

MYOPATHIC CHANGES

Morphology • injury–repair • diagnostic interpretation

Skeletal muscle pathology

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Learning objectives

- Explain how focal myofiber necrosis initiates macrophage clearance and satellite-cell repair.
- Recognize regeneration, chronic fiber loss, fibrosis, fatty replacement, and abnormal inclusions.
- Distinguish selected myopathic patterns from denervation and identify illustrative etiologies.

The scope of a myopathic pattern

Intrinsic myofiber injury

Segmental necrosis

Regeneration

Fibrosis / fat in chronic injury

Loss of innervation

Motor-unit dropout

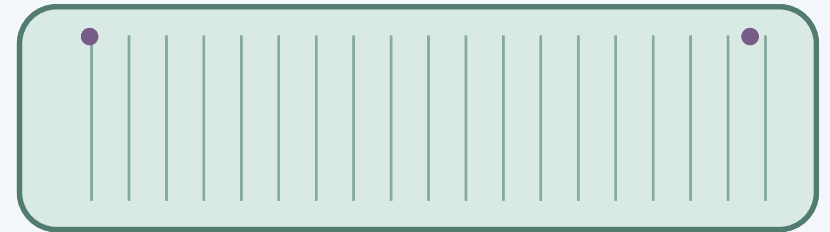
Grouped angular atrophy

Fiber-type grouping

A myofiber is a multinucleated cell

- Myoblast fusion produces elongated multinucleated myotubes and mature myofibers.
- Myofibers contain organized contractile sarcomeres along their length.
- One fiber can undergo damage in only part of its length.

Segment of a multinucleated myofiber



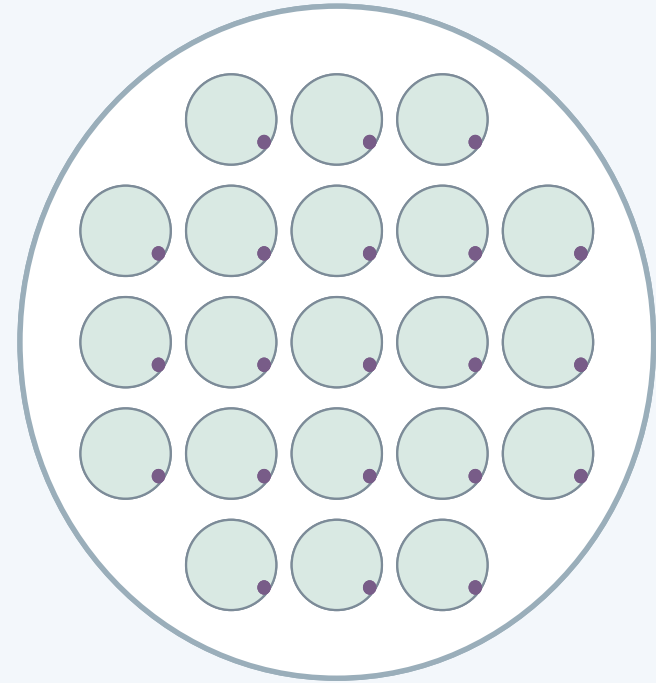
Ordered sarcomeres

Schematic — not a clinical or histologic specimen

Fascicles organize myofibers

- Individual myofibers are grouped in fascicles.
- The endomysium surrounds individual fibers; Connective tissue also separates fascicles.
- This arrangement makes fiber loss, fibrosis, and perifascicular patterns recognizable.

Arrangement within a muscle fascicle



Schematic — not a clinical or histologic specimen

Satellite cells support repair

- Small tissue stem-cell populations reside in adult skeletal muscle.
- After injury, activated satellite cells provide a cellular source for regeneration.
- Regeneration depends on the remaining tissue framework and continued injury burden.

Cellular repair at the myofiber surface

Satellite cell



A reserve for injury-induced regeneration

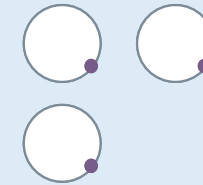
Schematic — not a clinical or histologic specimen

Fiber types serve distinct functions

- Type I fibers: Sustained force, high oxidative capacity, high fatigue resistance.
- Type II fibers: Rapid movement, greater power, greater glycolytic capacity.
- Relative fiber proportions and atrophy patterns carry diagnostic information.

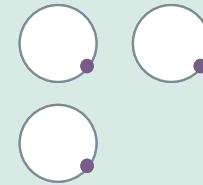
Type I / type II muscle fibers

Type I



Oxidative • sustained
force

Type II



Glycolytic • rapid
force

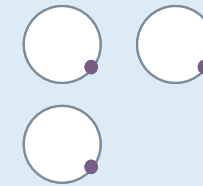
Schematic — not a clinical or histologic specimen

Histochemical fiber typing

- NADH-TR activity is darker in type I fibers and lighter in type II.
- ATPase at pH 9.4 shows the opposite contrast: Type I light, type II dark.
- Stain and assay conditions must be known before interpreting color.

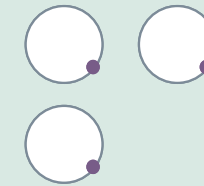
Type I / type II muscle fibers

Type I



Oxidative • sustained
force

Type II



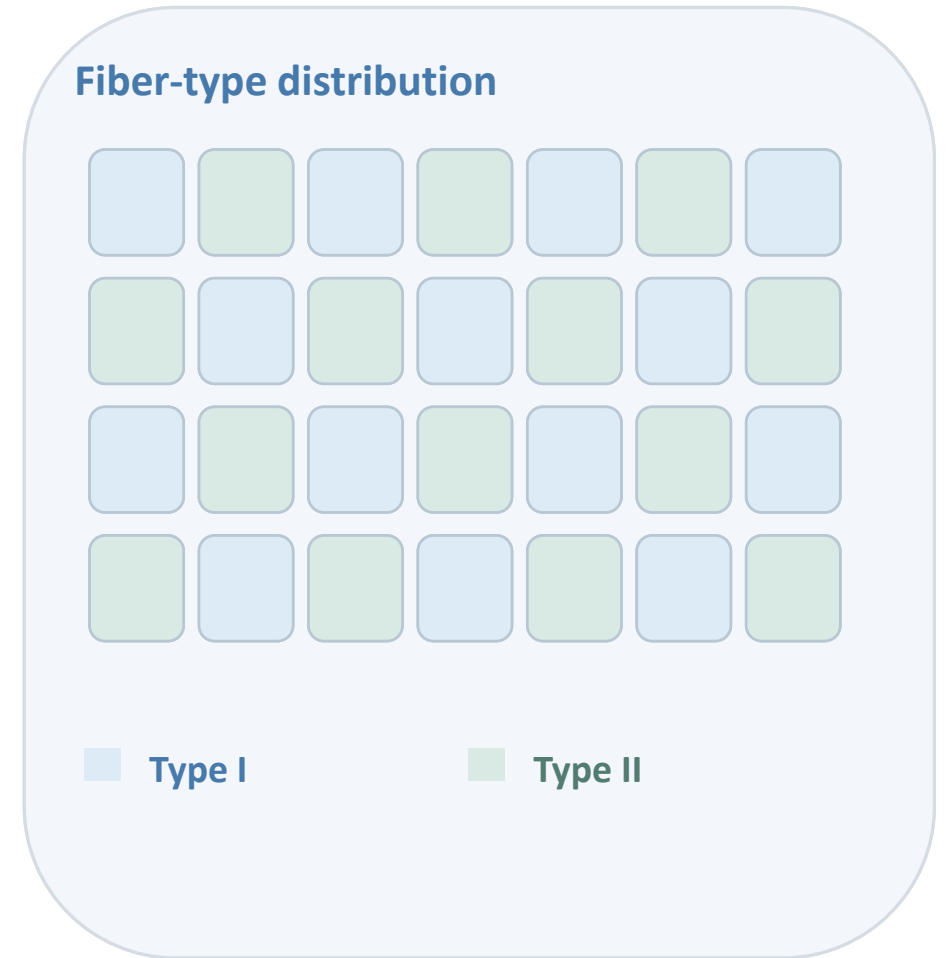
Glycolytic • rapid
force

NADH-TR: I darker | ATPase pH 9.4: II darker

Schematic — not a clinical or histologic specimen

Normal fibers form a checkerboard

- Type I and type II fibers are admixed throughout healthy muscle.
- Opposite-type fibers appear intermingled rather than clustered into large uniform groups.
- Marked fiber-type grouping is instead a clue to previous denervation and reinnervation.

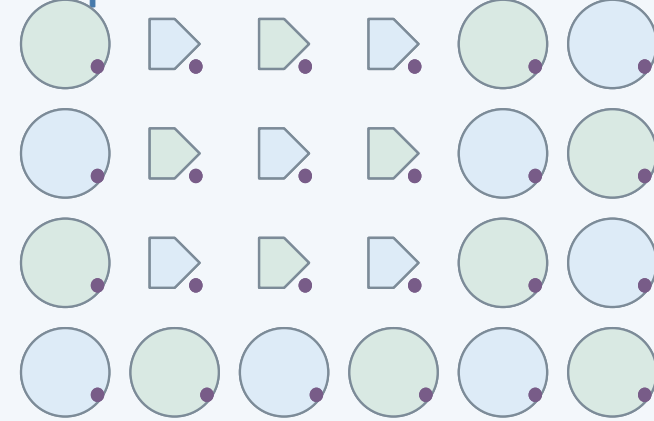


Schematic — not a clinical or histologic specimen

Muscle atrophy is not disease-specific

- Reduced myofiber size occurs after loss of innervation, disuse, aging, cachexia, and myopathy.
- The spatial distribution of small fibers is more informative than atrophy alone.
- Interpret muscle atrophy together with other injury and repair features.

