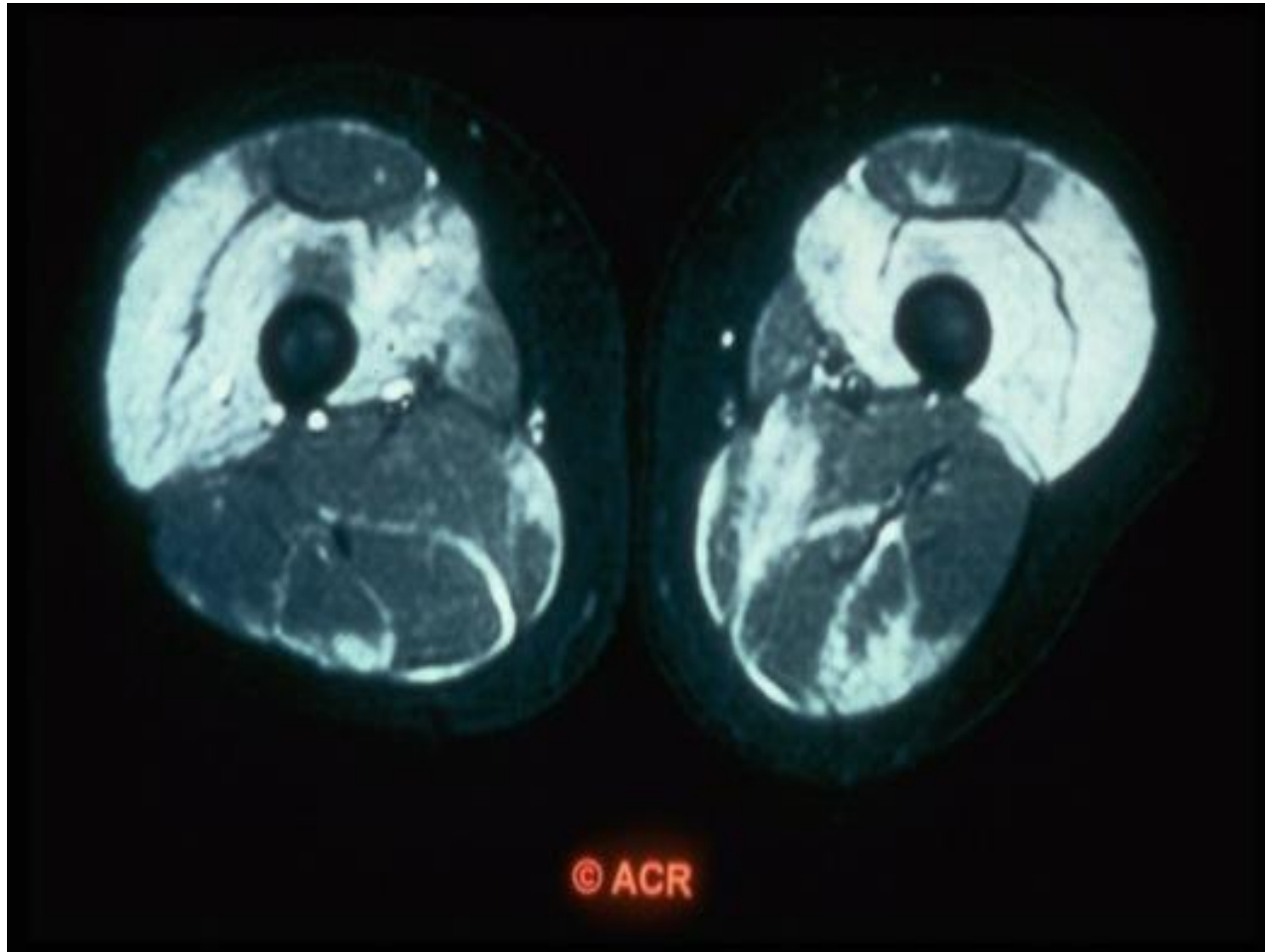
Assessment of Muscle Weakness

- Patient report of effect on activities
- Manual muscle strength testing
- Physiologic testing
- Functional tests
 - Timed stands
 - 6 minute walk
 - Functional Index-2

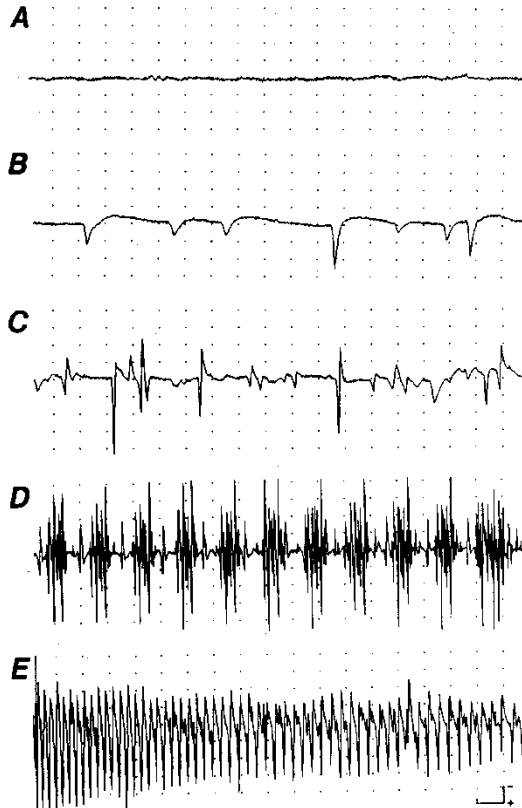
Evaluation of Muscle Disease: Laboratory Tests

- CK – Creatine kinase (CPK)
- Aldolase
- LDH – Lactate dehydrogenase
- AST – aspartate aminotransferase
- ALT – alanine aminotransferase

Muscle MRI can show inflammation or scarring



Resting EMG



Normal muscle - no resting activity

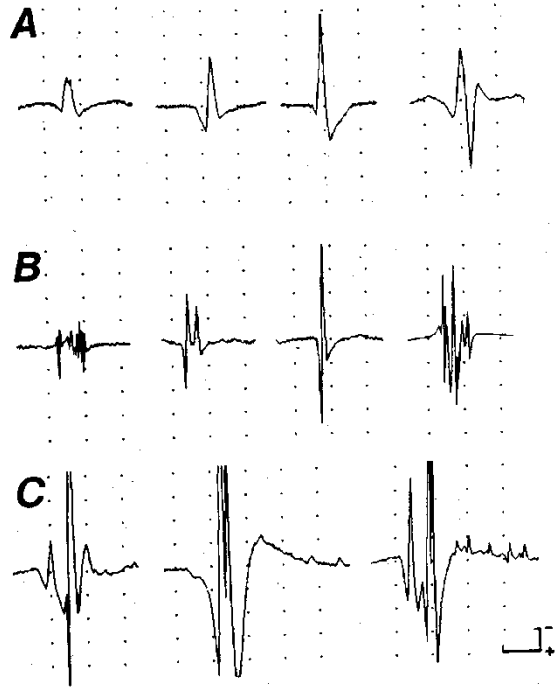
Positive waves

Fibrillation potentials and occasional positive waves

Complex repetitive discharges

Myotonic discharge

Motor Unit Action Potentials (MUAPs)



Normal MUAPs

Myopathy: Low amplitude, short, polyphasic MUAPs

Neuropathy: Large, long duration, polyphasic MUAPs

Dermatomyositis: characterized by rash

- Heliotrope
- Gottron's papules
- Shawl sign & others
- Calcinosis cutis

Heliotrope



Gottron's papules



Gottron's sign



Shawl sign



Periungual erythema



Calcinosis cutis



Amyopathic Dermatomyositis (Dermatomyositis siné myositis)

