Myopathies and Muscular Dystrophies

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Skeletal Muscle

- Three types of muscle:
  - Skeletal
  - Cardiac
  - Smooth

- Over 640 skeletal muscles in the human body
Anatomy of Skeletal Muscle

- **Muscles**
  - composed of

- **Fascicles**
  - which contain many

- **Fibers**
  - that are filled with

- **Myofibrils**
  - the contractile component of muscles
Nomenclature
Definition

• Muscular dystrophies are genetic, progressive, degenerative disorders of muscle
  ▫ Muscle weakness is the primary symptom
  ▫ Clinical and histologic criteria have been used in the past for classification
Definition

- Now muscular dystrophies are mostly classified on a genetic basis
- Thus, we often refer to them by the broader moniker of:
  - *Genetic muscle diseases*
Why Should We Care?

- 200+ genetic muscle diseases
- Overall minimum prevalence of symptomatic disease ~1 in 1,000 (100/100,000)
  - Similar to multiple sclerosis
    - Dystrophinopathies – 23/100,000
    - Myotonic dystrophies 1 & 2 – 14/100,000
    - FSHD – 18/100,000
    - LGMD – 7/100,000
    - All others - ~30/100,000
Pattern of Muscle Involvement Varies
Limb Girdle Muscular Dystrophies
Limb Girdle Weakness

- “Post-natal onset of progressive weakness and muscle atrophy affecting proximal muscles of the upper and lower extremities”
Limb Girdle Weakness

• >50 autosomal recessive LGMDs
• >10 autosomal dominant LGMDs
LGMD
Relative Prevalence in USA

- Calpain-3 = 15%
- Dysferlin = 10%
- Sarcoglycans = 10%
- FKRP = 10%
- Anoctamin-5 = 10%
- Lamin A/C = 5%
- All others 40%
  - Extracellular matrix-related proteins
  - Pompe disease
  - VCP
  - *RYR1*-related myopathies
RYR1
Not uncommon among LGMD patients
LGMD and Other Muscular Dystrophies

Multiple, overlapping phenotypes associated with numerous gene loci
Nomenclature (again)
Phenotype? Pathology? Genotype?

• Phenotype – what does the patient look like?
  ▫ Malignant hyperthermia or LGMD or exercise-induced rhabdomyolysis

• Histologic features – what does the muscle biopsy look like?
  ▫ Central core disease or multi-minicore disease or centronuclear myopathy

• Genetic – what protein or gene needs fixing???
  ▫ Ryanodine receptor related myopathy
  ▫ \textit{RYR1}-associated muscle disease
TREATMENT

=> Transition to Genetic Therapies
Successes in Genetic Therapies

• AON in DMD
• Viral vector gene therapy (DMD, LGMD 2B, 2C, 2D, 2E, 2L)
• Dual cassette viral vector mini-dystrophin
• Microdystrophin
  ▫ In the GRMD model
Adeno-Associated Virus (AAV)

• Non-pathogenic
  • Invades cells, but no disease

• Of over 100 AAV serotypes
  – Only ~6 widely used (AAV1, AAV5, AAV6, AAV8, AAV9, AAVrh74)
Adeno-associated Virus (AAV) is a Delivery Vehicle

Muscle fiber

AAV particle

nuclear penetration

uncoating

ssDNA

dsDNA

“Mini-chromosome” (Plasmid)
Viral Genes are Removed From AAV

Wild-type AAV

Remove rep, cap

Recombinant (r)AAV

LGMD gene

Plasmid
Non-Human Primate - Intramuscular

Dose escalation in 6 non-ambulatory LGMD2B patients

LGMD2E Gene Therapy - Gene Replacement for Beta Sarcoglycan

Human Phase 2 Systemic Therapy Trial Underway

=> 2 subjects dosed
83-98% transfection rates
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- Microdystrophin
  - In the GRMD model

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Long-term microdystrophin gene therapy is effective in a canine model of Duchenne muscular dystrophy

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Microdystrophin Gene Therapy
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6 month-old GRMD dog

Untreated