



MITOCHONDRIAL FITNESS SUSTAINS HEALTHY AGING



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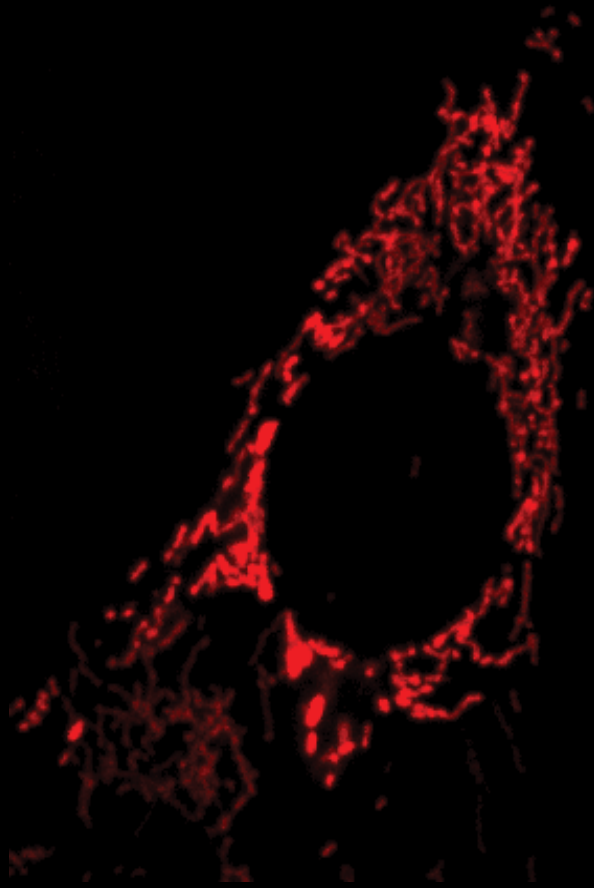
Facultat de Farmàcia
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CENTRO DE INVESTIGACIÓN BIOMÉDICA EN RED
Diabetes y Enfermedades Metabólicas Asociadas

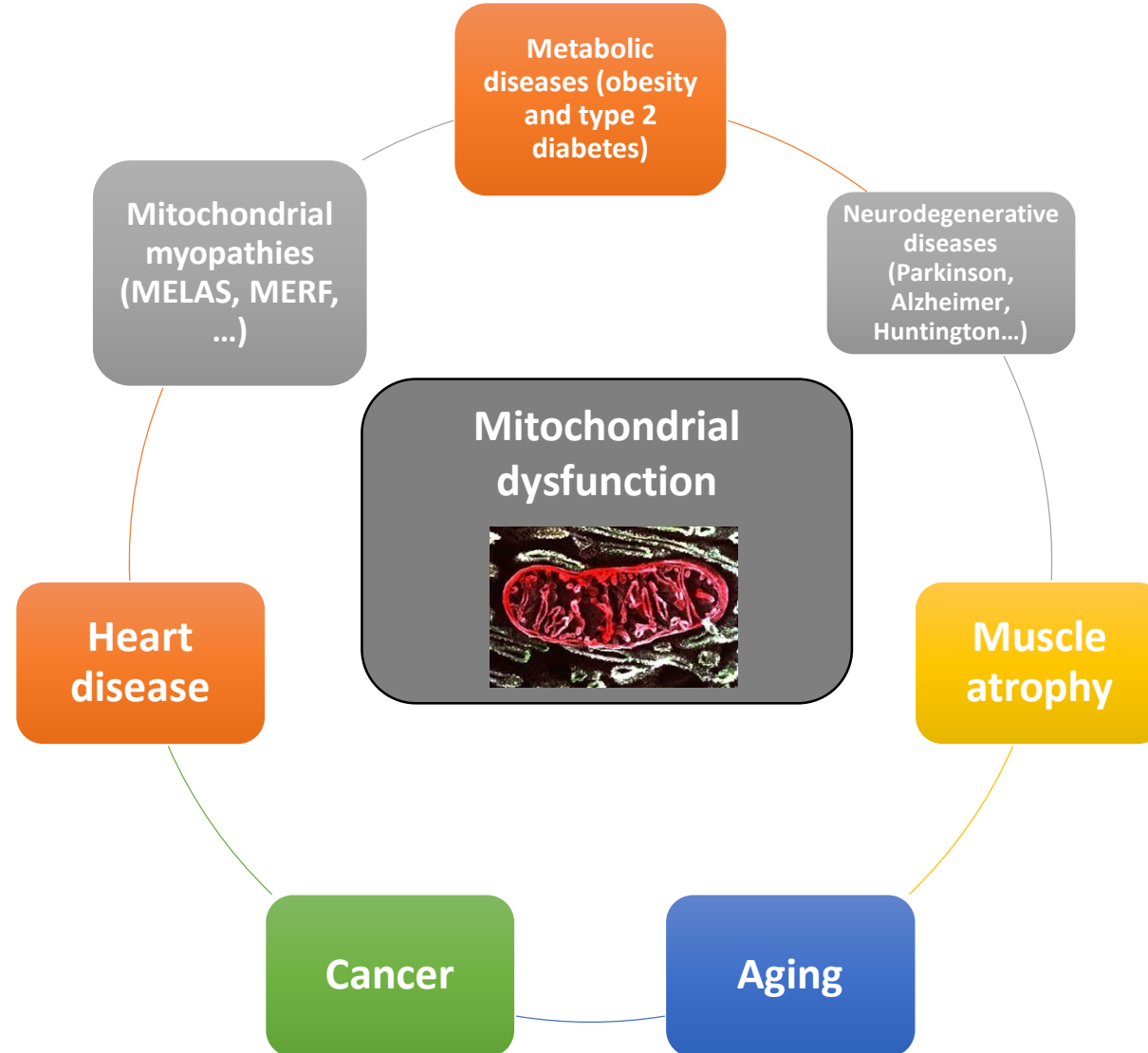
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Facultat de Farmàcia i Ciències de l'Alimentació
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Mitochondria: essential organelles in human health and disease

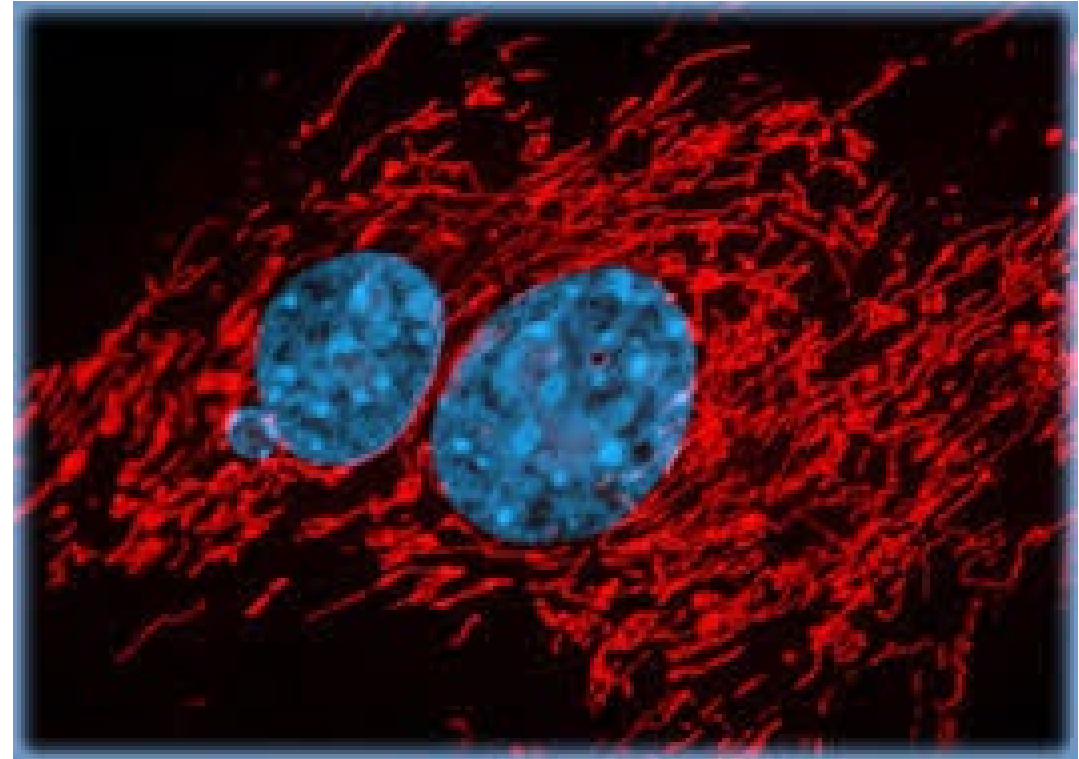
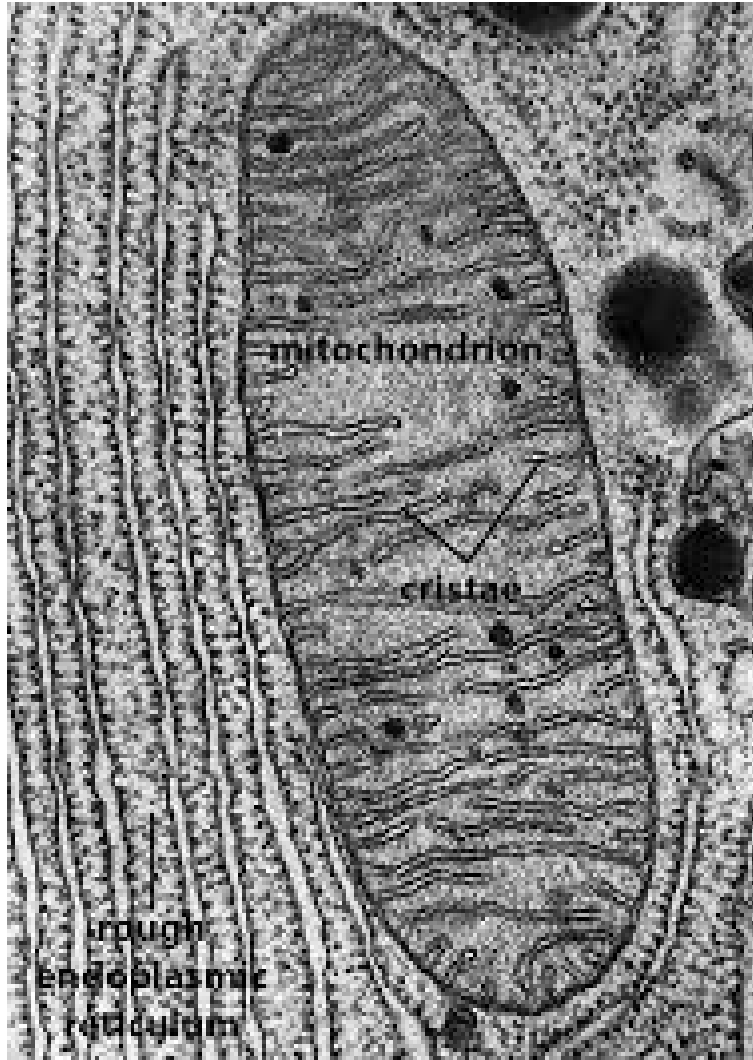


- major energy generator
- cell signaling
- interorganellar communication
- apoptosis
- interconversion of carbohydrates, lipids and amino acids
- haem biosynthesis
- iron-sulphur cluster biogenesis
- innate immunity

Mitochondrial dysfunction is at the core of several human pathologies



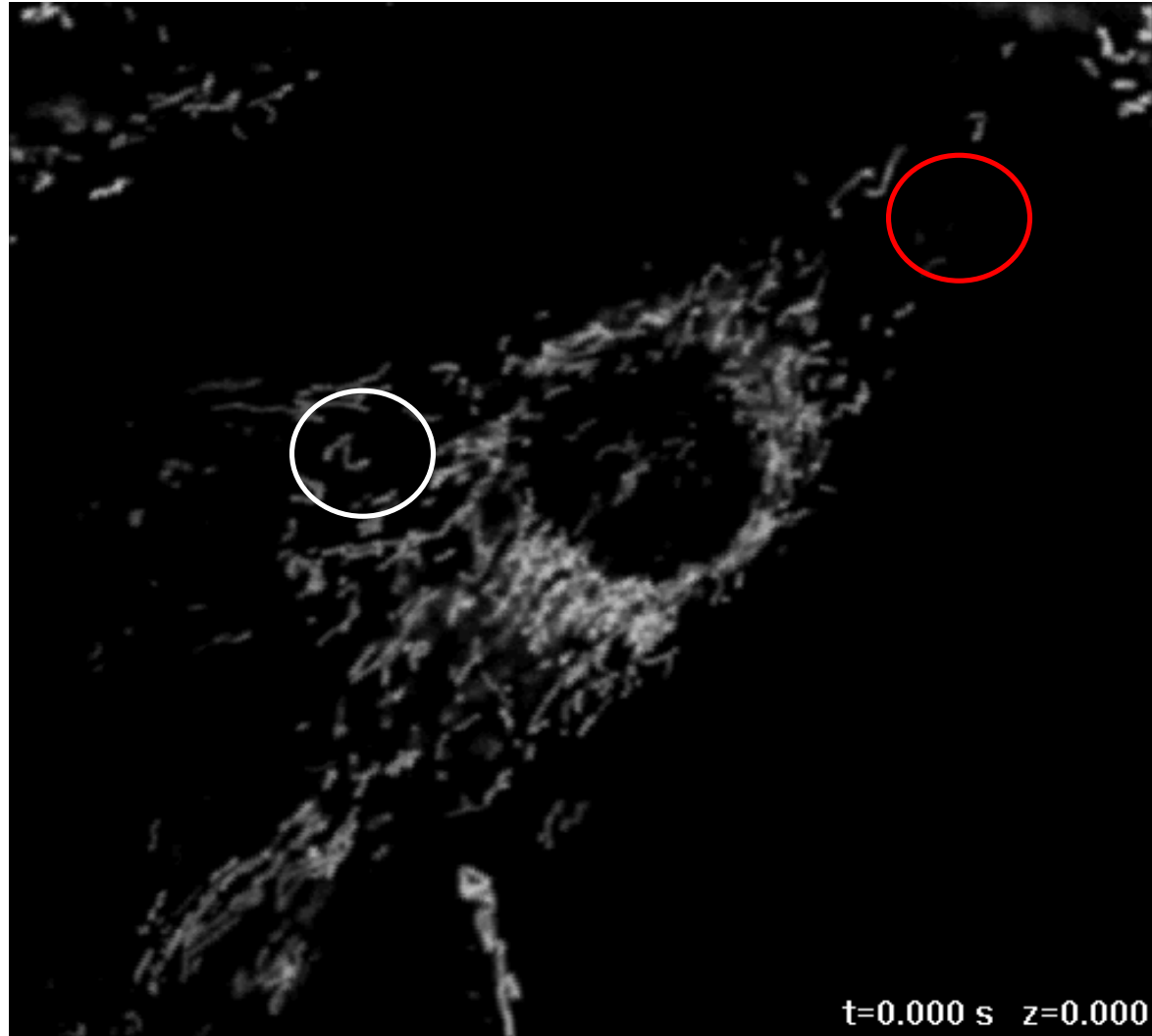
Mitochondria inside the cells



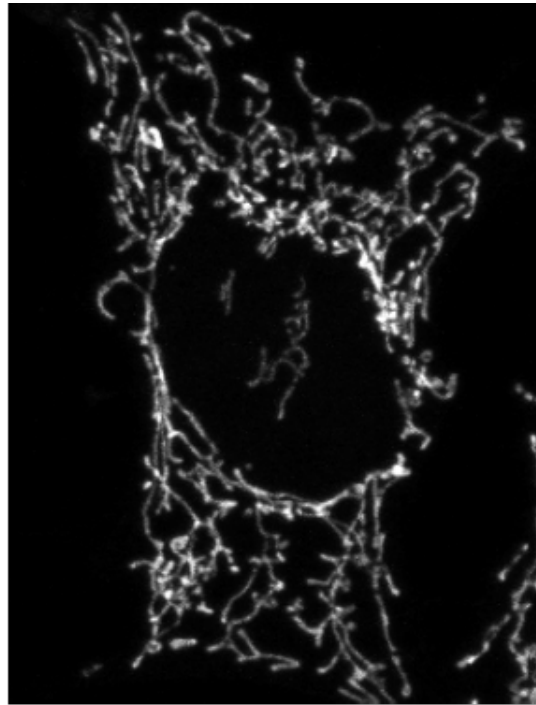
Mitochondria are very dynamic organelles