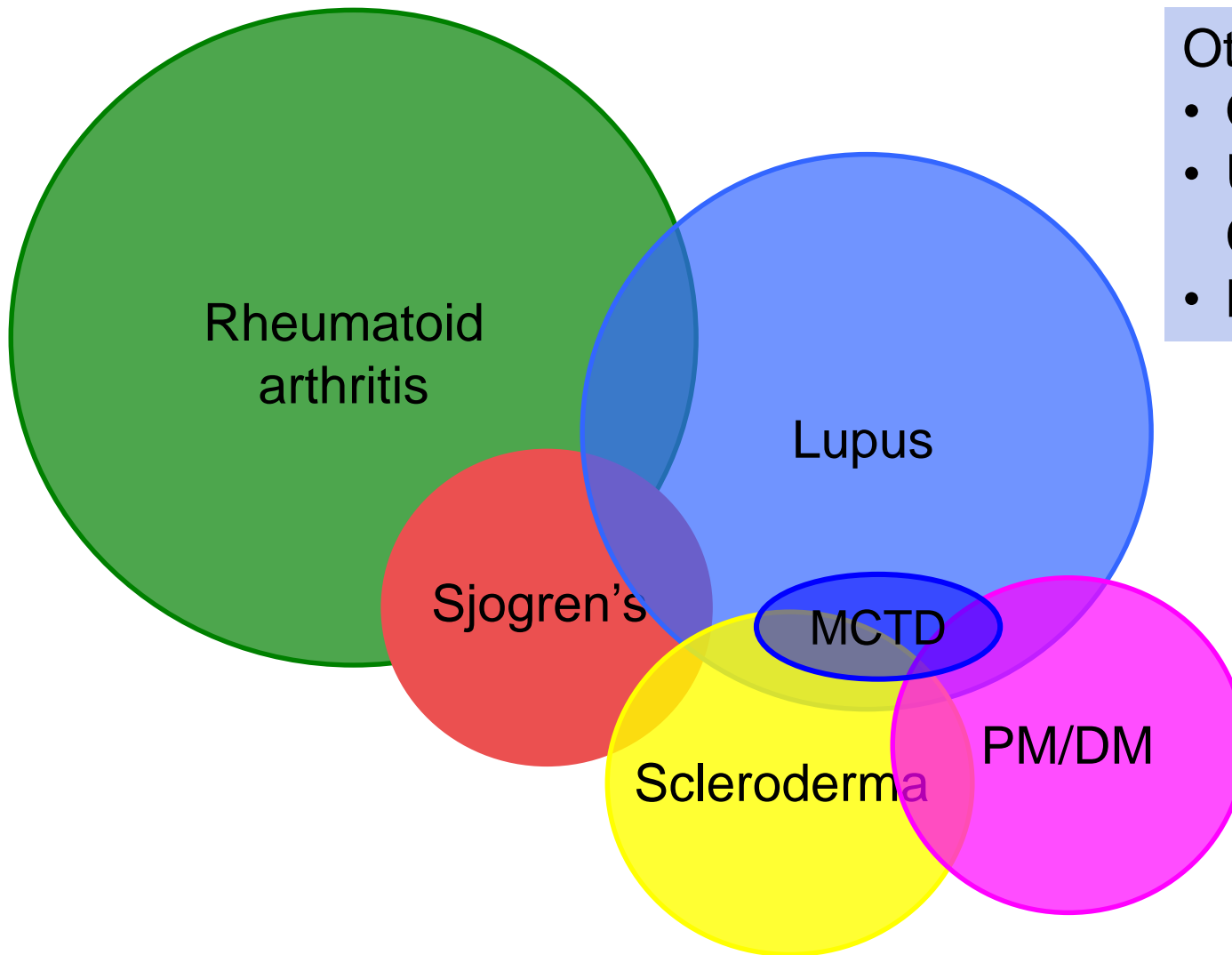
- Cutaneous features of DM
- No muscle weakness
 - Maybe elevated muscle enzymes or EMG, but not weak

Gerami et al., J Am Acad Dermatol 2006;54:597-613

Other organ system problems – mostly PM and DM

- Lung – interstitial lung disease
- Gastrointestinal – dysphagia, anorexia, reflux
- Heart – inflammation, fibrosis, rhythm
- Joints – arthritis, arthralgia, morning stiffness
- Raynaud's phenomenon
- Constitutional – fatigue, fever

Autoimmune Connective Tissue Diseases



Other terms:

- Overlap CTD
- Undifferentiated CTD
- Mixed CTD

Inclusion body myositis

- Muscle biopsy findings define the disorder

Myxovirus-Like Structures in a Case of Human Chronic Polymyositis

Abstract. Intranuclear and intracytoplasmic aggregates of filaments with tubular structures and transverse striations occurred in muscle tissues biopsied from a patient with chronic polymyositis. The filamentous tubules bear a close resemblance to the incomplete form of myxovirus in which the envelope is missing. Three biopsies from the same patient, taken during a period of 1½ years, all revealed these structures. This finding provides presumptive evidence that a chronic persistent viral infection may be involved in the pathogenesis of chronic polymyositis.

SHI-MING CHOU

*Department of Pathology and
Regional Primate Research Center,
University of Wisconsin
Medical School, Madison*

15 DECEMBER 1967

Inclusion Body Myositis

- First description 1967
- “IBM” term coined 1971
- Sporadic form (s-IBM)
- Several hereditary forms (h-IBM)
- Clinically similar:
 - Weakness: insidious, distal, atrophy
 - CK minimally to moderately elevated
 - EMG: myopathic +/- neurogenic
- Hereditary: younger; no inflammation

Clinical Features of sIBM

- Insidious onset
- ~6 years to diagnosis
- Weakness generalized or localized to limbs; may be asymmetric
- Reflexes normal initially, eventually diminished in 40%
- Dysphagia in 2/3 – late
- Myalgia uncommon but aching in thighs and knees in some



Typical involvement:

- Finger flexors
- Wrist flexors
- Knee extensors
- Ankle dorsiflexors

Needham & Mastaglia, Lancet Neurol 6: 620-31, 2007

Anti-synthetase Syndrome

- Anti-synthetase antibody – Jo-1, others
- PM/DM
- Interstitial lung disease
- Inflammatory arthritis
- Raynaud's phenomenon
- Mechanic's hands
- Fever

Mechanic's hands



Immune-mediated necrotizing myopathy

- Characterized by muscle biopsy with necrotic muscle fibers without inflammation
- Specific autoantibodies
 - Anti-SRP
 - Anti-HMGCR
 - Often associated with statin use

Christopher-Stine, et al. Arthritis Rheum 2010; 62: 2757-66
Mammen, et al. Arthritis Rheum 2011; 63: 713-21

IIM: Epidemiology

Incidence - 0.5 to 8/million

	Polymyositis/ Dermatomyositis	Inclusion Body Myositis
Age	Bimodal, 10-15 in kids 45-60 in adults	>50
Female:male	2:1	1:2

Epidemiology of IBM and PM Olmsted County, 1981-2000*

	IBM	PM
Incidence	0.79 (0.24-1.35)	0.41 (0.08-0.73)
Prevalence	7.06 (0.87-13.24)	3.45 (0.00-7.35)

*Age- and sex-adjusted rates per 100,000 population; (95% CI)

