From Skeletal Muscle Weakness to Functional Outcomes Following Critical Illness
A Translational Biology Perspective

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Disclosure

I have no conflicts of interest to disclose.

Within the last 24 months I have not had any type of financial arrangement or affiliation with commercial interests related to the content of this continuing education activity that requires disclosure.
Objectives

1. Update on mechanisms underpinning development & persistence of skeletal muscle loss/dysfunction

2. Highlight recent discoveries, contextualizing basic cellular mechanisms within clinical observations

3. Integrate challenges and opportunities implementing knowledge into novel therapeutics
Loss of strength and muscle in the ICU

- 1 week post-ICU admission, MRCSS <48 up to 60% patients

  e.g. De Jonghe et al JAMA 2002; 288(22)
  Lee et al Phys Ther 2012; 92(12)
  Vanpee et al Crit Care Med 2011; 39(8)

Nakanishi et al Int Care Med 2018, 44(2) 263
Variable muscle, strength and physical functional recovery

CT thigh
(mid femur cross section)

52 yo M

47 yo F

6 months
Post ICU discharge

Dos Santos et al. AJRCCM 2016 194 (7)

Herridge et al AJRCCM 2016 194 (7)
Protein degradation > Protein synthesis = Muscle wasting

Ubiquitin Proteasome System (UPS)

UPS stimuli intrinsic to critical illness
- Inflammation
- Oxidative stress
- Energy stress
- Abnormalities lipid metabolism

UPS introduced via ICU care
- Unloading (bedrest)
- Inactivity
- Pro-atrophy drugs

Modified from Meiners et al ERJ 2012 40
**UPS inhibitors**

* Velcade (Bortezomib), Carfilzomib (Kyprolis), Ixazomib (Ninlaro)
  26S proteasome inhibitors

* Velcade mitigates muscle wasting pre-clinical models
  

* mechanically ventilated animals partially inhibits diaphragm myofiber atrophy/weakness
  

* have narrow therapeutic range and toxicity precludes use for atrophy prevention

* development muscle specific Ub ligase inhibitors underway
Autophagy

Enhanced autophagy

Myocyte atrophy

Impaired autophagy

Muscle damage/dysfunction

Compliments of MBioInfo,
Mechanobiology Institute
National University of Singapore
Insufficient autophagy in critical illness associated with organ failure and mortality


Pharmacological regulators of autophagy (inducers, inhibitors) in development

Currently available drugs (eg metformin, chloroquine) impact autophagy machinery

*Autophagic balance is critical to muscle integrity and homeostasis.*

*Further research is required in critically ill patients to determine*

1) *appropriate timing*
2) *extent of*
3) *enhancement and/or inhibition of autophagy to maintain muscle mass and function*
** Caveat**

- Reports demonstrate **early muscle catabolism** confers a survival benefit by deprioritizing an energy dependent non-vital organ system and concurrently liberating amino acids for consumption.


- In view of possible benefits of an early catabolic response, attempts to inhibit proteolysis to spare muscle in the ICU will need to be carefully considered with respect to timing and extent.
Proteolysis > Protein synthesis = Muscle wasting
mTOR Signalling Network

mTOR signalling stimuli
- Mechanical loading
- Exercise/activity
- Essential nutrients
- Growth Factors
Anabolic Resistance in Early Critical Illness

- Well described

  Constantin D et al. J Physiol 2011;589:3883
  Puthucheary Z et al. Thorax 2018;73(10):926

- Limited muscle growth with appropriate substrates/exercise

- Results in part due to energy depletion
Muscle mitochondria ultrastructural injury & decreased biogenesis

Depletes ATP

Specifically decreases capacity for exercise to induce protein synthesis

? Can acutely critically ill patients generate adequate energy in order to facilitate and respond to exercise in the ICU
Precision nutritional supplements may protect muscle mass

- Nutritional substrates Leucine, \( \beta \)hydroxy- \( \beta \) methylbutyrate (HMB)
- Positively modulate mTOR signalling pre-clinical models
- Increase muscle protein synthesis
- Attenuate autophagy
One Size May Not Fit All

1. In health, the baseline nutritional & energy requirements necessary to enable activity to build protein and muscle varies tremendously.

2. Prospective studies are essential to better delineate the complex interaction between nutrition, exercise and the critically ill patient’s baseline metabolic status.

3. Precision individualized prescription of exercise and nutritional supplementation, and the timing of administration, will be required to overcome profound proteolytic push that occurs in early critical illness.
Satellite cells are decreased in critical illness survivors with sustained muscle wasting.

Dos Santos et al. AJRCCM 2016 194 (7)
? Does a depleted satellite cell pool causally contribute to persistent muscle atrophy in the critical illness survivor

SCs must
• self renew to maintain the population, and
• differentiate to make new muscle.

Defects in either process leads to impaired muscle regeneration.
Caspase-3 & retinoid receptors stimulate SC differentiation in pre-clinical models

- **Fernando P et al.** Proc Natl Acad Sci USA. 2002, 99
- **Hamed M et al.** Nucleic Acids Res 2017, 45

**Anti-Cancer Agents**

- PAC-1 – caspase 3 stimulator - in Phase 1 trials
- Targretin (Bexarotene) – retinoid receptor agonist

- Both could be repurposed for use in sustained muscle wasting if future studies identify functional deficits in SC
Lipolysis in Critical Illness

• Early catabolic state of critical illness, accelerated lipolysis increases circulating TG-rich lipoproteins & FFA

• In animal models muscle ectopic lipid accumulation induces proteasomal activity & muscle atrophy

• SC overexpression lipoprotein lipase obliterates myogenic potential & muscle regeneration in pre-clinical models

Clinical relevance of FFA to muscle in critical illness

- muscle mass & muscle ATP content not impacted by fatty acid supplementation in first 7 days post ICU admission
  
  *Puthucheary ZA, et al.. Thorax 2018;73(10):926*

- given potential for lipid-induced muscle toxicity, removal of fatty acid supplementation should be evaluated future trials
Impaired contractility – Diminished muscle specific force

Research in pre-clinical models demonstrates multifactorial cause of diminished muscle specific force

1) altered bioenergetics with depletion of ATP

2) altered muscle membrane excitability

3) excitation-contraction uncoupling.
Excitation-contraction coupling uncoupling occurs

i) altered muscle composition
ii) altered calcium dynamics and/or
iii) decreased myofilament Ca++ sensitivity/impaired function due to post-translational modifications
Chaperone Co-inducer BGP-15

• rat model of ventilator induced diaphragmatic dysfunction, BGP-15 restored depressed muscle specific force

• BGP-15 prevented post translational modifications of myosin that impair its function

  *Salah H et al. Sci Transl Med 2016;8(350):350ra103*

• ? Same effect in skeletal muscle

• BGP-15 should be evaluated in the pre-clinical models of ICUAW with potential for long-term outcomes
Summary

• Update recent advances delineating cellular biology muscle wasting/weakness critical illness

• Modulators of the UPS, autophagy, mTOR, lipolysis, excitation-contraction uncoupling +/- sc differentiation all serve as potential novel therapeutics