Role of exercise and mitochondria in determining muscle health with advancing age

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Musculoskeletal Health Education Forum, Brock University, Sept 30, 2023

1

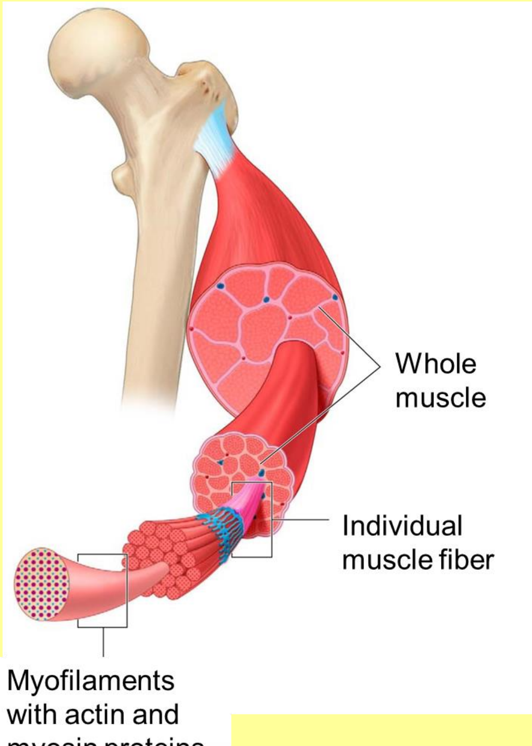
What are the essential components of **Muscle Health**

The molecular and cellular basis for:

1.Size and strength (prevention of atrophy)

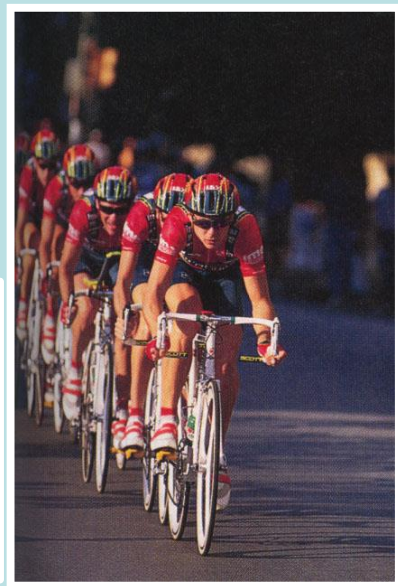
2.Endurance (fatigue resistance)

3. Metabolic efficiency (40% of body mass)



2

Exercise helps to maintain MUSCLE HEALTH in youth, adulthood, and as we age

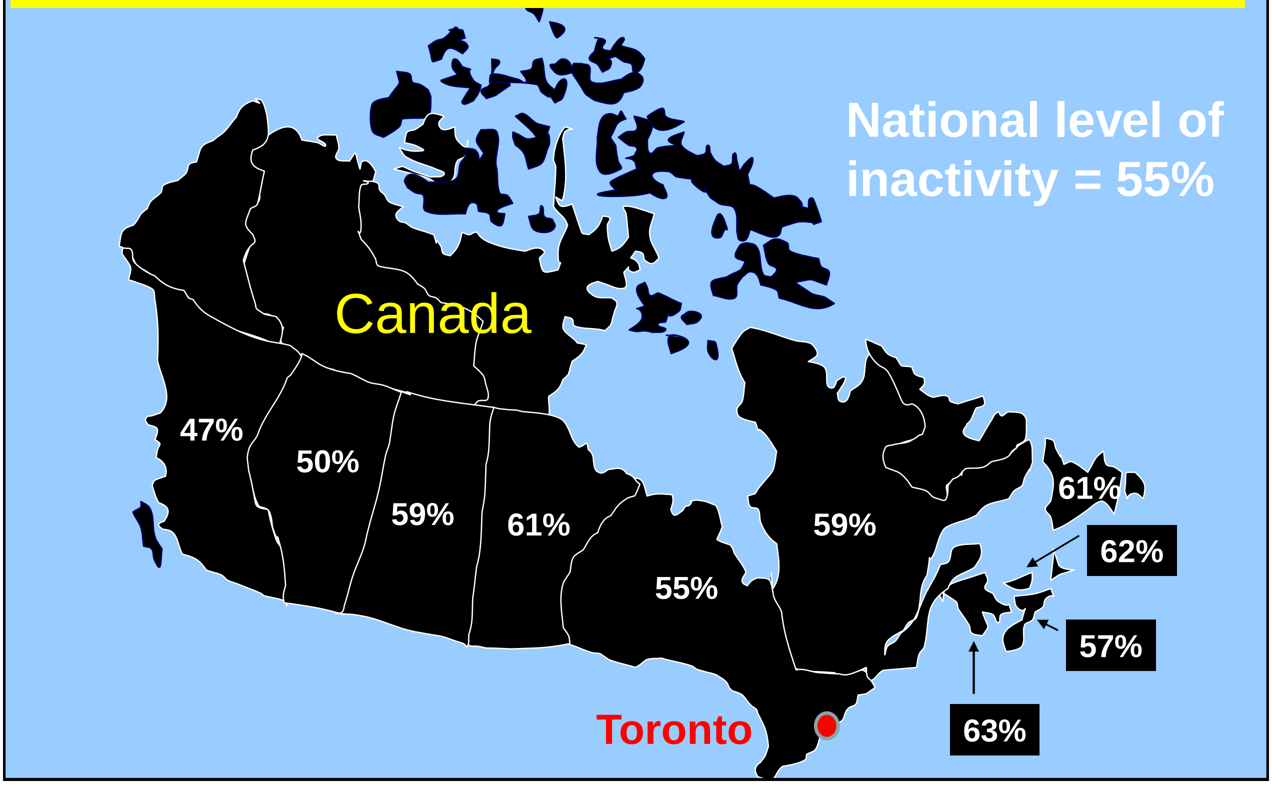


1. What are the mechanisms of how exercise maintains health?
2. Can exercise "attenuate aging", or improve disease conditions

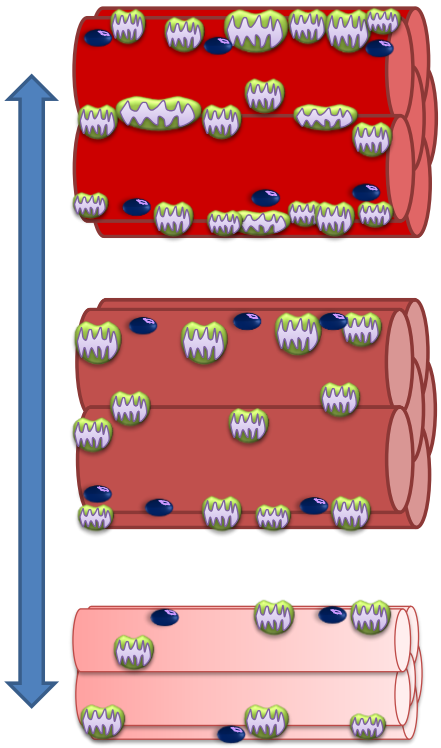
(eg. Obesity, Type 2 diabetes, Mitochondrial Myopathies, Muscle Disuse)?

This is important to consider for 3 reasons:

1. ***Our growing aging population***
2. ***Our national level of inactivity***



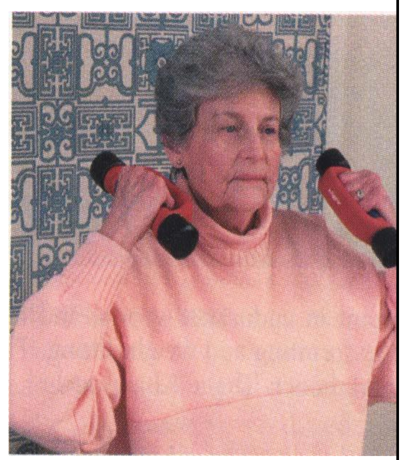
Exercise, mitochondria and muscle health



Very Healthy, regular exercise

Healthy

Age, Disease



➔Mitochondria exhibit Plasticity”

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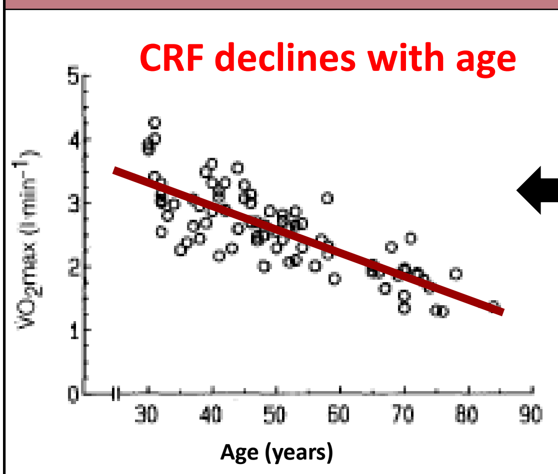
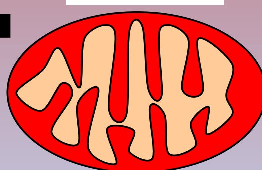
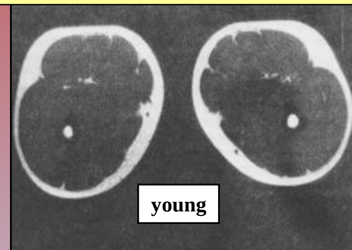
Mitochondrial dysfunction is involved in two important functional declines with age: Cardiorespiratory Fitness (CRF) and Sarcopenia



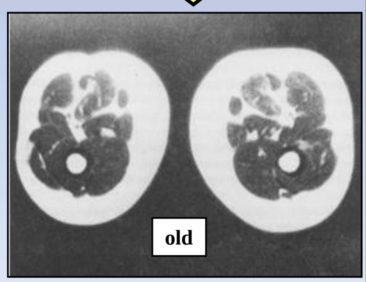
CRF is closely correlated with longevity!

