Mini-Symposium

Skeletal Muscle:
Development, Adaptation & Disease

“Gain Without Pain”

Rhonda Bassel-Duby, Ph.D.
Associate Professor of Molecular Biology
Myoglobin Immunohistochemistry
Subtypes of Skeletal Myofibers

- **Type I (slow)**
  - red, oxidative
  - fatigue-resistant
  - slow contraction
  - insulin-sensitive

- **Type IIa**
  - white, glycolytic
  - fatigue rapidly
  - rapid force development
  - insulin-resistant

- **Type IIb (fast)**
  - endurance training, nerve stimulation

  - inactivity, disease, hypogravity
Establishing Myofiber Specialization

Preprogramming of myoblasts

Pattern imposed by motor nerve

tonic

phasic
Cross-innervation Switches Fiber Types
Electrical Stimulation Model
unstimulated  stimulated
Molecular Marker of Muscle Plasticity

myoglobin

Stimulation (days)

C 1 3 7 14
Electrical Signals Alter Intracellular Calcium

10 Hz continuous

100 Hz intermittent

Type I fibers

Type II fibers
Genetic Reprogramming of Skeletal Muscle

neural activity

\( \text{Ca}^{2+} \)

MCIP \( \rightarrow \) calcineurin

GSK3 \( \rightarrow \) NFAT

HDAC \( \rightarrow \) MEF2

CaMK

PSC-1

Myofiber specialization (fiber type)
Genetic Manipulation of Signal Transduction Pathways in Muscle
Voluntary Running Cages
Voluntary Wheel Running Enhances Muscle Oxidative Capacity

<table>
<thead>
<tr>
<th>% fiber</th>
<th>Sedentary</th>
<th>Run</th>
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<tr>
<td>Type I</td>
<td>24.7+3.9</td>
<td>21.6+1.6</td>
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<tr>
<td>Type IIa</td>
<td>26.5+5.6</td>
<td>61.2+12.3</td>
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<tr>
<td>Type IIb</td>
<td>48.8+2.0</td>
<td>17.2+10.9</td>
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Genetic Reprogramming of Skeletal Muscle

neural activity $\rightarrow$ Ca$^{2+}$

calcineurin

NFAT

Myofiber specialization (fiber type)
Genetic Manipulation of Signal Transduction Pathways in Muscle
Calcineurin Promotes Slow Fiber Transformation

Genetic Reprogramming of Skeletal Muscle

neural activity

\[ \text{Ca}^{2+} \]

CaMK

MEF2

Myofiber specialization (fiber type)
Expression of CaMKIV* in Skeletal Muscle

MCK 4.8 kb  CaMKIV*  hGH

brain  heart  lung  liver  stomach  kidney  spleen  testis  sk. muscle

Wild-type  MCK-CaMK

soleus  PLA  EDL  WV  soleus  PLA  EDL  WV

CaMKIV*

tubulin
CaMK Promotes Slow Fibers Transformation

Wild-type

MCK-CaMK

CaMK Stimulates Mitochondrial Biogenesis

MCK-CaMK Muscle Shows Improved Function

Genetic Reprogramming of Skeletal Muscle

neural activity

Ca^{2+}

calcineurin

NFAT

CaMK

MEF2

PGC-1

Myofiber specialization (fiber type)
PGC-1α Promotes Slow Fiber Transformation

MCK 4.8 kb

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<tr>
<th>Hind limb</th>
<th>Soleus/Gastrocnemius</th>
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<td>Pl</td>
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PGC-1α


myoglobin

Tn I-slow

cytochrome c

tubulin
PGC-1α Promotes Slow Fiber Transformation

Wild-type

MCK-PGC-1

metachromatic stain  anti-myosin (slow)
MCK-PGC-1 Muscle is More Resistant to Fatigue

Genetic Reprogramming of Skeletal Muscle

neural activity

\[ \text{Ca}^{2+} \]

Calcineurin

CaMK

NFAT

MEF2

PGC-1

Myofiber specialization (fiber type)
Calcineurin Enhances Insulin-Stimulated Glucose Transport in Muscle

Ryder et al. JBC, 2003
Calcineurin Modulates Insulin-Stimulated Glucose Uptake in Muscle
Genetic Reprogramming of Skeletal Muscle

neural activity → Ca\(^{2+}\) → MCIP → calcineurin → GSK3

CaM kinase (CaMK) → HDAC → MEF2 → PGC-1

Myofiber specialization (fiber type)
Skeletal Muscle Regenerates

satellite cells
Muscle Regeneration

- Quiescent satellite cells
- Proliferating satellite cells

Muscle Injury

Maturation

Differentiation
Growing Muscle on Synthetic Fibers
# Acknowledgements

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<tr>
<th>Hai Wu</th>
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<td>Fritz Thurmond</td>
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*Harvard Medical School*

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Jeffrey Ryder