Simplified cross-sectional pattern



Qualitative pattern only; Not a tissue section

Schematic — not a clinical or histologic specimen

Three informative patterns of atrophy

Morphologic finding	Interpretation
Grouped small fibers	Denervation / neurogenic
Perifascicular small fibers	Dermatomyositis
Type II selective atrophy	Corticosteroids / disuse

Myopathic versus neurogenic injury

Myopathic mechanism

Direct injury

Muscle enzyme release

Repair may restore sarcomeres

Neurogenic mechanism

Loss of trophic input

Angulated grouped atrophy

Reinnervation reorganizes fiber type

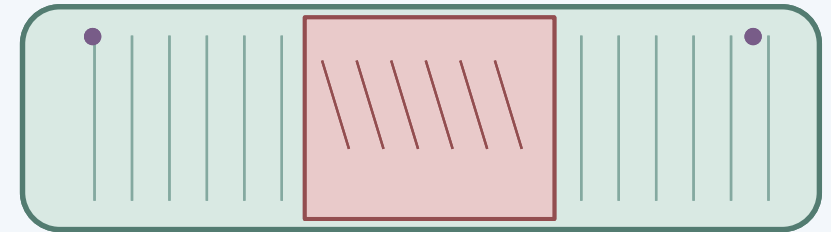
Primary myopathy: The morphologic vocabulary

Morphologic finding	Interpretation
Segmental fiber necrosis	Damage
Basophilia + prominent nuclei	Repair
Endomysial collagen / fat	Chronic remodeling
Vacuoles / aggregates	Selected structural disorders

Segmental necrosis spares part of the fiber

- A myofiber is long and tube-like; Injury can be confined to a short segment.
- Degeneration disrupts sarcomeres and other structures within the injured region.
- Surviving portions of the same fiber can participate in restoration.

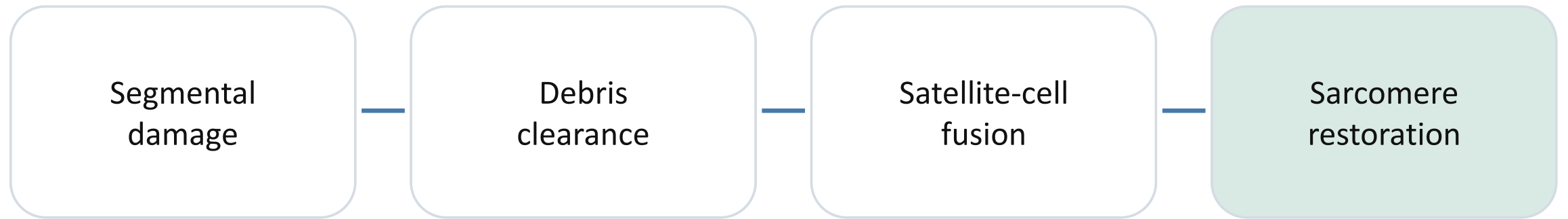
Segment of a multinucleated myofiber



Local segment disrupted; Remainder persists

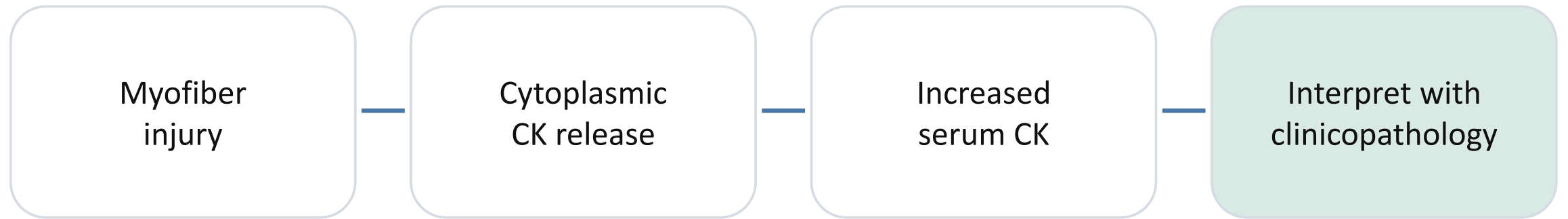
Schematic — not a clinical or histologic specimen

Injury–repair sequence



Conceptual sequence — no numeric timing or quantitative scale

Creatine kinase reflects myofiber damage



Conceptual sequence — no numeric timing or quantitative scale

CK: Injury signal, not a diagnosis

What CK helps establish

Muscle injury is occurring

Supports destructive fiber injury

Can guide further evaluation

What CK cannot establish

Specific immune vs toxic etiology

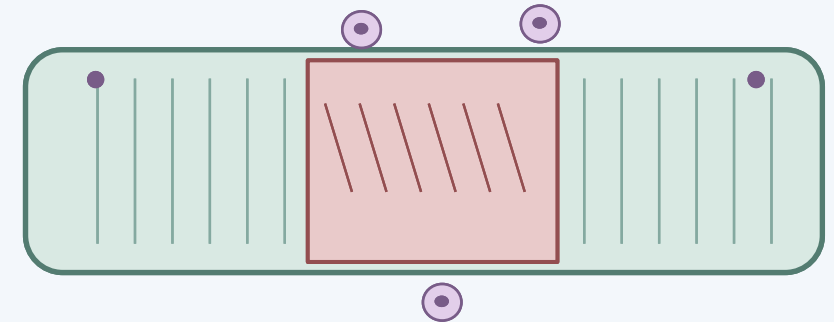
The histologic distribution

The presence of a particular inclusion

Macrophages clear a necrotic segment

- Macrophages engulf damaged sarcomeres and other necrotic fiber contents.
- This removal process is termed myophagocytosis.
- The fiber's connective-tissue context helps orient the repair sequence.

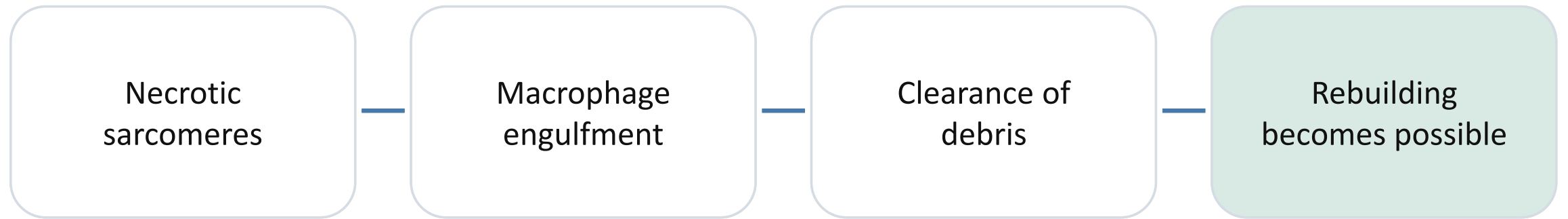
Segment of a multinucleated myofiber



Macrophages remove damaged contractile material

Schematic — not a clinical or histologic specimen

Myophagocytosis precedes regeneration



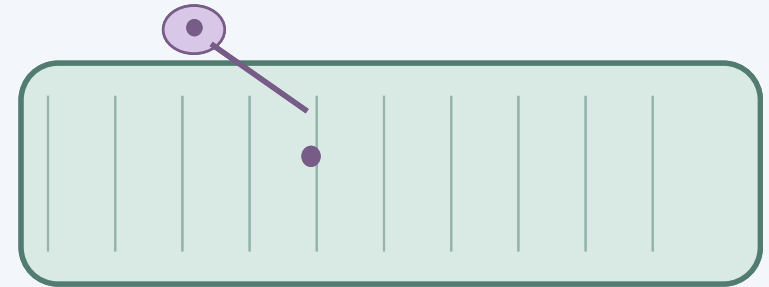
Conceptual sequence — no numeric timing or quantitative scale

Satellite-cell fusion repairs the fiber

- After activation, satellite-cell progeny fuse with damaged myofibers.
- The resulting regenerated portion gains the capacity to produce new sarcomeres.
- Repair is a cellular rebuilding process, not simple scar formation.

Cellular repair at the myofiber surface

Satellite cell



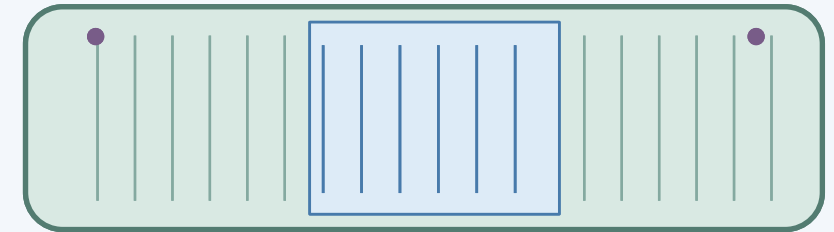
Activation → fusion → repair

Schematic — not a clinical or histologic specimen

New sarcomeres restore contractile continuity

- Replacement of lost contractile elements follows removal of necrotic material.
- In favorable acute injury, the original fiber becomes structurally continuous again.
- Repeated injury may outpace this restorative process.

