BIOCH 755: Biochemistry I Fall 2015

7.2 Muscle Proteins

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7.2 Muscle Contraction

- **Key Concepts 7.2**
  - Myosin is a motor protein that undergoes conformational changes as it hydrolyzes ATP.
  - The sliding filament model of muscle contraction describes the movement of thick filaments relative to thin filaments.
  - The globular protein actin can form structures such as microfilaments and the thin filaments of muscle.

Skeletal Muscle Organization

- Muscle fibers: long multi-nucleated cells; run the length of muscle
- Myofibrils: bundles of alternating thick and thin filaments

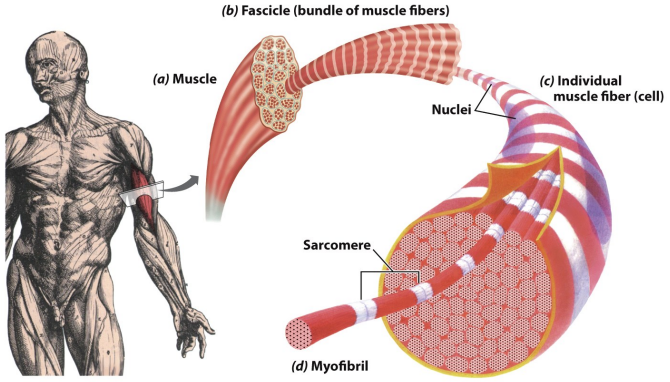


Figure 7-22

Myofibrils: Interdigitated Thick and Thin Filaments

- Repeating units of "sacromeres"
- Bundled by Z and M disks
- A band: thick filaments of ~150 Å in diameter
- I band: thin filament of ~70 Å in diameter

- Contracting muscle: up to 1/3 shorter while becoming thicker (volume constant)
- Simultaneous reduction of H zone and I band (while A band remains constant)

=> "Sliding Filament Model"

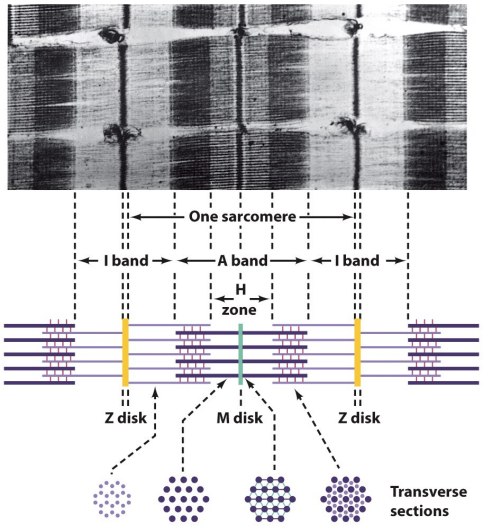


Figure 7-23

Sliding Filament Model

- First observed and proposed by Hugh Huxley in 1954
- Explains ~1/3 maximal contraction

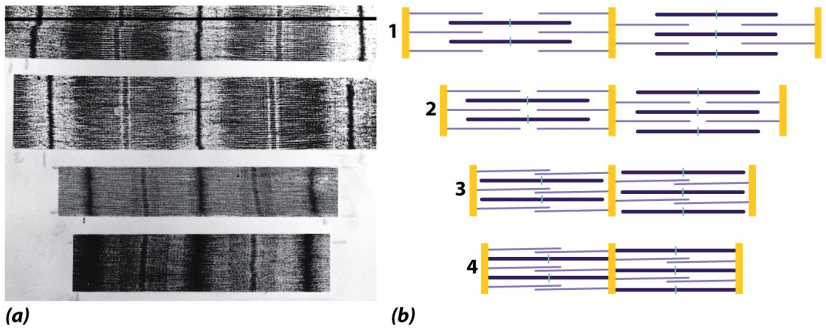


Figure 7-24

Myosin: the Motor

- Myosin: main component of thick filament
  - 6 polypeptide chains
  - 2x 220KD heavy chain
  - 2 pairs of light chains: essential and regulatory light chains (ELC and RLC), ~ 15-22 KD
  - C-terminal coiled coil
  - N-terminal: ATPase activity