Wilson et al., J Rheumatol 2008; 35:445-7

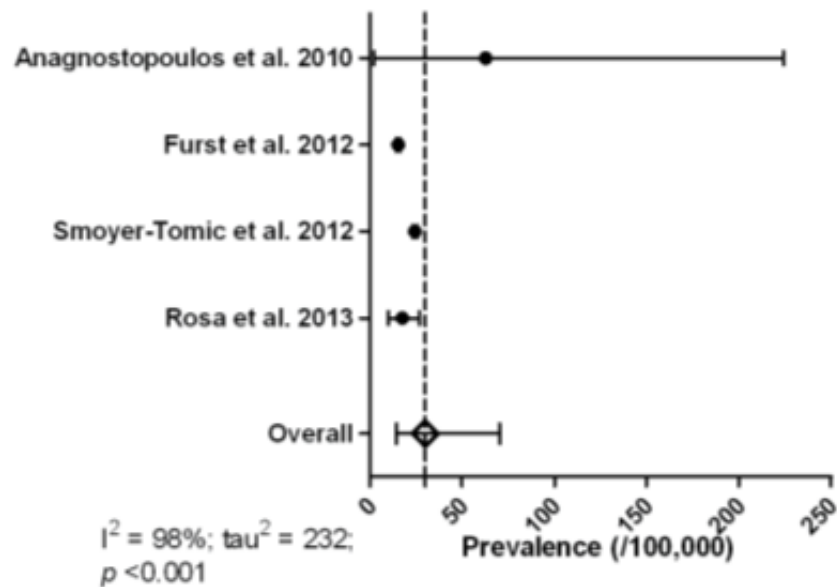
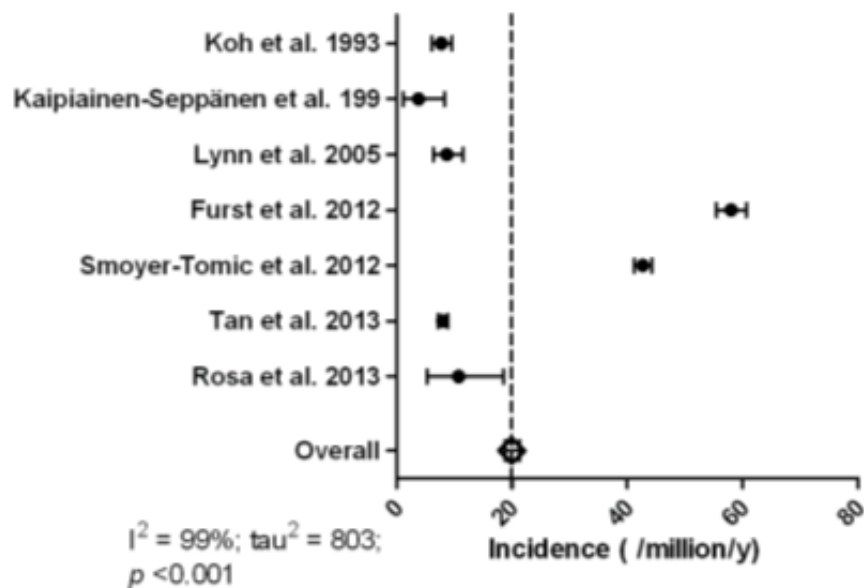
Epidemiology of DM Olmsted County, 1976-2007*

	DM	CADM
Incidence	0.96 (0.61-1.32)	0.21 (0.04-0.38)
Prevalence	2.14 (1.31-2.98)	

*Age- and sex-adjusted rates per 100,000 population; (95% CI)

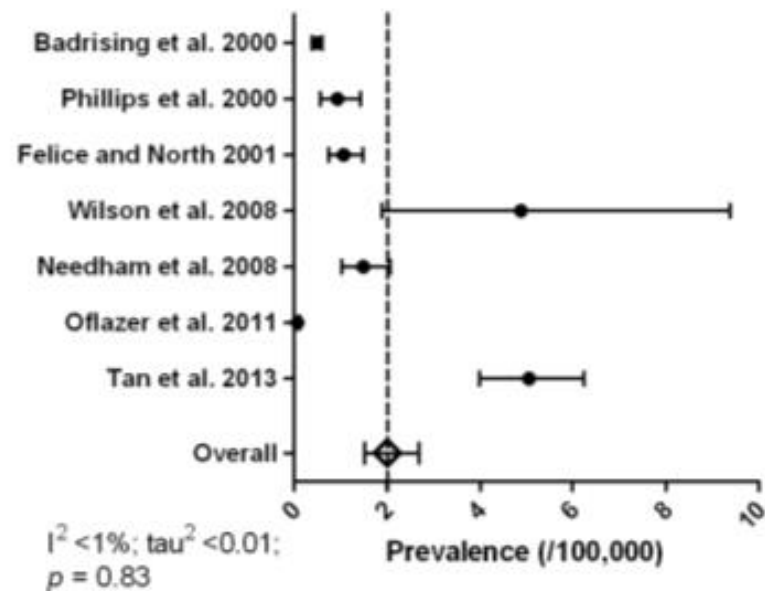
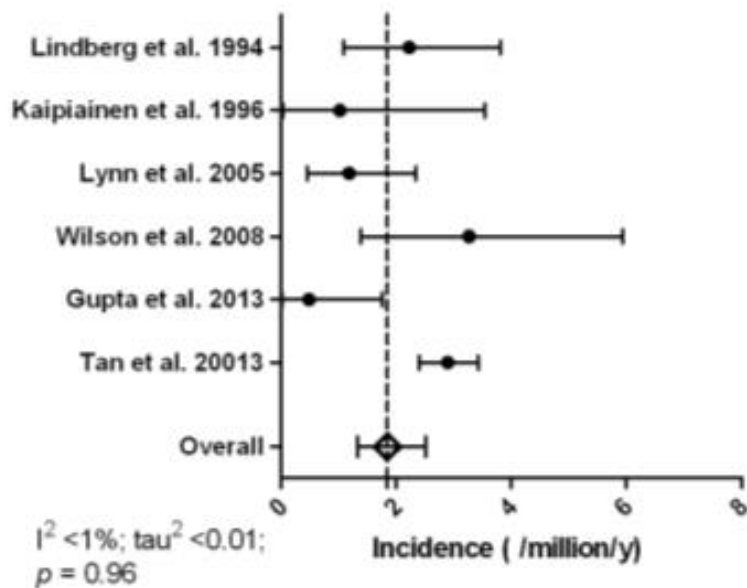
Bendewald et al., Arch Dermatol 2010; 146: 26-30

Systematic Review: Adult IIM



Meyer et al., Rheumatology 2015; 54: 50-63

Systematic Review: sIBM



Meyer et al., Rheumatology 2015; 54: 50-63

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PM/DM Classification Criteria

- Proximal muscle weakness
- Elevated serum levels of skeletal muscle enzymes
- Myopathic changes on EMG
- Muscle biopsy evidence of inflammation
- Skin rash