Segment of a multinucleated myofiber



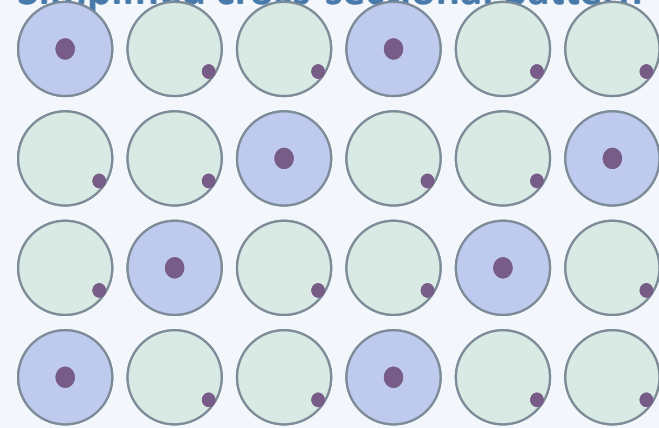
New sarcomeres span the repaired segment

Schematic — not a clinical or histologic specimen

Recognizing a regenerating fiber

- Regenerating myofibers are rich in RNA.
- In hematoxylin and eosin sections, this RNA-rich cytoplasm appears basophilic.
- Regeneration can be recognized alongside degenerating fibers in an active lesion.

Simplified cross-sectional pattern



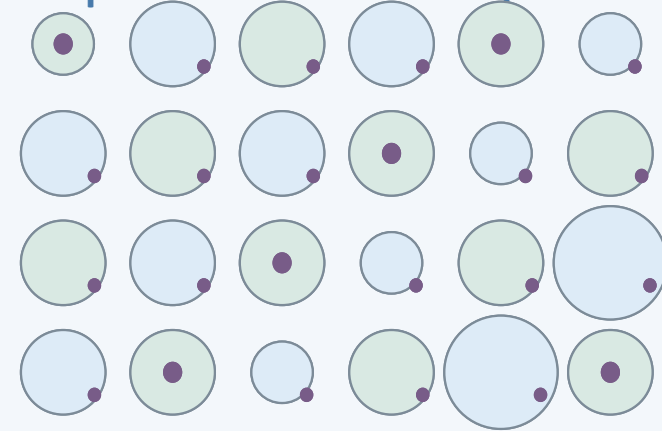
Blue-gray fibers designate RNA-rich regeneration

Schematic — not a clinical or histologic specimen

Regenerating nuclei are conspicuous

- Regenerating fibers contain enlarged nuclei with prominent nucleoli.
- Nuclei may lie at varied positions within the cytoplasm.
- This contrasts with the usual subsarcolemmal placement of mature myofiber nuclei.

Simplified cross-sectional pattern



Qualitative pattern only; Not a tissue section

Schematic — not a clinical or histologic specimen

Basophilia and internal nuclei: Interpretation

Mature myofiber

Relatively peripheral nuclei

Established contractile apparatus

Not strongly basophilic

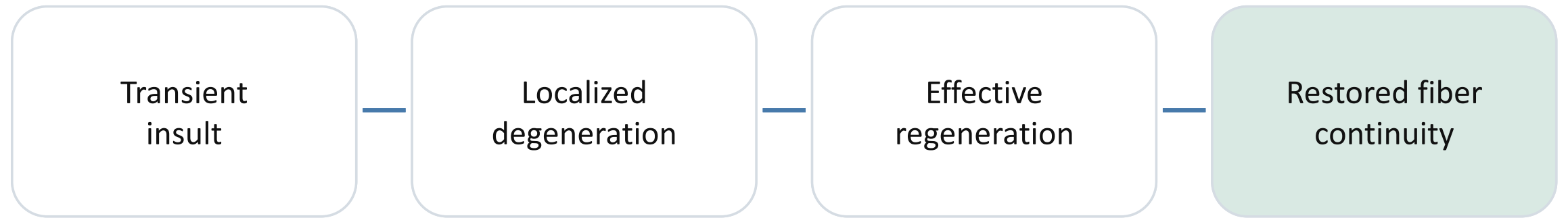
Regenerating myofiber

RNA-rich basophilic cytoplasm

Large nucleolated nuclei

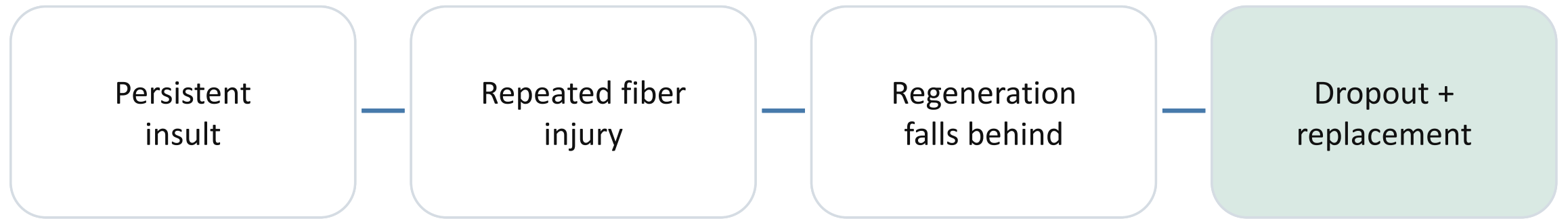
Nuclei may be internal

Acute injury can heal structurally



Conceptual sequence — no numeric timing or quantitative scale

Chronic injury exceeds repair capacity

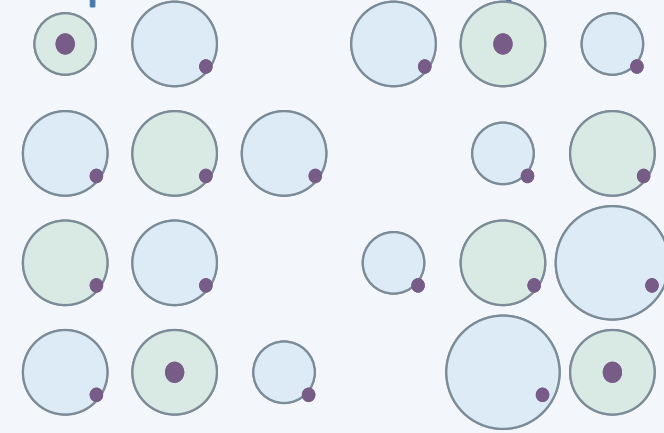


Conceptual sequence — no numeric timing or quantitative scale

Myofiber dropout reduces contractile mass

- Dropout refers to loss of fibers that are not replaced by successful regeneration.
- The resulting deficit contributes to chronic muscle weakness.
- Dropout is often accompanied by increased interstitial connective tissue.

Simplified cross-sectional pattern



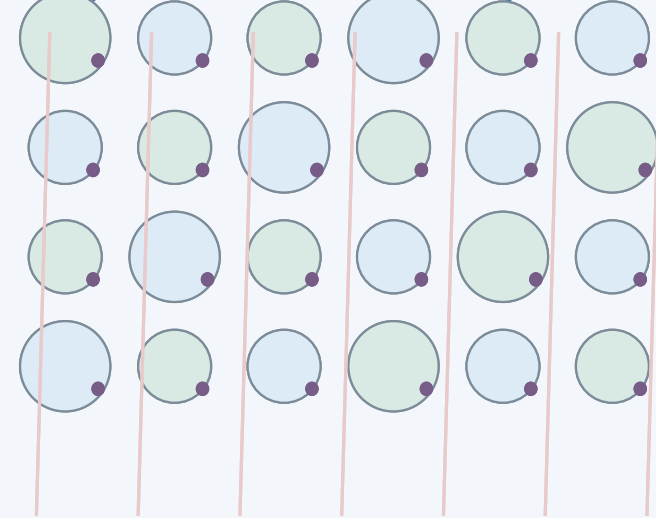
Qualitative pattern only; Not a tissue section

Schematic — not a clinical or histologic specimen

Endomysial fibrosis replaces lost fibers

- Fibrosis is deposition of collagen in the endomysial compartment.
- It is a prominent marker of chronic, incompletely repaired muscle injury.
- Fibrosis separates residual fibers rather than recreating contractile elements.

Simplified cross-sectional pattern



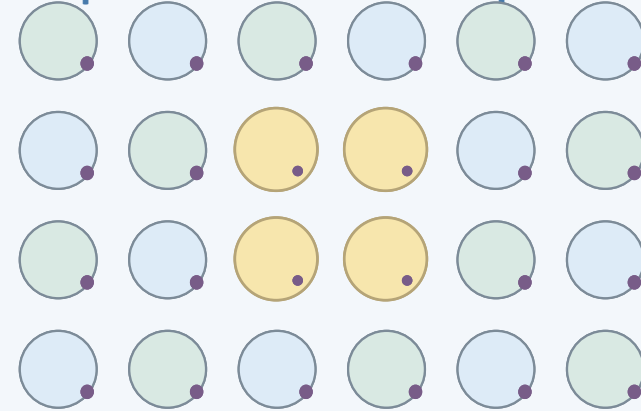
Qualitative pattern only; Not a tissue section

Schematic — not a clinical or histologic specimen

Fatty replacement marks chronic remodeling

- Adipose tissue can occupy regions of lost skeletal muscle.
- Fibrosis and fatty replacement frequently coexist in long-standing disease.
- They reflect tissue remodeling, not active fiber regeneration.