**Fission: white
circle**

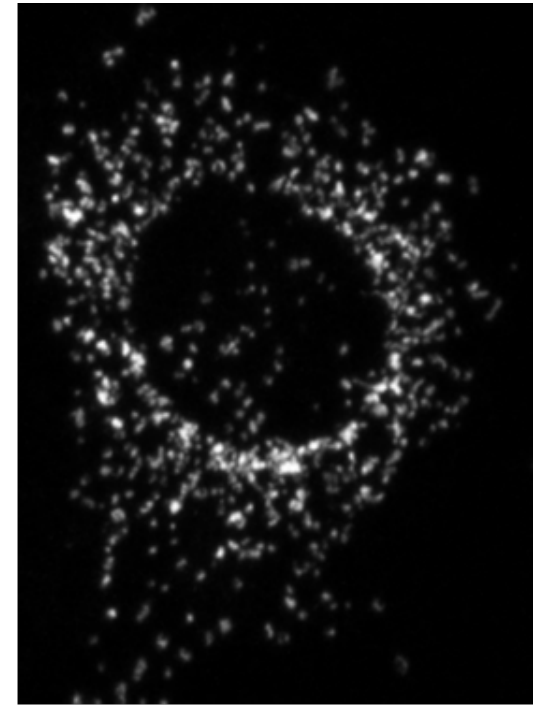
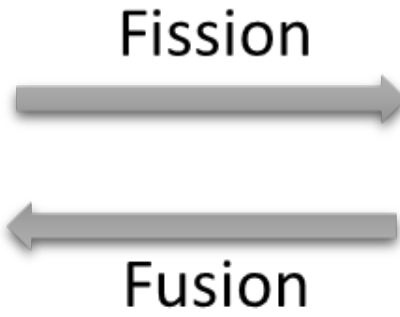
**Fusion: red
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Mitochondrial dynamics regulates mitochondrial morphology

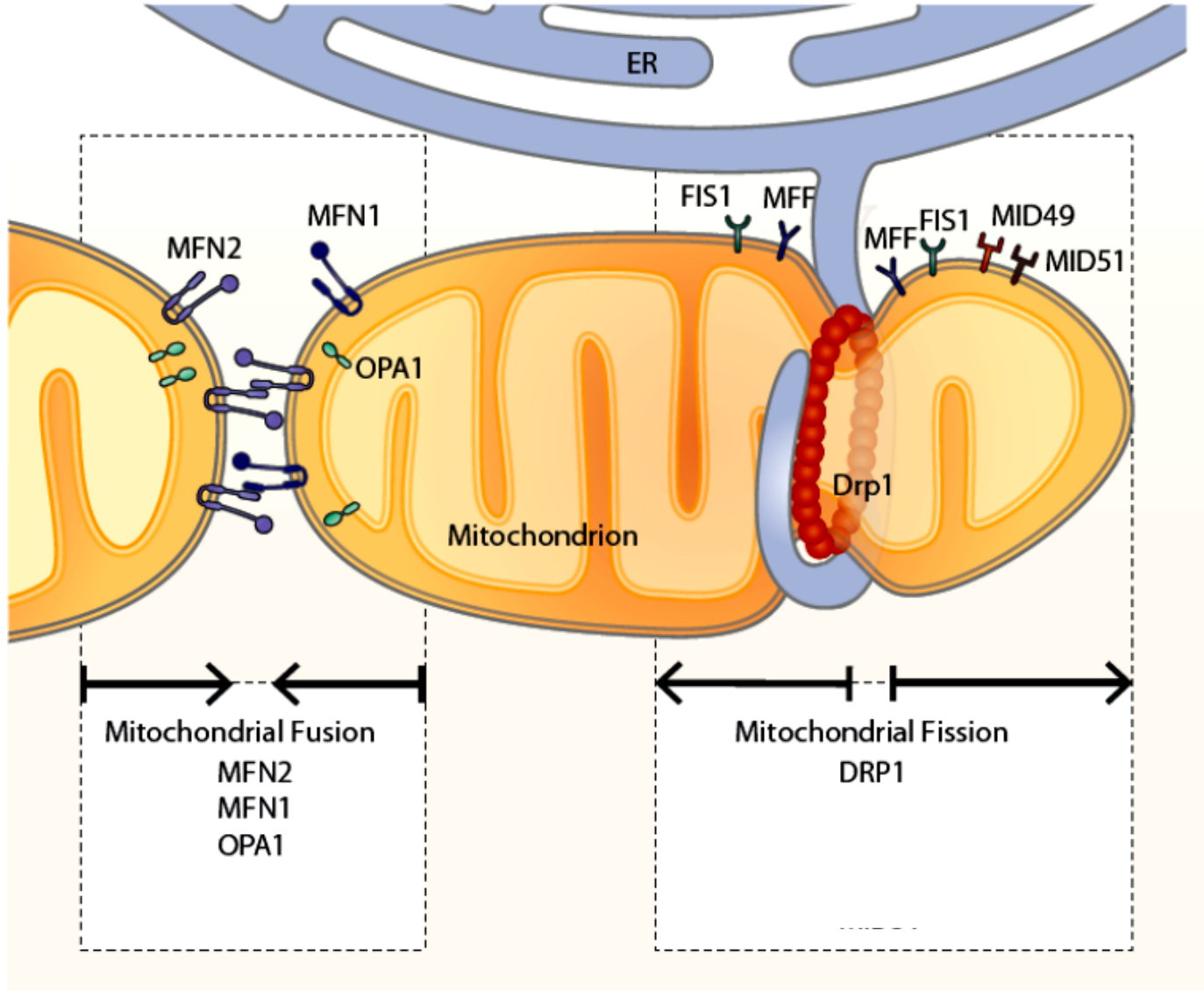


Elongated mitochondrial network

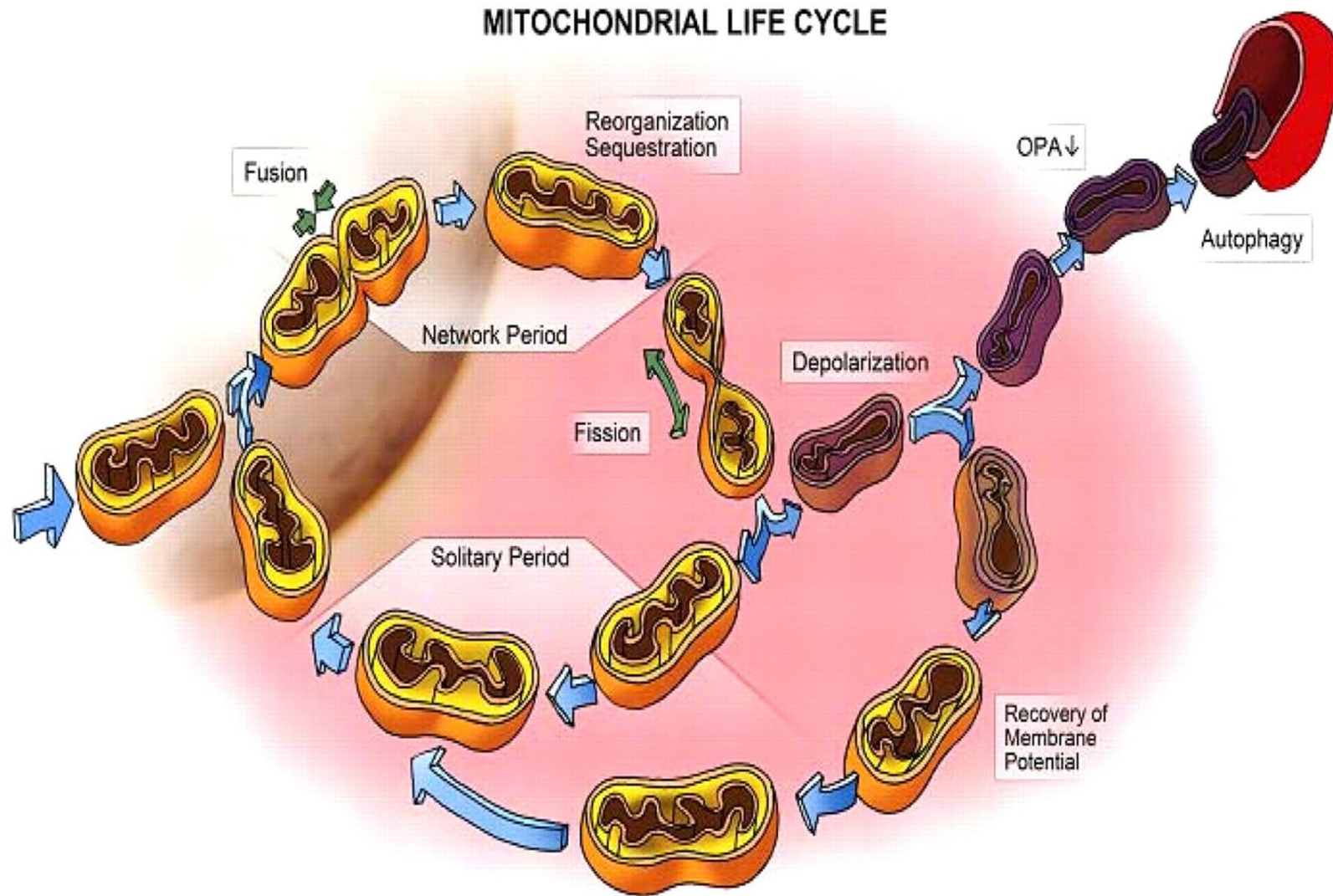


Fragmented mitochondrial network

Mitochondrial dynamics is controlled by mitochondrial fusion and fission proteins

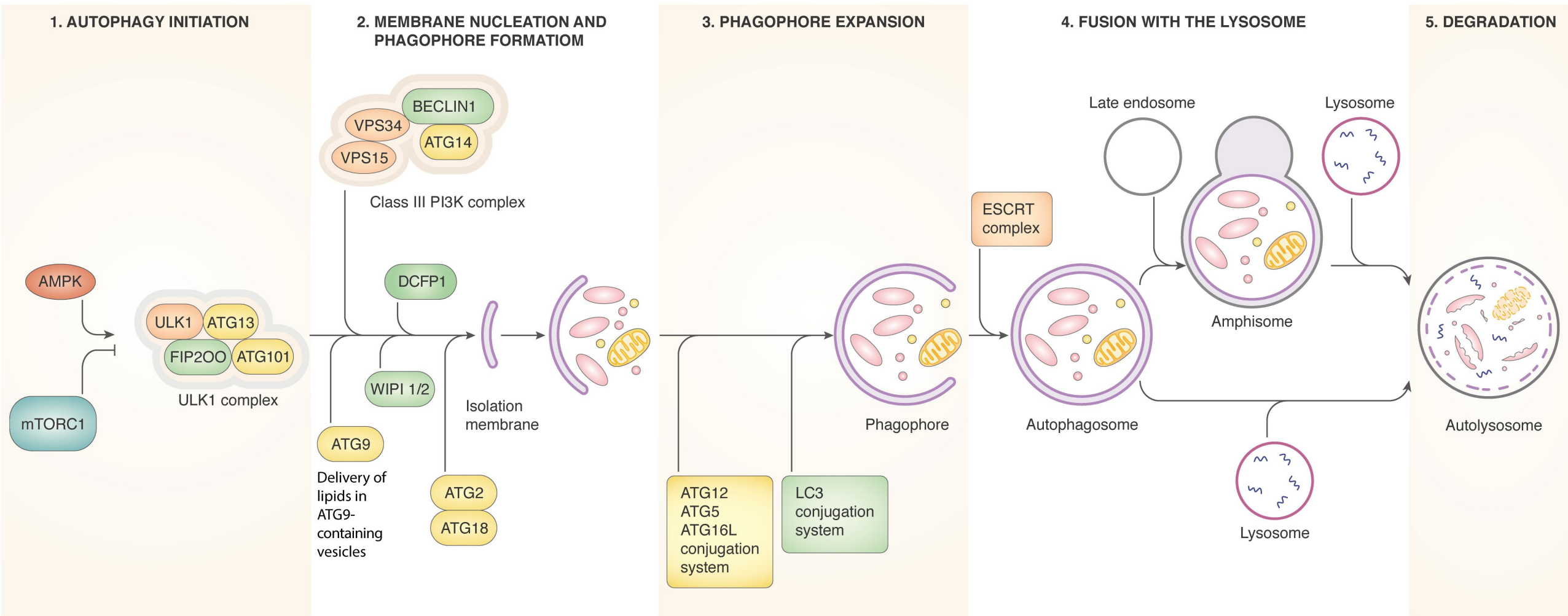


Mitochondrial dynamics and the mitochondrial life cycle



Autophagy

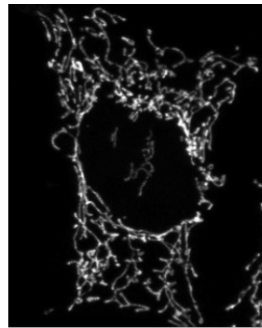
FIGURE 1
Molecular regulation of autophagy



