



68° CONGRESSO NAZIONALE SIGG

Ritorno al futuro

FIRENZE, 13-16 DICEMBRE 2023
PALAZZO DEI CONGRESSI



SARCOPENIA E DISFUNZIONE MITOCONDRIALE: VERSO LA «TARGET THERAPY»

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Dipartimento di Scienze Mediche e Chirurgiche - Università di Foggia





AGENDA

1

L'impatto dell'età sul muscolo scheletrico

2

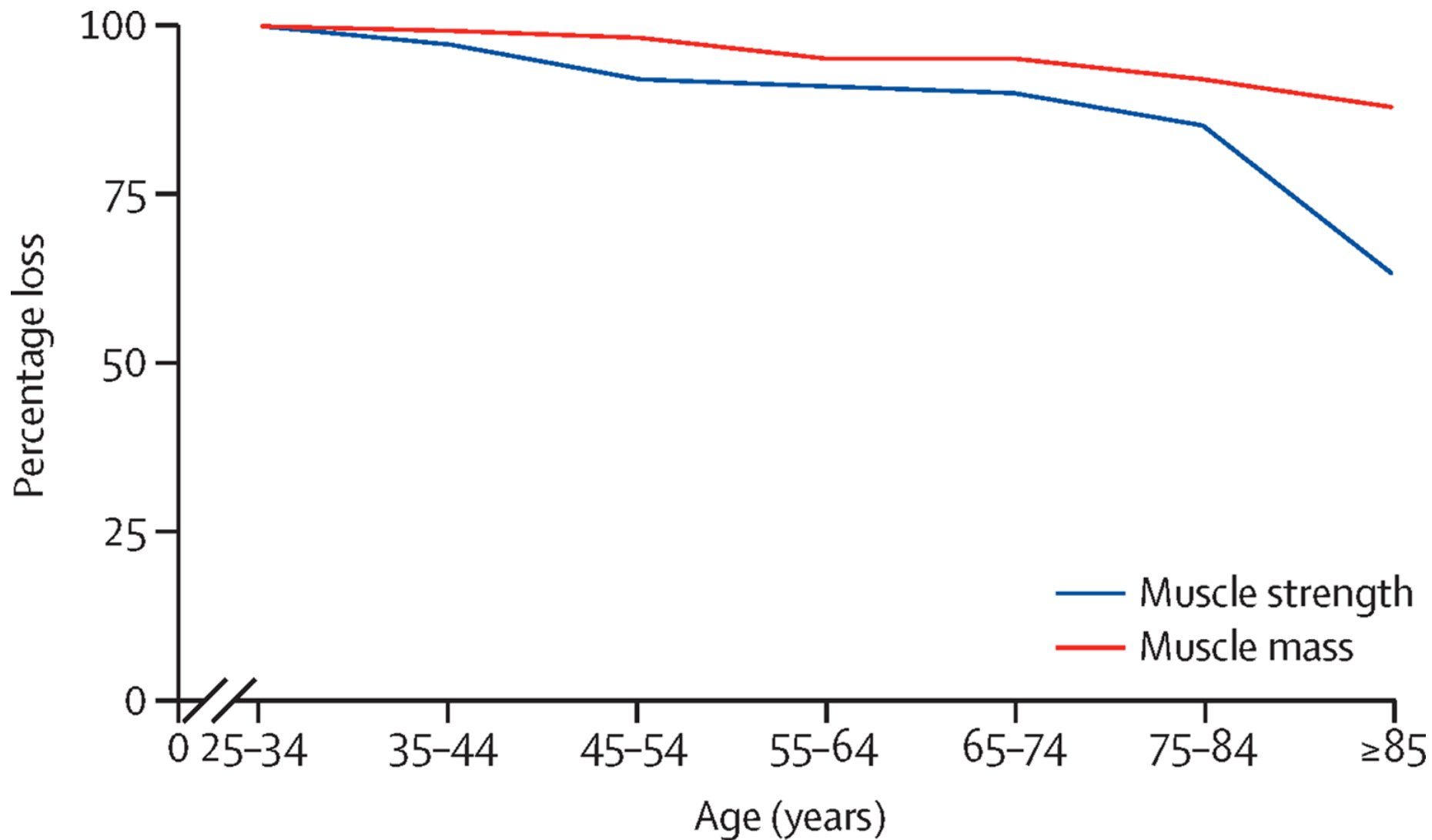
Alterazioni del bilancio redox nella sarcopenia