Simplified cross-sectional pattern



Yellow cells represent fatty replacement

Schematic — not a clinical or histologic specimen

A chronic injury trajectory

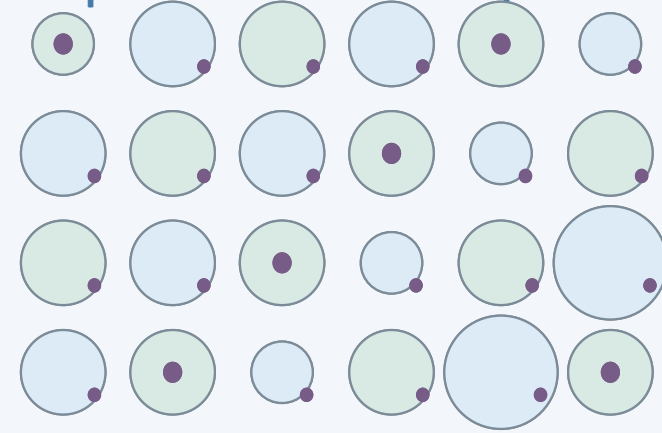


Conceptual sequence — no numeric timing or quantitative scale

Atrophic fibers may coexist with regeneration

- The nature of the primary insult determines whether atrophic fibers are also present.
- A single biopsy may show injury, repair, and chronic remodeling concurrently.
- Do not infer uniform timing for all fibers in a diseased muscle.

Simplified cross-sectional pattern



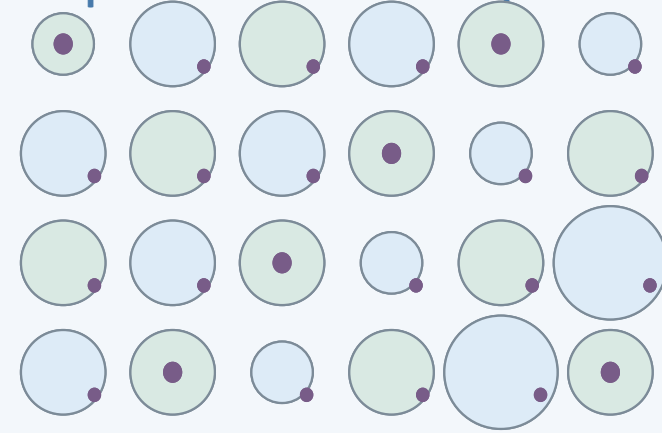
Qualitative pattern only; Not a tissue section

Schematic — not a clinical or histologic specimen

Hypertrophy is not always pathologic

- Physiologic activity can enlarge muscle fibers.
- Some chronic myopathies also feature fiber hypertrophy.
- An enlarged fiber has meaning only in its tissue and clinical context.

Simplified cross-sectional pattern



Qualitative pattern only; Not a tissue section

Schematic — not a clinical or histologic specimen

Chronic myopathy can show compensatory enlargement

Physiologic enlargement

Exercise-linked adaptation

Not sufficient for diagnosis

Evaluate normal surrounding muscle

Chronic myopathy

May contain enlarged survivors

Can coexist with fiber dropout

Interpret with necrosis and repair

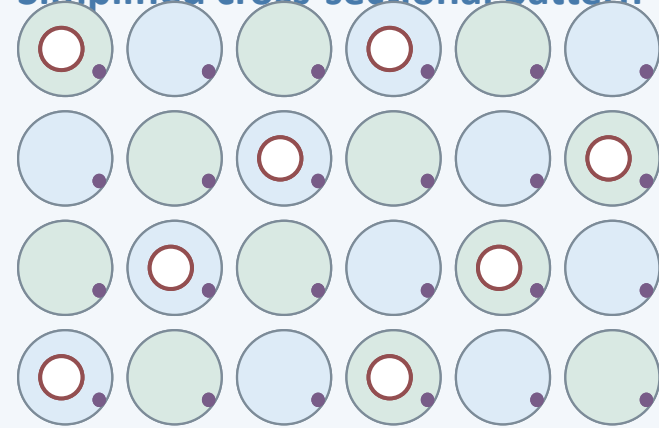
Inclusions point toward specific mechanisms

Morphologic finding	Interpretation
Vacuolar change	Lysosomal / inclusion body examples
Protein aggregates	Sporadic inclusion body myositis
Clustered organelles	Specific primary myopathies

Vacuoles are a structural finding

- A vacuole appears as an altered or empty-appearing region within myofiber cytoplasm.
- Certain drug-associated and inclusion body myopathies produce vacuolar changes.
- Vacuoles require context: Different pathogenic pathways can yield similar spaces.

Simplified cross-sectional pattern



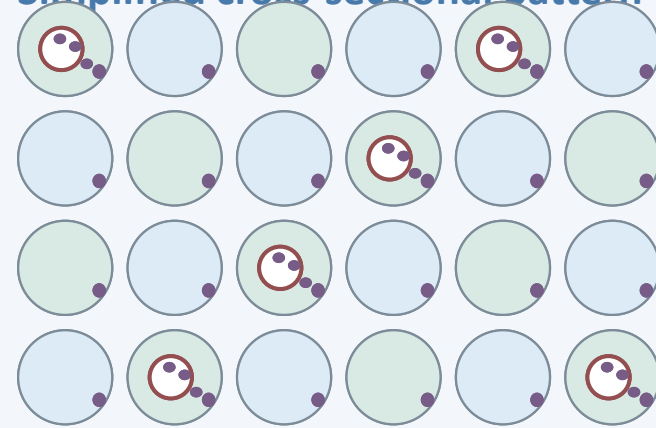
Qualitative pattern only; Not a tissue section

Schematic — not a clinical or histologic specimen

Protein aggregates change the differential

- Some myopathies accumulate abnormal cytoplasmic proteins.
- Inclusion body myositis combines rimmed vacuoles with abnormal protein aggregates.
- The source describes β -amyloid, TDP-43, and ubiquitin among these aggregates.

Simplified cross-sectional pattern



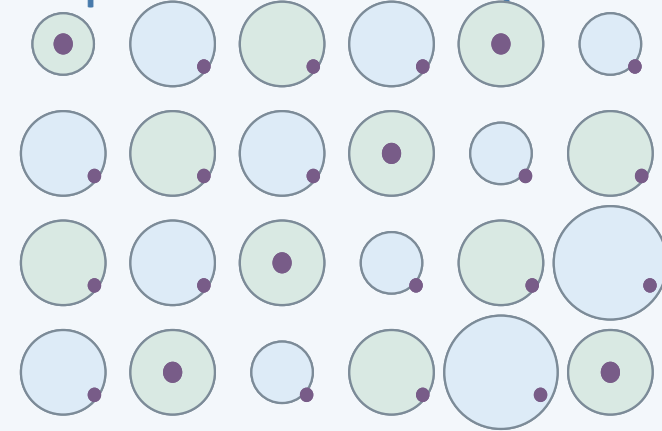
Qualitative pattern only; Not a tissue section

Schematic — not a clinical or histologic specimen

Clustered organelles can be pathologic

- Abnormal distributions of cellular organelles are an inclusion category.
- Mitochondrial and lysosomal disorders provide mechanistic examples.
- The precise ultrastructural lesion matters more than merely noting an inclusion.