Mitochondrial health is key in the maintenance of cellular homeostasis

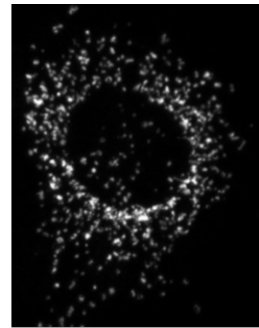
Mitochondrial morphology
and movement

Mitochondrial
dynamics



Elongated mitochondrial network

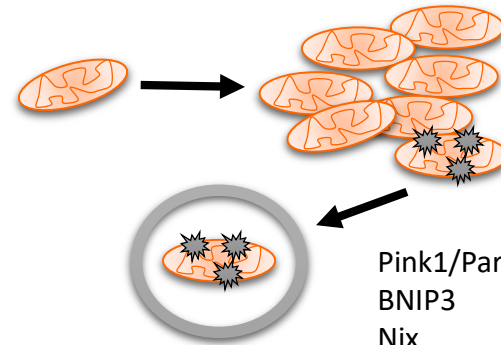
Drp1
Fission
Fusion
Mfn1/2, OPA1



Fragmented mitochondrial network

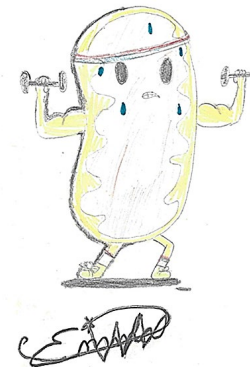
Mitochondrial mass
and quality

Mitochondrial
biogenesis and
mitophagy



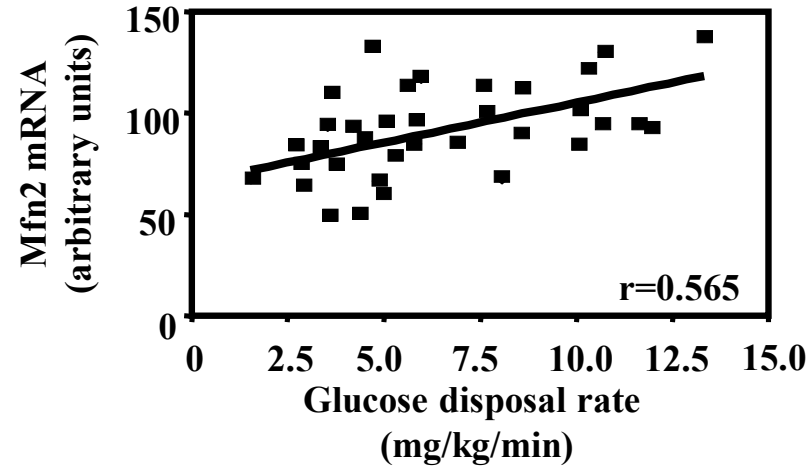
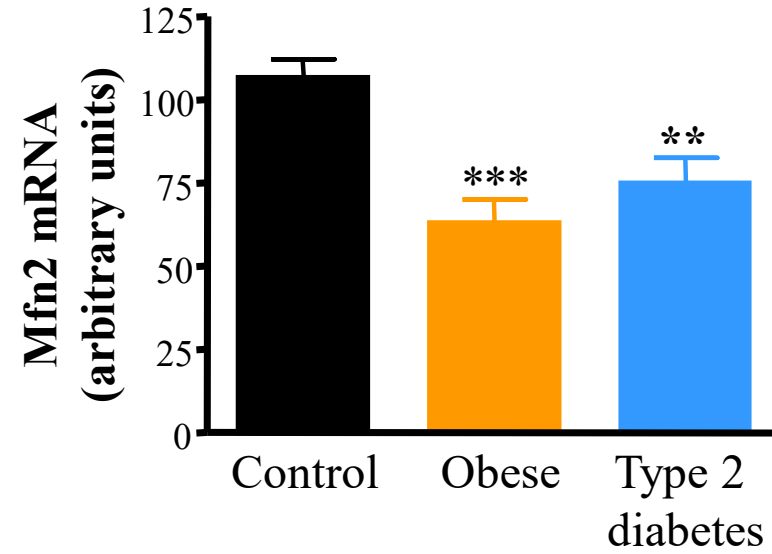
Pink1/Parkin
BNIP3
Nix
FUNDC1
OPTN
NDP52

Mitochondrial
fitness

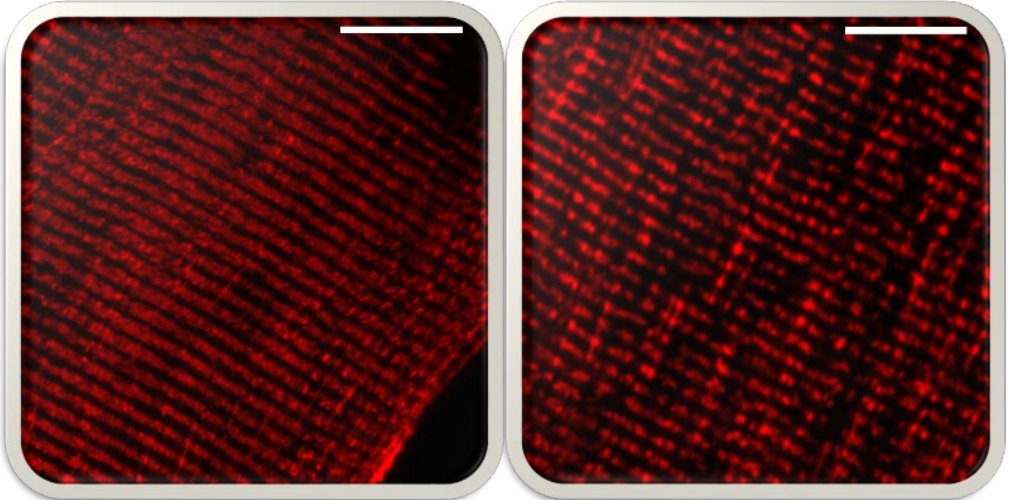


Role of mitochondrial fitness in metabolic disease

Muscle Mfn2 expression is lower in obesity and type 2 diabetes and is correlated with insulin sensitivity



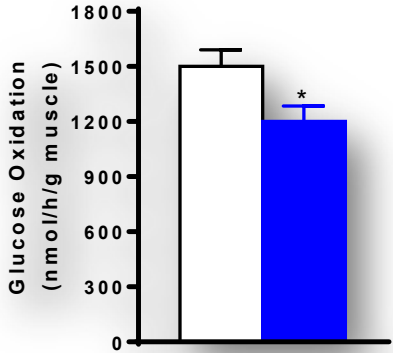
Mfn2 deficiency causes defective mitochondrial metabolism in skeletal muscle



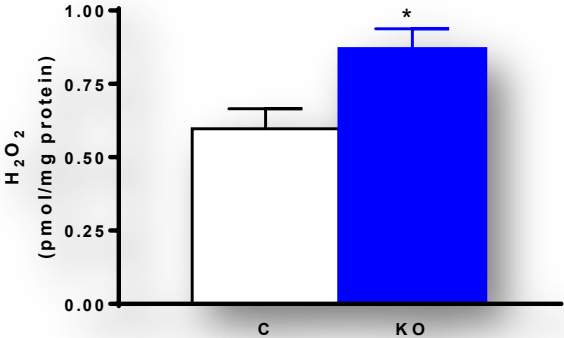
Control

Mfn2 KO

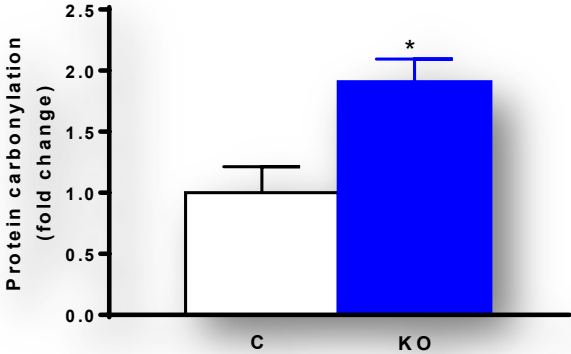
Glucose oxidation



H2O2 levels

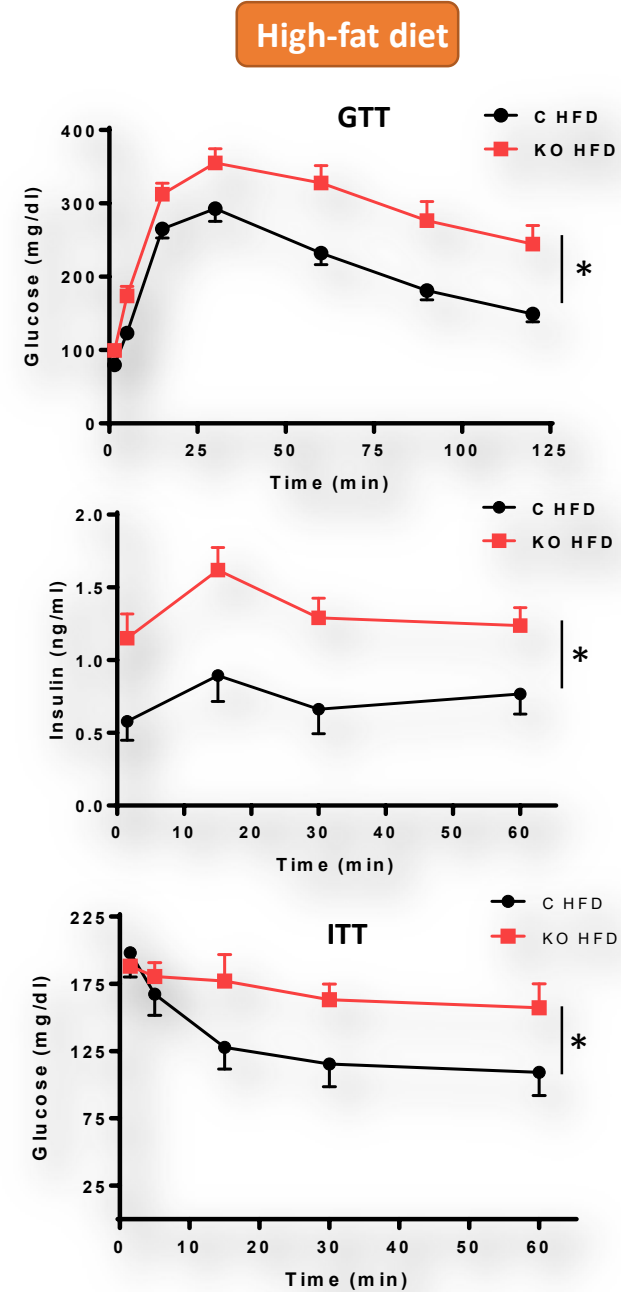
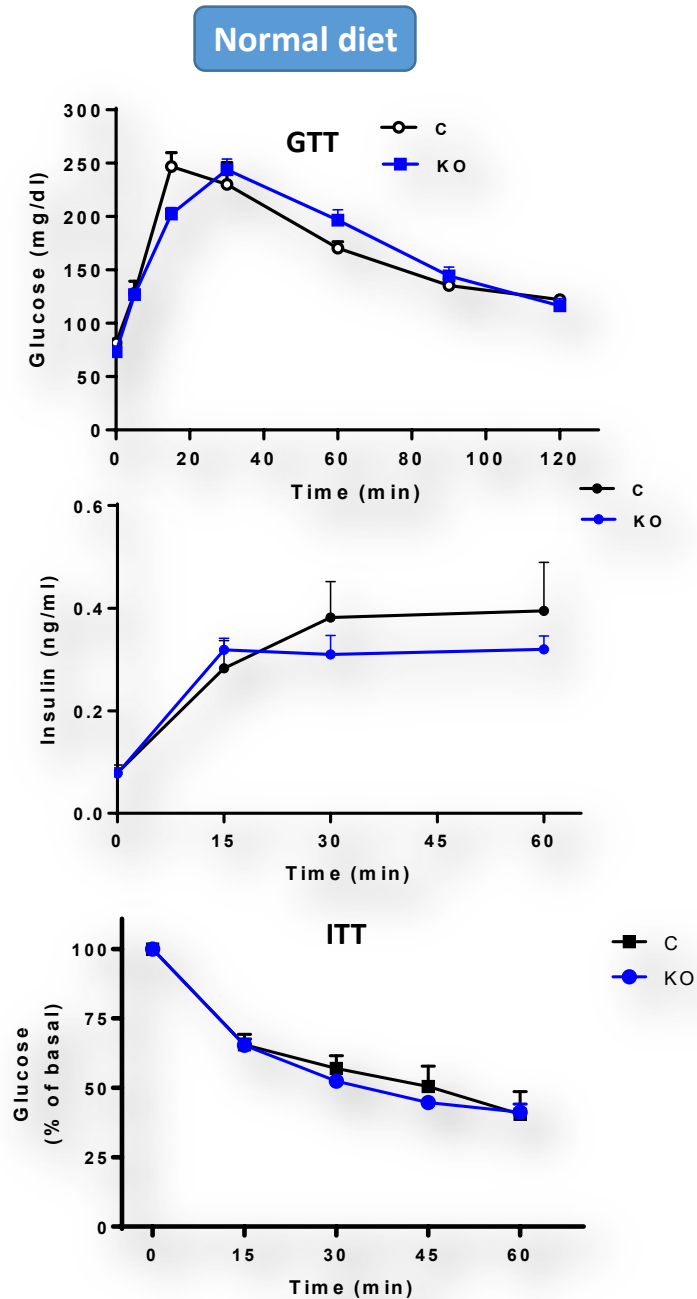


