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# Target Mitochondria Metabolism and Energy Expenditure in Muscle Atrophy, Sarcopenia and Cachexia

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**Objective** Muscle atrophy is a common and clinically important outcome of many diseases and hospitalization bed rest. Mechanical unloading of skeletal muscles may result in a rapid loss of muscle mass and mitochondria dysfunction. And the recovery from disuse muscle atrophy is usually complete in young healthy adults but is delayed and often incomplete in older patients. However, the mechanisms underlying poor recovery of aged muscle following disuse remain to be delineated. Recent evidence suggests that mitochondrial energetics play an important role in regulation of muscle mass. To this end, we employed multiple approaches to address the role of mitochondrial function and metabolism in muscle atrophy and sarcopenia. And we are also engaged to develop novel mitochondria-targeted antioxidant peptides to mitigate this mitochondria-related functional impairment by ROS and improve the recovery from muscle atrophy and cachexia.
**Methods** Tail Suspension Hind Limb Unloading for adult mice (6-month-old) and aged mice (22-24month old). Cardiometabolic Phenotyping： Measurement of fat and lean mass (g) is accomplished using a LF90II TD-NMR (Bruker, Madison, WI). Locomotor activity measurements are obtained using a Promethion Mouse Multiplexed Metabolic System(Sable Systems International, Las Vegas, NV).Mitochondrial Respiration :Respirometry assays were conducted using an Oxygraph-2k (Oroboros Instruments, Innsbruck, Austria), Mitochondria H2O2 emission was measured with Amplex Red reagent which reacts with H2O2 to produce the stable fluorescent compound resorufin. Resorufin fluorescence was monitored using a Fluorescence. A continuous, spectrophotometric assay was utilized to measure mitochondrial calcium retention capacity (CRC) within soleus fiber bundles. RNA Sequencing and Informatics, KEGG Pathway and Upstream Regulator Analysis, Real-Time Quantitative-PCR. Multidimensional mass spectrometry-based shotgun lipidomics was employed to measure and characterize the lipid patterns inmouse soleus muscle. Metabolomics Acylcarnitines A panel of acylcarnitines was quantitated by LC/ MS/MS (Agilent 1290 HPLC/6490 triple quadrupole mass spectrometer). Amino Acids. Quantitation of amino acids was achieved using LC/MS/MS (Agilent 1290 HPLC/6490 triple quadrupole mass spectrometer).
**Results** Old mice have impaired early recovery of soleus mass following unloading induced muscle atrophy. And mitochondrial function and metabolism does not Improve during early recovery in aged Mice. Divergent metabolomic response was found between adult and aged Mice during unloading and recovery. However, transcriptomic response to unloading and reloading is similar in adult and aged Mice.
**Conclusions** Here, we report that aged mice with low muscle mass and low glucose clearance rate also display poor early recovery of muscle mass after disuse muscle atrophy. We used unbiased and targeted approaches to identify changes in energy metabolism gene expression, metabolite pools and mitochondrial phenotype and show for the first time that persistent mitochondrial dysfunction, dysregulated fatty acid β-oxidation and elevated H2O2 emission occur concomitantly with poor early recovery of muscle mass following a period of disuse in old mice. Importantly, this is linked to more severe whole-body insulin resistance, as determined by insulin tolerance test. Our findings also showed cellular metabolic changes during muscle atrophy and sarcopenia may induce higher production of oxygen radicals that play a significant role in the progression of age-related sarcopenia.

These findings suggest that muscle fuel metabolism and mitochondrial energetics could be a focus for mining therapeutic targets to improve recovery of muscle mass following periods of disuse. We are engaged to develop novel mitochondria-targeted antioxidant peptides to mitigate this mitochondria-related functional impairment by ROS and improve the recovery from muscle atrophy and cachexia. Co-administration of other targeted compounds was also promising to improve recovery from muscle atrophy and cachexia.