Dysfunction





Sarcopenia with age



➔ Frailty, weakness, instability

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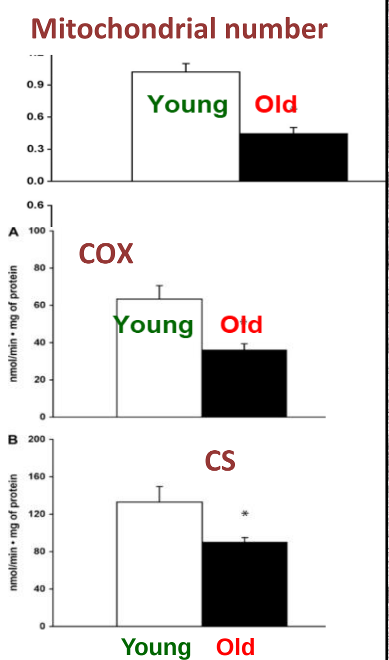
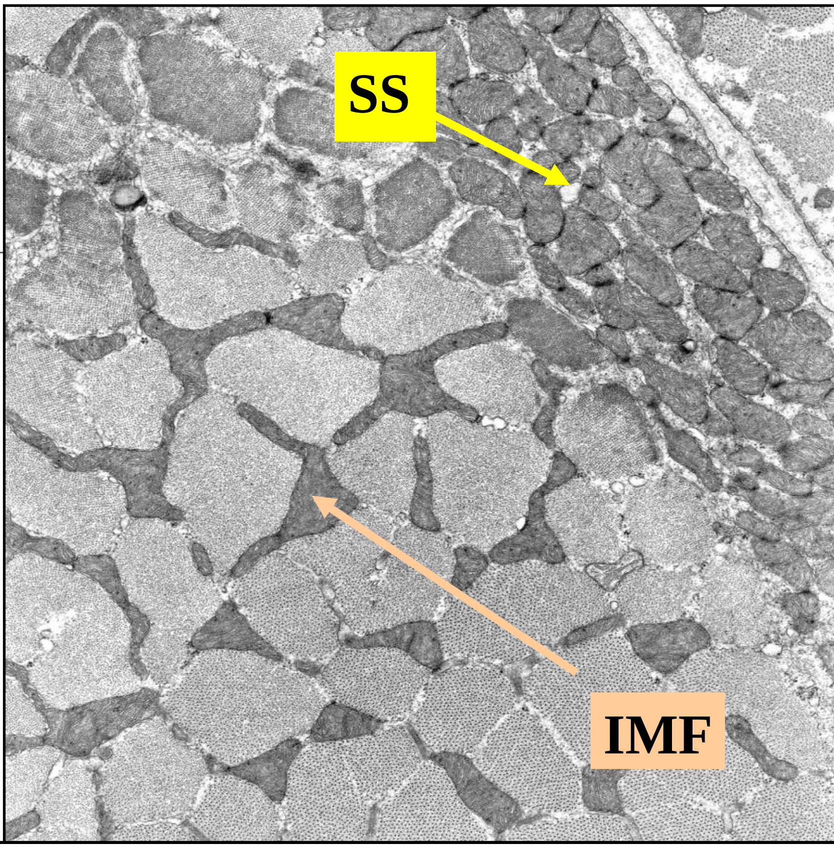
What happens to mitochondria with AGE?

Mitochondrial *content and function* decline and organelle fragmentation





Crane J D et al. J Gerontol A 2009

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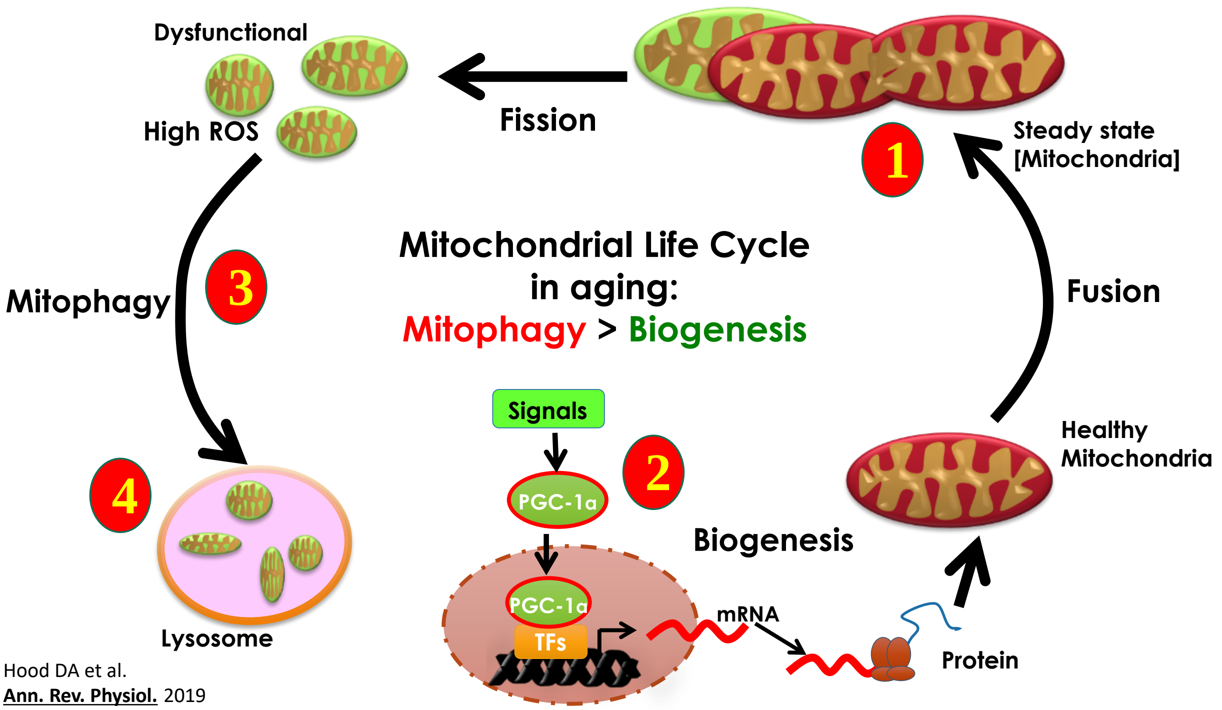

Hood DA et al.
Ann. Rev. Physiol. 2019

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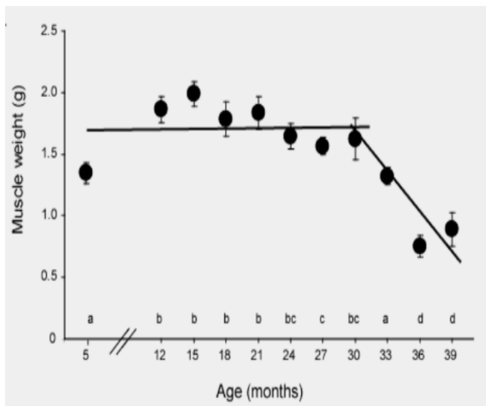
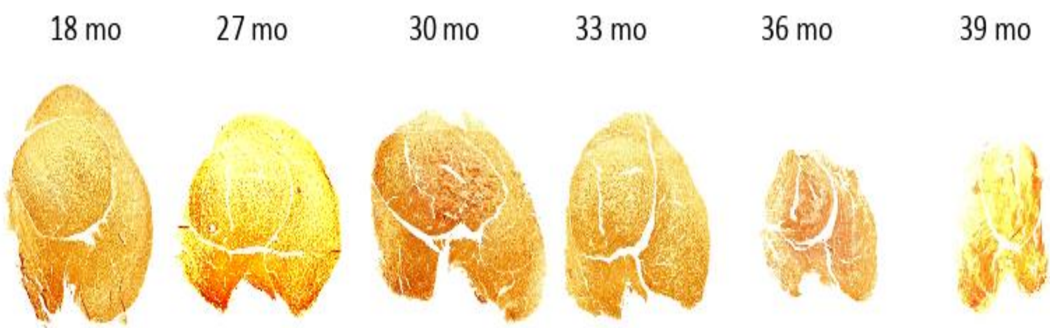
Animal models of human aging are continuously sought
Example: the F344BN rat



Young, Adults : 6 Months
Senescent : 35-36 Months



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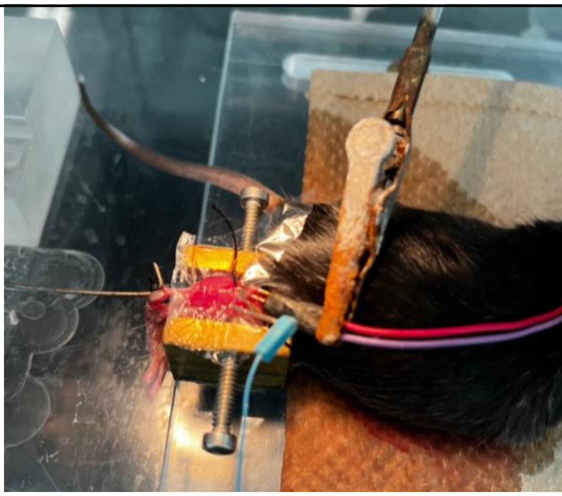