Simplified cross-sectional pattern



Qualitative pattern only; Not a tissue section

Schematic — not a clinical or histologic specimen

Do not equate every vacuole with necrosis

Inclusion or vacuolar pattern

Vacuolated cytoplasm

Storage / lysosomal pathway clues

May not indicate active necrosis

Destructive injury pattern

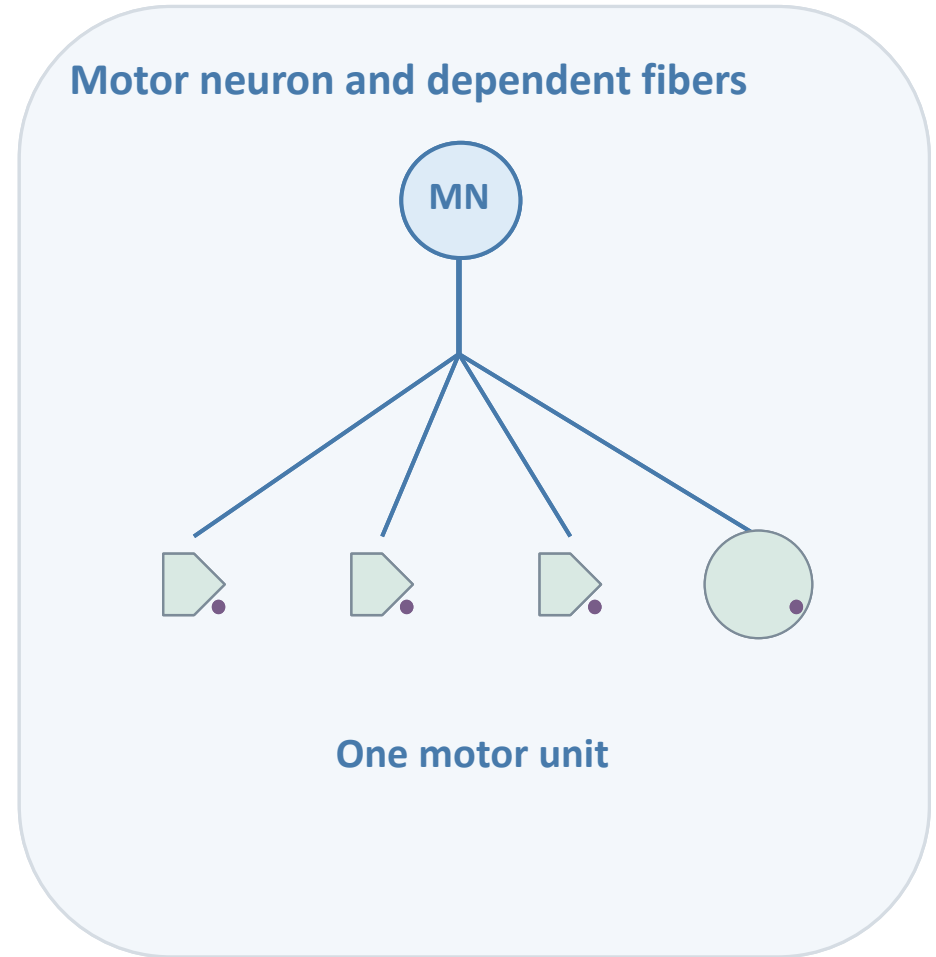
Segmental degeneration

Macrophage myophagocytosis

Can raise serum CK

Neurogenic atrophy starts with denervation

- Loss of a motor axon deprives its fibers of trophic input.
- Affected fibers become smaller and often angulated.
- Groups of similarly affected fibers can arise because motor units are lost together.

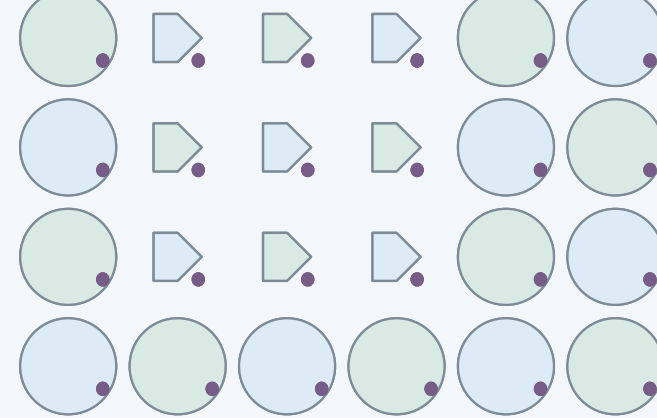


Schematic — not a clinical or histologic specimen

Grouped angulated fibers favor denervation

- Clustered small, flattened, angulated fibers are a classic neurogenic pattern.
- Group atrophy differs from isolated or scattered fiber shrinkage.
- This comparison prevents an overdiagnosis of primary myopathy.

Simplified cross-sectional pattern



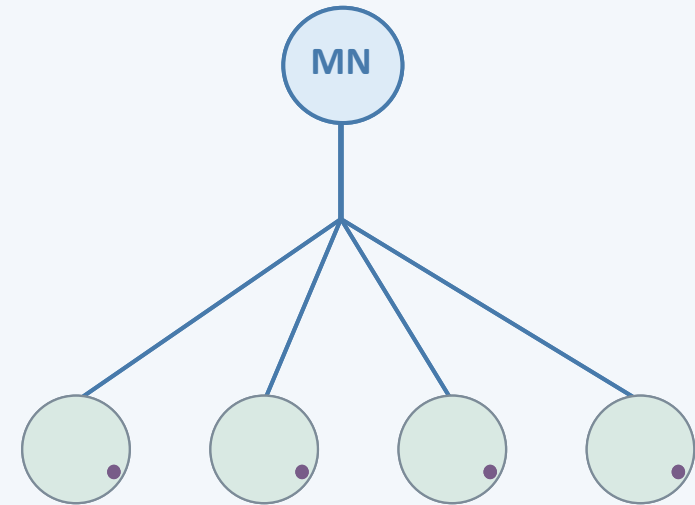
Qualitative pattern only; Not a tissue section

Schematic — not a clinical or histologic specimen

Reinnervation reorganizes motor units

- Surviving axons may capture formerly denervated myofibers.
- Motor-unit size increases and reinnervated fibers may adopt a different fiber type.
- The resulting distribution becomes less checkerboard-like.

Motor neuron and dependent fibers

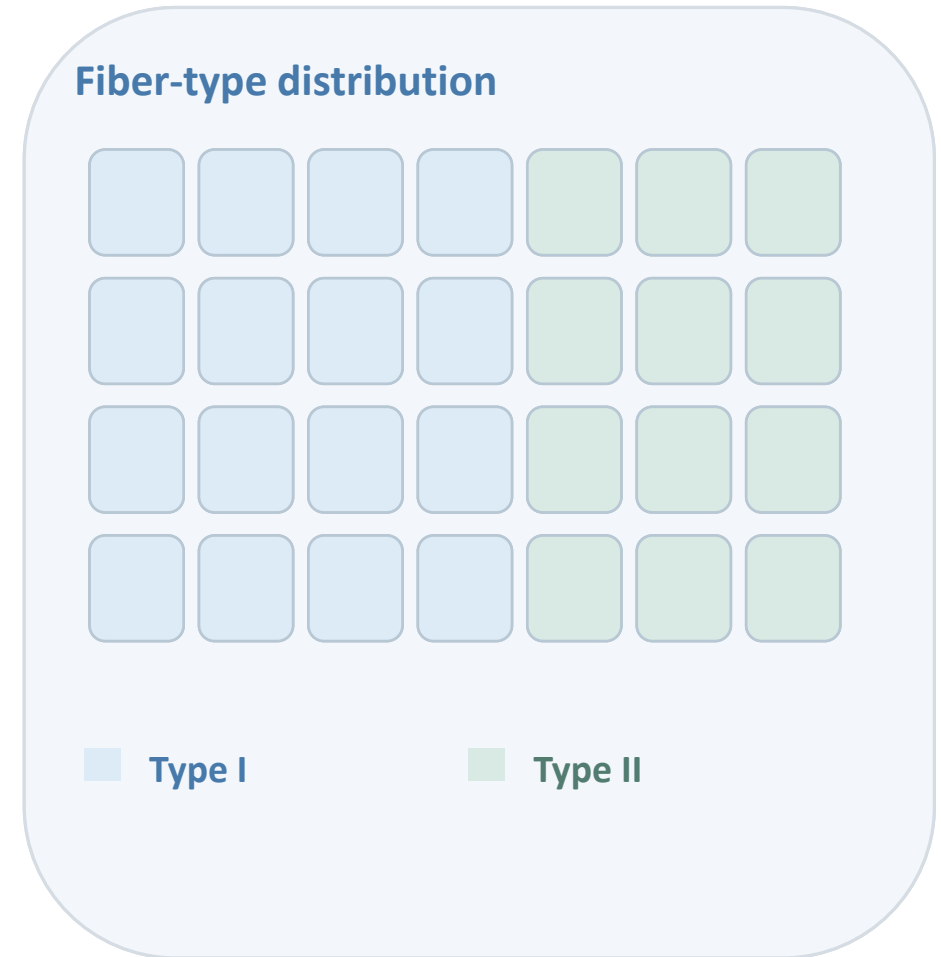


One motor unit

Schematic — not a clinical or histologic specimen

Fiber-type grouping records reinnervation

- One motor neuron innervates fibers of a single functional type.
- Reinnervation can produce large adjacent regions of one fiber type.
- Ongoing denervation of the expanded unit may produce subsequent grouped atrophy.