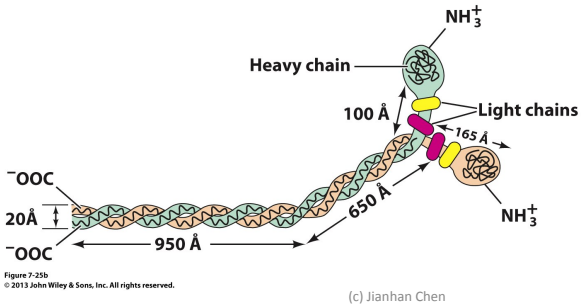


Figure 7-25b

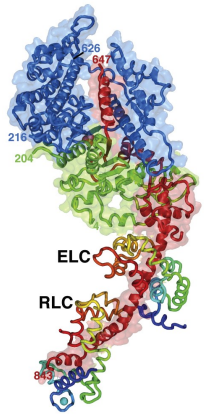


Figure 7-25a

Myosin: the Motor

- Myosin: main component of thick filament
  - ~500 myosin heads per thick filament (~250 myosin dimers)

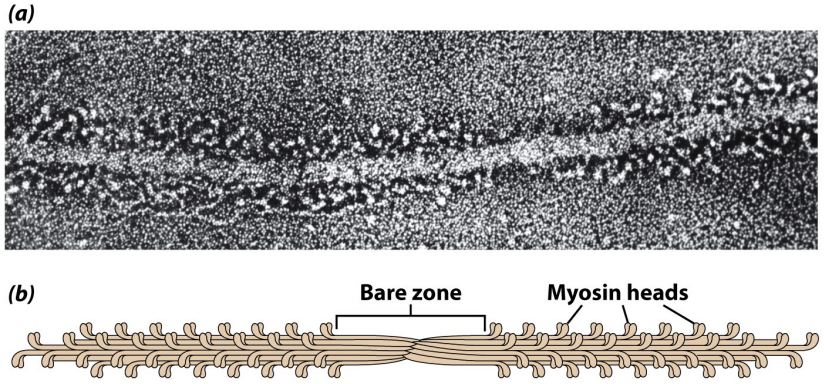
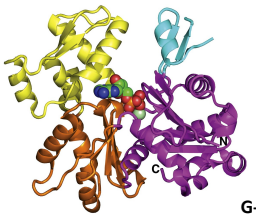


Figure 7-26

Actin Filament: the Track

- Actin: 375-residue protein, most abundant in eukaryotes (G-actin)
  - Four domains, bind ATP (and Ca^{2+})
- Referred to as F-actin when polymerized
  - No ATP hydrolysis required
  - cyroEM
  - + end binds to Z disk
  - Binds myosin head via hydrophobic interactions



G-actin
PDBid 3HBT

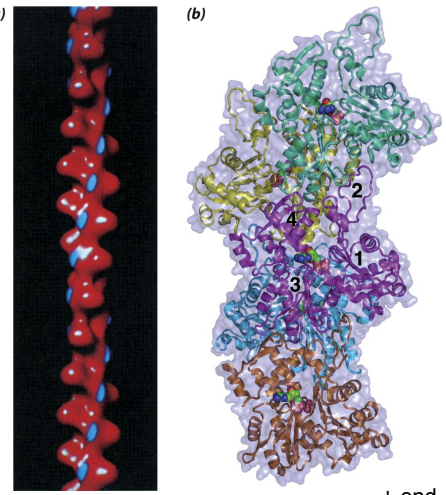
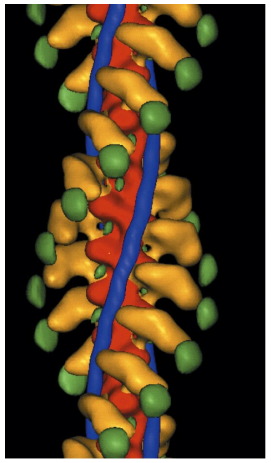