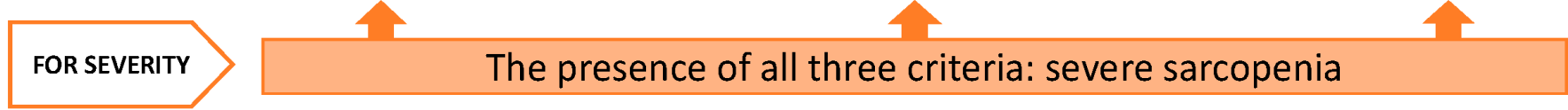
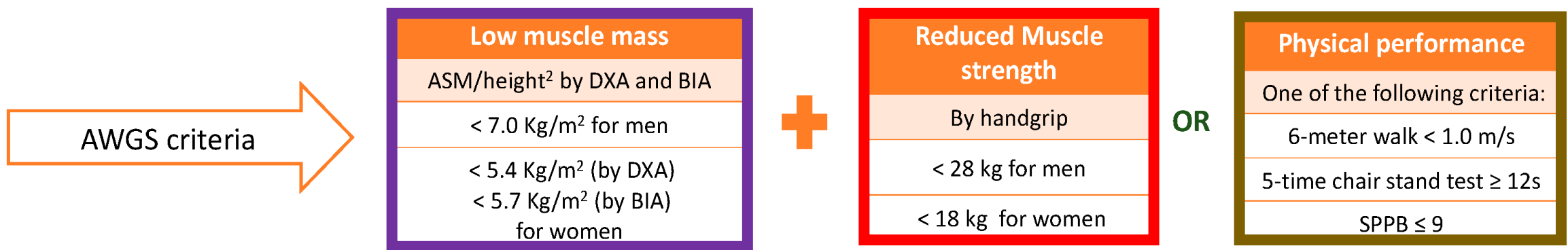
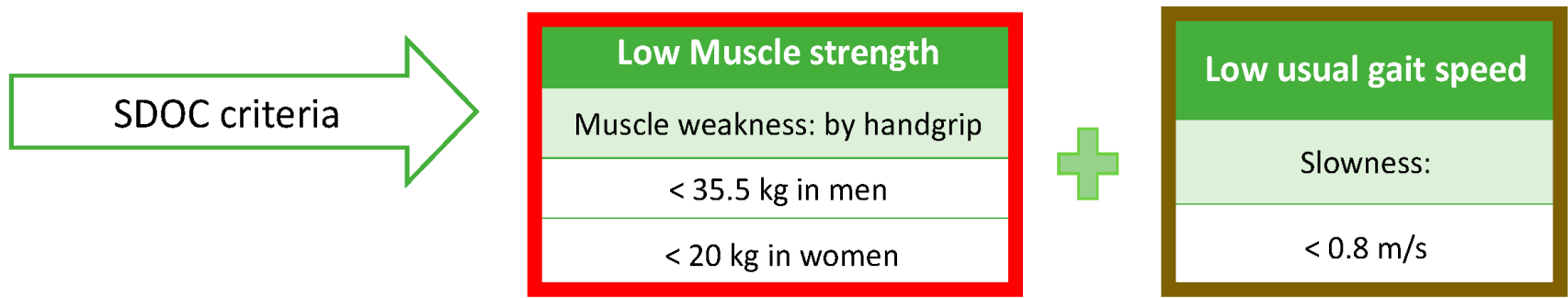
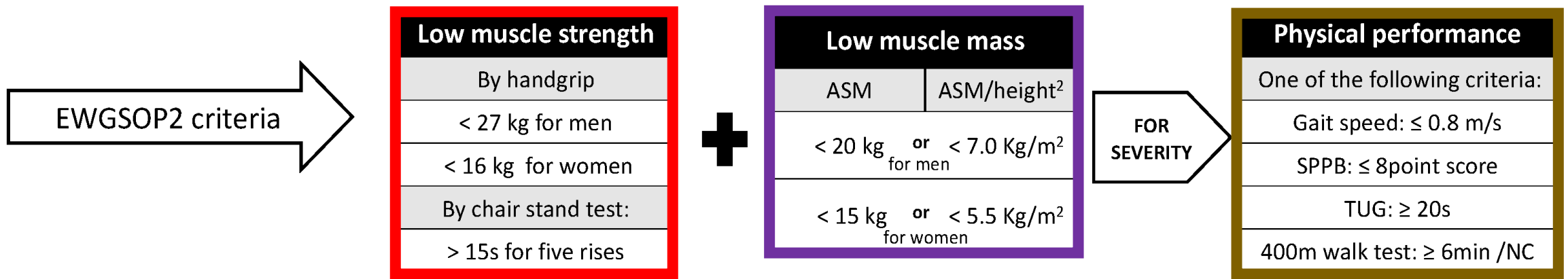