Definite PM or DM: 4 criteria

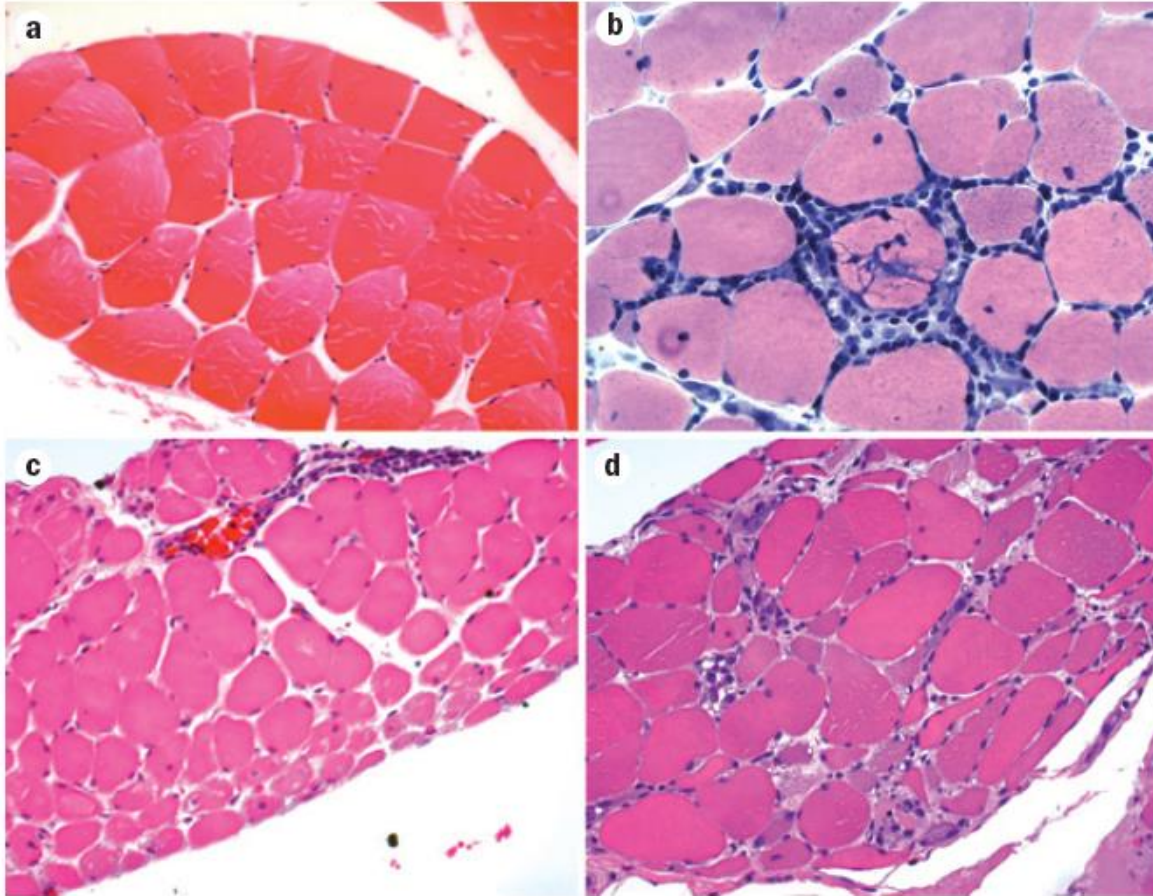
Probable PM or DM: 3 criteria

Possible PM or DM: 2 criteria

Bohan & Peter, N Engl J Med 292: 344, 405, 1975

Bohan et al., Medicine 56: 255, 1977

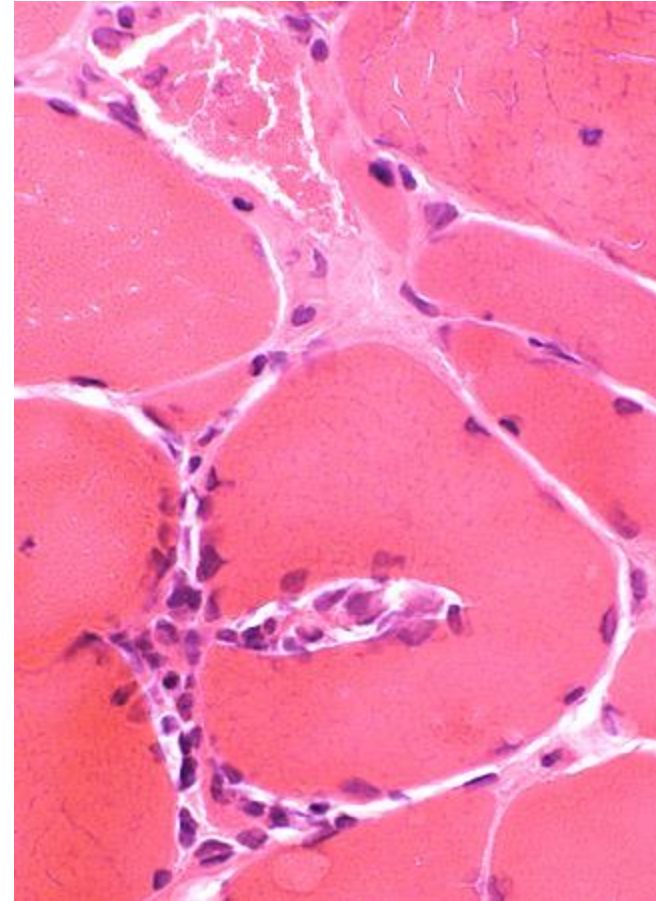
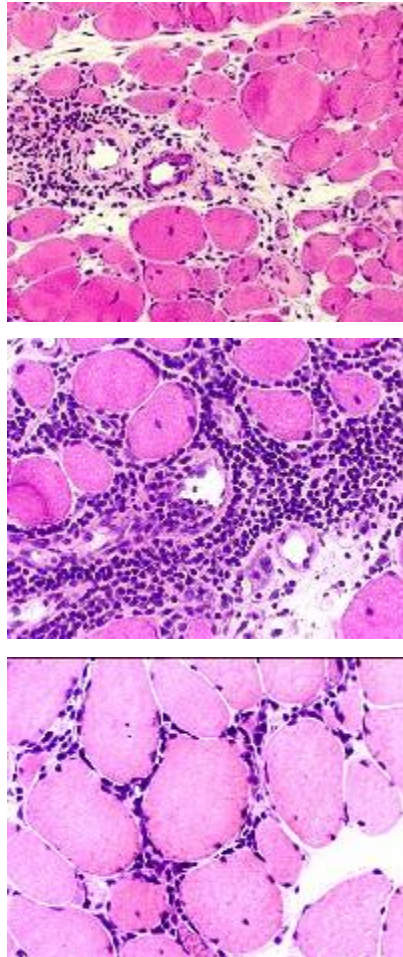
Muscle histopathology



- a) Normal muscle
- b) PM – endomysial inflammation
- c) DM – perifascicular atrophy
- d) Necrotizing myopathy