Protein carbonylation

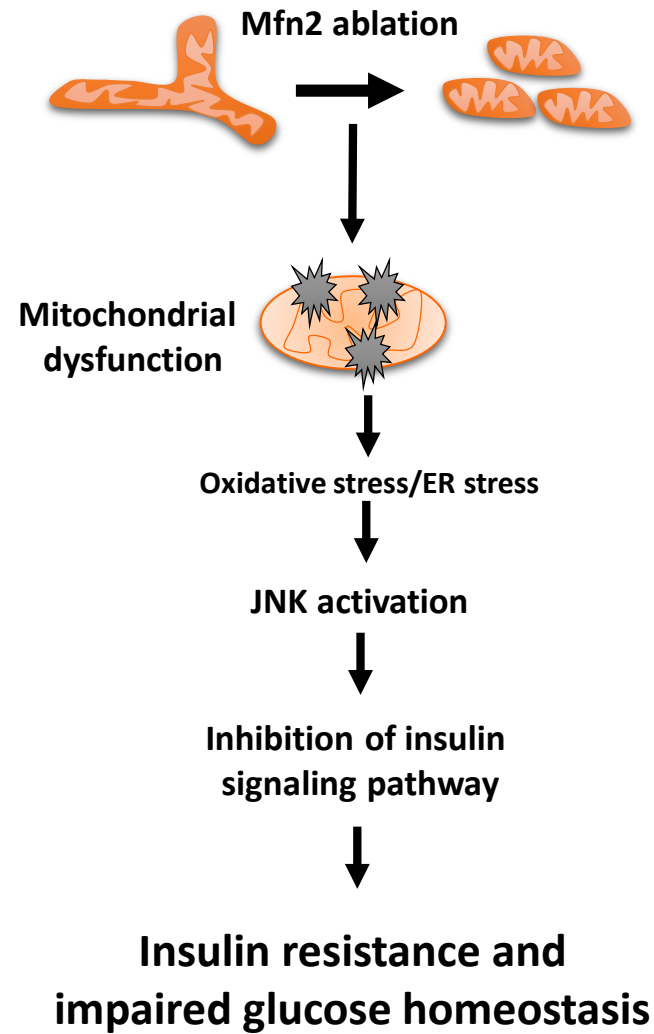


(Sebastián et al., PNAS 2012)

Mfn2 deficient mice show glucose intolerance and insulin resistance in response to HFD

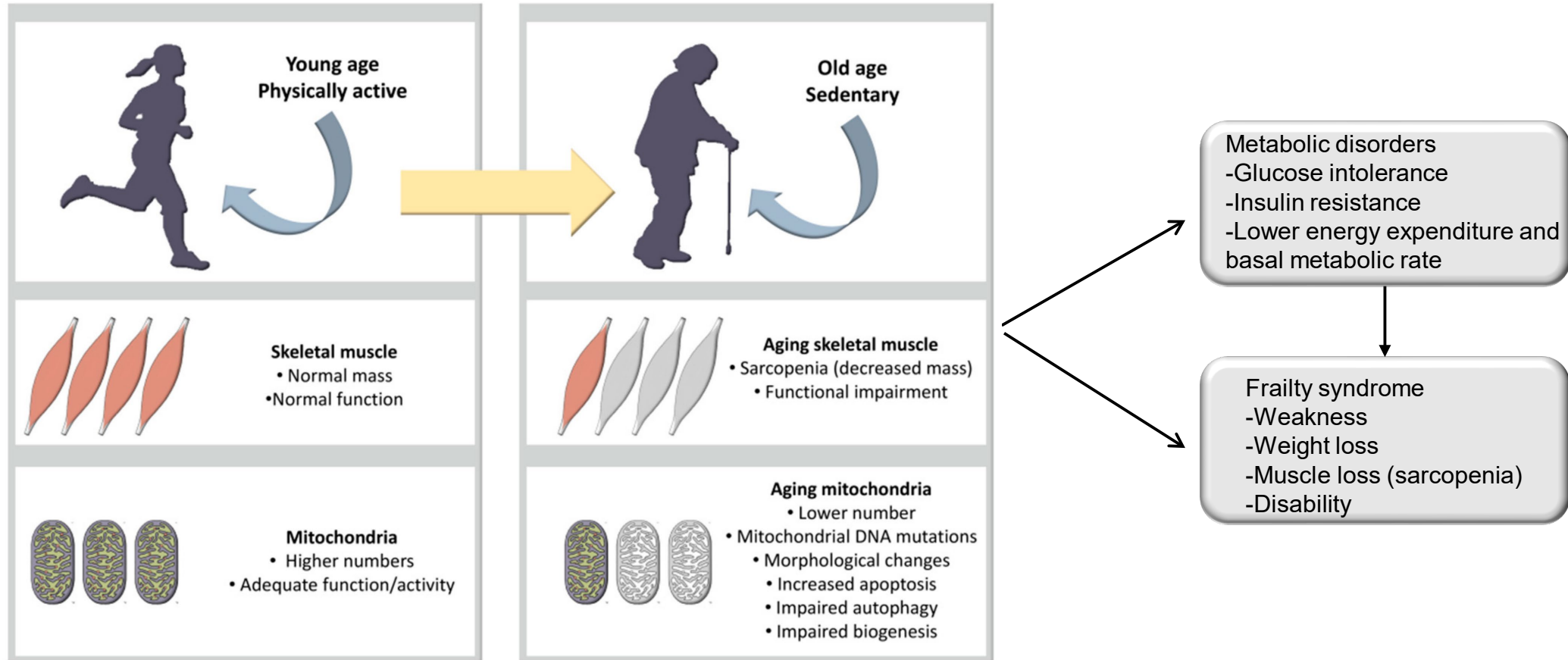


Mfn2 is essential for normal insulin sensitivity and glucose homeostasis

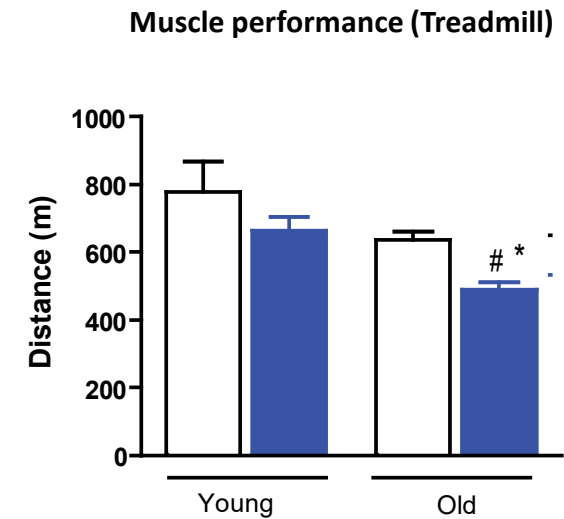
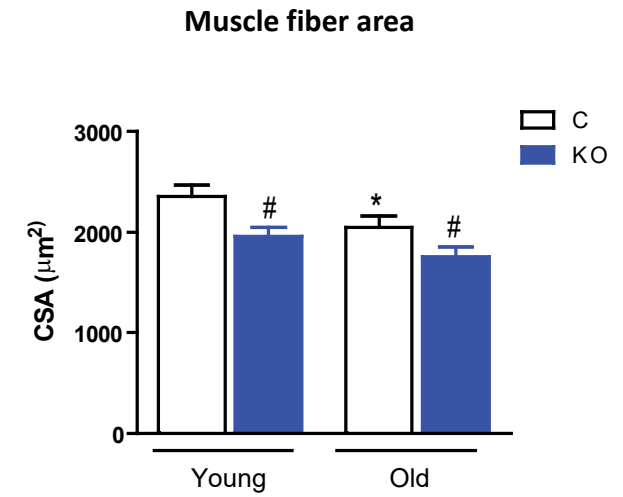
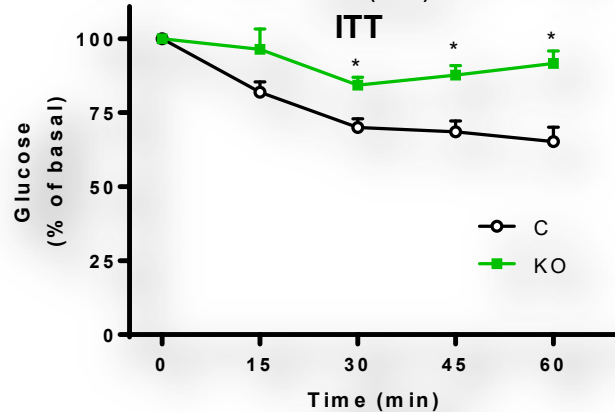
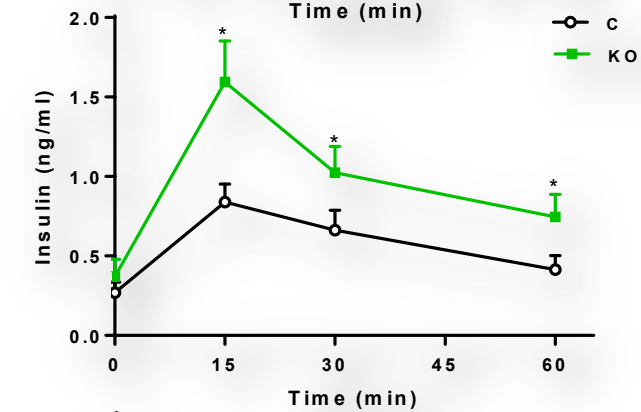
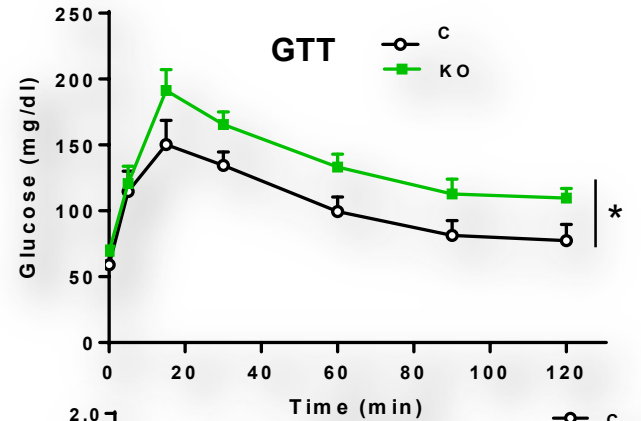
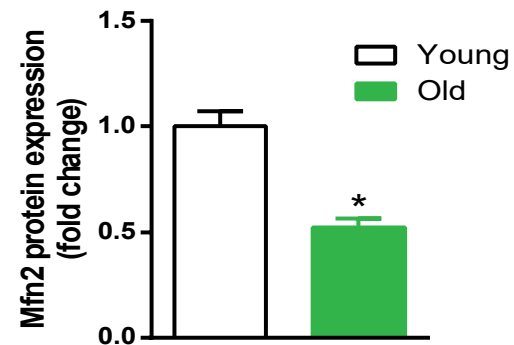
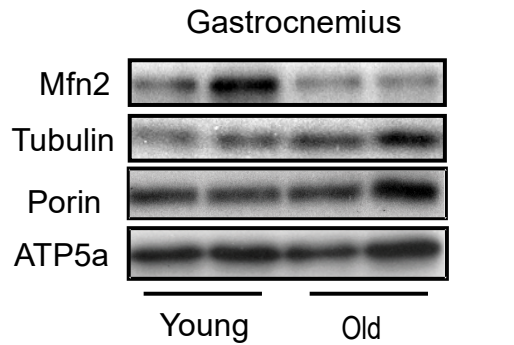


Role of mitochondrial fitness in aging

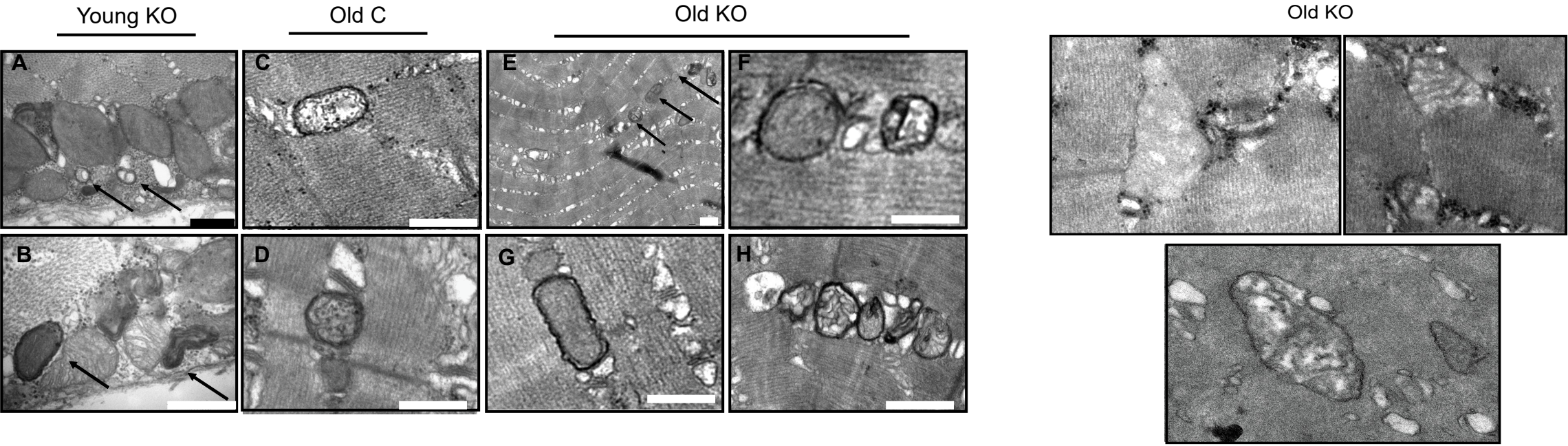
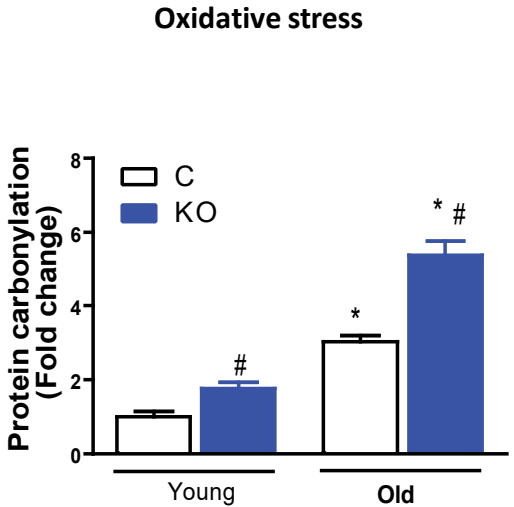
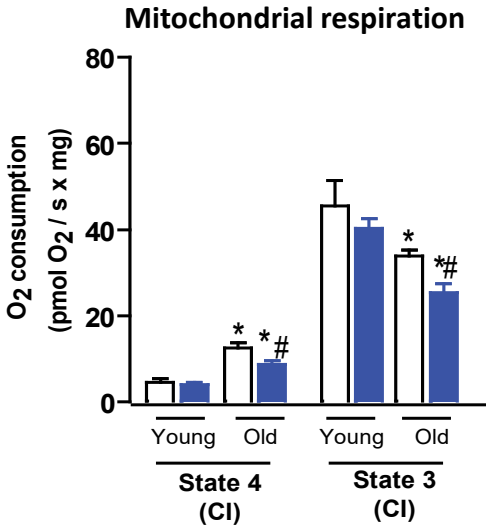
Physiologic changes in skeletal muscle during aging: the role of mitochondria