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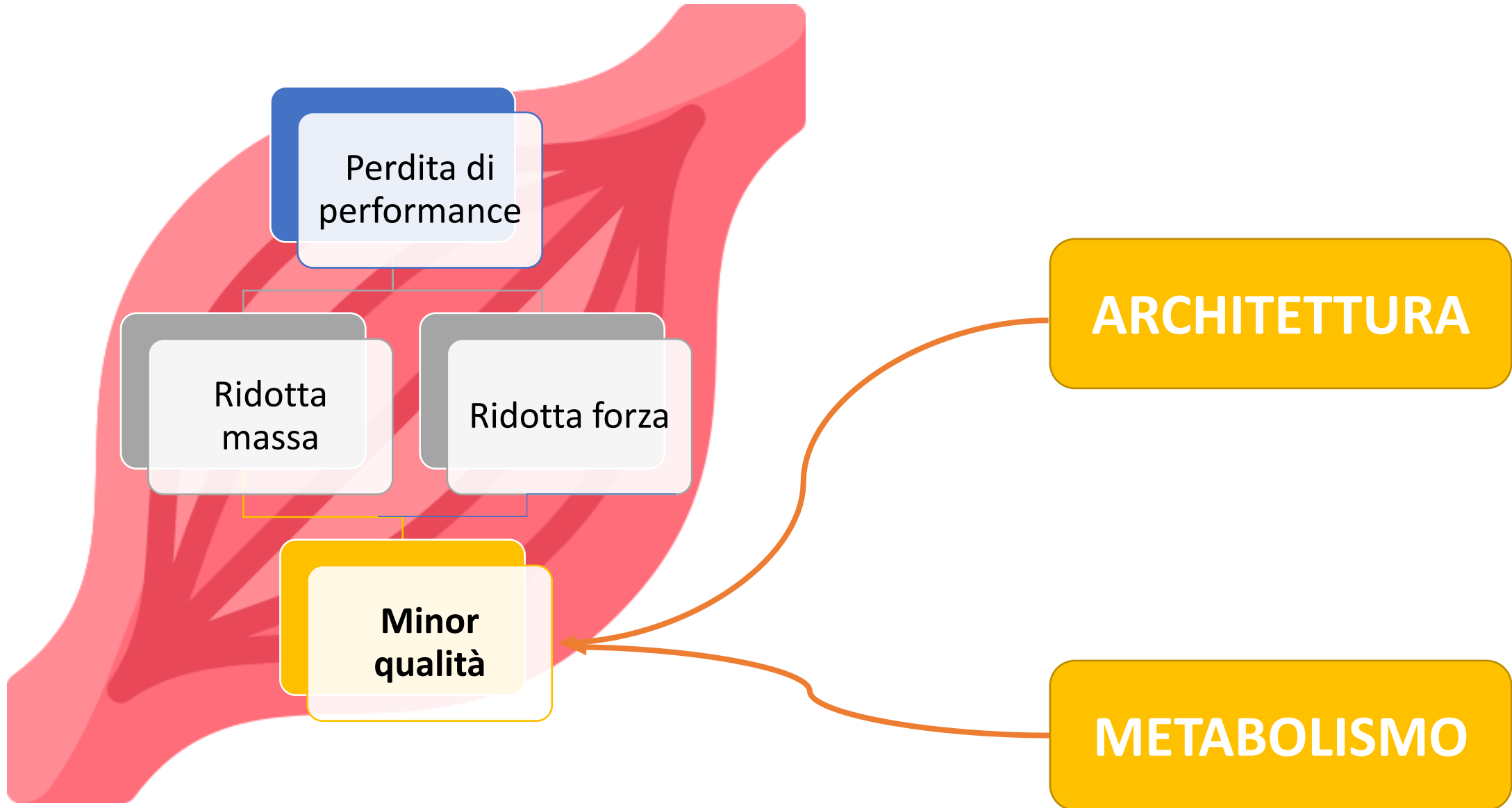
Compromissione muscolare e mitocondri