Figure 7-28

Model of Myosin-Actin Interaction



e 7-30
esy of Ronald Milligan, The Scripps Research Institute, La Jc

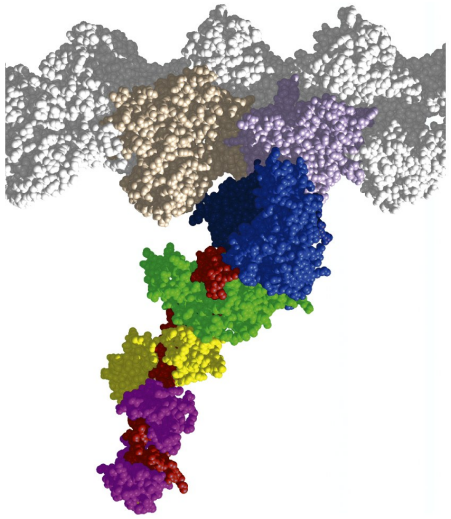
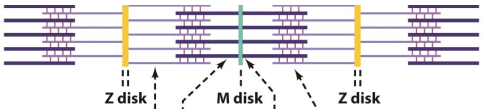
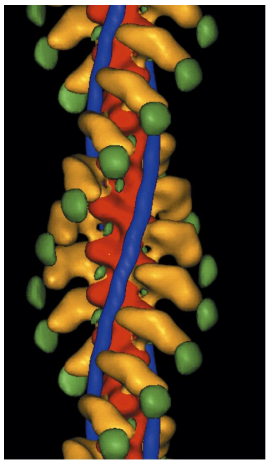


Figure 7-29
Modified from a drawing by Ivan Rayment and Hazel Holden, University of Wisconsin

Other Components of Muscle

- Myosin and actin account (only) for about 60-70% and 20-25% of total muscle proteins
- Tropomyosin: line the groove of actin filament (blue ribbon in the right figure)
- Troponin: links tropomyosin, Ca^{2+} sensing!
- Titin: longest known protein (34,350 residues), spanning ~1 μm between M and Z disks; thought to resist sacromere over extension
- Several other proteins that form Z and M disks and the linkages of other proteins to these junction points

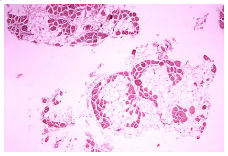




e 7-30
esy of Ronald Milligan, The Scripps Research Institute, La Jc

Duchenne and Becker Muscular Dystrophy (DMD and BMD)

- Muscle wasting diseases
  - Muscle degeneration exceeds regeneration, leading to progressive muscle weakness and eventually lung/heart failure and death
  - DMD: onset age of 2-5 years, expected life span < 25 yr
  - BMD: onset age 5-10 years, less progressive and longer life expectancy
- Caused by mutations that lead to either degraded (in DMD) or semi-functional (in BMD) dystrophin
  - On X-chromosome, thus mostly affect men
  - BMD: 1 in every 3600 male birth
  - DMD: 3-6 incidence per 100K male birth



- Dystrophin (~0.002% of muscle tissue): helps to anchor F-actin to extracellular matrix and prevents membrane damage during muscle contraction
- No treatment: ongoing research on stem cell or gene therapy

Mechanism of Force Generation in Muscle

YouTube animations:
https://www.youtube.com/watch?v=oHDRIwRZRVI

- Muscle contraction involves myosin walking (literally!) on actin filament
- Driven by ATP hydrolysis
- The current model involves 6 steps (see diagram)
- Whole cycle ~ 0.2 second during a strong muscle contraction
- Contraction triggered by Ca^{2+} pulse (from 10^{-7} to 10^{-5} M)
- Tropomyosin-troponin

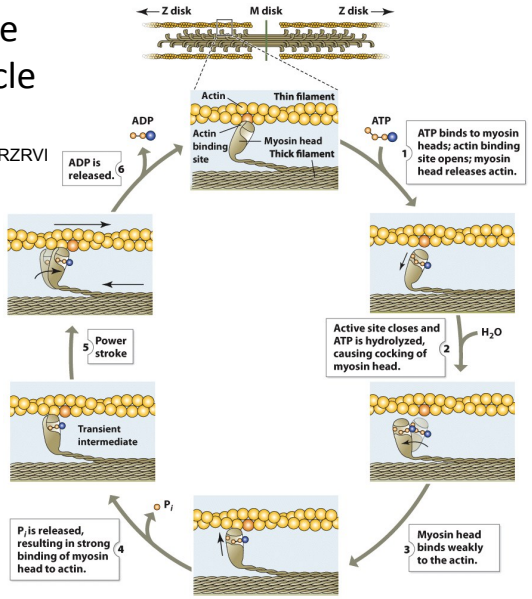
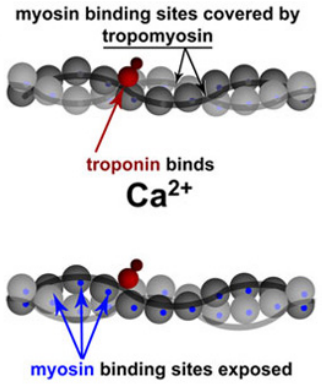


