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

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”
Sliding Filament Model

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

Myosin: the Motor

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

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
Model of Myosin-Actin Interaction

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

Mechanism of Force Generation in Muscle

- 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 $10^{-6}$ M)
- Tropomyosin-troponin

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

YouTube animations: https://www.youtube.com/watch?v=oHDRIwRZRVI
Ca\(^{2+}\) Regulates Muscle Contraction by Altering Tropomyosin Position on Thin Filament

- Actin the most abundant protein in eukaryotic cells: \(\sim 5\text{-}10\%\) of total protein content!
- Forms microfilaments of \(\sim 70\ \text{Å}\) 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!

Actin Microfilaments in Nonmuscle Cells

Microfilament Treadmilling

Crawling Macrophage
Summary

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