4

Medicina mitocondriale per la sarcopenia

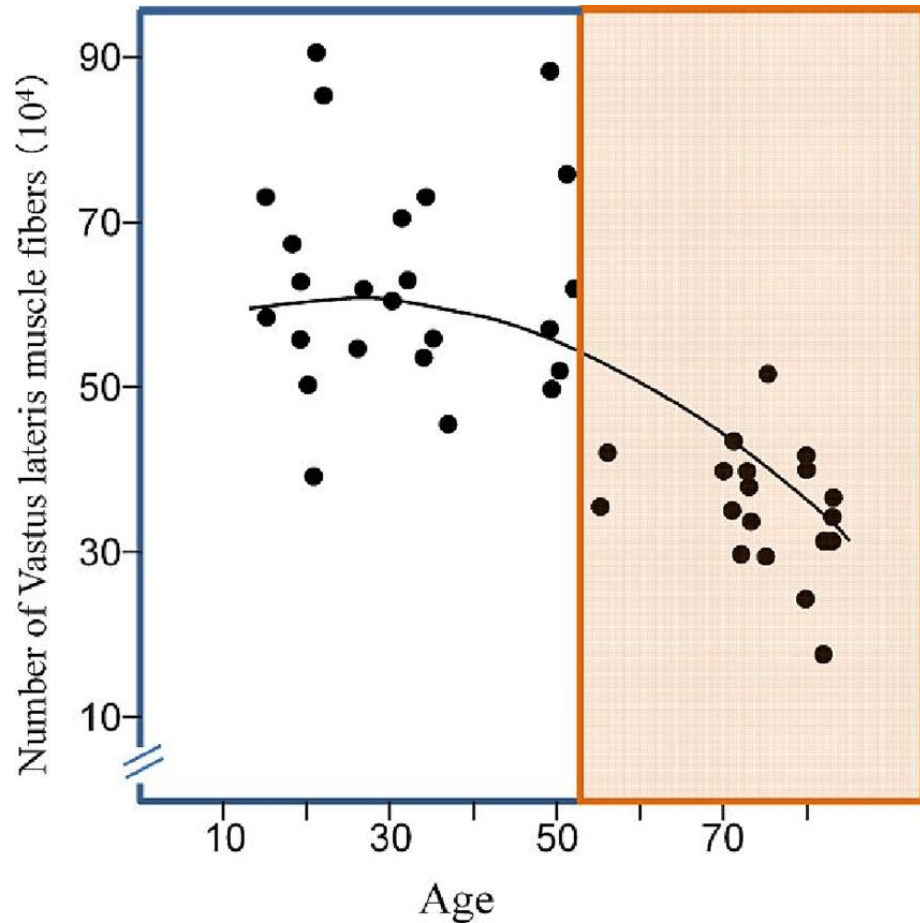




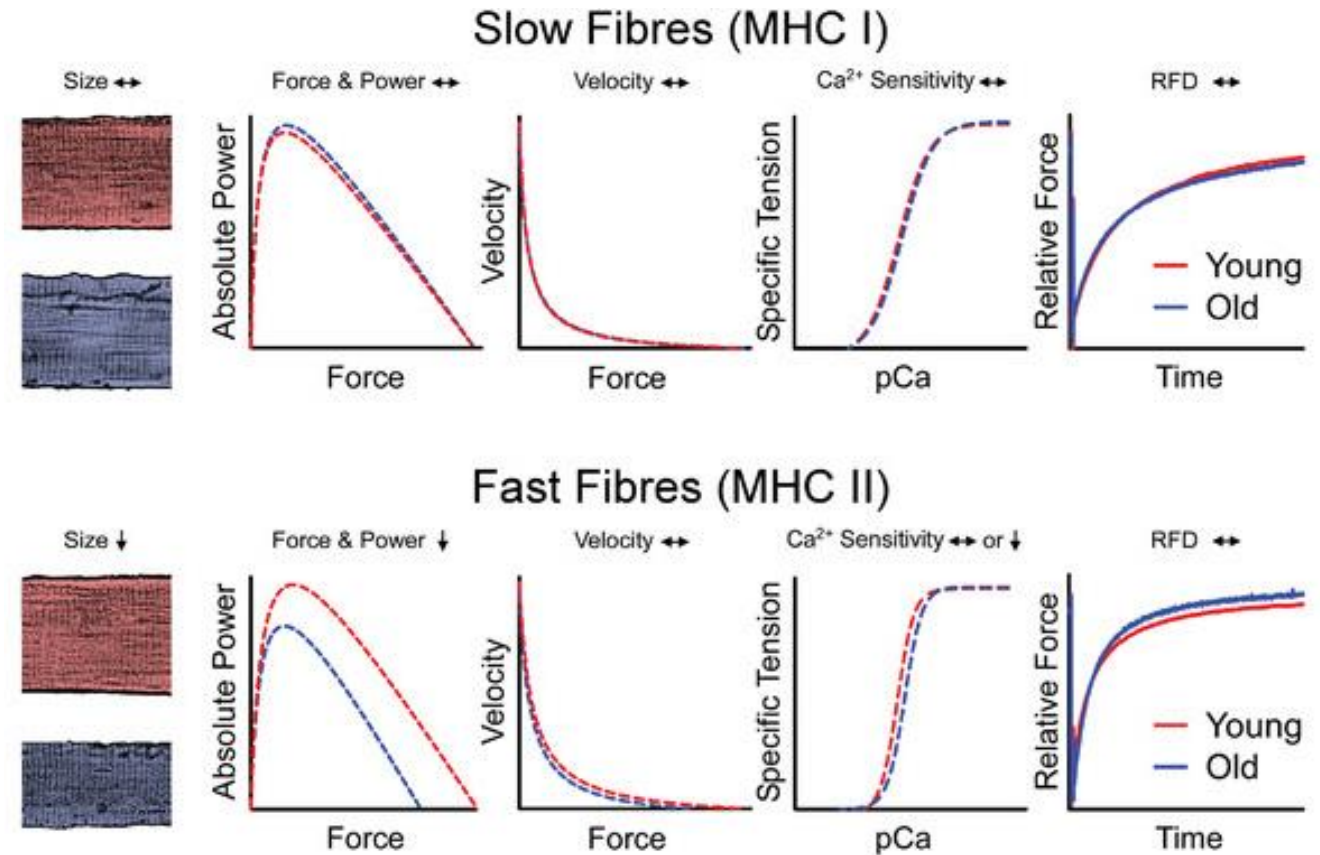