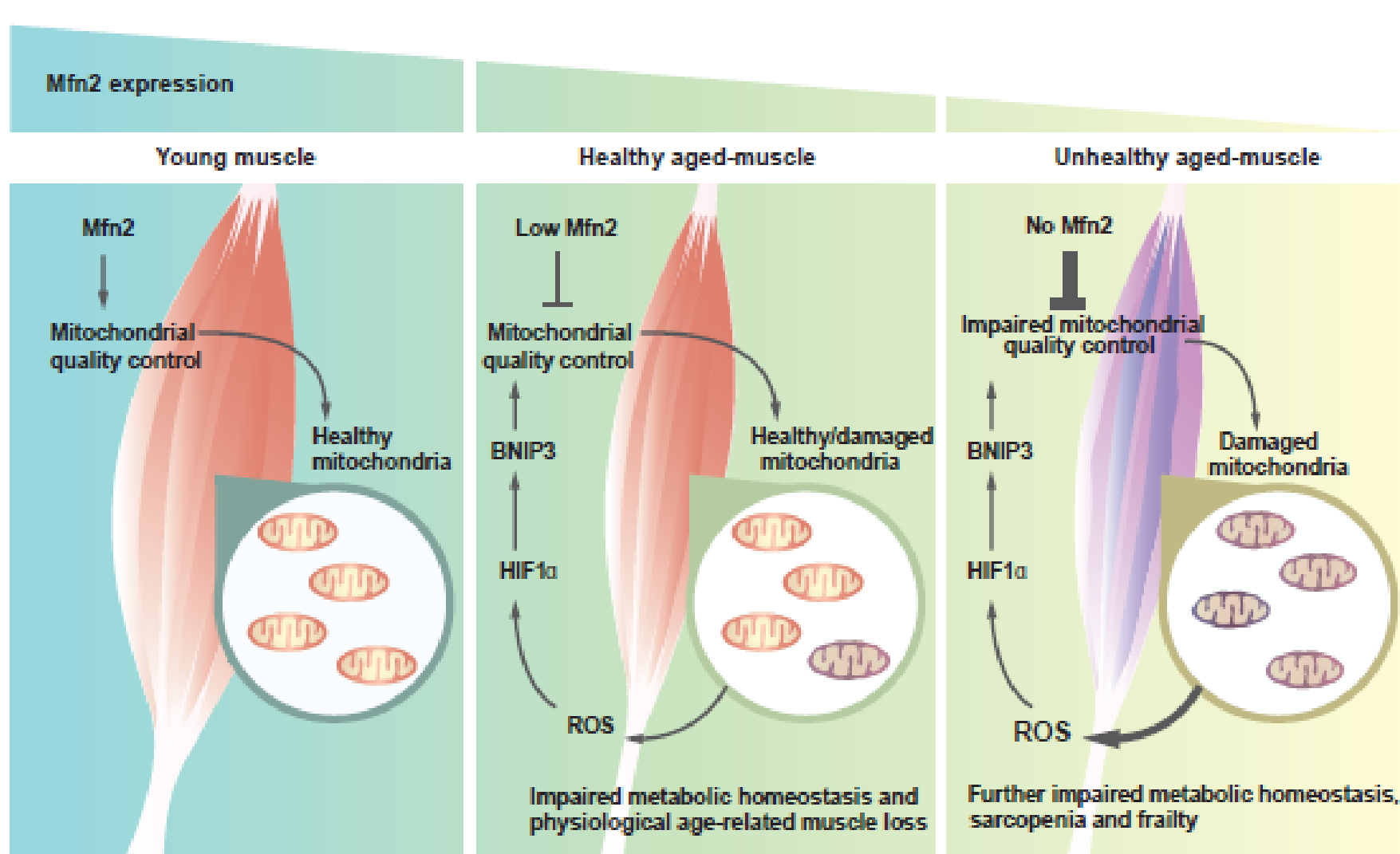
Mfn2 expression in skeletal muscle decreases during aging and associates with metabolic deregulation and sarcopenia



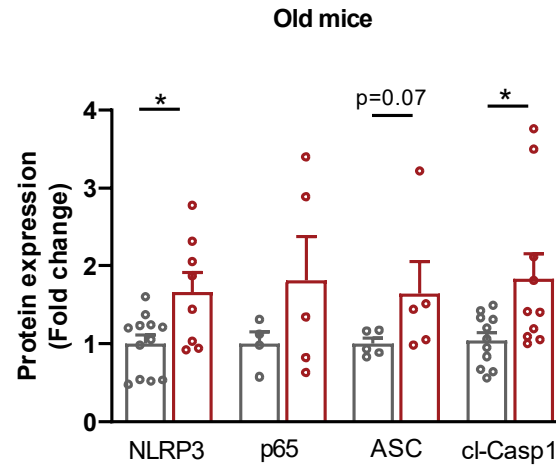
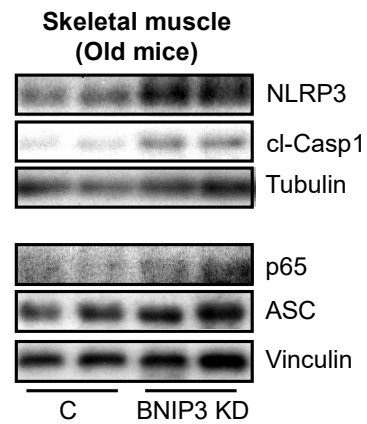
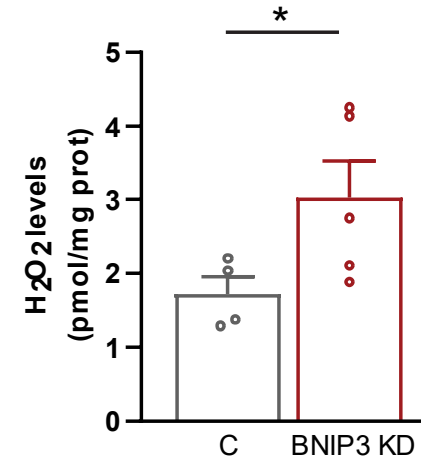
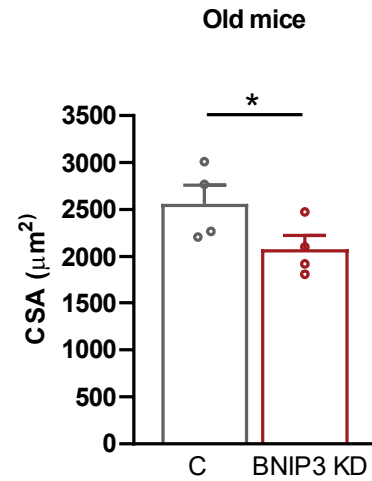
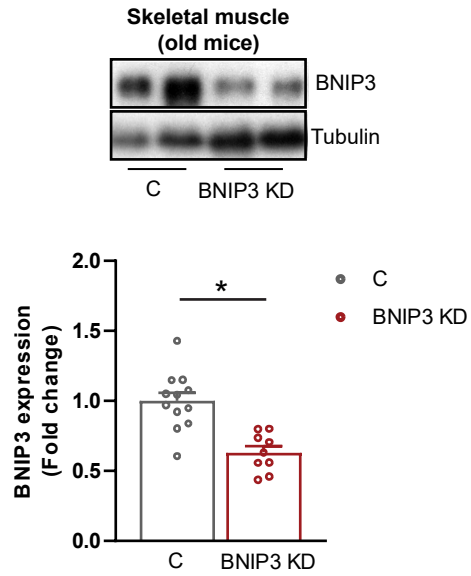
Mfn2 deficiency in skeletal muscle impairs mitochondrial quality



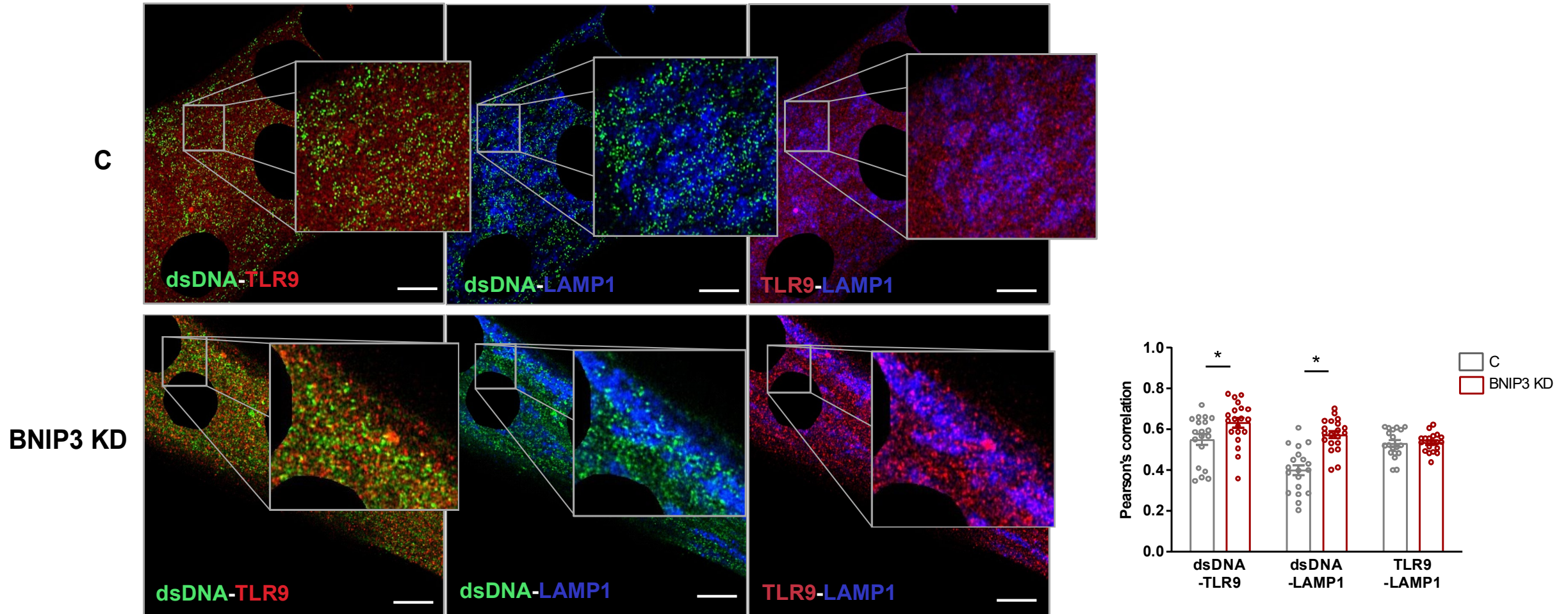
Mfn2 is determinant for healthy aging by controlling mitochondrial health



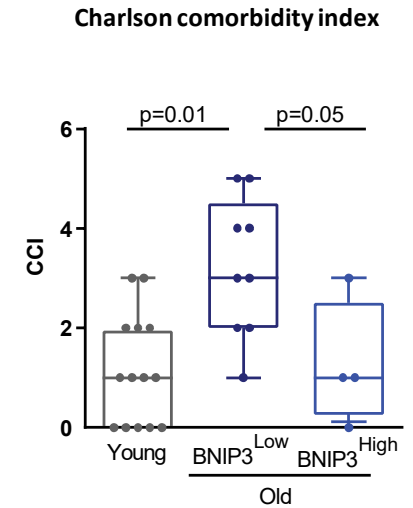
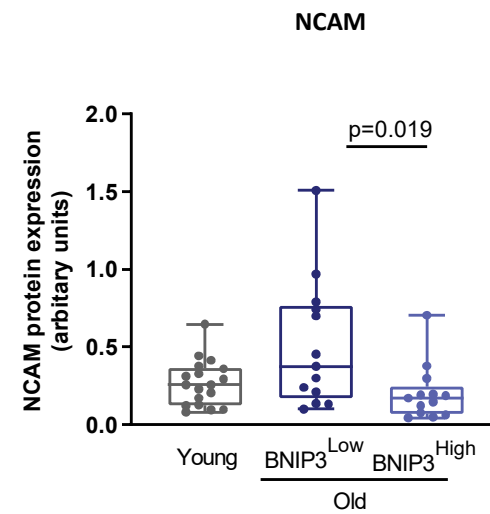
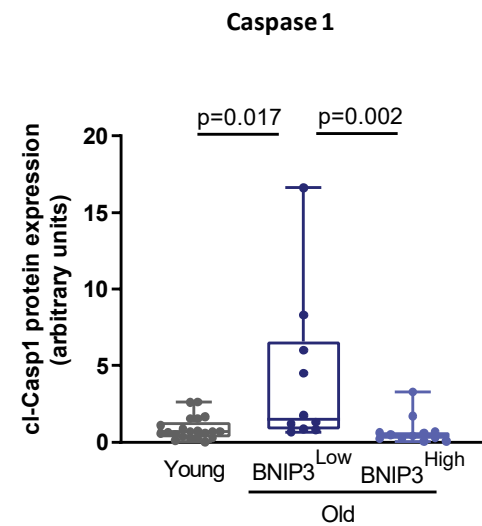
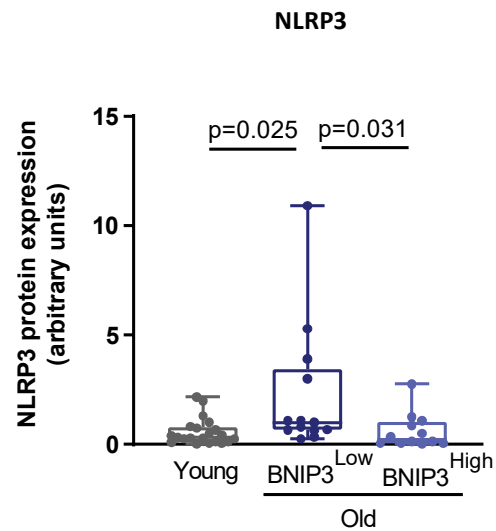
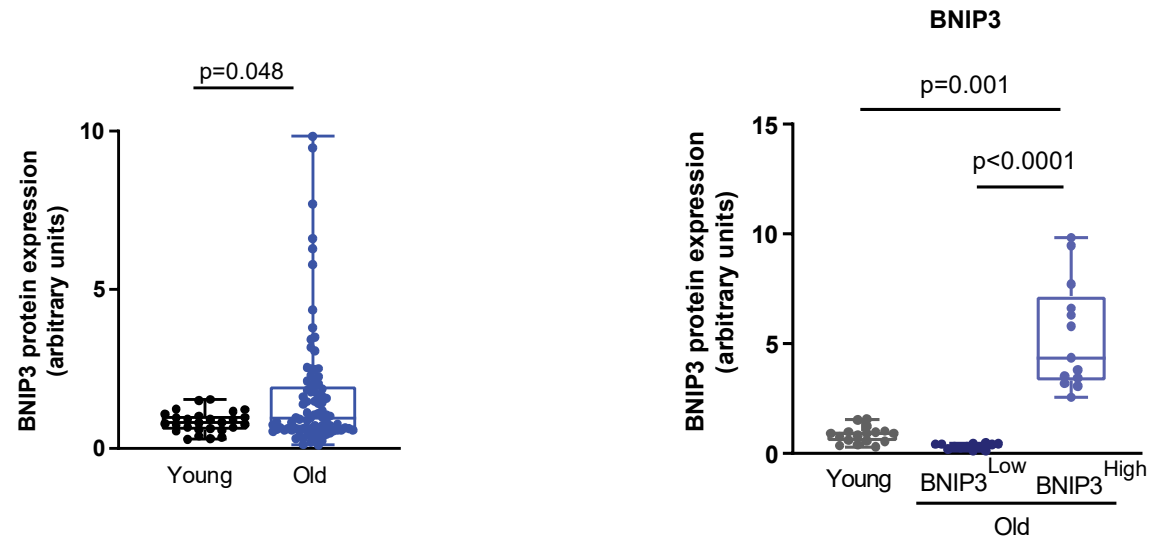
Downregulation of BNIP3 in old mice exacerbates muscle atrophy, mitochondrial dysfunction and inflammation