Schematic — not a clinical or histologic specimen

A paired comparison of biopsy patterns

Myopathic pattern

Necrosis and regeneration

Hypertrophy / atrophy

Some distinctive inclusions

Neurogenic pattern

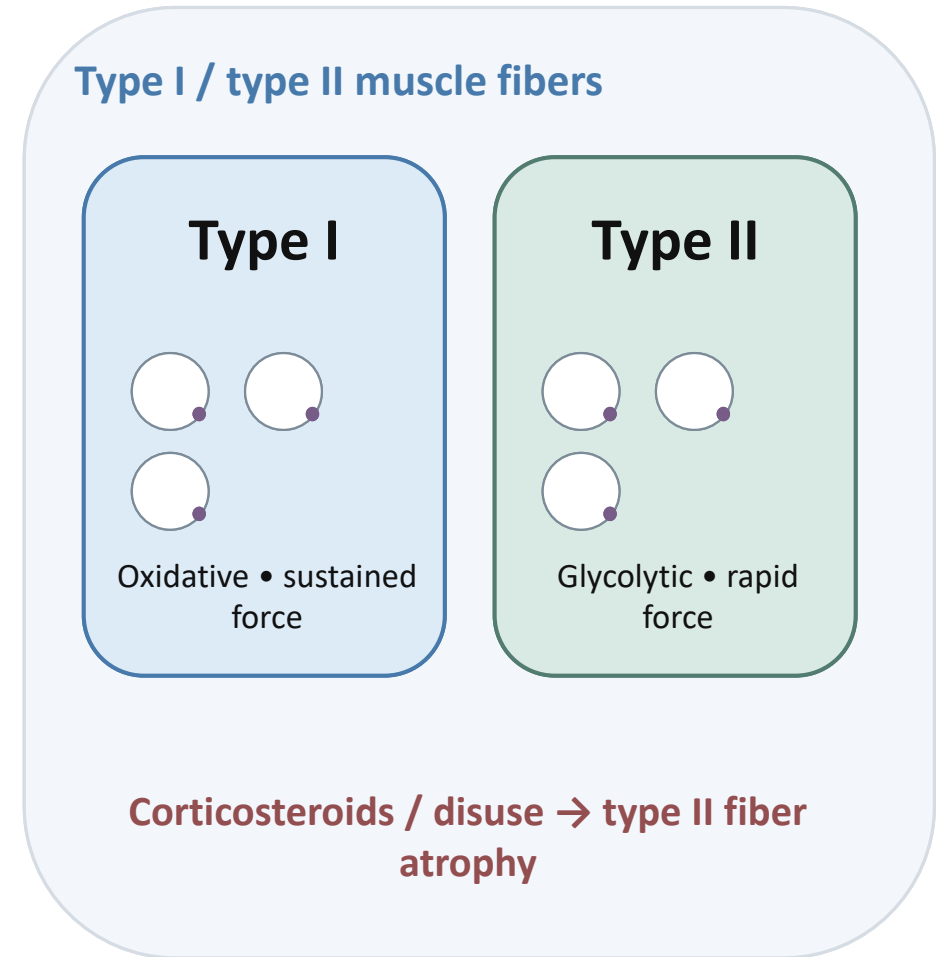
Grouped angular atrophy

Reinnervation / type grouping

Motor-unit dependence

Type II atrophy illustrates another mechanism

- Prolonged corticosteroid treatment can preferentially reduce type II fiber size.
- Disuse may yield a similar selective pattern.
- Selective atrophy differs from the segmental necrosis–regeneration sequence.

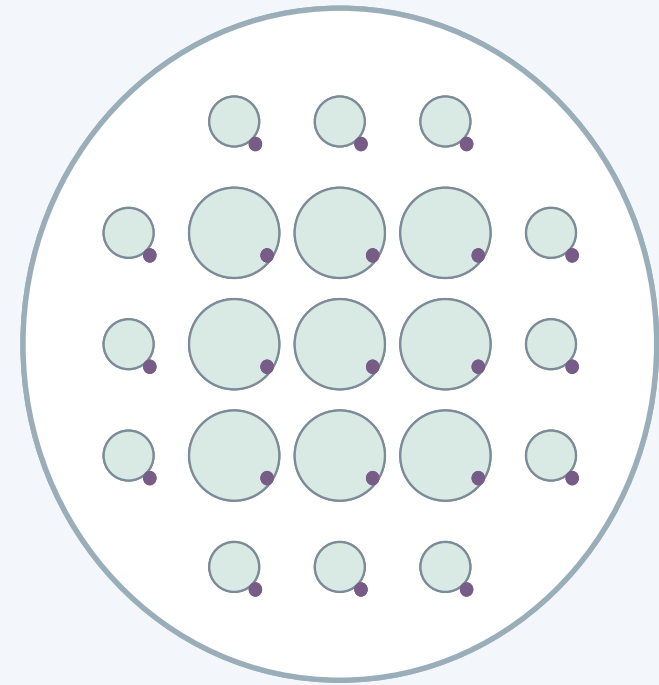


Schematic — not a clinical or histologic specimen

Distribution can suggest dermatomyositis

- Perifascicular atrophy refers to preferentially small fibers at fascicle margins.
- The pattern is a recognized lesion in dermatomyositis.
- It is not present in every case and should be integrated with other findings.

Arrangement within a muscle fascicle



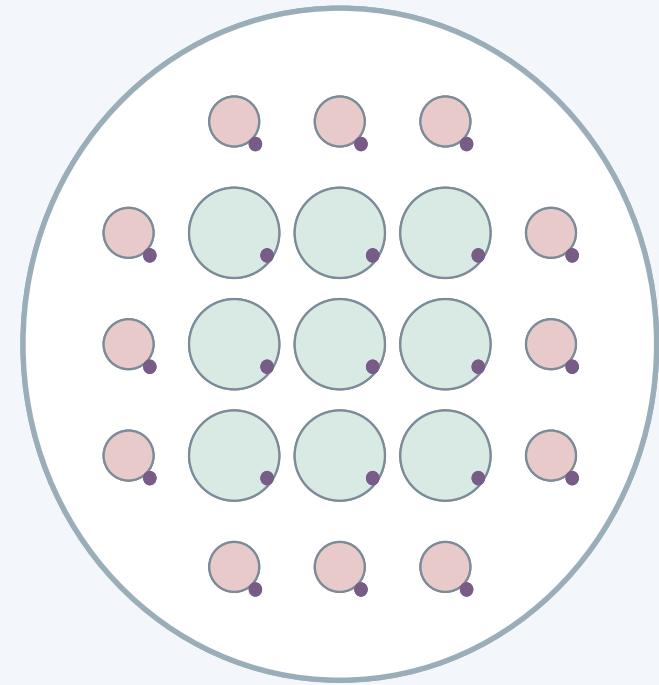
Small fibers near fascicle edge

Schematic — not a clinical or histologic specimen

Perifascicular injury: Why location matters

- In dermatomyositis, vascular and interferon-associated abnormalities accompany muscle injury.
- Perifascicular atrophy highlights the arrangement of damage within the fascicle.
- The source emphasizes that mechanisms remain incompletely established.

Arrangement within a muscle fascicle



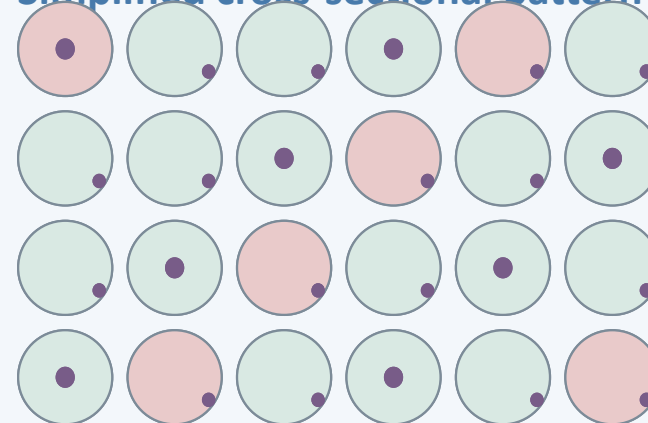
Small fibers near fascicle edge

Schematic — not a clinical or histologic specimen

Necrosis may dominate despite sparse inflammation

- Immune-mediated necrotizing myopathy features extensive fiber necrosis and regeneration.
- Inflammatory infiltrates are often relatively scant.
- The presence of myonecrosis does not require dense inflammation on the biopsy.

Simplified cross-sectional pattern



Pink fibers designate schematic injury

Schematic — not a clinical or histologic specimen

Necrotizing myopathy: Clinical integration

Necrotizing pattern

Prominent myofiber injury

Relatively scant inflammation

Immune or toxic possibilities

Disease context

Anti-SRP / anti-HMGCR antibodies

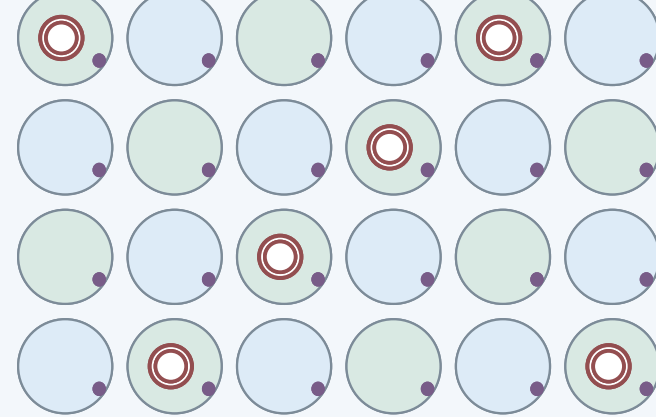
Progressive weakness

Serum CK and drug history

Rimmed vacuoles in inclusion body myositis

- Rimmed vacuoles are characteristic abnormal cytoplasmic inclusions.
- Established sporadic cases may also show endomysial T-cell inflammation.
- Fibrosis and fatty replacement are frequent chronic features.