Età e architettura muscolare



Lexell J et al., *J Neurol Sci*, 1988

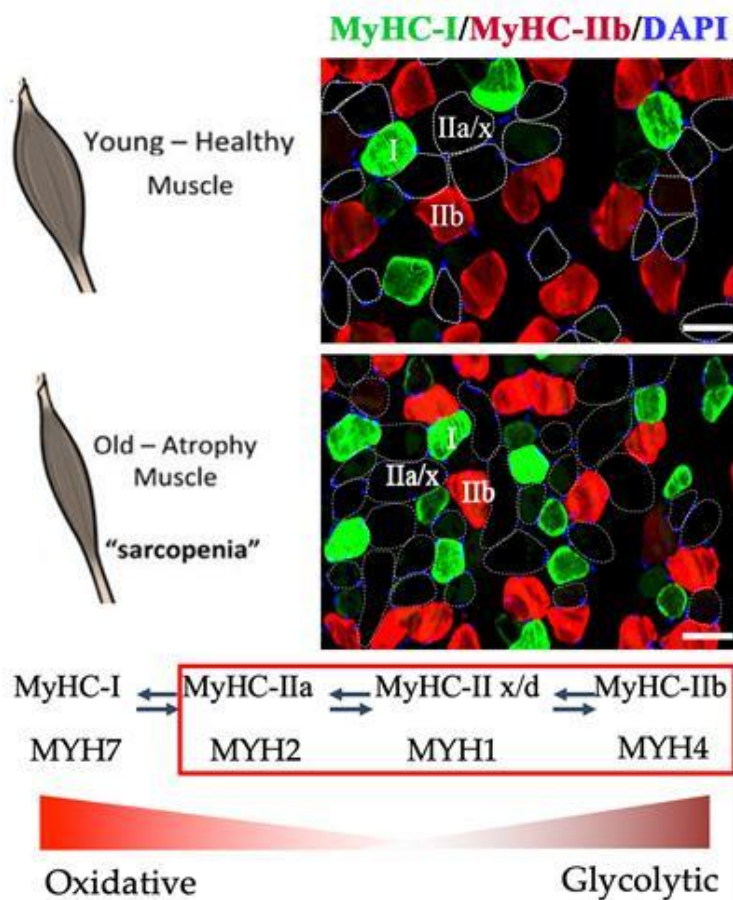