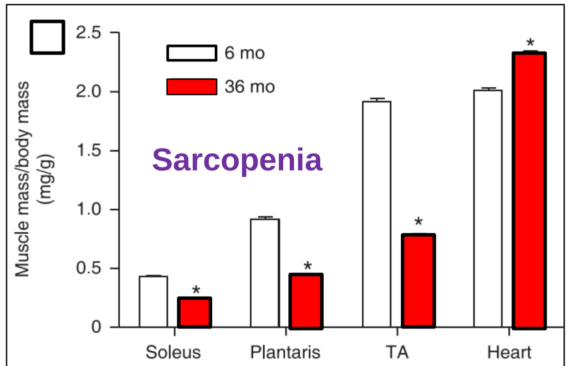

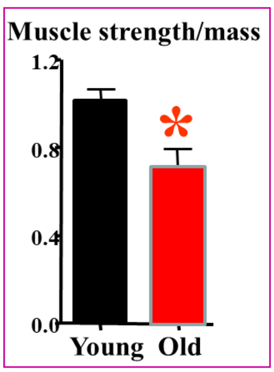

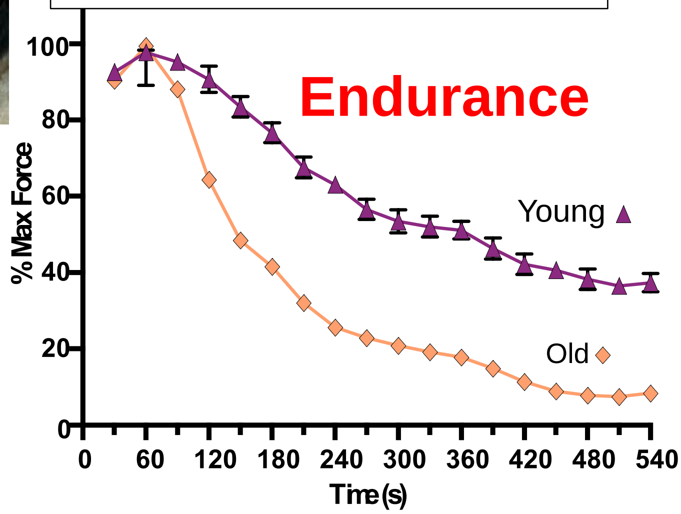

"Aged" muscle is smaller, weaker and has less endurance than "young" muscle

Chabi, B et al. **Aging Cell** 7: 2-12, 2008

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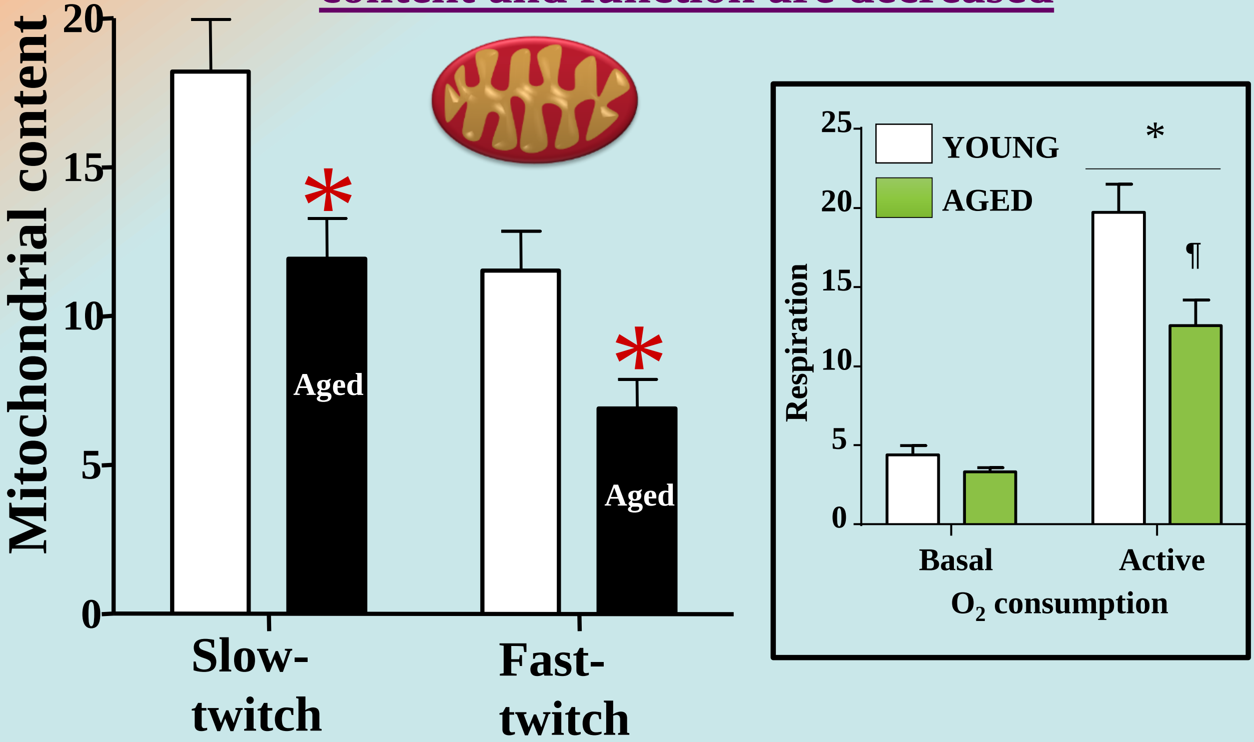
Endurance is reduced because mitochondrial content and function are decreased



Mitochondrial content is determined by its Life Cycle (turnover)

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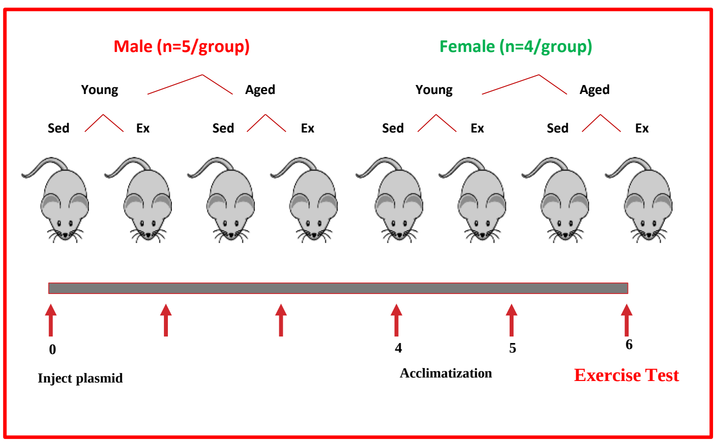
Are there sex differences in mitochondrial function with age?


Triolo et al. Skeletal Muscle (2022) 12:13
https://doi.org/10.1186/s13395-022-00296-7
Skeletal Muscle

RESEARCH Open Access

The influence of age, sex, and exercise on autophagy, mitophagy, and lysosome biogenesis in skeletal muscle

Matthew Triolo[1,2], Ashley N. Oliveira[1,2], Rita Kumari[1,2] and David A. Hood[1,2*]



Young – 4-6mo
Aged – 22-24mo

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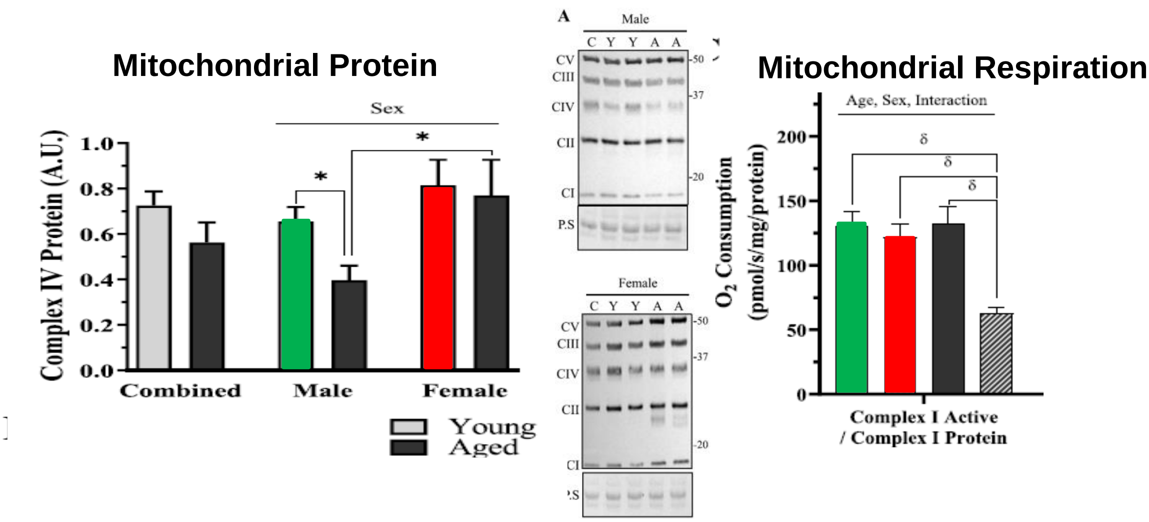
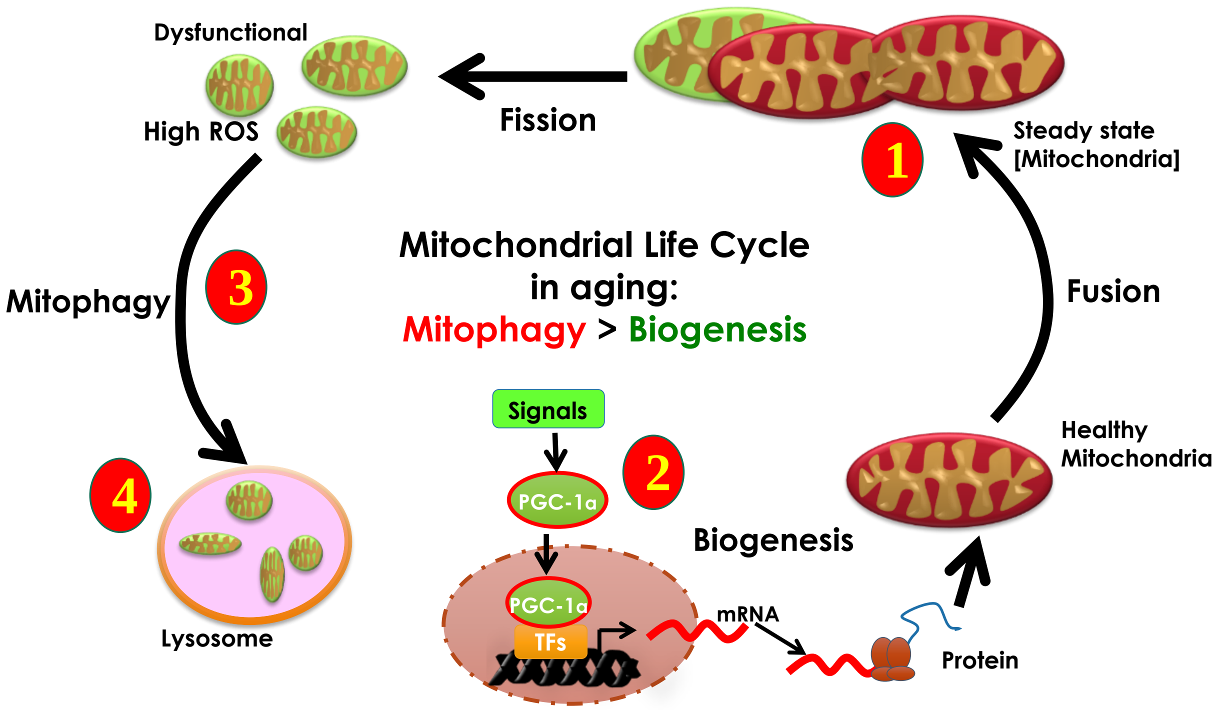
Females have more mitochondrial protein but lower function per mitochondrion with age



Biological sex differences exist in mitochondrial content and function with age



Hood DA et al. **Ann. Rev. Physiol.** 2019

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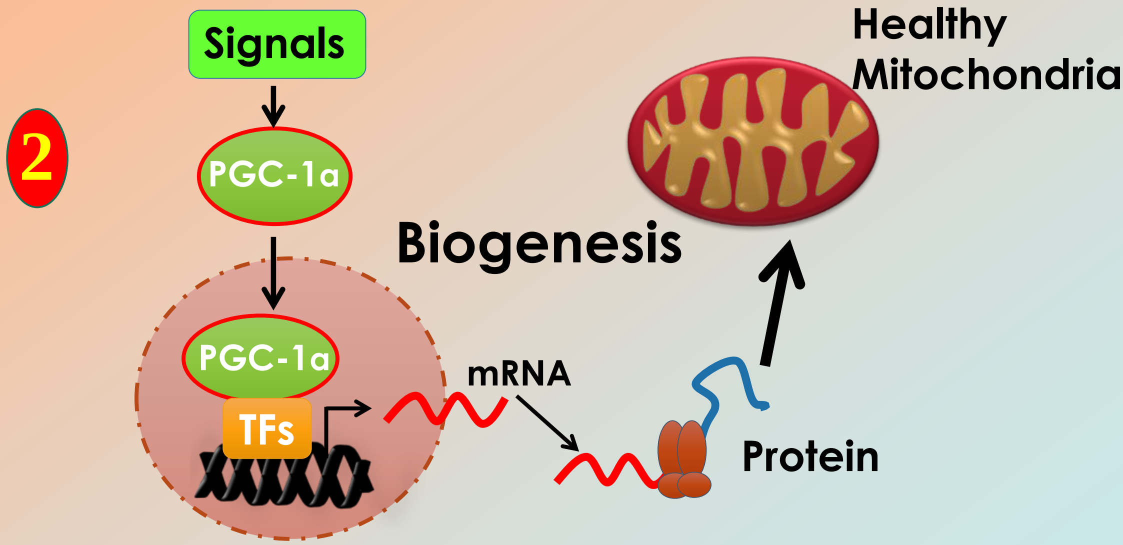
Is there a "Special" protein that regulates mitochondrial content in muscle?