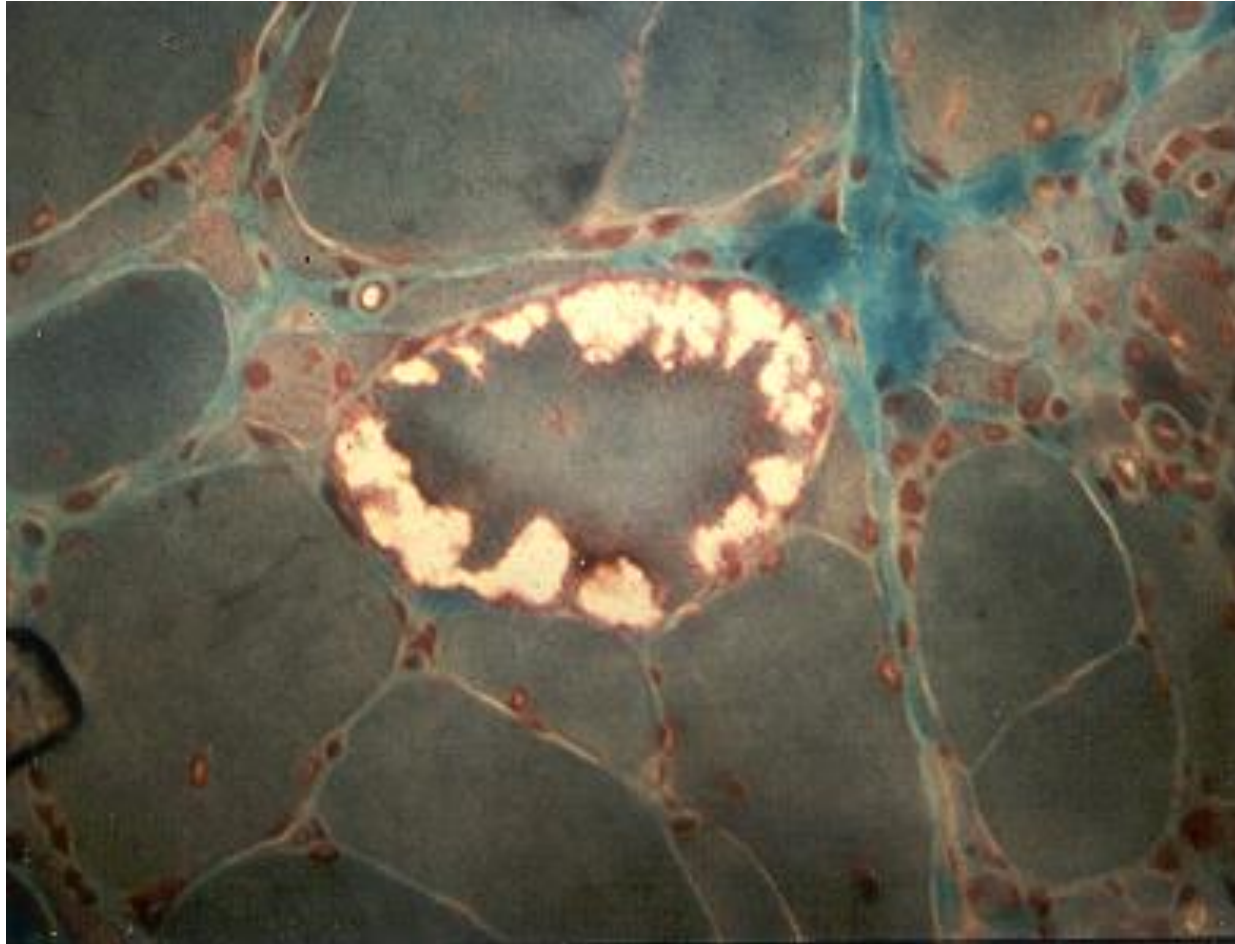
Mammen, Nat Rev Neurol 2011; 7:343-54

Myositis = muscle inflammation

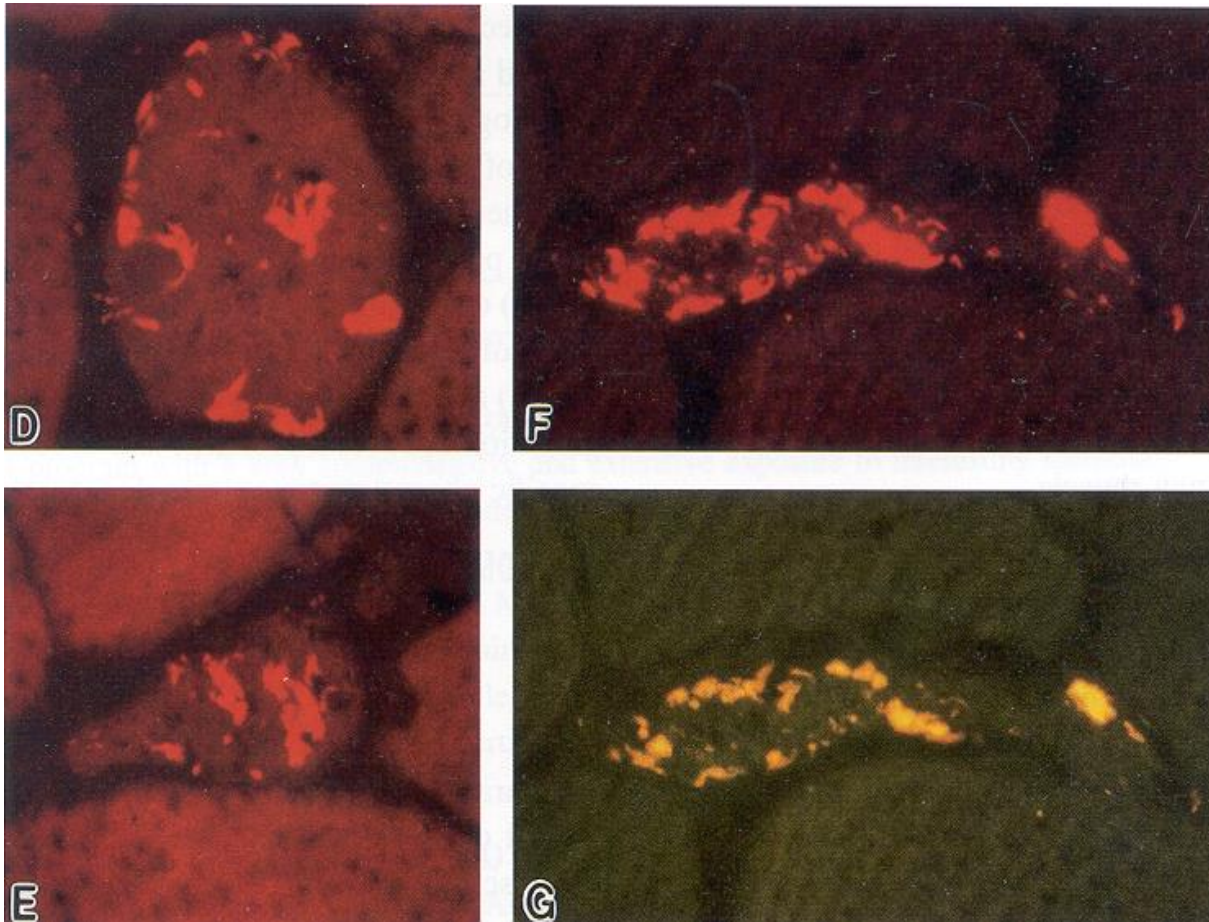


<http://www.neuro.wustl.edu/neuromuscular/pathol/inflammation.htm>

IBM: Vacuoles



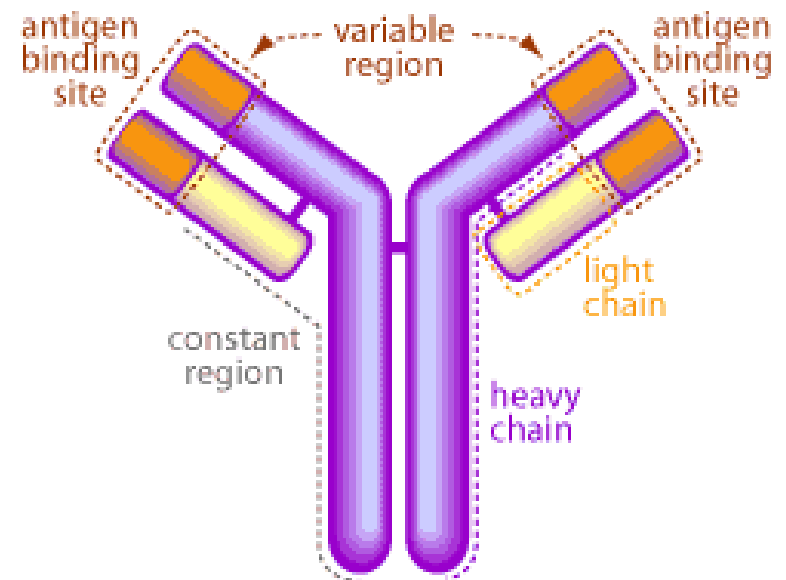
IBM Congo red staining



Askansas & Engel, J Neuropathol Exp Neurol 60:1, 2001

Antibodies

- Immunoglobulin
- Produced by plasma cells in the immune system
- Identify and neutralize viruses and bacteria
- Each recognizes a unique protein (antigen)