Figure 7-32

Ca^{2+} Regulates Muscle Contraction by Altering Tropomyosin Position on Thin Filament



Green: w/ Ca^{2+}

Figure 7-33
Courtesy of William Lehman, Boston University School of Medicine

Actin Microfilaments in Nonmuscle Cells

- Actin the most abundant protein in eukaryotic cells: ~5-10% of total protein content!
- Forms microfilaments of ~70 Å in diameter: dynamic!
- Crucial for many functions: maintaining cell shapes, cell division, endocytosis, organelle transport etc
- Treadmilling: constant grow at the + end and dissociate at the – end
  - Directional growth and cell locomotion!

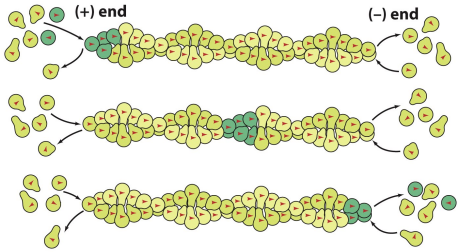


Figure 7-35
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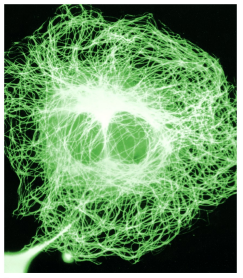
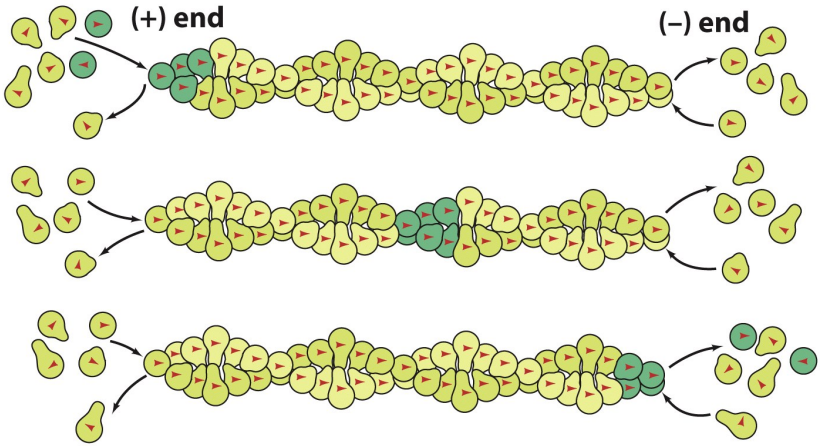


Courtesy of John Victor Small, Austrian Academy of Sciences, Salzburg

Microfilament Treadmilling



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Crawling Macrophage

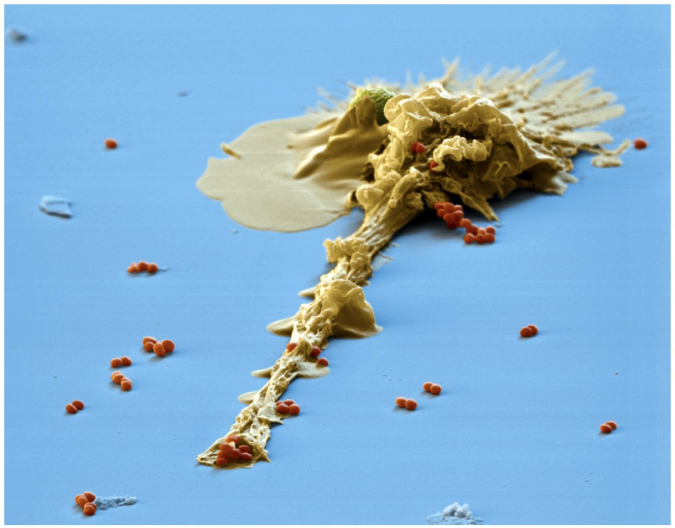

Figure 7-36
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Summary

- Muscle organization
- Key proteins: myosin and actin
  - Basic properties and major functional roles
  - Others proteins
- Force generation mechanism
- Calcium sensing
- Actin microfilaments