➔ PGC-1α



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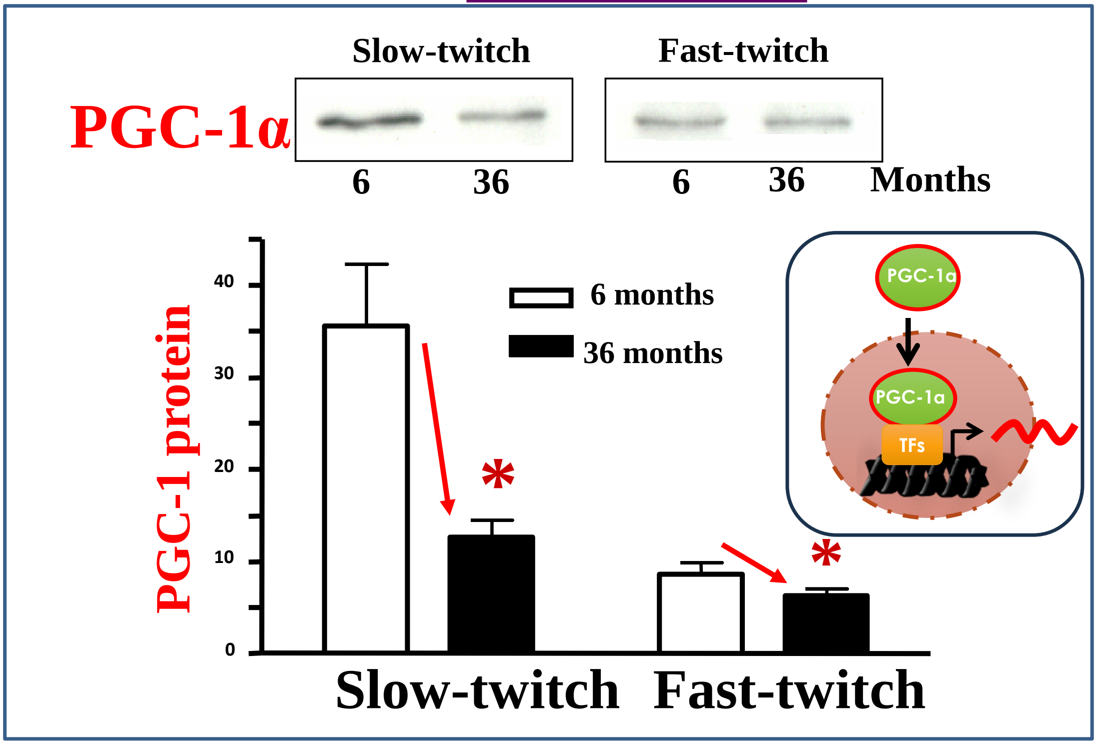
PGC-1α overexpression

➔Mitochondrial biogenesis, improved endurance, VO2max and lipid metabolism

PGC-1α knockout

➔Mitochondrial dysfunction, reduced content, increased apoptotic susceptibility

Decreased mitochondrial content in aging muscle is partly due to reduced PGC-1α



Chabi, B et al. **Aging Cell** 2008

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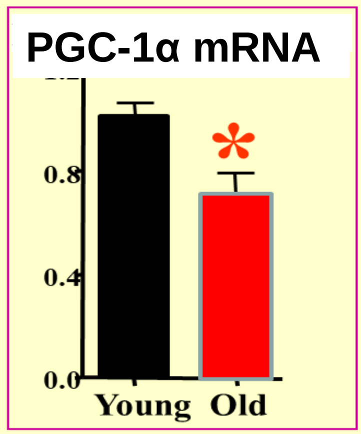
What is the mechanism involved in the decrease in PGC-1α protein in AGED muscle?

↓ mRNA

PGC-1 Gene

↓ Transcription

[PGC-1 mRNA] →



↓ Translation

[PGC-1 Protein]

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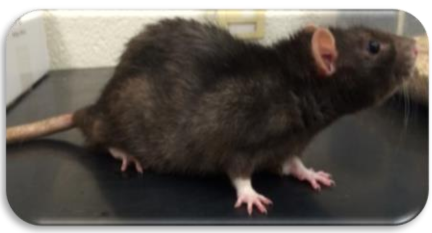
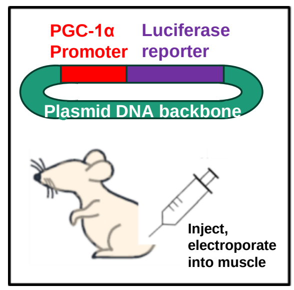
What about transcription?