Simplified cross-sectional pattern



Qualitative pattern only; Not a tissue section

Schematic — not a clinical or histologic specimen

Inclusion body myositis spans two patterns

Inflammatory elements

Endomysial CD8-rich cells

Invasion of fibers

MHC class I upregulation

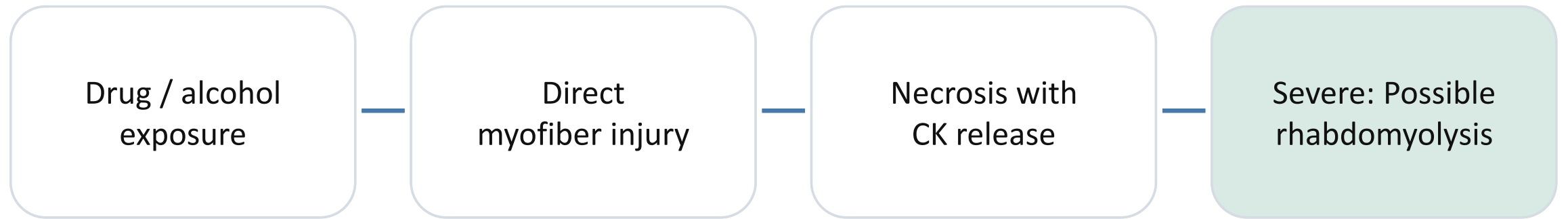
Degenerative elements

Rimmed vacuoles

Protein aggregates

Fibrosis / fatty replacement

Direct toxic damage can cause myonecrosis



Conceptual sequence — no numeric timing or quantitative scale

Statin injury: Distinguish two processes

Direct toxicity

Acute necrotic injury

Exposure or dose context

May improve after withdrawal

Immune-mediated myopathy

Necrosis despite sparse inflammation

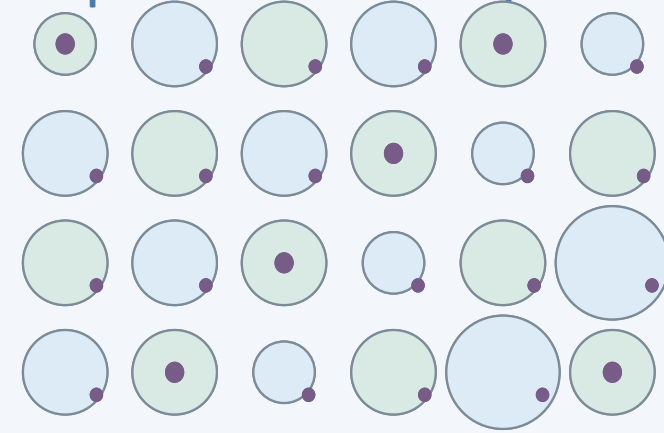
Anti-HMGCR can be present

Requires integrated assessment

Lysosomal interference produces vacuolar change

- Hydroxychloroquine and chloroquine can cause an insidious vacuolar myopathy.
- Type I fibers may be predominantly affected.
- Ultrastructural whorled lamellar membrane aggregates help characterize the lesion.

Simplified cross-sectional pattern



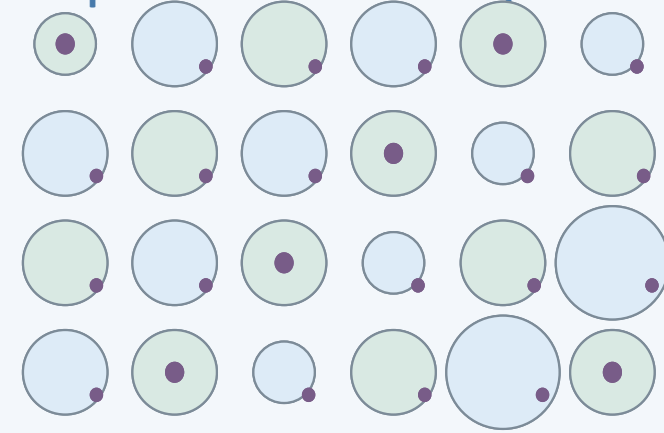
Qualitative pattern only; Not a tissue section

Schematic — not a clinical or histologic specimen

Mitochondrial injury is another route to myopathy

- Zidovudine is cited as a drug capable of producing acquired mitochondrial myopathy.
- Mitochondrial disturbance is mechanistically distinct from denervation.
- Structural clues must be matched to exposure history.

Simplified cross-sectional pattern



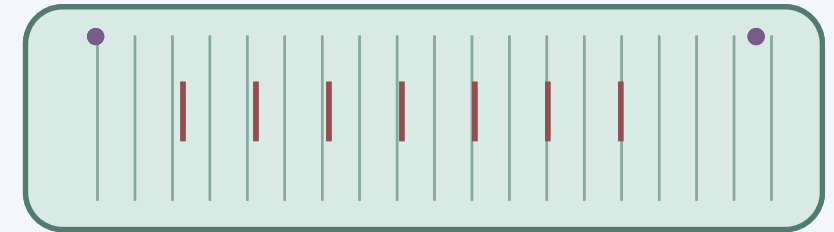
Qualitative pattern only; Not a tissue section

Schematic — not a clinical or histologic specimen

Critical illness myopathy affects the sarcomere

- Critical illness myopathy may feature selective loss of myosin thick filaments.
- This is termed myosin-deficient myopathy in the source.
- The resulting weakness can complicate recovery from mechanical ventilation.

Segment of a multinucleated myofiber



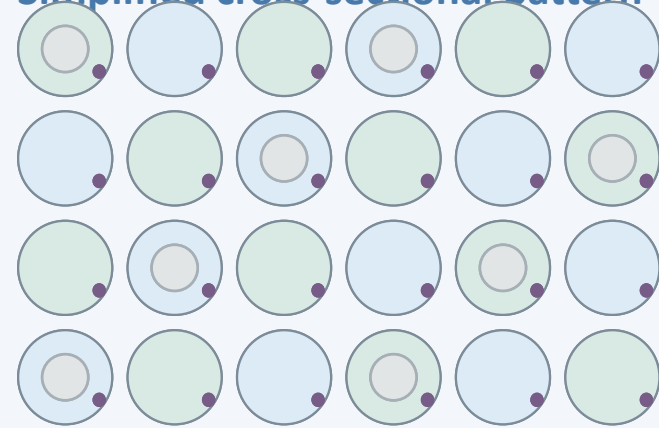
Disrupted thick-filament component

Schematic — not a clinical or histologic specimen

Congenital core myopathy: Disrupted architecture

- Central core disease features defined areas with disrupted sarcomeric arrangement.
- These core regions contain fewer mitochondria.
- The pattern contrasts with nonspecific segmental necrosis and regeneration.

Simplified cross-sectional pattern



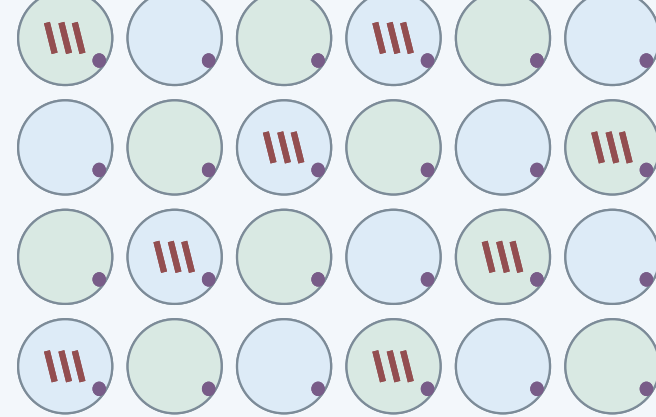
Qualitative pattern only; Not a tissue section

Schematic — not a clinical or histologic specimen

Nemaline rods are structural inclusions

- Nemaline myopathy produces spindle-shaped rods derived from Z-band material.
- The source notes prominence in type I fibers.
- Modified Gömöri trichrome or electron microscopy helps visualize the rods.

Simplified cross-sectional pattern



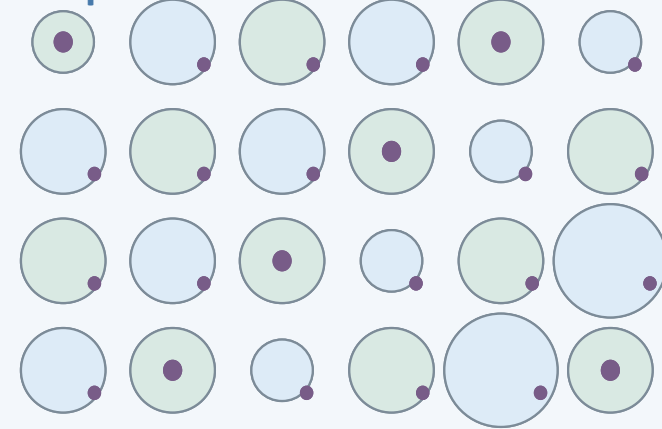
Qualitative pattern only; Not a tissue section

Schematic — not a clinical or histologic specimen

Central nuclei have different interpretations

- Large nuclei with prominent nucleoli can indicate regeneration.
- Centronuclear myopathies show nuclei persistently near the geometric center of fibers.
- The nuclear finding must be interpreted with age, morphology, and context.