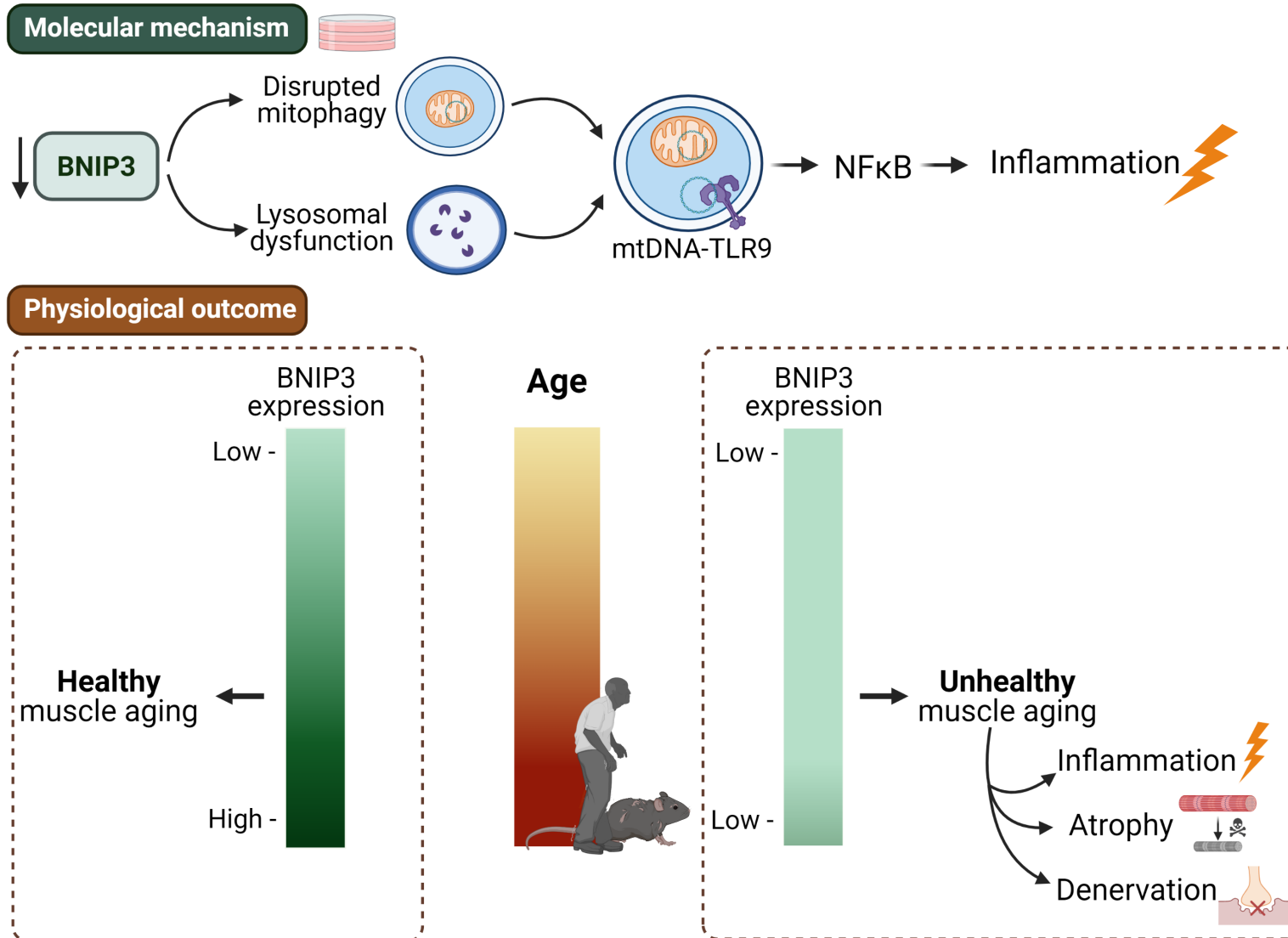
BNIP3 deficiency induces a mtDNA-TLR9 dependent inflammation



High muscle BNIP3 expression protects from inflammation and is associated with healthy aging in humans

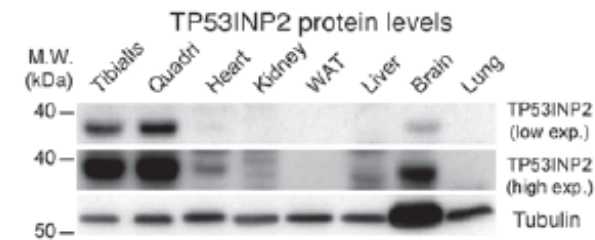
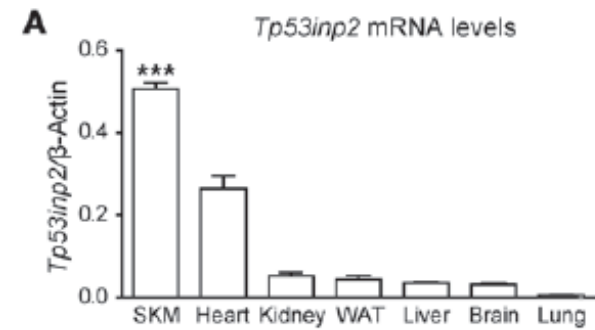
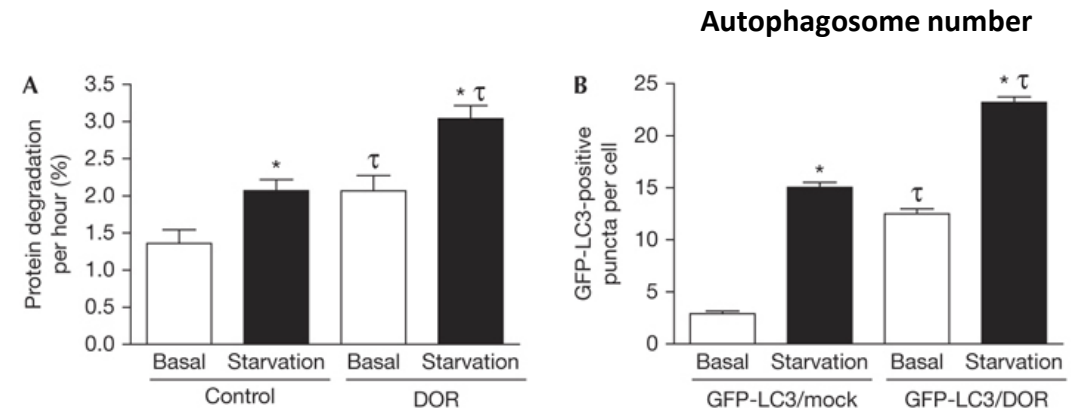
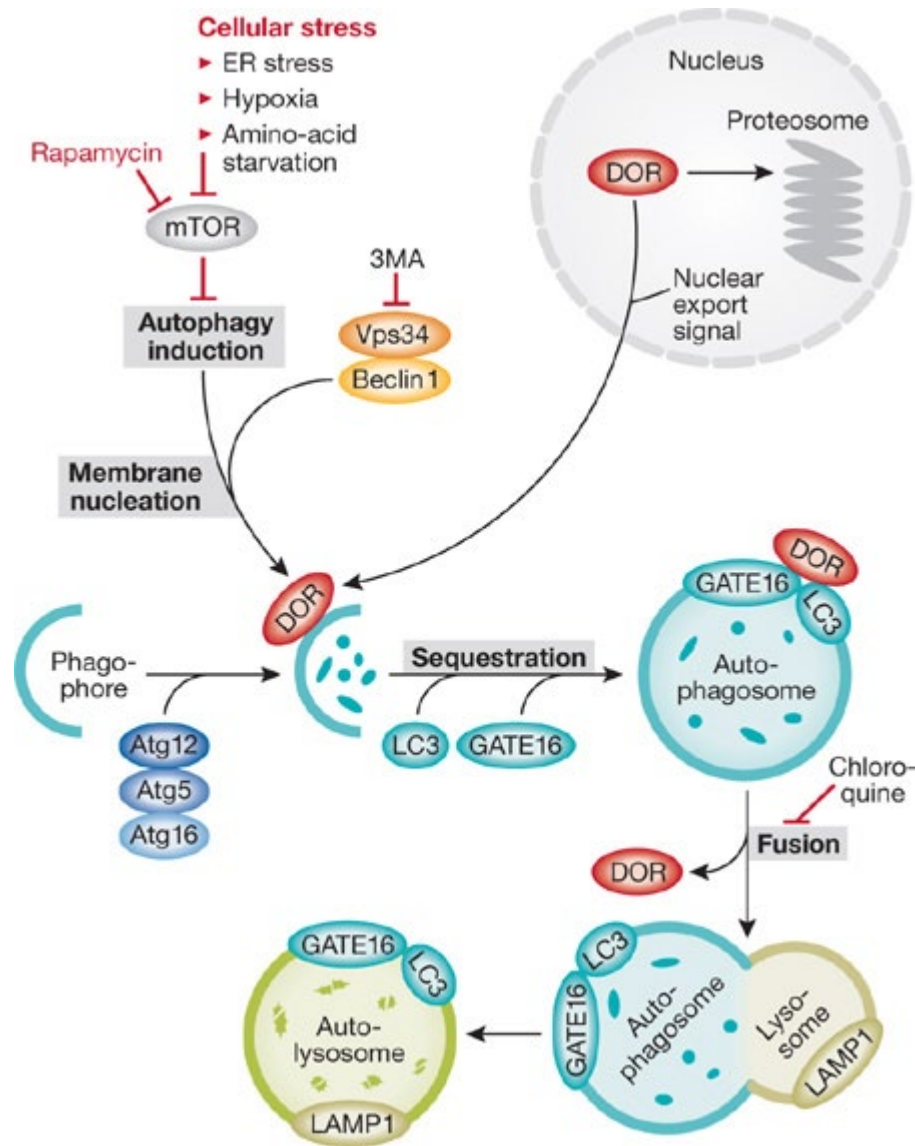


Coordination of mitochondrial and lysosomal homeostasis mitigates inflammation and muscle atrophy during aging



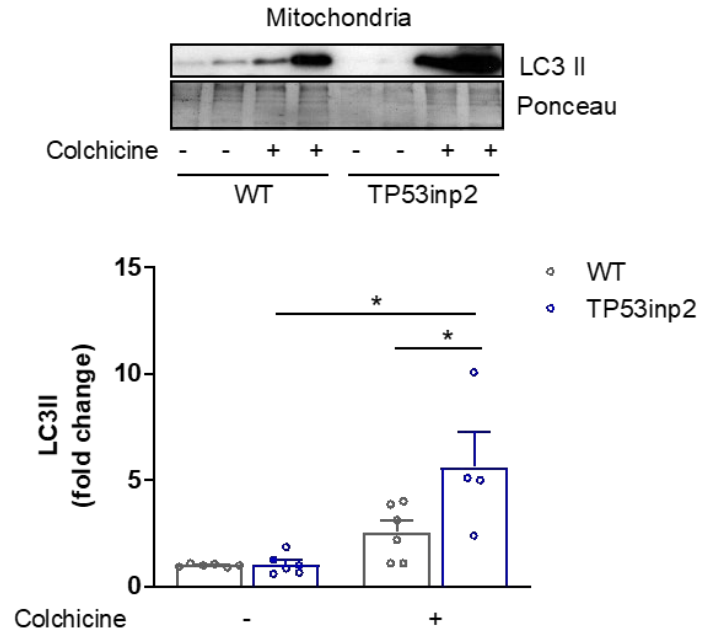
Could increased mitochondrial fitness protect from age-related metabolic disease and sarcopenia?