Inject the PGC-1a “Promoter” and examine the contractile activity response

Electroporate1.5kb PGC-1α promoter-luciferase construct

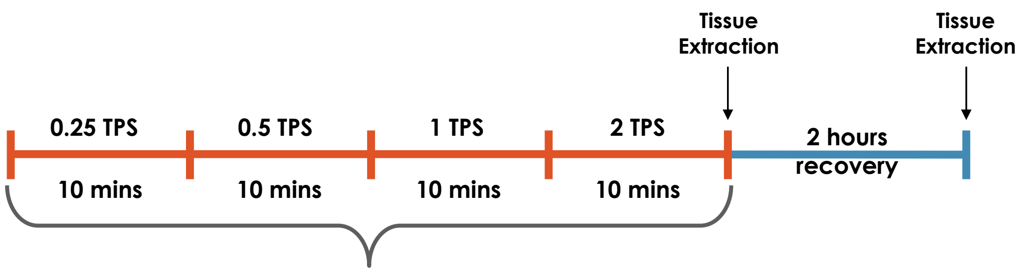


Fischer 344 Brown Norway rats
6-7 months vs. 34-35 months



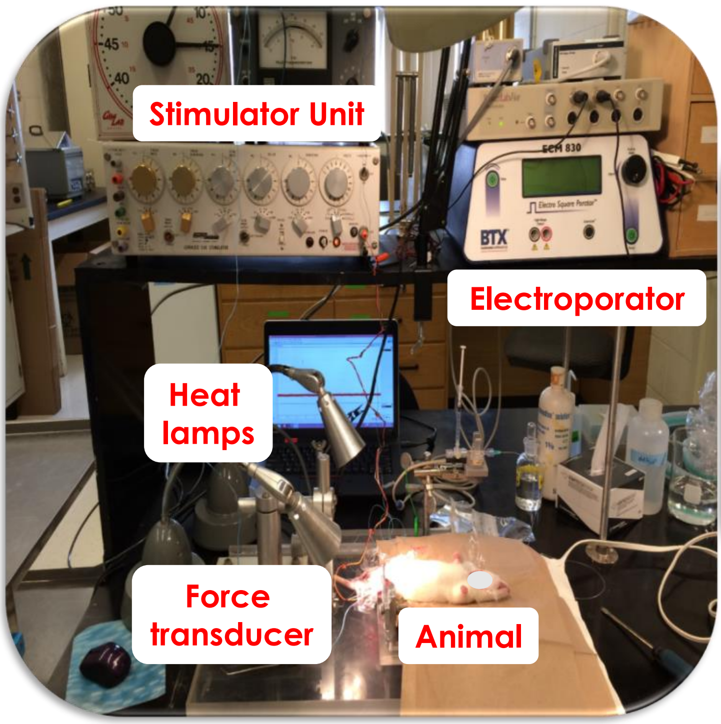
7 days for gene expression

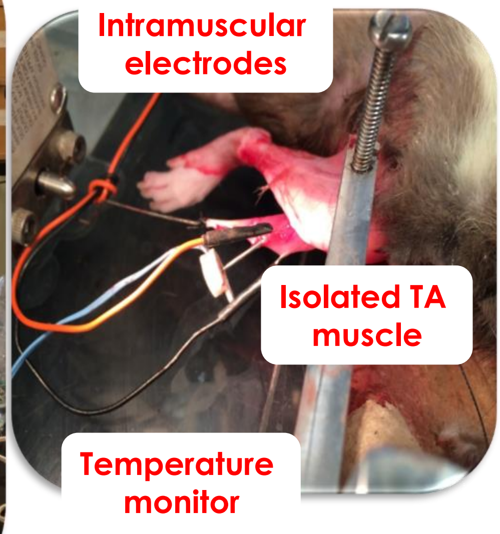
In situ muscle stimulation



40 mins total *in situ* contractile activity
to elicit muscle fatigue

In situ contractile activity of <u>young</u> and <u>aged</u> muscle





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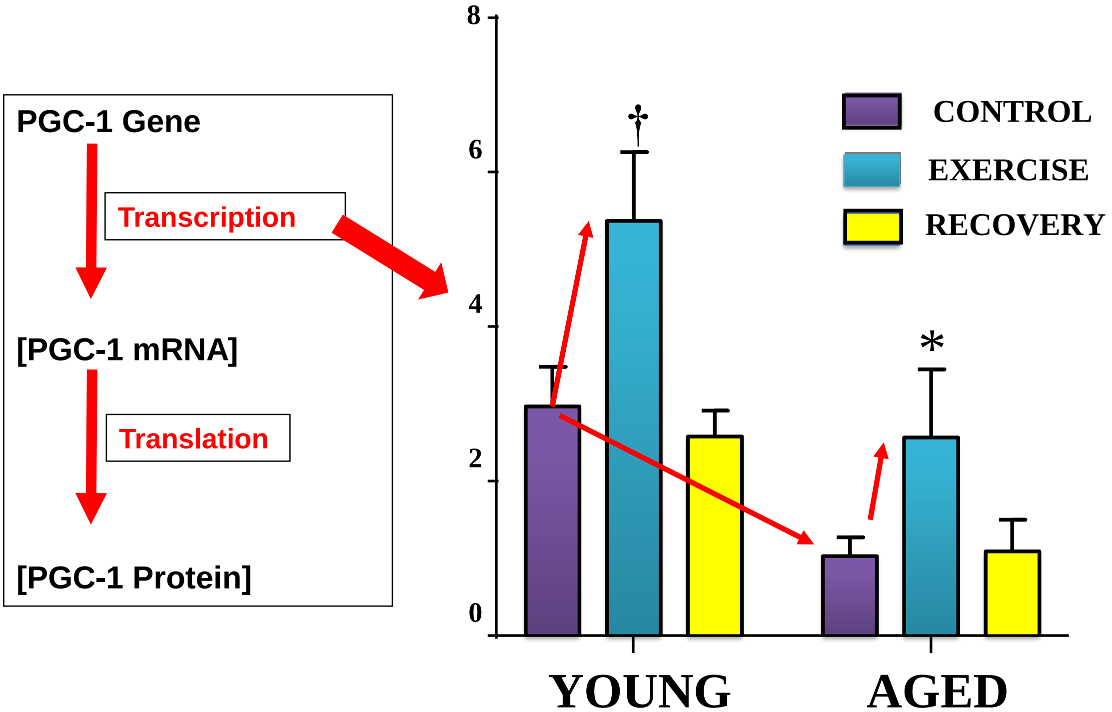
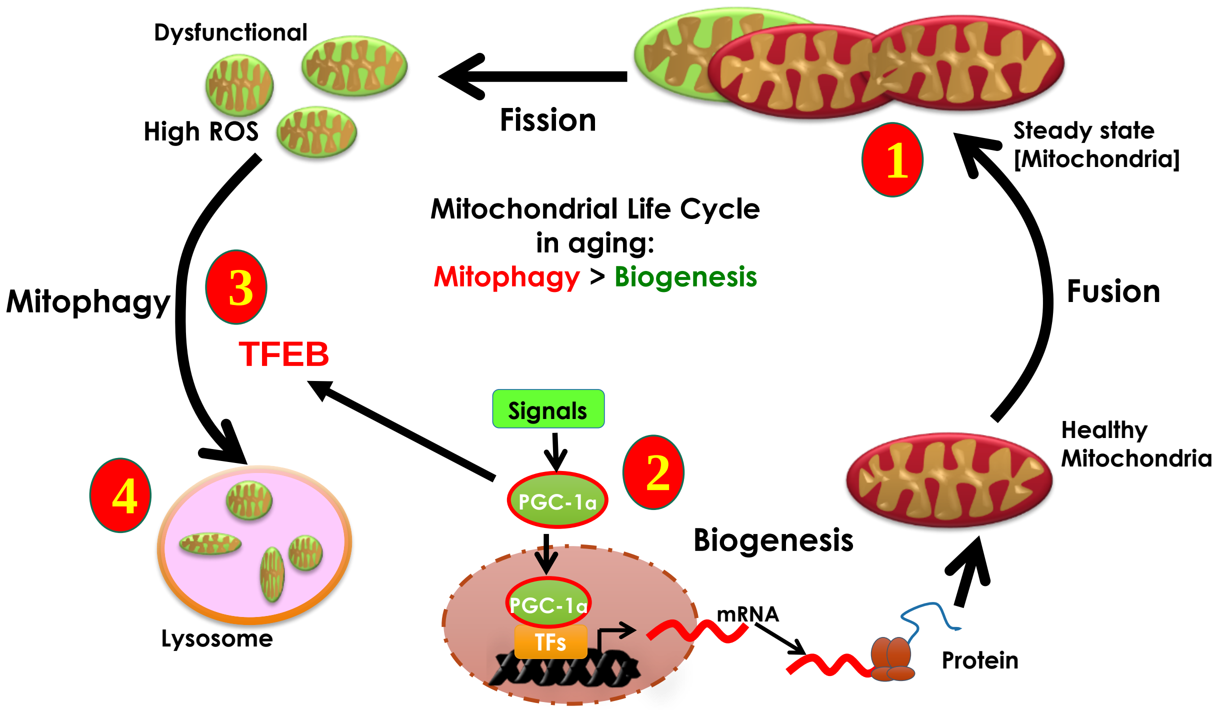
Transcription of PGC-1α is reduced with age, but "rescued" by one exercise bout



Carter HN et al. **J. Appl. Physiol.** 2018



Hood DA et al.
Ann. Rev. Physiol. 2019

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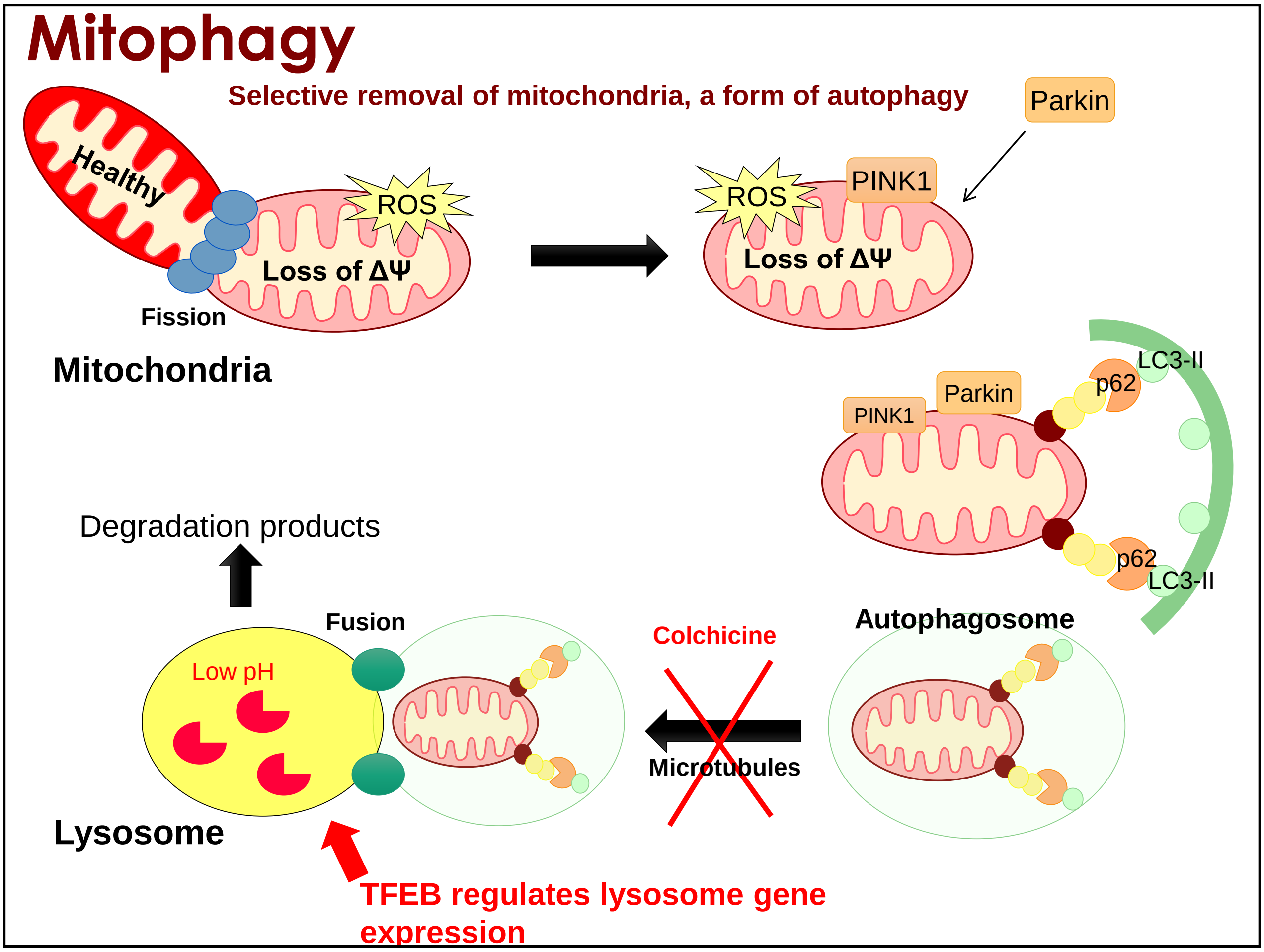

Mitophagy
Selective removal of mitochondria, a form of autophagy
Parkin
Healthy
ROS
Loss of ΔΨ
Fission
ROS
PINK1
Loss of ΔΨ
Mitochondria
LC3-II
p62
Parkin
PINK1
p62
LC3-II
Degradation products
Fusion
Autophagosome
Colchicine
Low pH
Microtubules
Lysosome
TFEB regulates lysosome gene expression

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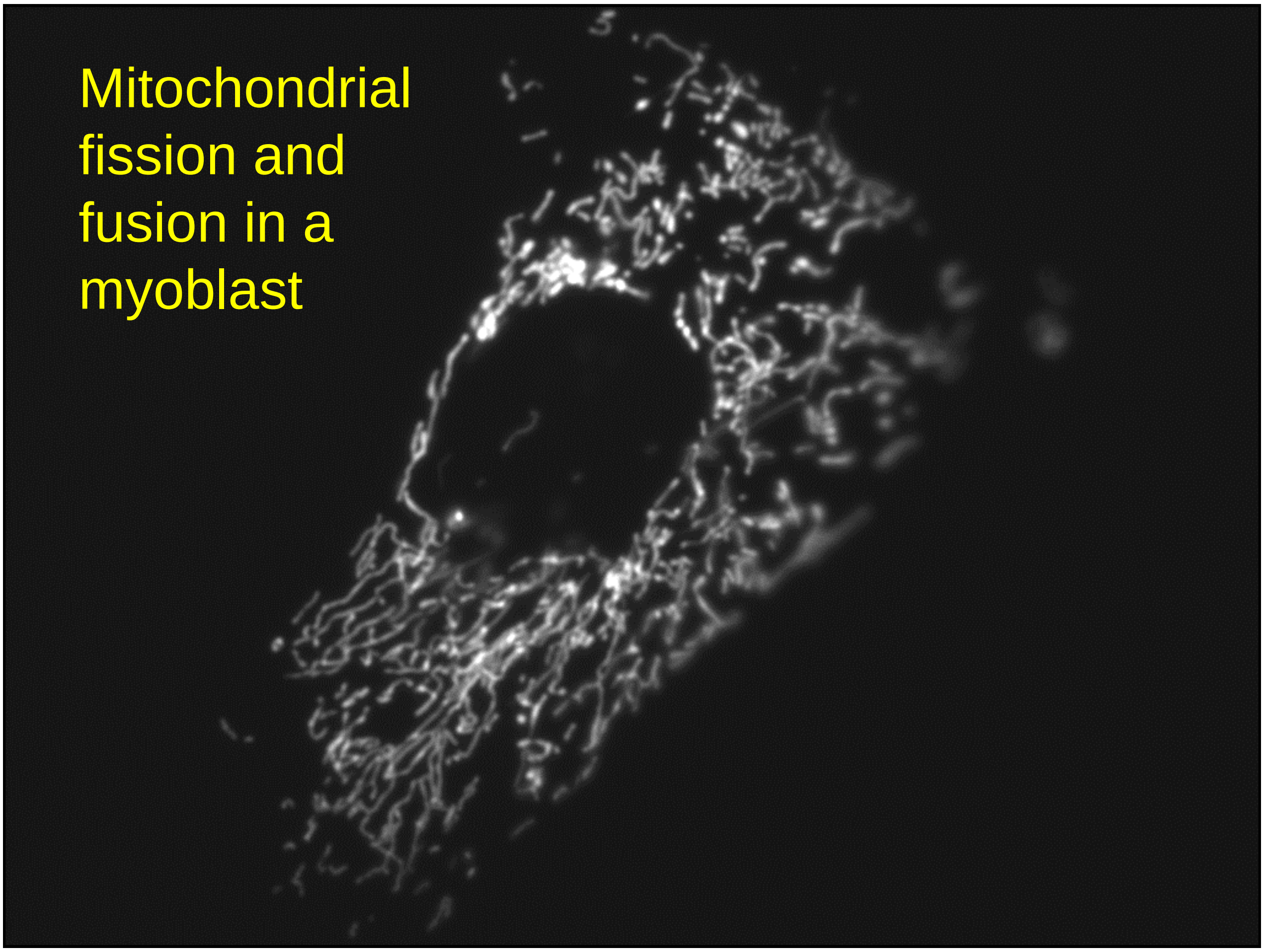