Grosicki CGJ et al., *J Physiol*, 2022



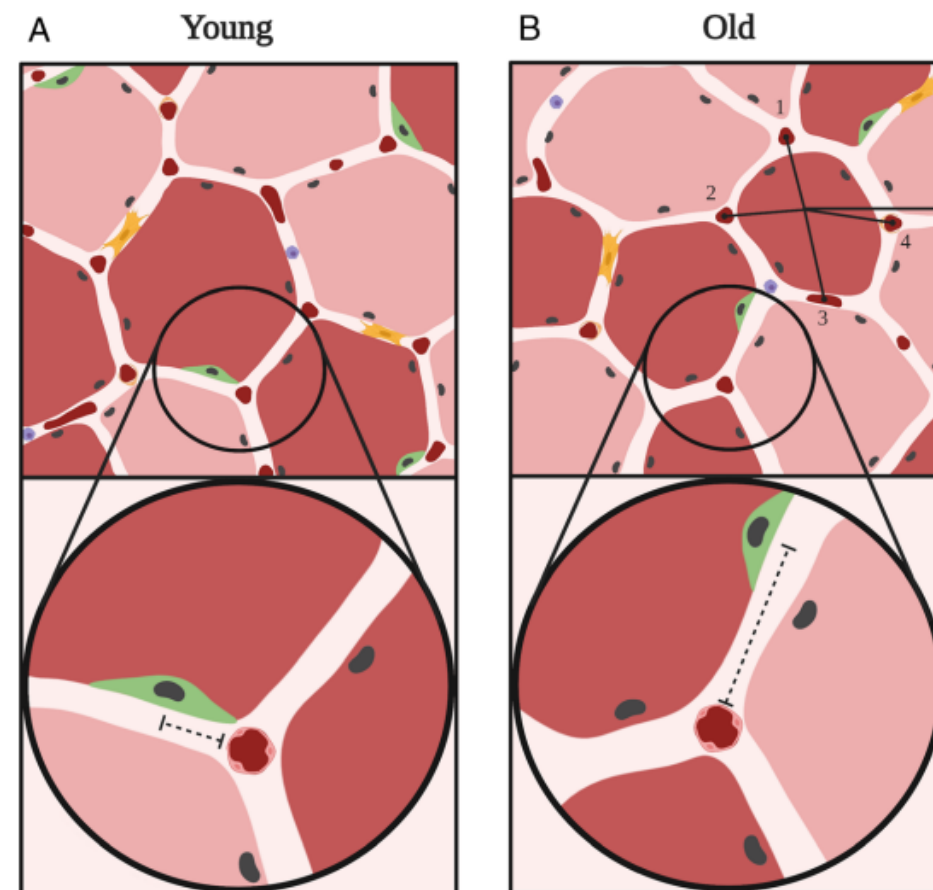
Età e metabolismo muscolare (1)