Autoantibodies

- Antibodies directed toward an individual's normal proteins
- Autoantibodies may:
 - Cause disease
 - Simply be markers of disease

Autoantibody	Target	Disorder
Antinuclear antibodies (ANA)	Contents of cell nuclei	Lupus and related conditions
Rheumatoid factor (RF)	IgG	Rheumatoid arthritis
Anti-Jo-1	Histidyl tRNA synthetase	Polymyositis with ILD
Anti-PR-3 (c-ANCA)	Neutrophil proteinase-3	Granulomatosis with polyangiitis
Anti-thyroid antibodies	TPO Thyroglobulin	Hashimoto's thyroiditis
Anti-AChR	Acetylcholine receptor on muscle	Myasthenia gravis
Anti-TTG	Tissue transglutaminase	Celiac disease

Non-specific Autoantibodies in Myositis

Percent of Patients with Various Autoantibodies

Antibody	All (n=212)	PM (n=58)	DM (n=79)	CTM (n=36)	CAM (n=13)	IBM (n=26)
ANA	52	40	62	77	31	23
ds-DNA	5	3	3	11	8	4
SSA/Ro	12	12	11	17	0	12
SSB/La	8	5	6	19	8	8
Sm	3	0	1	17	0	0
U1RNP	11	7	13	25	0	0
PM/Scl	2	0	4	3	0	0
RF	6	5	8	8	0	4

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

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%

Antisynthetase antibodies

Antigen	tRNA synthetase	JDM*	Frequency (%)	
			ADM*	Non-white
Any		1-5	30	AA 29
Jo1	Histidyl-	2-5	25-30	AA13
PL12	Alanyl-	1-3	<5	
PL7	Threonyl-	<1	<5	Japanese 17
EJ	Glycyl-	<1	<5	
OJ	Isoleucyl-	<1	<5	
KS	Asparagynyl-	NA	<1	
HA	Tyrosyl-	NA	<1	
ZA	Phenylalanyl-	NA	<1	

*Caucasian

Robinson & Reed, Nat Rev Rheumatol 2011; 7: 664-75

Serologic Subgroups in IIM 2

- Anti-TIF-1 γ (anti-transcription intermediary factor 1 γ ; anti-p155): DM, including JDM, malignancy
Targoff et al., Arthritis Rheum 2006; 54: 3682-3689
Trallero-Araguas et al., Medicine 2010; 89: 47-52
- Anti-MDA-5 (anti-melanoma differentiation-associated protein 5; anti-CADM): CADM, rapidly progressive ILD
Sato et al., Arthritis Rheum 2005; 52:1571-6
- Anti-NXP2 (anti-nuclear matrix protein 2; anti-MJ): JDM, especially with calcinosis, malignancy
Gunawardena et al., Arthritis Rheum 2009; 60: 1807-14

Gunawardena et al., Rheumatology 48: 607-12, 2009

Autoantibodies in IBM

Anti-cytoplasmic 5'-nucleotidase 1A

- Initially detected as 43 kd autoantibody
 - 13/25 (52%) IBM + vs 0/40 controls

Salajegheh, et al., PLoS One 2011; 6(5): e20266

- Antigen identified as cN1A
 - Most abundant in skeletal muscle
 - Catalyzes nucleotide hydrolysis to nucleosides
 - Perinuclear and vacuole accumulation of cN1A

Larman, et al., Ann Neurol 2013; 73: 408-18

Anti-cN1A Verification

Table 1 Sensitivity and specificity of anti-cN-1A autoantibodies

Sera	Number	Anti-cN-1A reactivity*	
		n	Per cent
Inclusion body myositis	238	88	37
Polymyositis/dermatomyositis	185	8	4
Polymyositis/scleroderma overlap	12	0	0
Neuromuscular diseases	93	4	4
Sjögren's syndrome	22	8	36
Systemic lupus erythematosus	44	9	20
Scleroderma	44	1	2
Rheumatoid arthritis	44	1	2
Multiple sclerosis	40	2	5
Type 1 diabetes	40	0	0
<i>Disease control†</i>	458	16	3

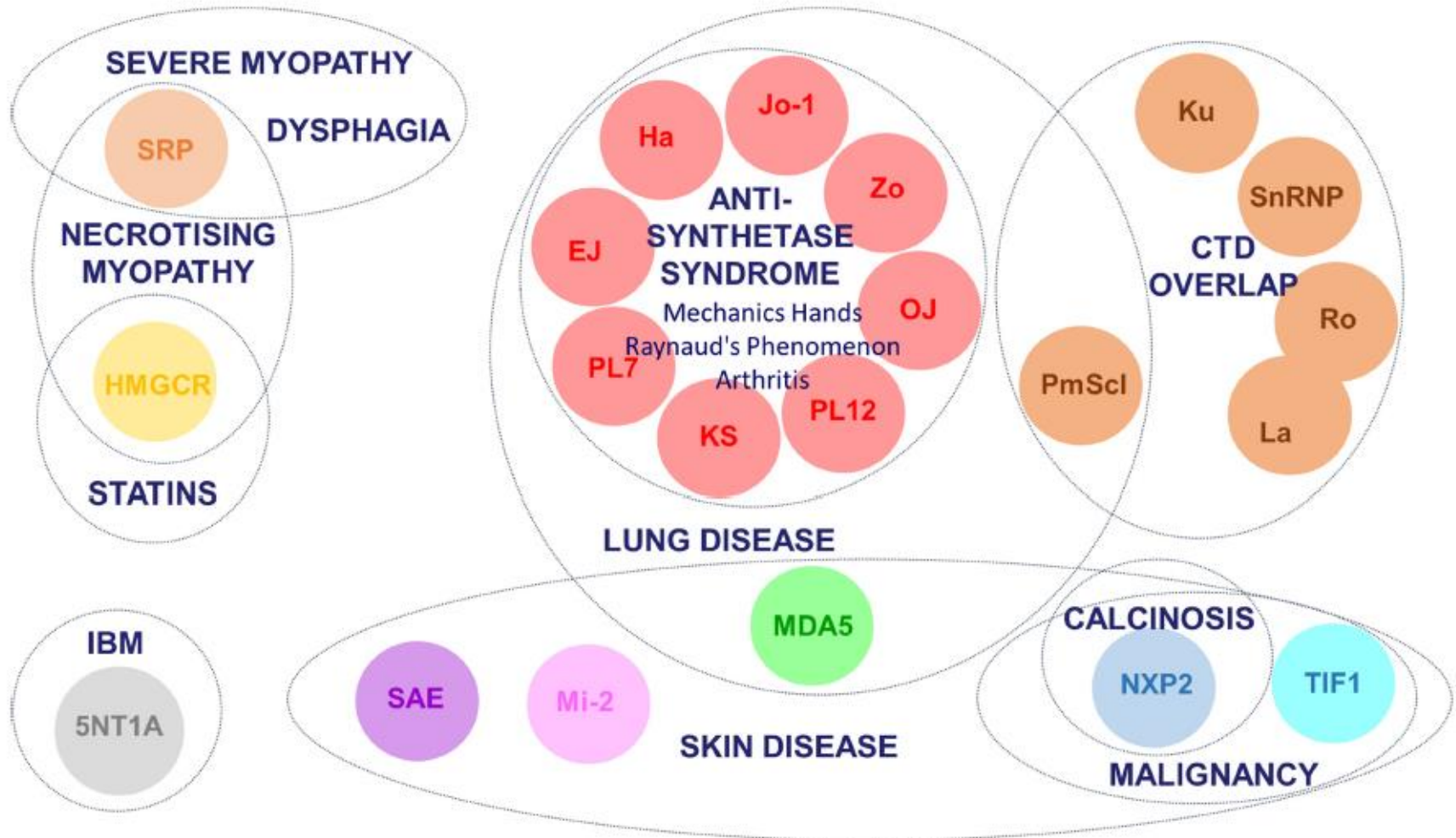
*Reactivity with at least one of the three cN-1A peptides higher than cut-off.

