Aging and exercise

- As we age muscles atrophy.
- There is reduction in muscle fiber cross section area.
- Loss of muscle fibers by apoptosis
- Reduced nerve connections.

- CAN WE SLOW THE EFFECT?
• This age-related muscle atrophy, termed **sarcopenia**, is associated with muscle weakness and can have significant effects on an individual’s health and quality of life.

• affects a growing population, occurring in 10-25% of individuals under the age of 70 and in more than 40% of the elderly over the age of 80.
• specific skeletal muscles may undergo a ~40% decline in muscle mass between the ages of 20 and 80 years.
• 25% decrease in cross-sectional area of vastus lateralis is consistently seen in comparisons of 70- to 75-year-olds with 20- to 30-year-olds. Large declines also occur in the number of fibers.
Inflammatory Cytokines

Sarcopenia
- Increased motor unit denervation
- Age-related loss of spinal motor neuron function
- Decreased physical activity
- eased o acid ake
- Age-related decline in anabolic hormone levels (e.g. testosterone, vitamin D, GH, IGF-1)

Cachexia
- Increased REE
- Host humoral factors: glucortic and angiontensin II
- Ano
• MUSCLE ACTION REVISITED
B

~10-nm step

Nature Reviews | Molecular Cell Biology
myosin binding sites covered by tropomyosin

Troponin binds Ca$^{2+}$

Myosin binding sites exposed
• Muscle building as a normal process involves myocytes that become myofibers.
• Myocytes are progenitor cells and their ability to differentiate is reduced in aging.
ENERGY IN MUSCLE CAN BE STORED BY REVERSIBLE TRANSFER OF THE TERMINAL PHOSPHATE OF ATP TO CREATINE
THE MITOCHONDRIAL VICIOUS CYCLE THEORY

• Oxidative stress induces mutations in mtDNA
• This gives even higher ↑ in ROS production
• Leading to ↓ ETC activity Mito dysfunction
• And causing apoptosis.
Telomere shortening/Aging

activate p53

↓ Growth arrest/apoptosis

↓ Senescence

↓ PGC-1α/β expression

↓ Mitochondrial number/function

↑ Age-related pathologies
Cytochrome c oxidase enzyme activity (average ± S.E.) in young and old in skeletal muscles, liver, and heart

### Cytochrome c oxidase activity (μmol/min · g protein)

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Young</th>
<th>Old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrocnemius medial</td>
<td>187 ± 62</td>
<td>162 ± 13</td>
</tr>
<tr>
<td>Gastrocnemius lateral</td>
<td>232 ± 22</td>
<td>166 ± 6(^{1-a})</td>
</tr>
<tr>
<td>Liver</td>
<td>455 ± 18</td>
<td>444±-11</td>
</tr>
<tr>
<td>Heart</td>
<td>1136 ± 60</td>
<td>1194 ± 61</td>
</tr>
</tbody>
</table>
ROS is most highly generated in circumstances such as reperfusion and where O2 levels are increased after decreased, e.g. after going anaerobic by exercise and then re-oxygenating.
• MANY ANIMALS ARE EXPOSED TO VARIABLE METABOLIC/ENERGY DEMANDS AND DIFFERENT OXYGEN TENSIONS, HOW DO THEY ADAPT?
• Hibernation is characterized by a profound decrease in oxygen consumption and metabolic demand during torpor that is punctuated by periodic rewarming episodes, during which oxygen consumption increases dramatically. The surge in oxygen consumption during arousal increases production of reactive oxygen species, making hibernation a potentially injurious process.

• Elephant seals can go very deep in the ocean where O2 levels are low then rise to the surface quickly. Also they can fast for very long periods and then start metabolism on feeding HOW?
Resistance to OXSTRESS in the elephant seal.

Change in O$_2$ or Prolonged fasting

Angiotensin II

NADPH oxidase

O$_2^{−}$, H$_2$O$_2$ → Nrf2

Cu,ZnSOD catalase

GGT

MnSOD

NADPH

NADP+$^+$

Oxidative damage

GCL

GSH

GSSG

GR

GST

PrxVI

GPx
Ca+ induced mitochondrial retrograde response
Ca++ release from the ER (called sarcoplaasmic reticulum in muscle) causes activation of Ca++ channels in the plasma membrane, which leads to loss of Ca++.

Ca++ is required for muscle functioning.
RETROGRADE SIGNALING INVOLVING ROS AND RNS

ROS/RNS

- Hypoxia
- H2O2
- O2-
- NO
- ONOO

S-NITROSYLATION OF IKK BETA

BECLIN RELEASE FROM BCL2

P-AMPK

INACTIVATION OF mTOR

AUTOPHAGY/MITOPHAGY

BECLIN DISSOCIATES FORM BCL2

BNIP3

ATG4

ATG13

HIF1

SOD1
SOD2
Glutathione reductase
Peroxyredoxin

H2O2
O2-
ONOO

ROS/RNS
• EXERCISE AND DIET: THE LINK TO A LONGER, HEALTHIER LIFE.
Mito biogenesis  Protein synthesis  Protein degradation
CREATINE SUPPLEMENTATION and HIGH INTENSITY EXERCISE

• Short term use of creatine with weight bearing exercises has been shown to improve muscle mass and fatigue resistance in the elderly. Also improves cognitive performance.

• Conjugated linoleic acid also improves muscle mass.
RESVERITROL (RED WINE) AND HISTONE DEACETYLASE INHIBITORS REDUCE AGING EFFECTS IMPLYING A ROLE FOR SIRT 1 AND SIRT 3.