Aumento del metabolismo ossidativo



Yang Q et al., *Aging and Disease*, 2022

Ridotta capillarizzazione

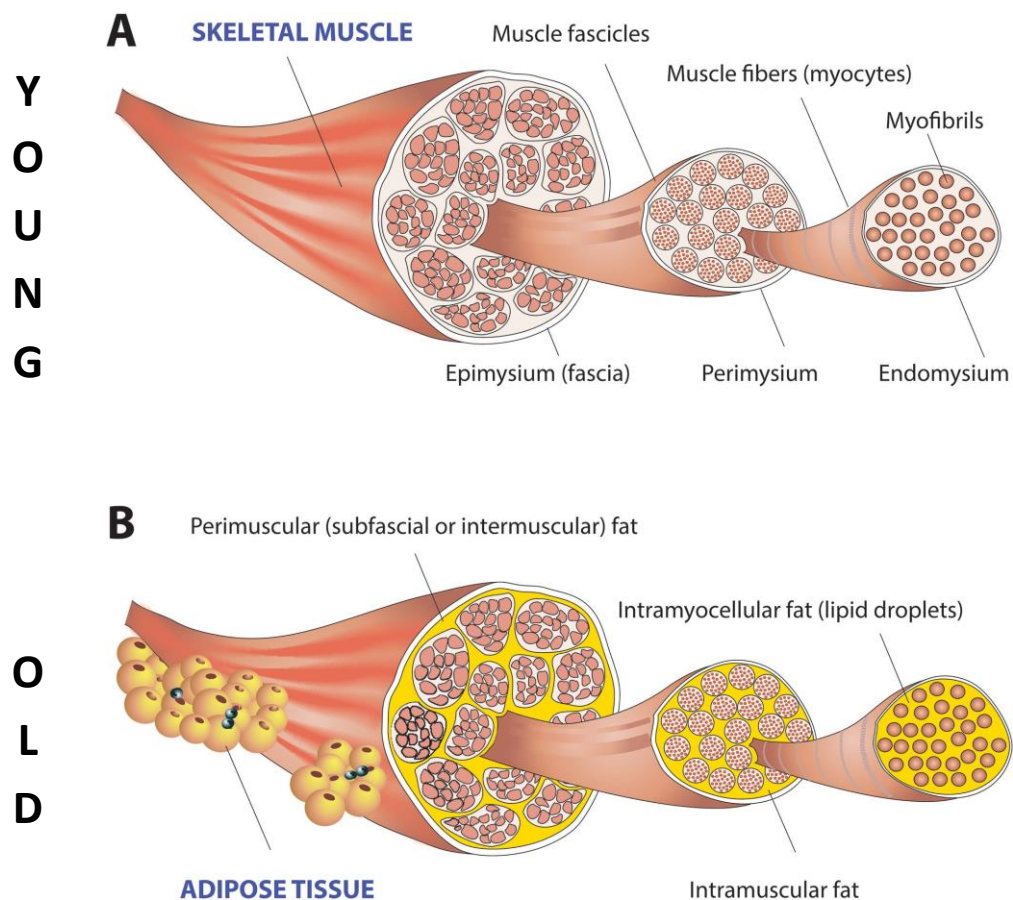


Nederveen JP et al., *Exerc Sci Sport Sci*, 2021



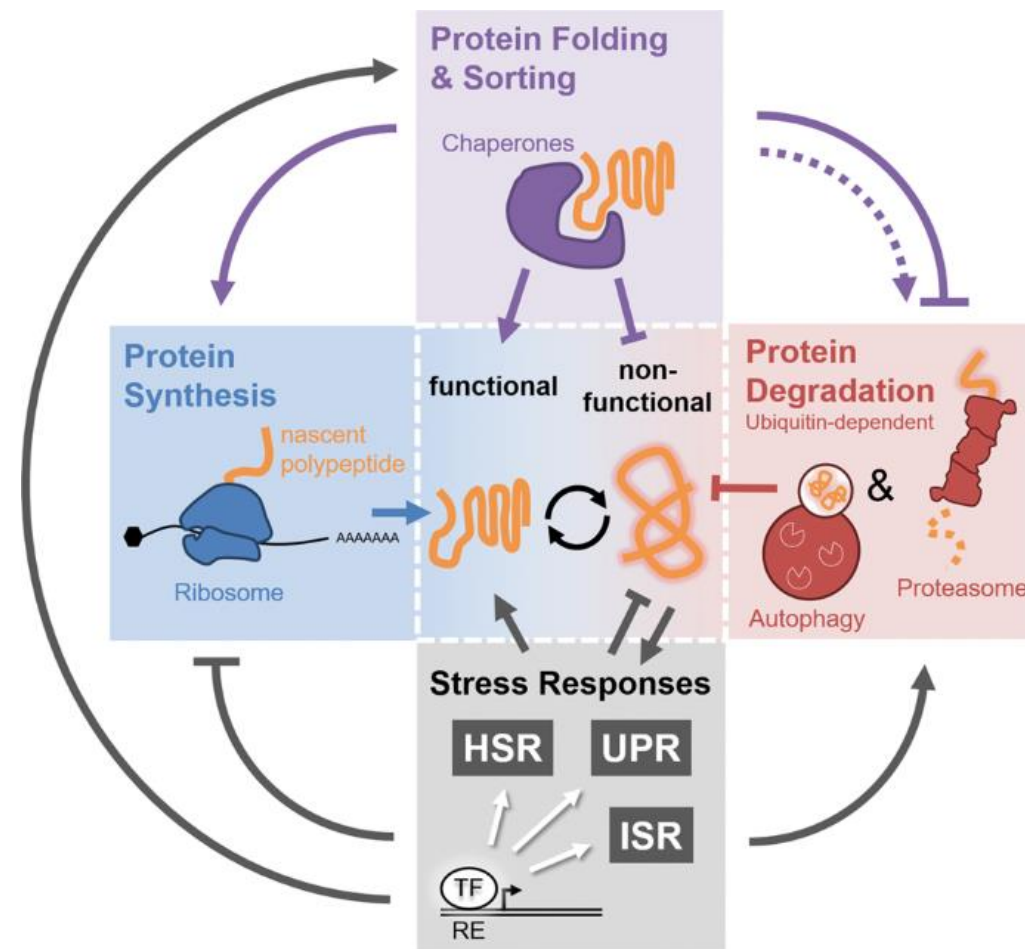
Età e metabolismo muscolare (2)

Insulino-resistenza e steatosi



Tucker MZ et al., Am J Endocrinol Metab, 2003

Perdita della proteostasi



Ottens F et al., Cell Death Differ, 2021



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Alterazioni del bilancio redox nella sarcopenia