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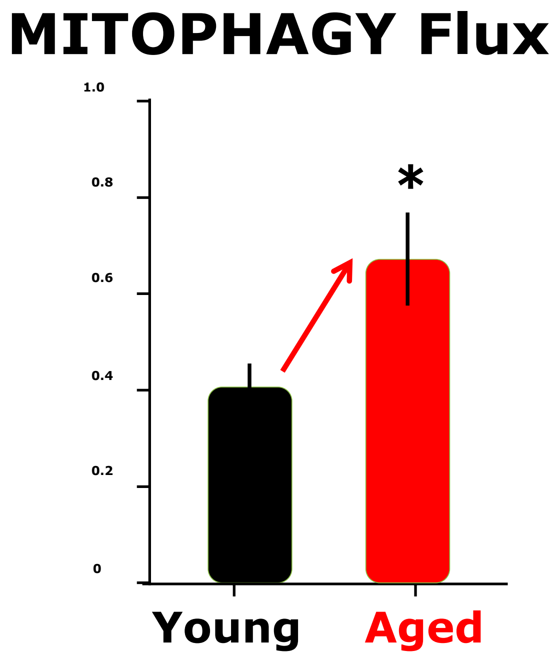
What happens to MITOPHAGY in AGED muscle?



Higher Mitophagy in aged muscle ➔
Decreased [mitochondria] in aged muscle

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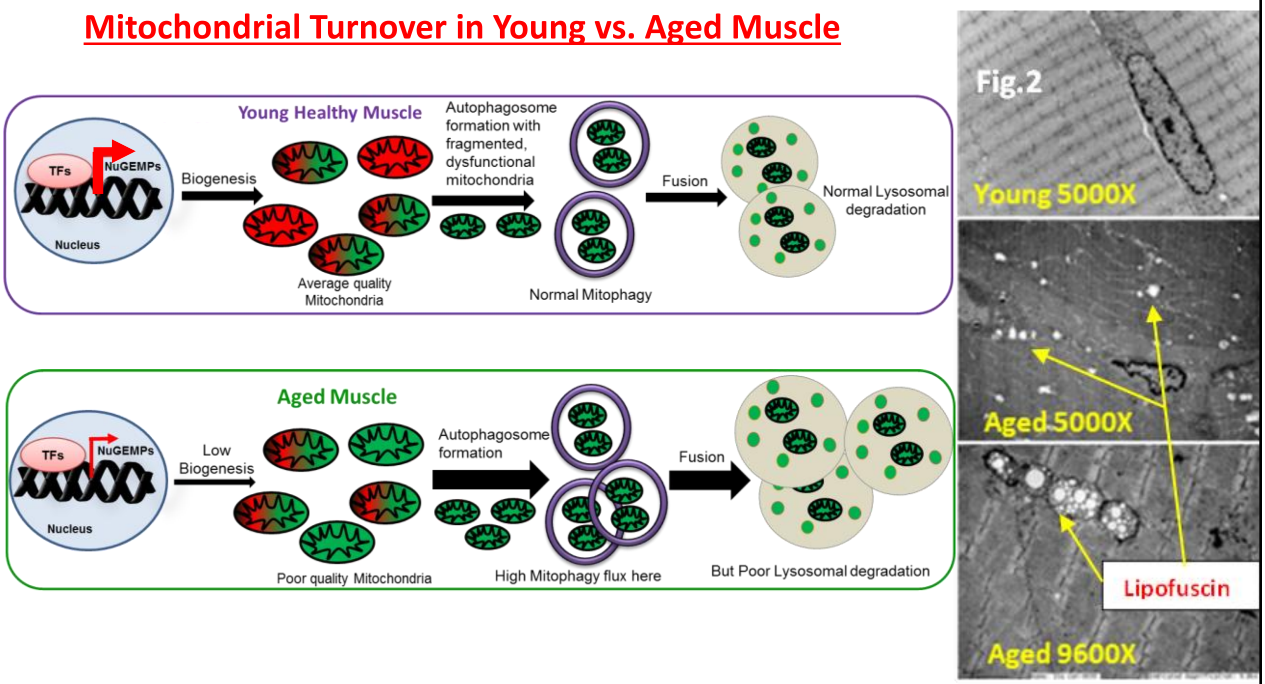
Mitochondrial Turnover in Young vs. Aged Muscle



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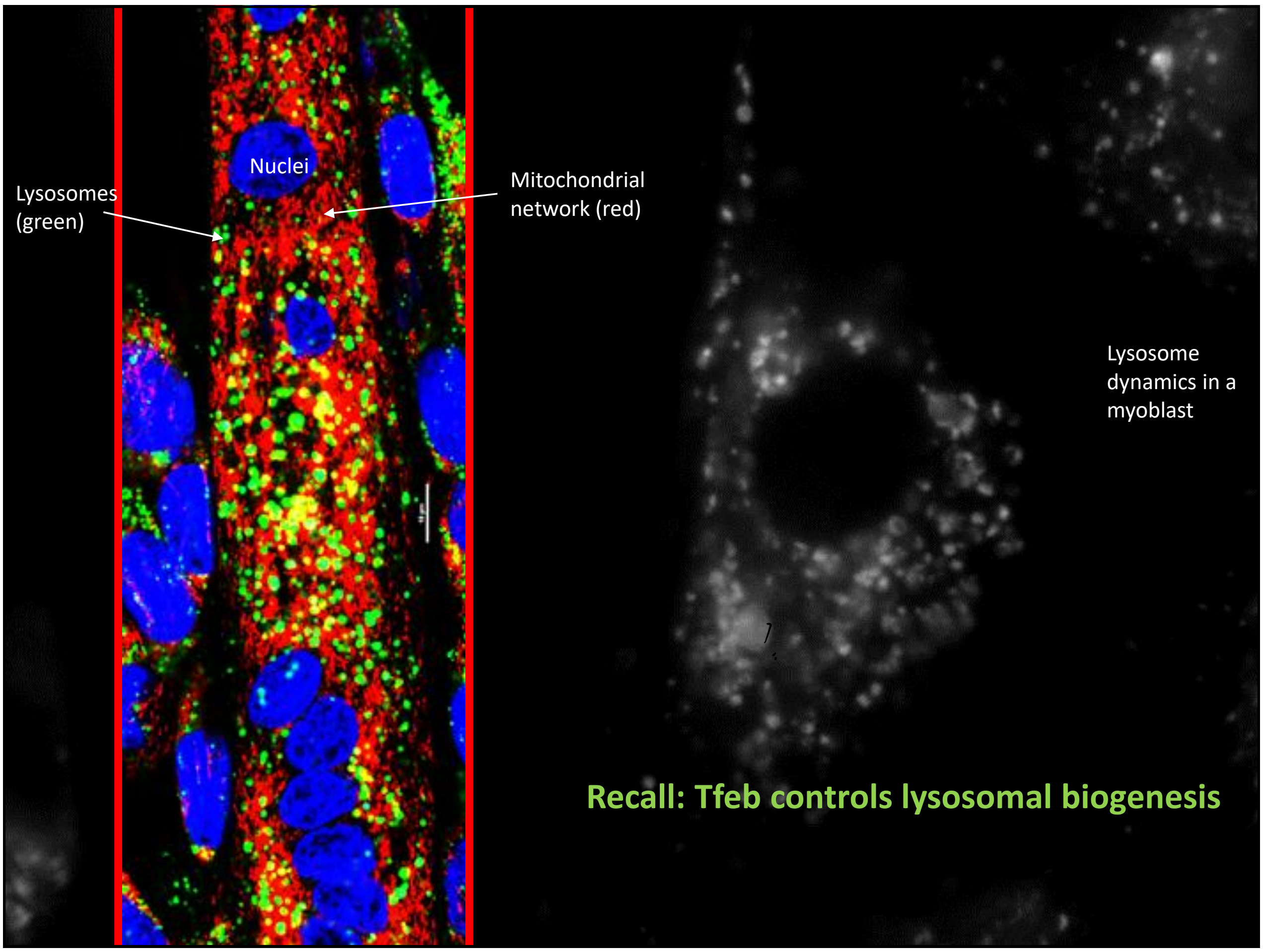
Nuclei
Lysosomes (green)
Mitochondrial network (red)
Lysosome dynamics in a myoblast
Recall: Tfeb controls lysosomal biogenesis

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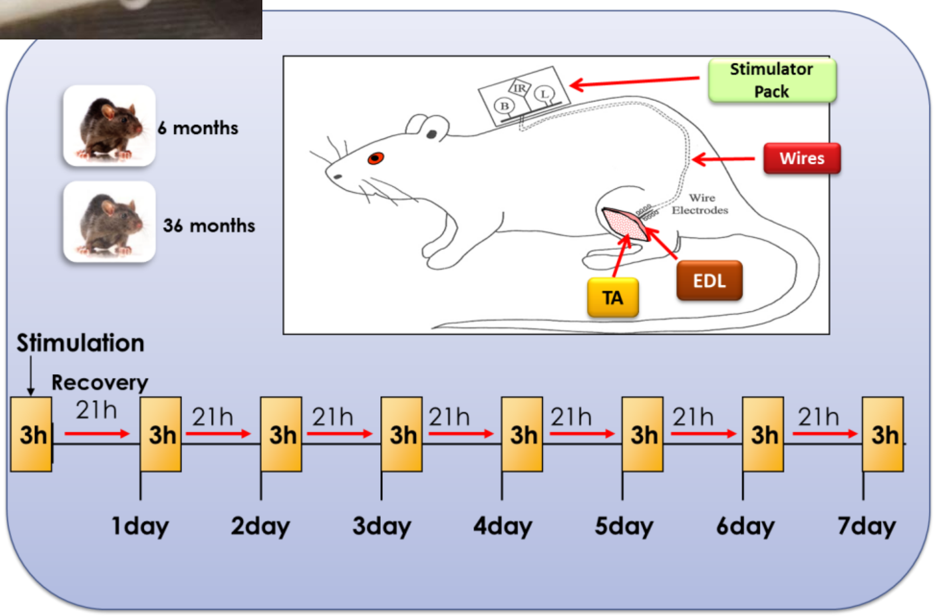
How can "Exercise" improve muscle health in Aged Muscle?