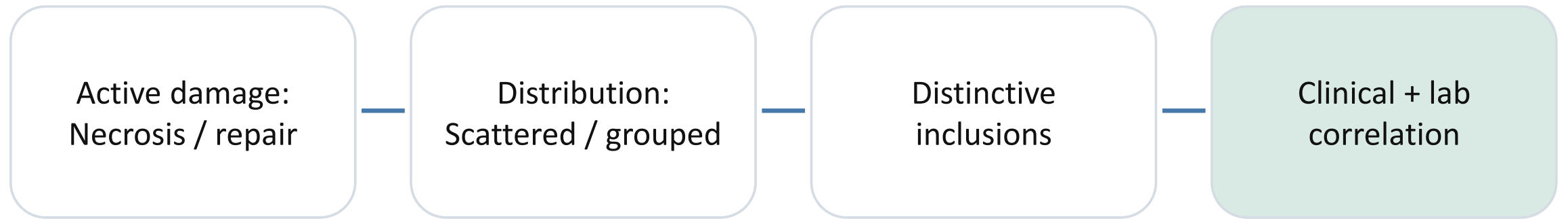
Simplified cross-sectional pattern



Qualitative pattern only; Not a tissue section

Schematic — not a clinical or histologic specimen

A diagnostic pattern-first approach



Conceptual sequence — no numeric timing or quantitative scale

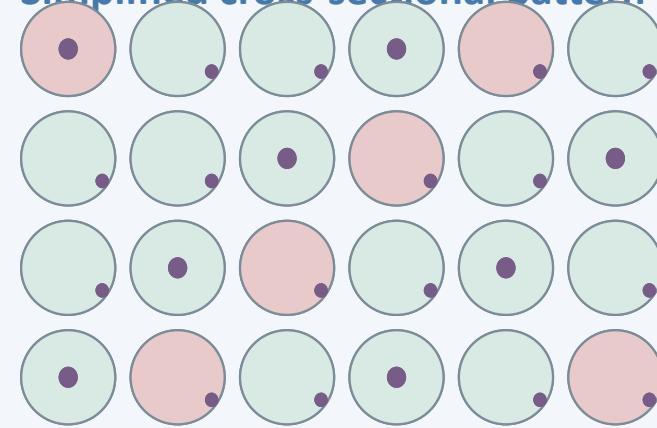
Biopsy patterns should be interpreted together

Morphologic finding	Interpretation
CK ↑	Damage signal; not subtype
Fiber distribution	Neurogenic vs myopathic clues
Necrosis + regeneration	Active injury–repair
Inclusions + remodeling	Subtyping and chronicity

Teaching case: Elevated CK and necrotic fibers

- Hypothetical patient with progressive weakness and increased CK.
- Biopsy: Numerous necrotic and regenerating fibers but few inflammatory cells.
- Question: Which source-described inflammatory-myopathy category warrants consideration?

Simplified cross-sectional pattern

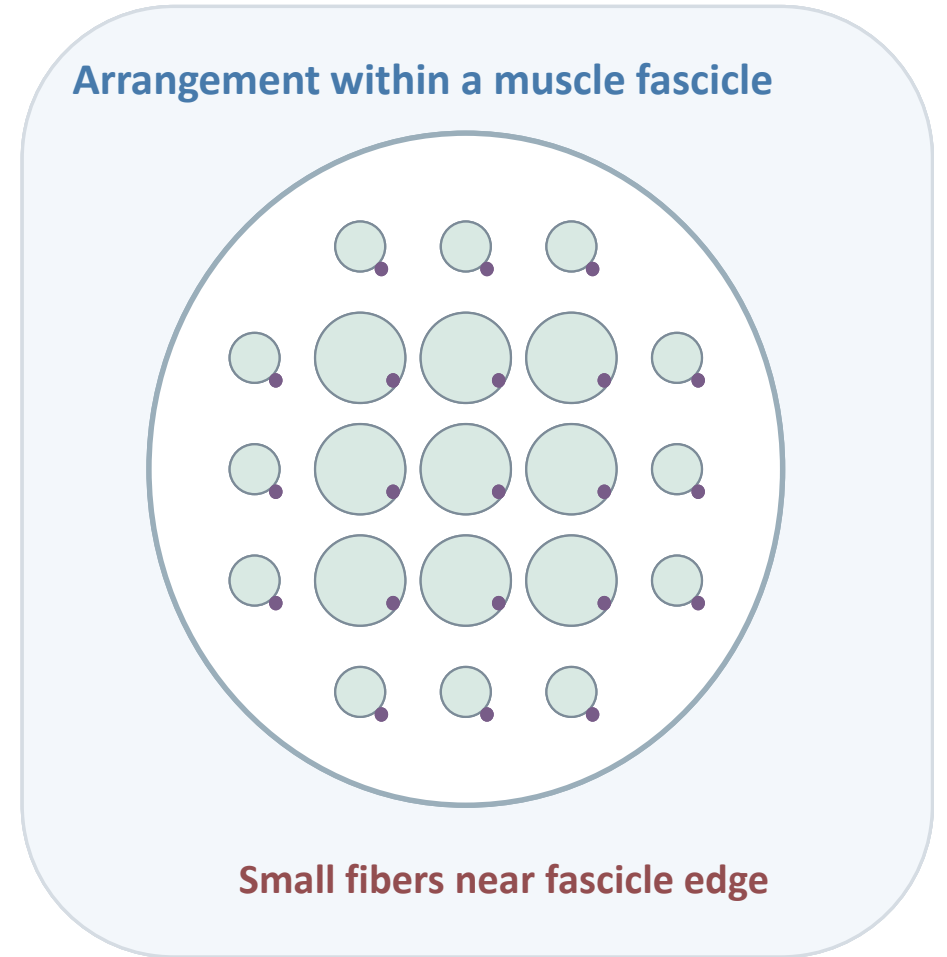


Pink fibers designate schematic injury

Schematic — not a clinical or histologic specimen

Teaching case: Small fibers at fascicle edge

- Hypothetical patient with proximal weakness and a cutaneous eruption.
- Biopsy schematic: Peripheral fascicle fibers are selectively small.
- Question: Which spatial atrophy pattern and disease association are illustrated?

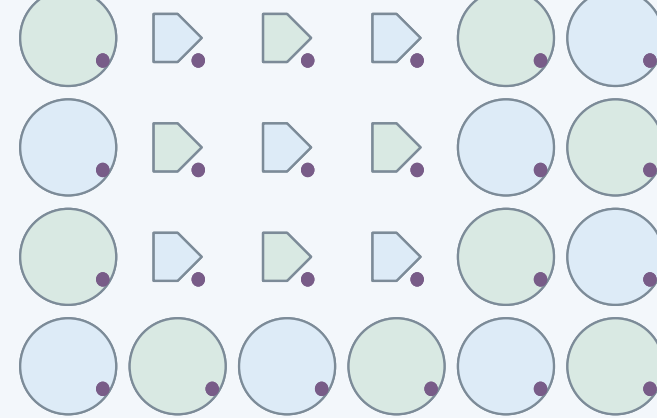


Schematic — not a clinical or histologic specimen

Teaching case: Angulated fiber clusters

- Hypothetical patient with progressive weakness and a peripheral neuropathic syndrome.
- Biopsy schematic: Clusters of angulated atrophic myofibers.
- Question: Does this favor primary myofiber degeneration or loss of innervation?

Simplified cross-sectional pattern



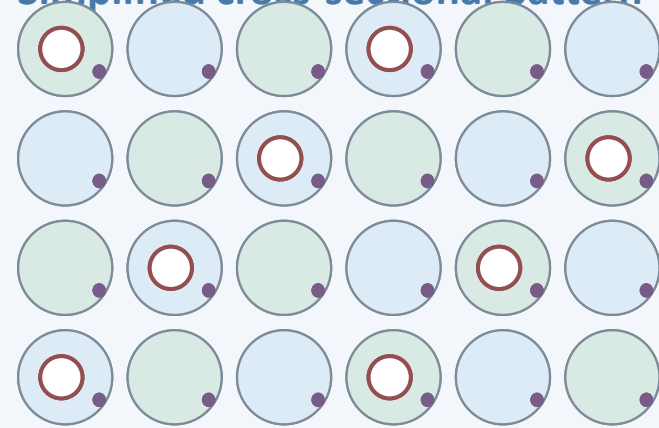
Qualitative pattern only; Not a tissue section

Schematic — not a clinical or histologic specimen

Teaching case: Vacuoles in a treated patient

- Hypothetical patient receiving long-term hydroxychloroquine.
- Muscle biopsy shows conspicuous vacuoles and unusual lysosomal structures.
- Question: What exposure-related mechanism should be evaluated?

Simplified cross-sectional pattern



Qualitative pattern only; Not a tissue section

Schematic — not a clinical or histologic specimen

What the pathology report must communicate

Morphologic finding	Interpretation
Activity	Necrosis / myophagocytosis / regeneration
Chronicity	Dropout / fibrosis / adipose tissue
Topography	Grouped / perifascicular / selective
Specificity	Vacuoles, aggregates, clinical correlation

Integrated summary

- Direct myofiber injury causes segmental degeneration with CK release and macrophage clearance.
- Satellite-cell fusion and sarcomere rebuilding drive regeneration; Chronic injury can end in fibrosis and fat.
- Distribution and inclusion patterns discriminate among etiologies and neurogenic mimics.

Primary reading

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- Chapter 27: Diseases of Skeletal Muscle; neurogenic and myopathic changes, with adjoining disease examples.
- All diagnostic illustrations in this lecture are native editable schematics, not photographs of human biopsies.