TP53INP2/DOR is a modulator of autophagy highly expressed in skeletal muscle

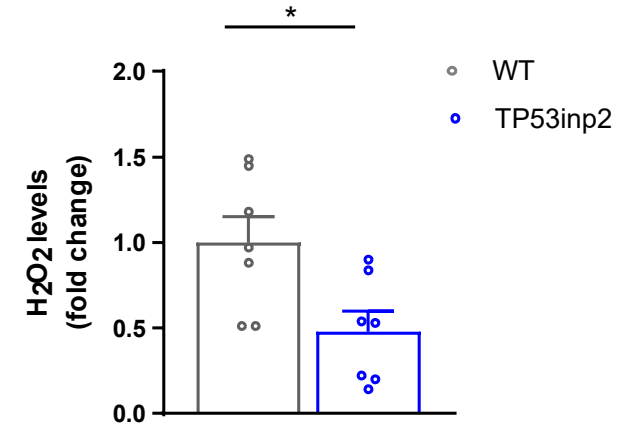
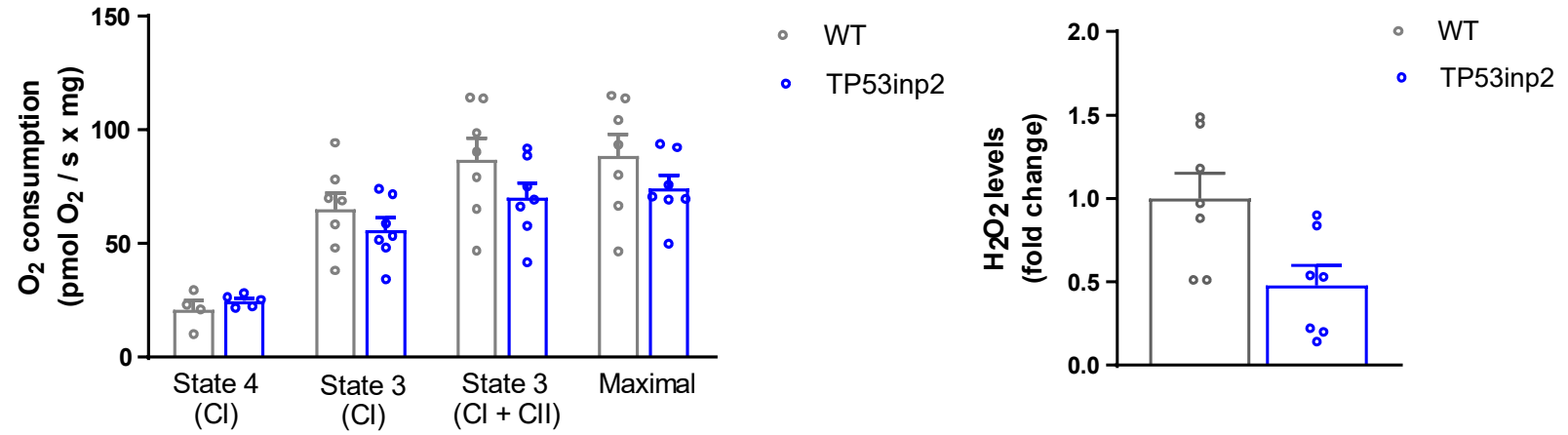


DOR/TP53INP2 overexpression enhances mitophagy and improves mitochondrial quality in old mice

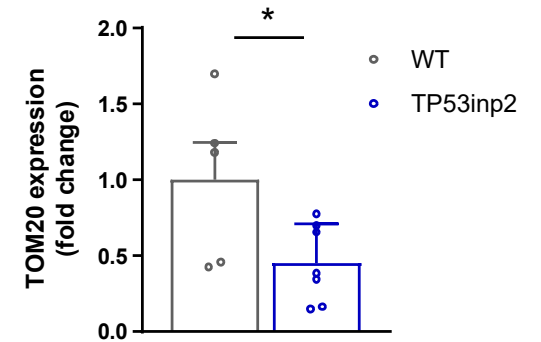
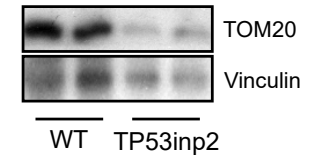
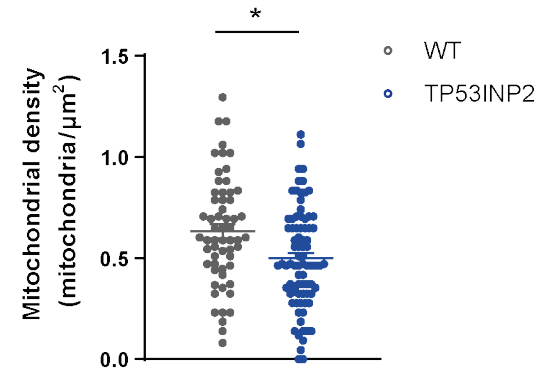
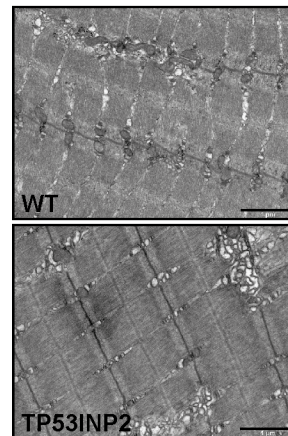
Mitophagic flux



Mitochondrial respiration

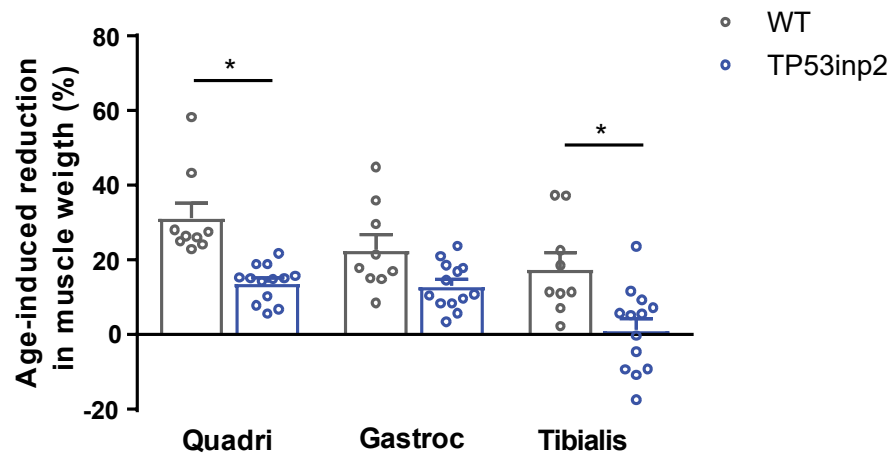


Mitochondrial mass

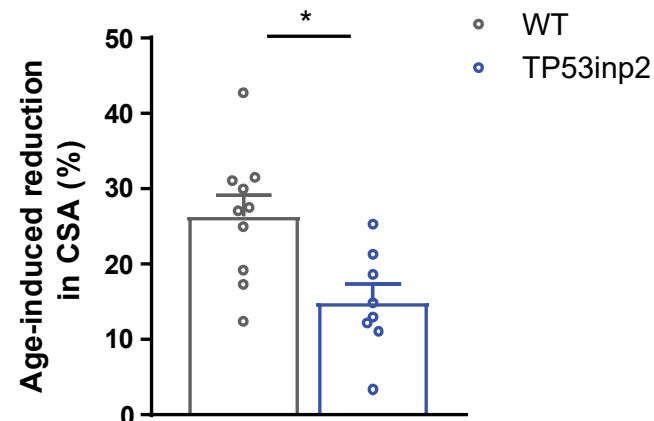


TP53INP2/DOR TG mice are protected from sarcopenia and age-related metabolic disease

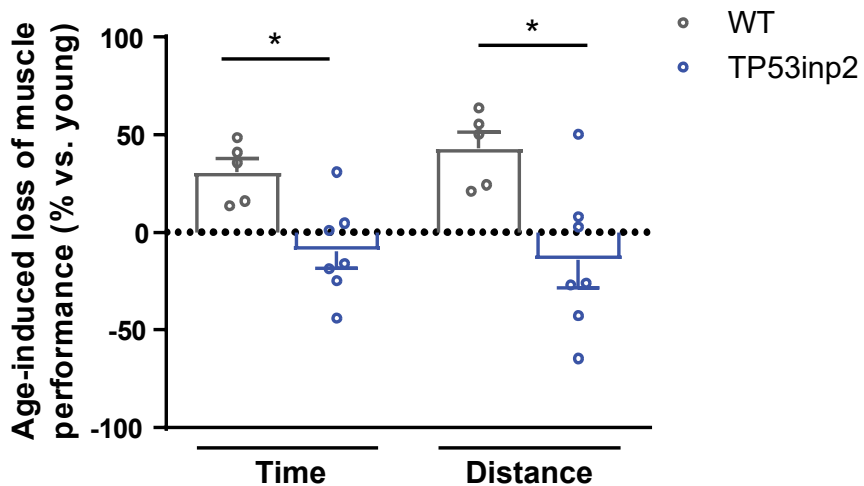
Age-induced reduction in muscle weight



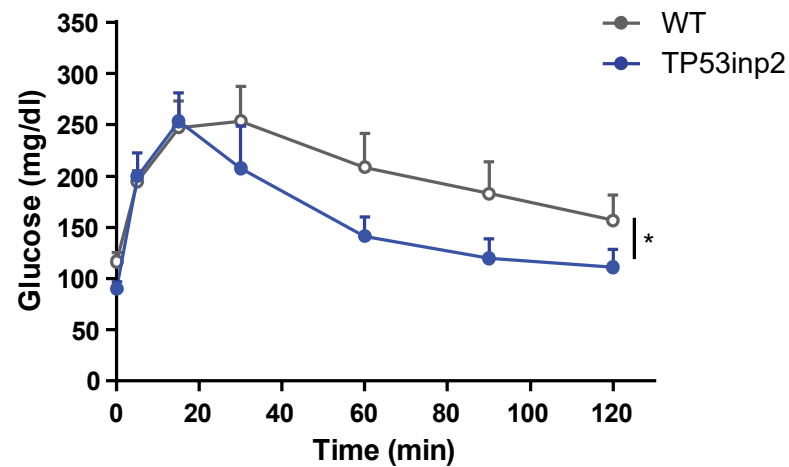
Age-induced reduction in CSA



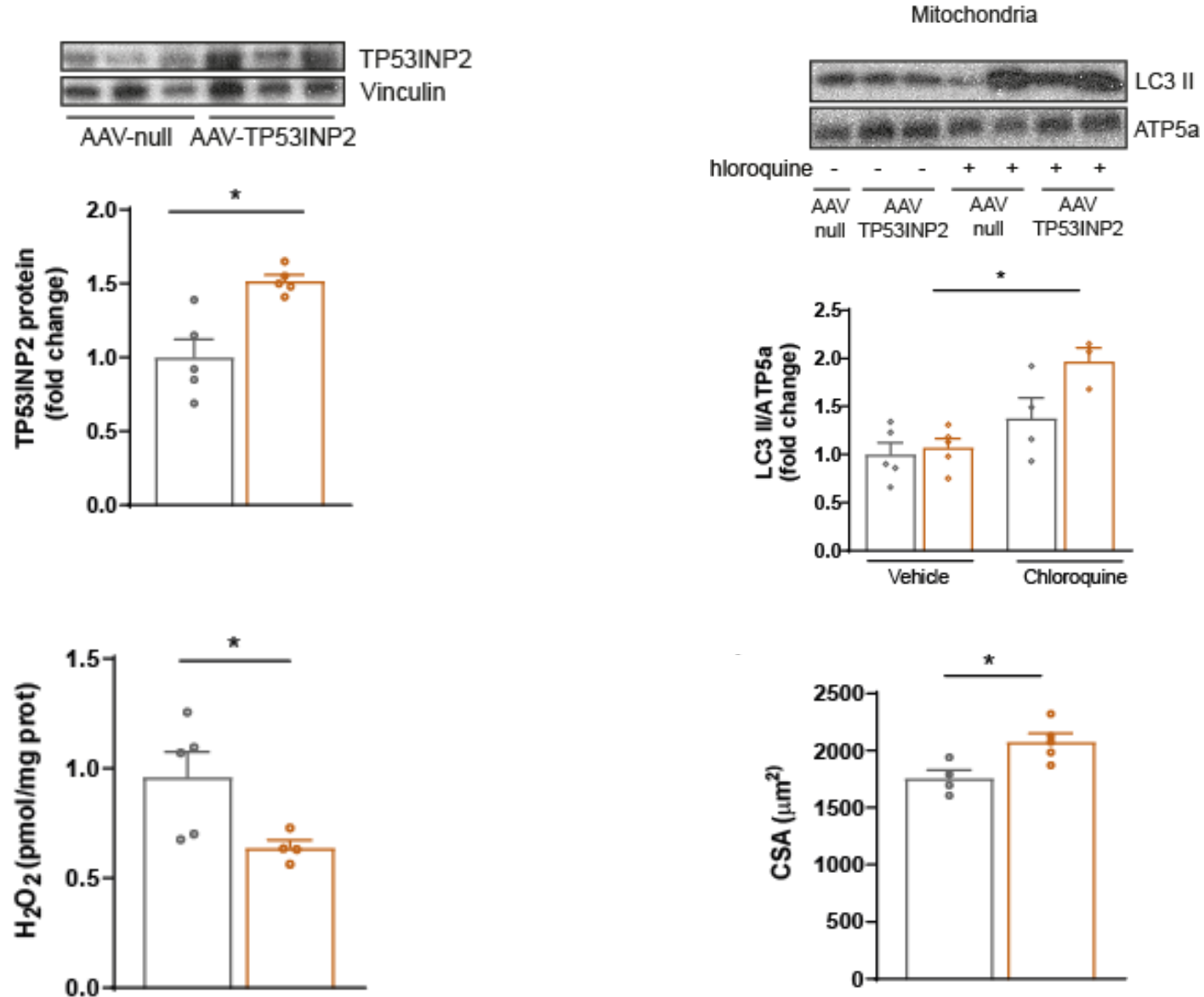
Age-induced reduction in muscle performance