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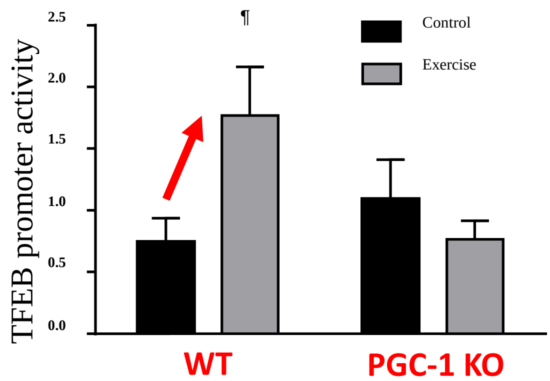
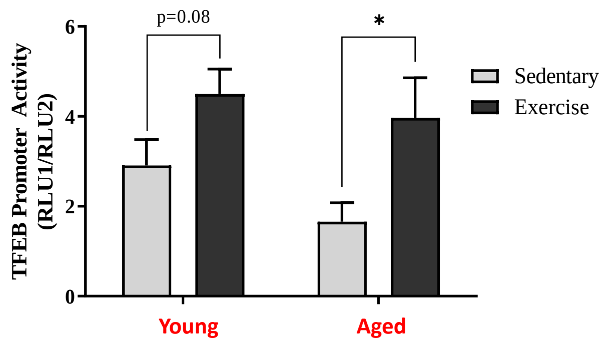
Acute exercise increases the transcription of Tfeb

-- in a PGC-1 dependent manner

Erlich, A. et al. **Am. J. Physiol.** 2017



-- even in older animals



Triolo, M. et al. **Skeletal Muscle** 2018

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Chronic Contractile Activity

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Sarcopenia and “pink-to-red” transformation in YOUNG and OLD muscle

YOUNG

AGED

Carter, HN and DA Hood, <u>Journal of Physiology (London)</u> 2018

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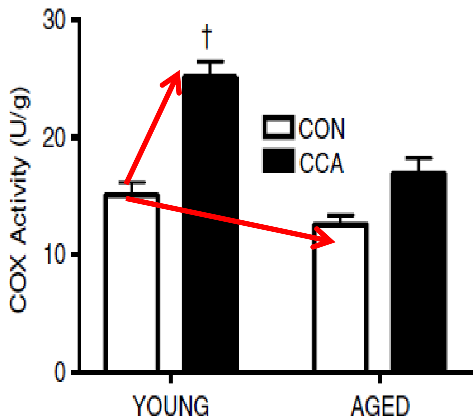
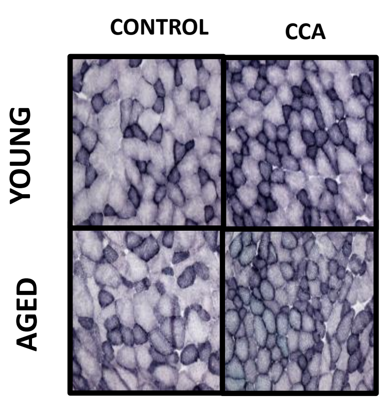
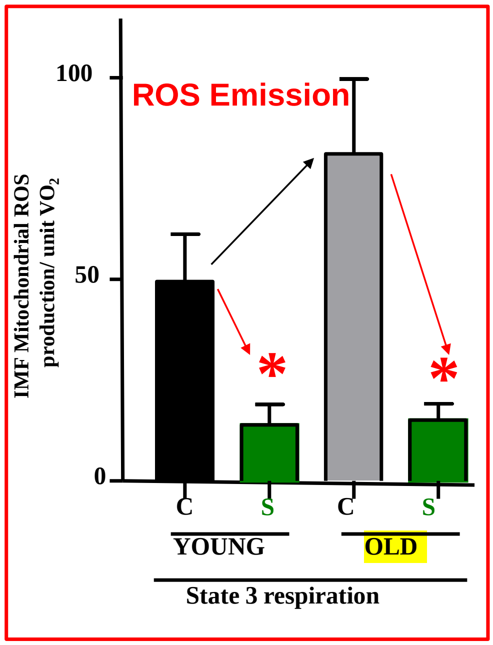
Mitochondrial content and function improve with CCA in aged muscle

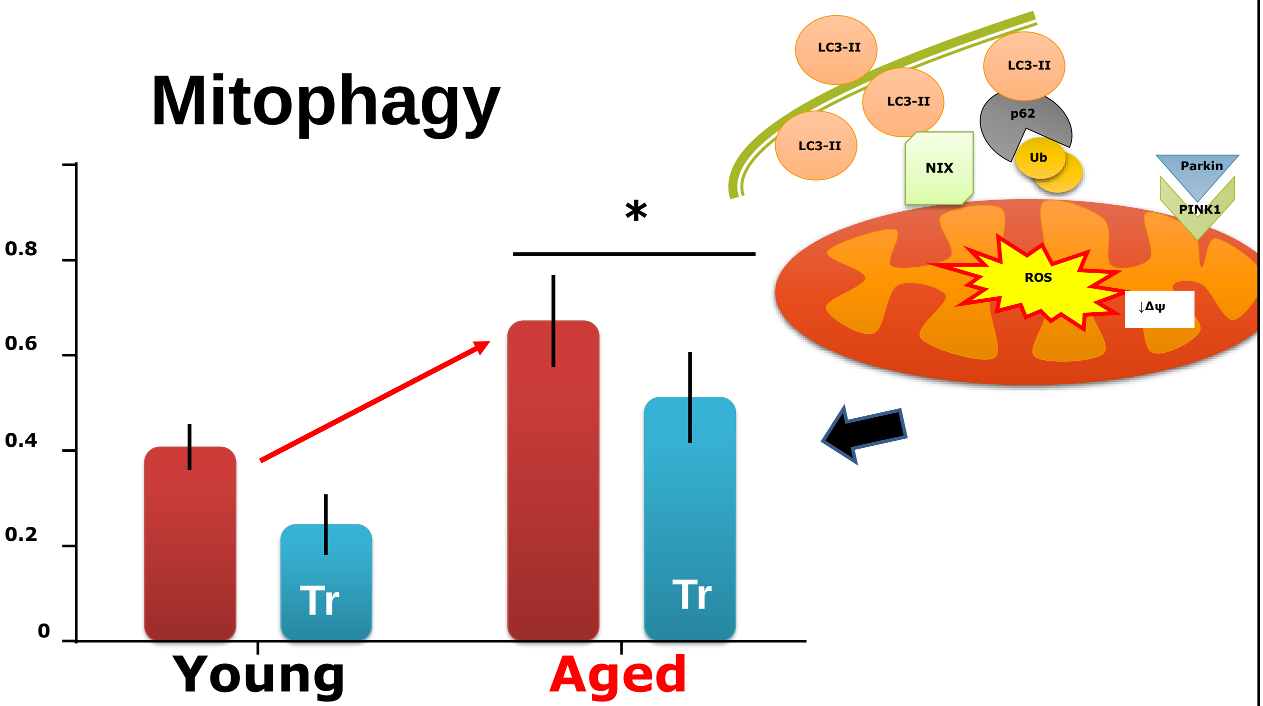






Carter, HN and DA Hood, J. Physiol. (London) 2018

What happens to MITOPHAGY as a result of "Training"?



Higher Mitophagy flux in aged muscle ➔
Is attenuated by chronic exercise because exercise stimulates the production of high quality mitochondria ➔ reduced signaling

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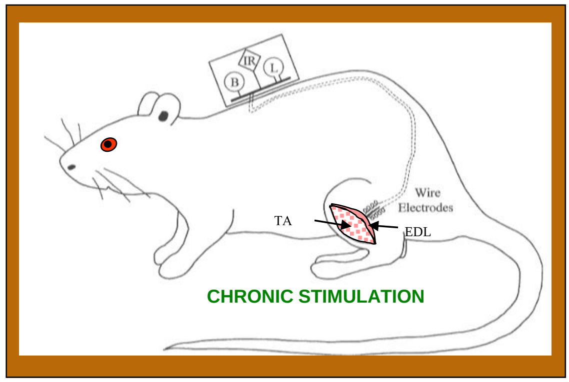
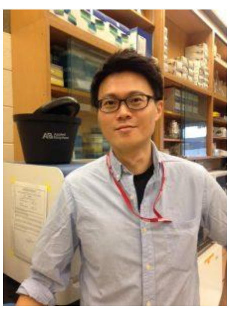
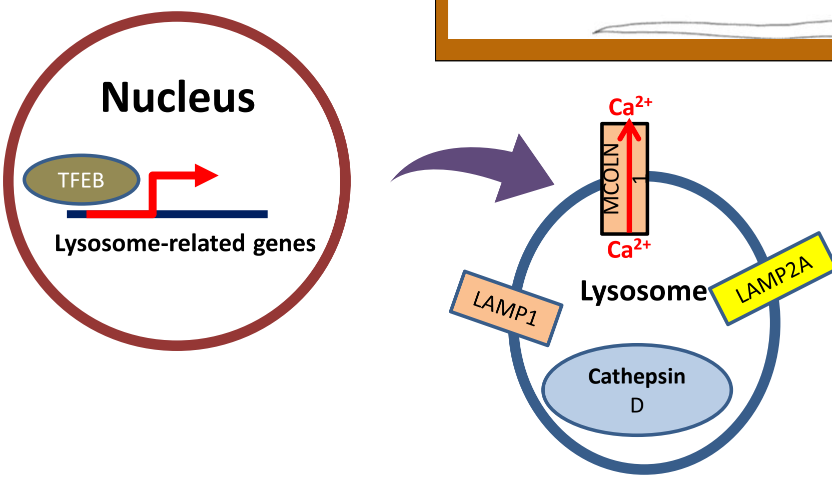
Regular Exercise produces Lysosomal adaptations







Kim, Y. and D.A. Hood, Physiol. Rep. 2017

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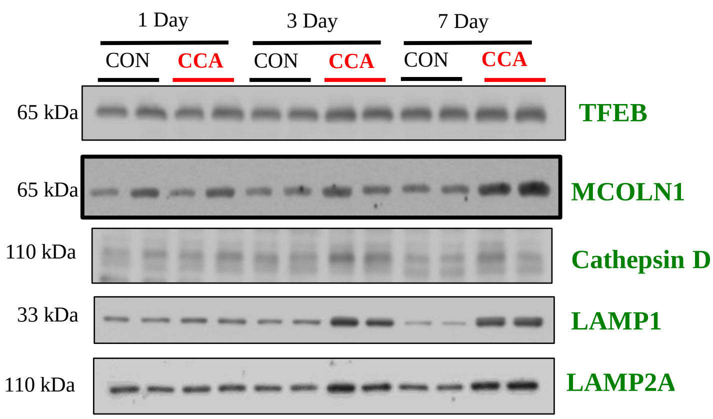
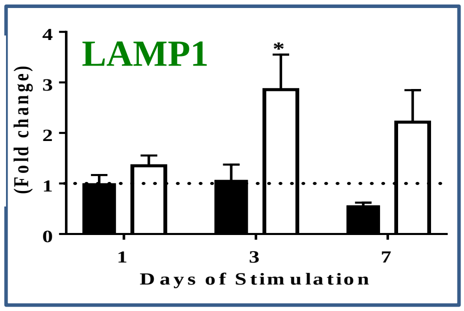
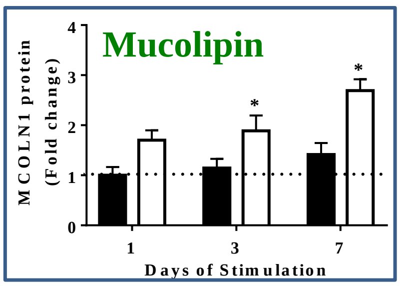
Exercise increases lysosomal degradation capacity







➔ reverse lysosomal dysfunction associated with age??