†Disease controls: total of all disease control groups except IBM, SLE and SjS.

cN-1A, cytosolic 5'-nucleotidase 1A; IBM, inclusion body myositis; SjS, Sjögren's syndrome; SLE, systemic lupus erythematosus.

Herbert, et al., Ann Rheum Dis 2016; 75:696-701

Myositis Specific Autoantibodies



Betteridge & McHugh, J Intern Med 2015; Epub

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General Approach to Treatment of Myositis

PM, DM, ASS, Overlap myositis



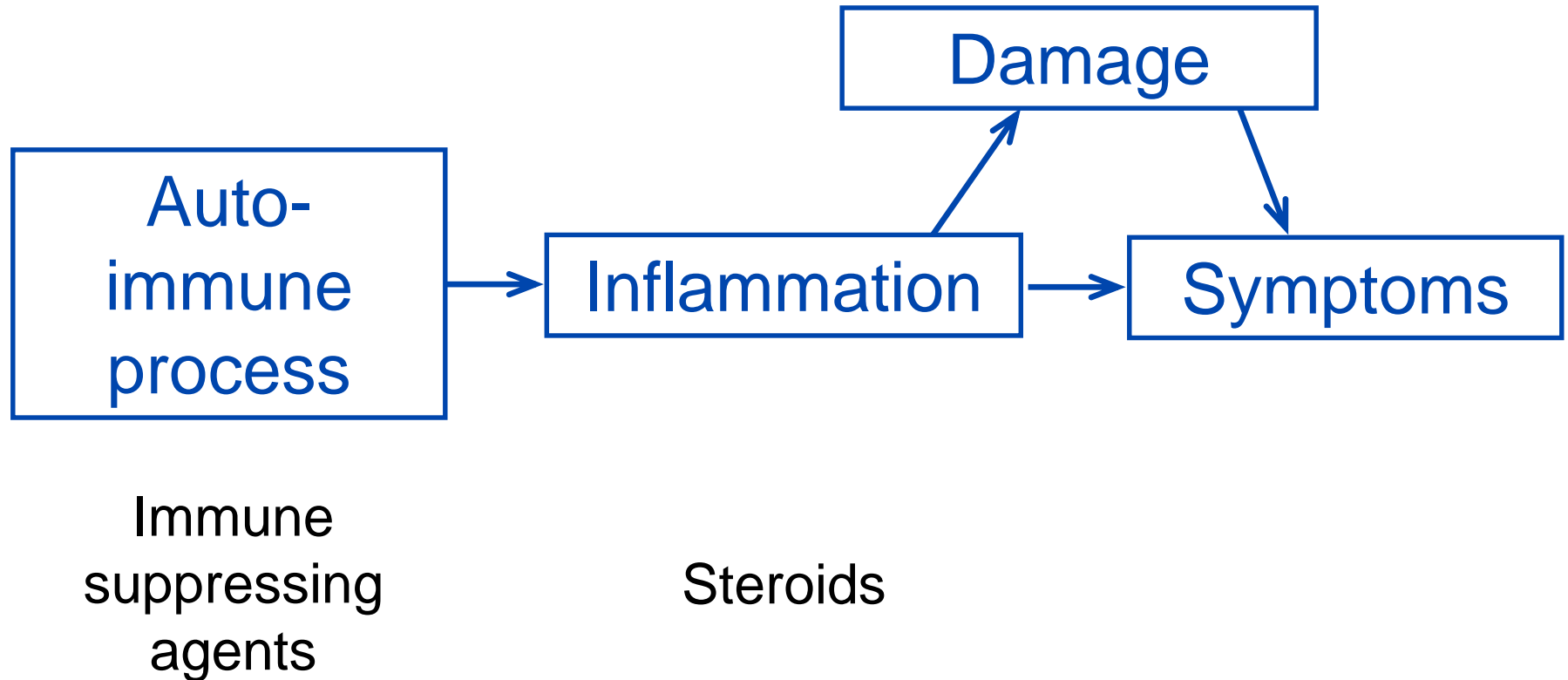
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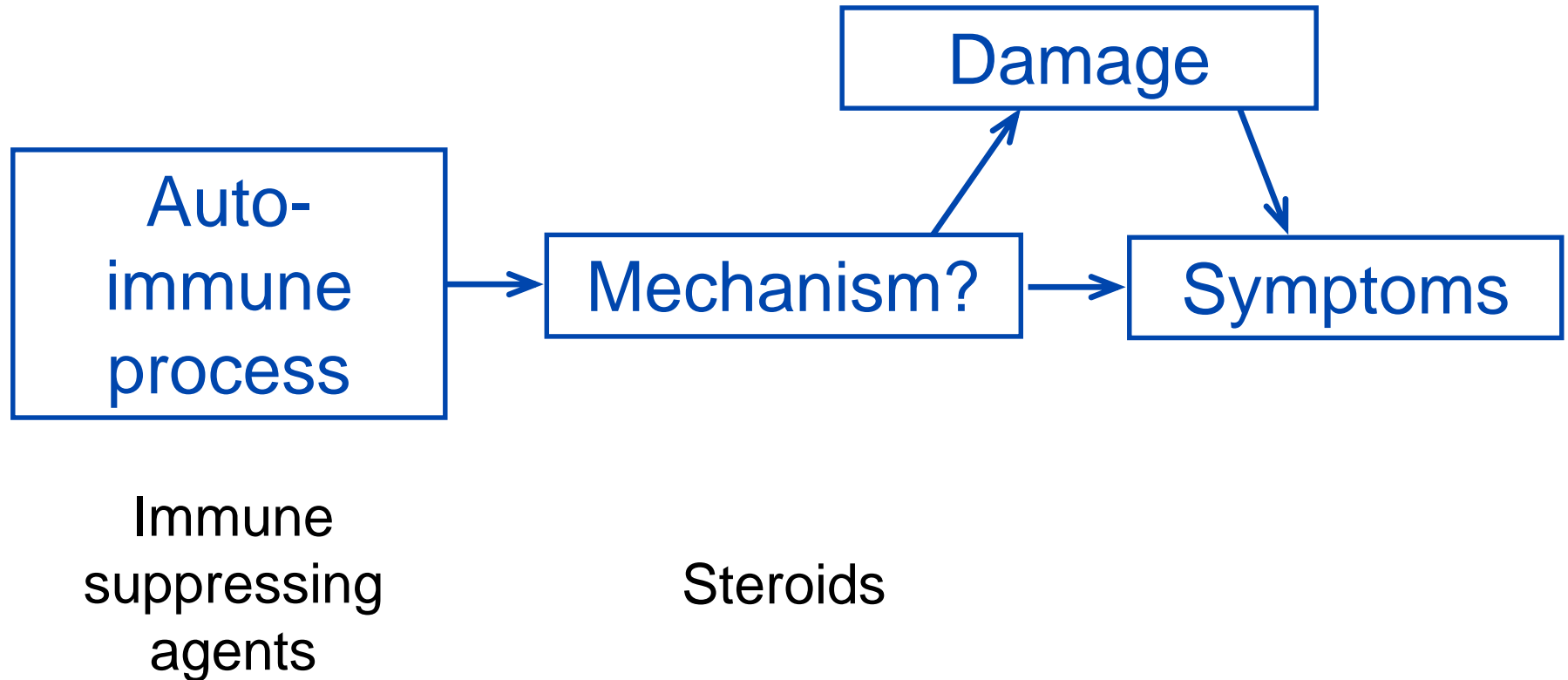
General Approach to Treatment of Myositis