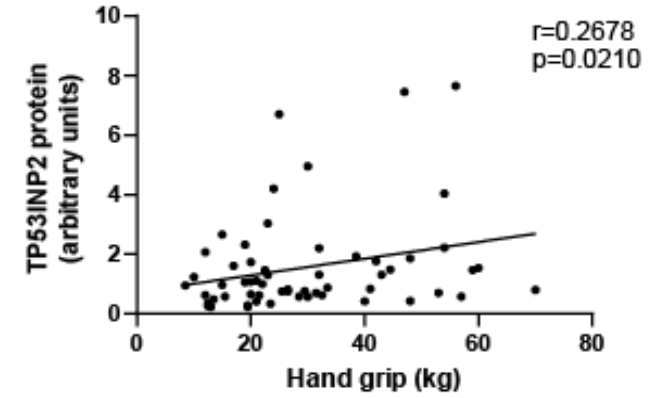
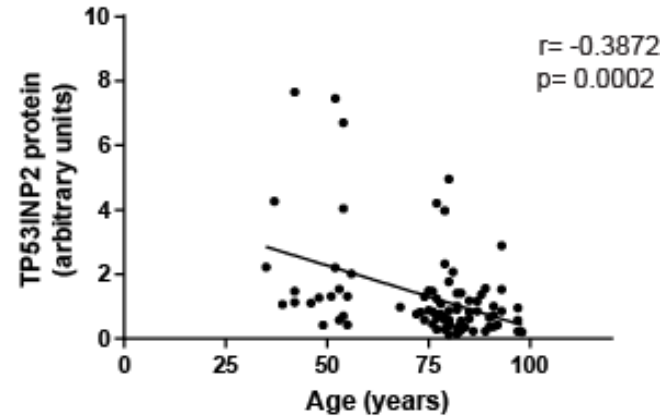
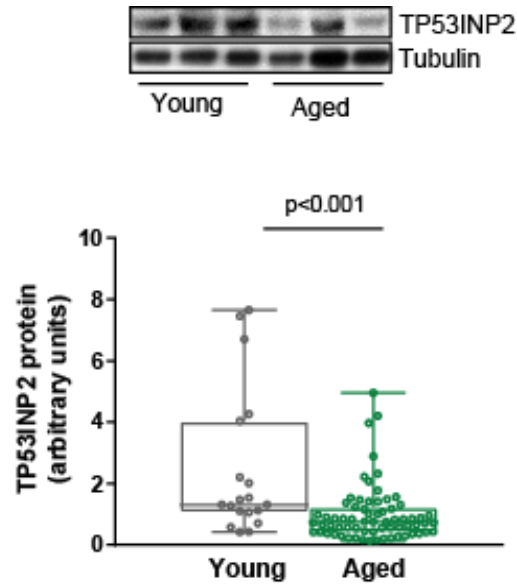
Glucose tolerance test



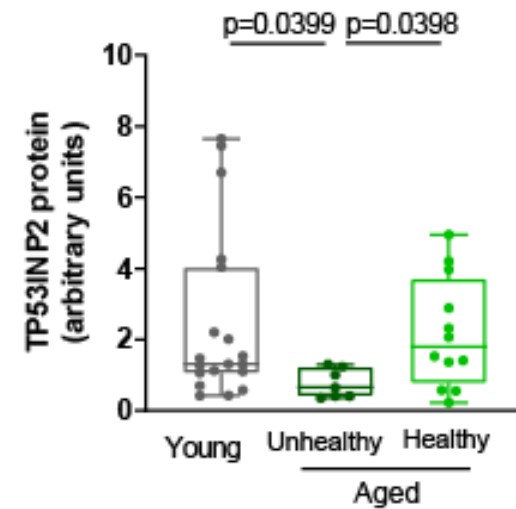
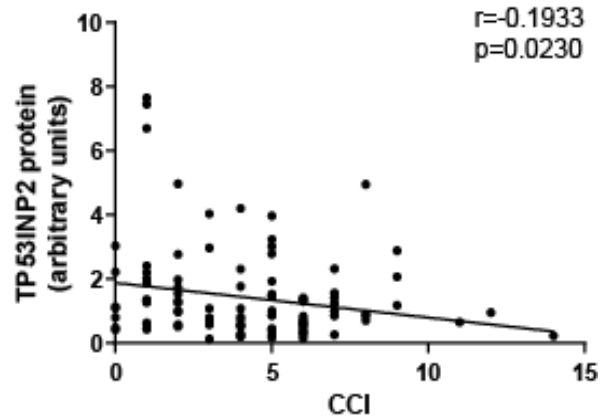
Acute overexpression of DOR/TP53INP2 in old mice induces mitophagy and improves muscle atrophy



TP53INP2/DOR expression decreases during aging and it is associated with sarcopenia and unhealthy aging in humans

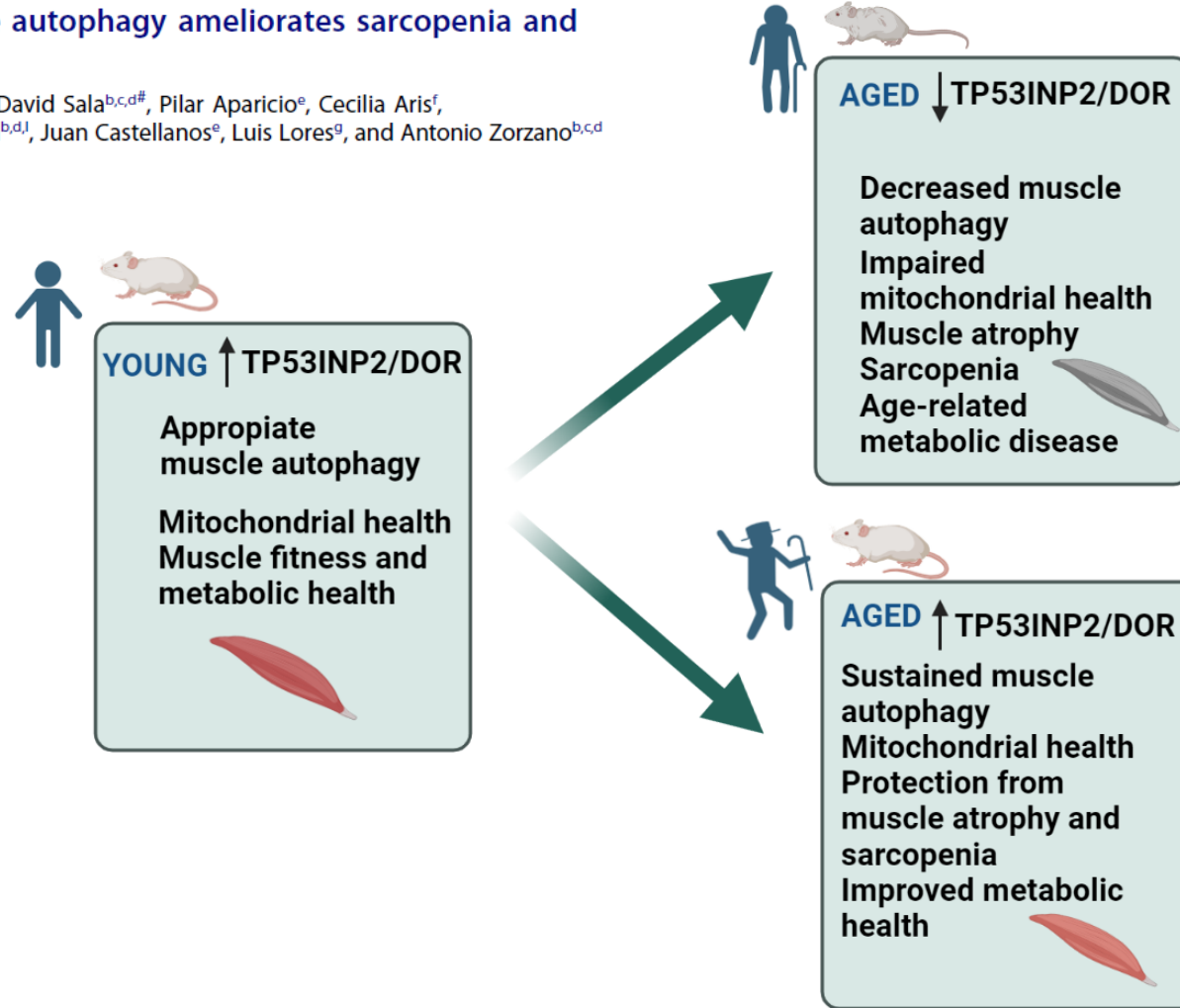


Charlson co-morbidity index

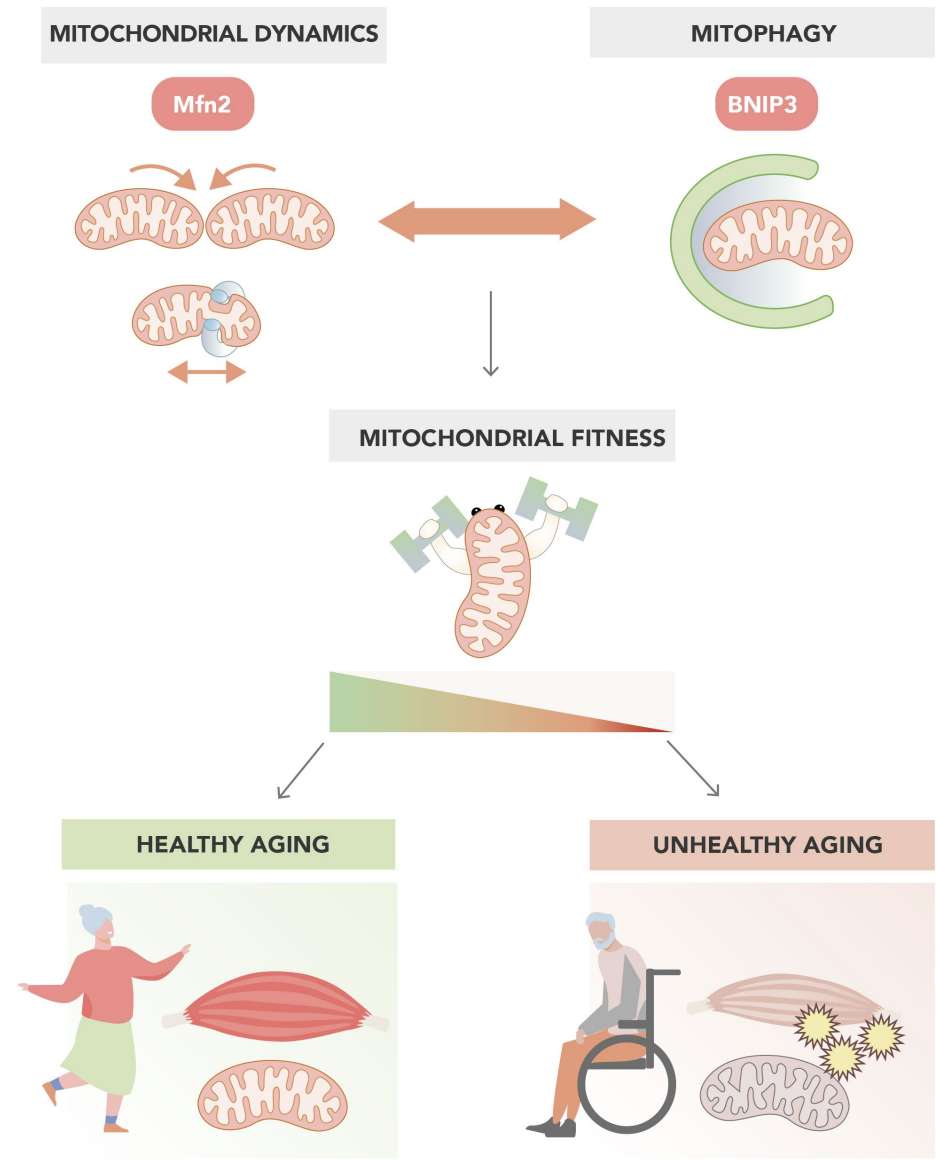
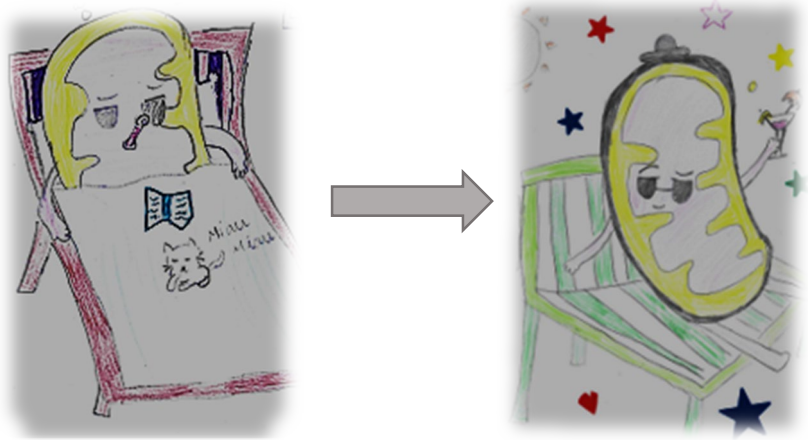


TP53INP2-dependent activation of muscle autophagy ameliorates sarcopenia and promotes healthy aging

David Sebastián^{a,b,c}, Marc Beltrà^{b,c,d}, Andrea Irazoki^{b,c,d*}, David Sala^{b,c,d#}, Pilar Aparicio^e, Cecilia Aris^f, Esmail Alibakhshi^{g,h,i}, Maria Rubio-Valera^{j,k}, Manuel Palacín^{b,d,l}, Juan Castellanos^e, Luis Lores^g, and Antonio Zorzano^{b,c,d}



Mitochondrial fitness sustains healthy muscle aging



- Mitochondria dysfunction
- Inflammation
- Muscle atrophy
- Sarcopena

Acknowledgements



Antonio Zorzano's lab

Post-docs:

Marc Beltrà

Manuela Sanchez-Feutrie

Saska Ivanova

Montserrat Romero

Sergio Rius

PhD students:

Andrea Irazoki

Aikaterini Danezi

Paula Sánchez

Jia Liang Sun Wang

Dragana Radivojevikj

Lab Technician

Jorge Manuel Seco

IRB Platforms

Advanced Digital Microscopy

Histopathology



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Agustina Creus (Post-doc)

Shrestha Mohapatra (PhD student)

Susana Redondo (Technician)

Josefine Munch (Master's student)



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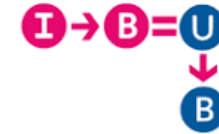
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Collaborators:

Parc Sanitari Sant Joan de Déu

Luis Lores

Juan Castellanos

School of Pharmacy and Food Sciences

Betaoxi Lab

Laura Herrero

María del Mar Romero

Marijana Todorcevic

Ana Corral

Ivonne Palacios

Marc Reina

Iván García

Susana Redondo