Kim, Y. et al. **Physiol. Rep**. 2017

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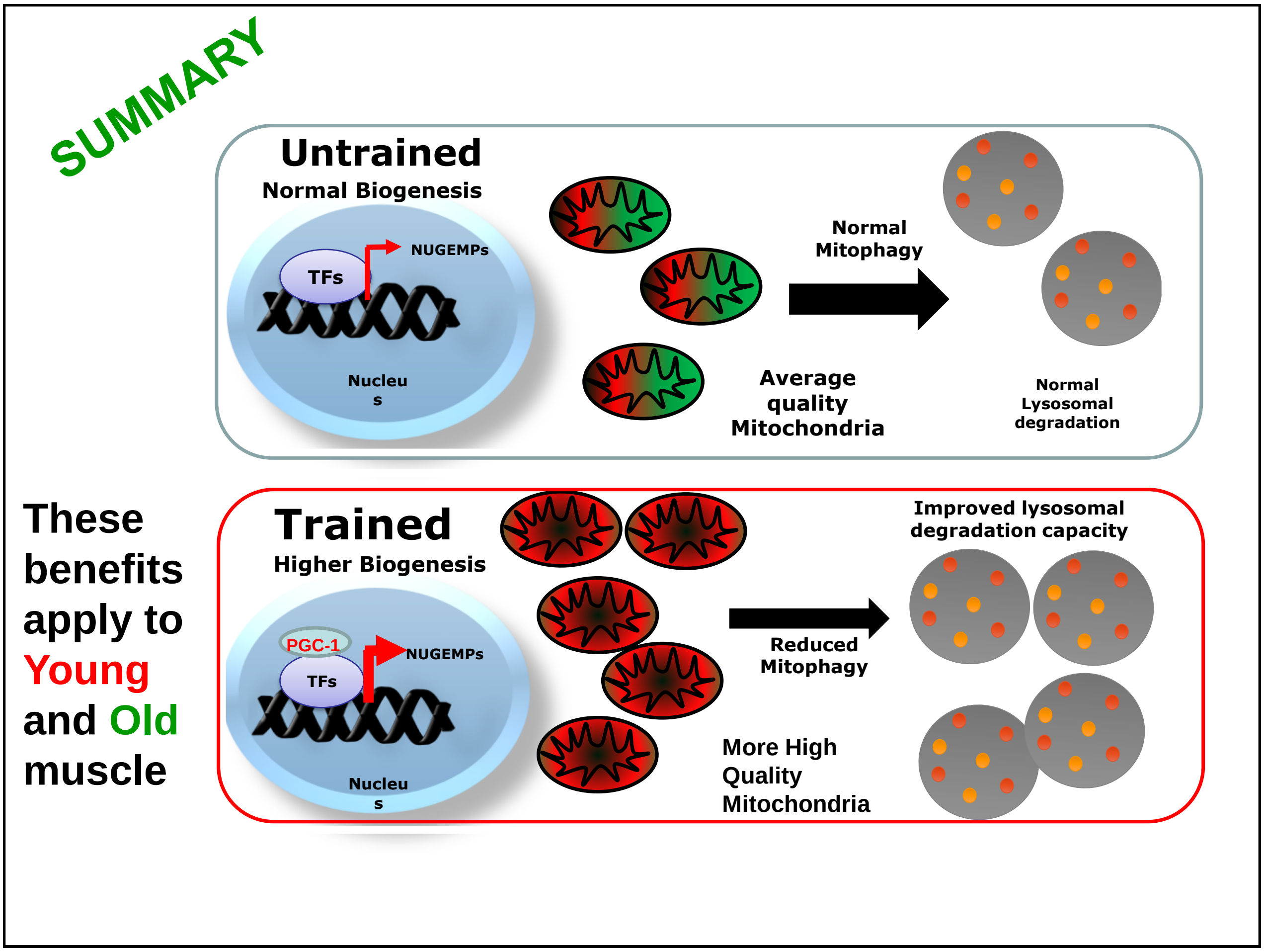
SUMMARY
Untrained
Normal Biogenesis
TFs
NUGEMPs
Nucleu
s
Normal
Mitophagy
Average
quality
Mitochondria
Normal
Lysosomal
degradation
These
benefits
apply to
Young
and Old
muscle
Trained
Higher Biogenesis
PGC-1
TFs
NUGEMPs
Nucleu
s
Reduced
Mitophagy
More High
Quality
Mitochondria
Improved lysosomal
degradation capacity

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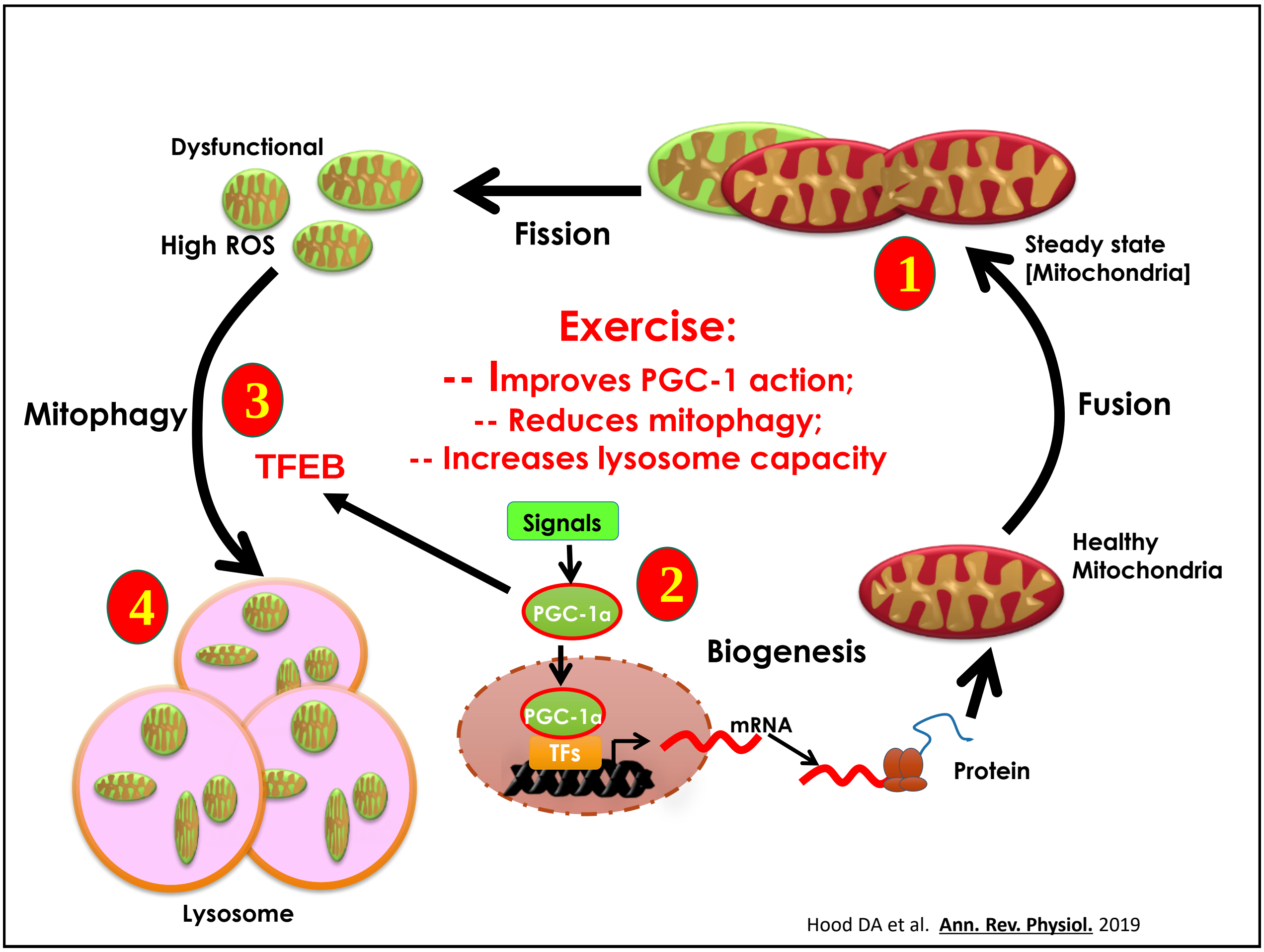
Dysfunctional
High ROS
Fission
Steady state
[Mitochondria]
1
Exercise:
-- Improves PGC-1 action;
-- Reduces mitophagy;
-- Increases lysosome capacity
Mitophagy
3
TFEB
Fusion
Signals
2
PGC-1α
Healthy
Mitochondria
4
Biogenesis
PGC-1α
TFs
mRNA
Protein
Lysosome
Hood DA et al. Ann. Rev. Physiol. 2019

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Conclusions:

1. Reduced mitochondrial content / function in aged muscle is due to:

Mitophagy > Biogenesis

2. Biogenesis is reduced, in part, due to impaired PGC-1α transcription;

4. Exercise reverses mitochondrial decay in aged muscle ➔ increased content and better function, but the response is attenuated compared to young muscle;

5. Chronic exercise reduces elevated basal mitophagy in aged muscle due to enhanced production of good quality mitochondria ➔ less signaling to mitophagy;

6. Exercise increases lysosomal biogenesis and degradation capacity to help reverse the accumulation of defective mitochondria.

➔ Exercise in Muscle Mitochondrial (and Lysosomal) Medicine

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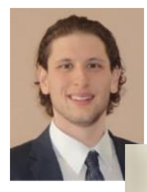

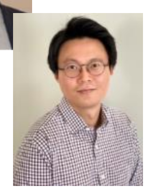

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Muscle Health & Research Centre
Adaptation • Development • Metabolism • Disease

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