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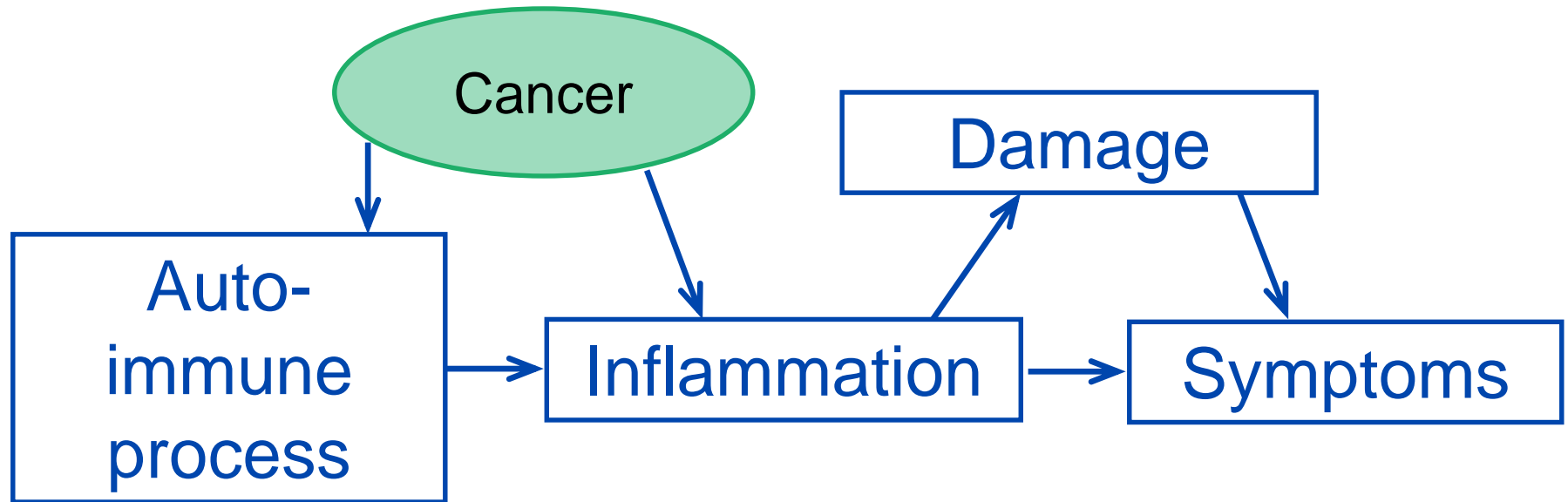
General Approach to Treatment of Myositis

Immune-mediated necrotizing myopathy



General Approach to Treatment of Myositis

Cancer-associated myositis

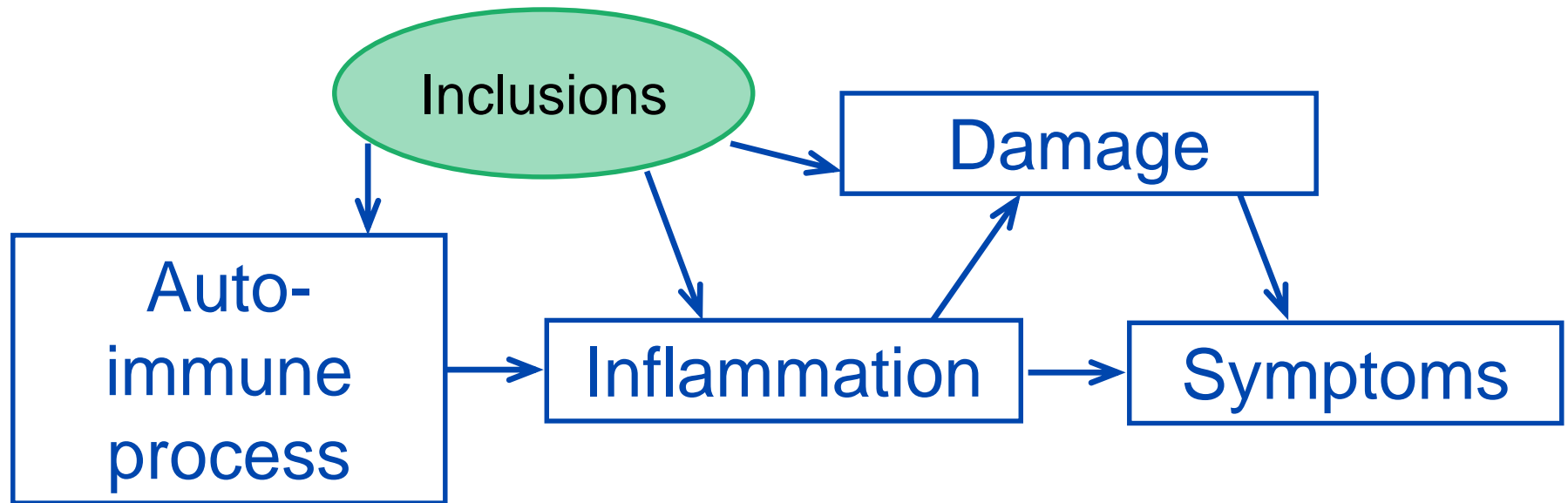


Immune
suppressing
agents?

Steroids?

General Approach to Treatment of Myositis

Inclusion body myositis



Immune
suppressing
agents?

Steroids?

Approach to Management

- Start with high-dose prednisone (e.g., 1 mg/kg/day)
 - Consider IV to begin
 - Consider split daily dose
- Continue about 1 month with slow taper
- Use an immunosuppressive agent
- Attention to side effects of therapy (e.g., osteoporosis, infection)

My Approach to Prednisone

- Begin 1 mg/kg/d (usually max 80 mg/d)
- Continue 1 month
- 2 weeks each:
 - 40 mg/d
 - 30 mg/d
 - 25 mg/d
 - 20 mg/d
 - 17.5 mg/d
 - 15 mg/d
 - 12.5 mg/d
- 10 mg/d and then decide what next

My Approach to Immunosuppressives

First-line agents

- Methotrexate
- Azathioprine (Imuran)
- Mycophenolate mofetil (CellCept)

Second-line agents

- IVIg
- Rituximab (Rituxan)
- Tacrolimus (Prograf)
- Cyclosporine A (Neoral, Sandimmune)
- Leflunomide (Arava)

Severe disease

- Cyclophosphamide (Cytoxan)

Studies

- Abatacept (Orencia)
- Tocilizumab (Actemra)
- Belimumab (Benlysta)

Never used

- ACTHAR gel

Also remember

- Pneumocystis pneumonia prophylaxis when on high dose prednisone
- Influenza, pneumococcal, and other immunizations
- Osteoporosis attention: calcium and vitamin D; bone density
- Mobility and assistive devices; fall prevention
- Dysphagia
- Exercise

I hope to answer some common questions:

- What is myositis?
- What causes myositis?
- What does myositis do to patients?
- How is myositis diagnosed?
- How is myositis treated?

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Questions?