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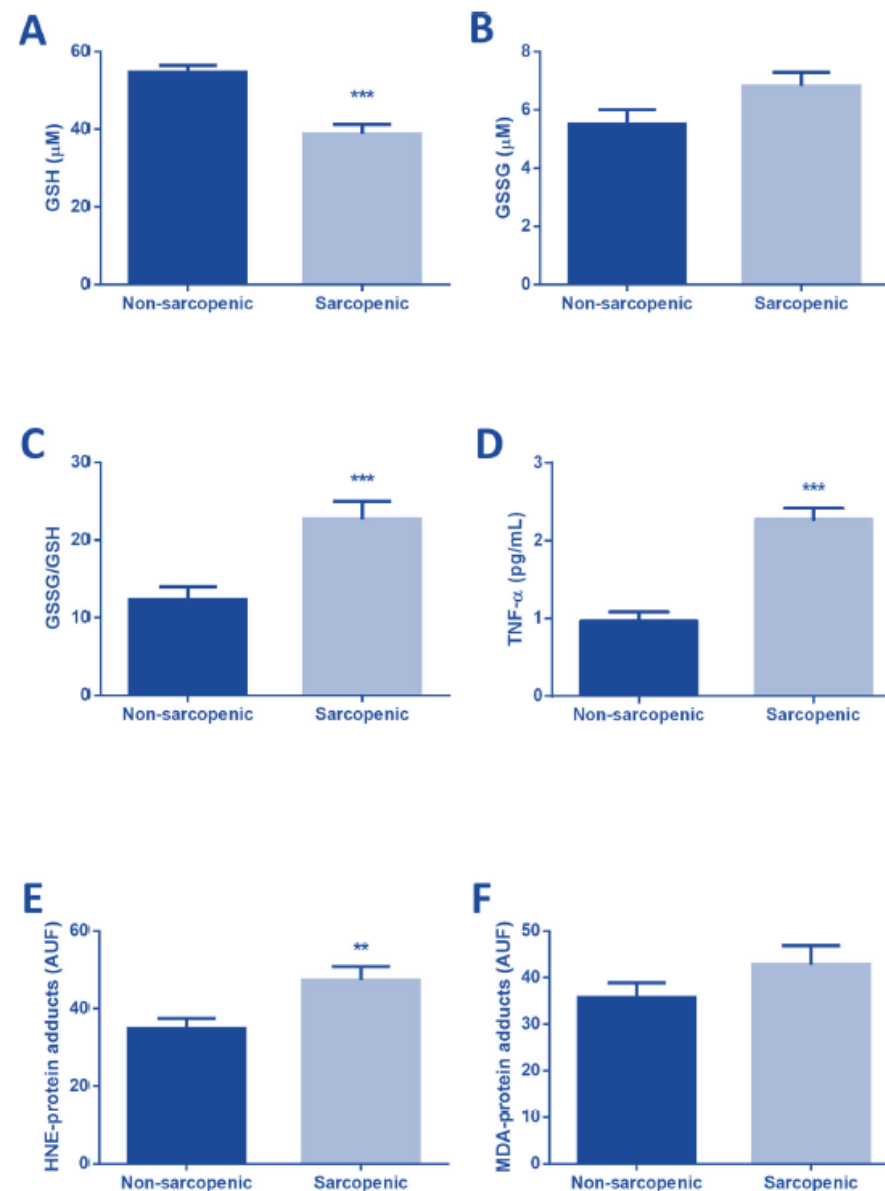
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Medicina mitocondriale per la sarcopenia



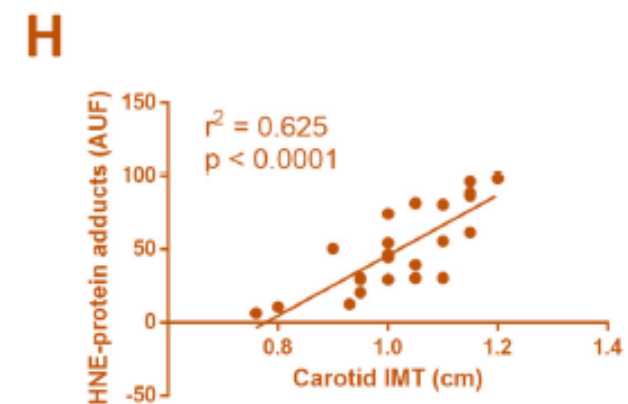
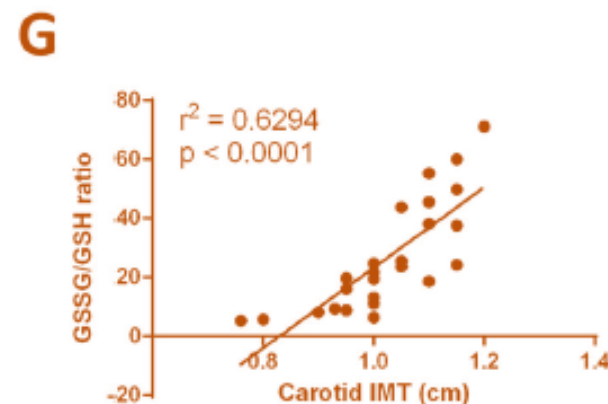
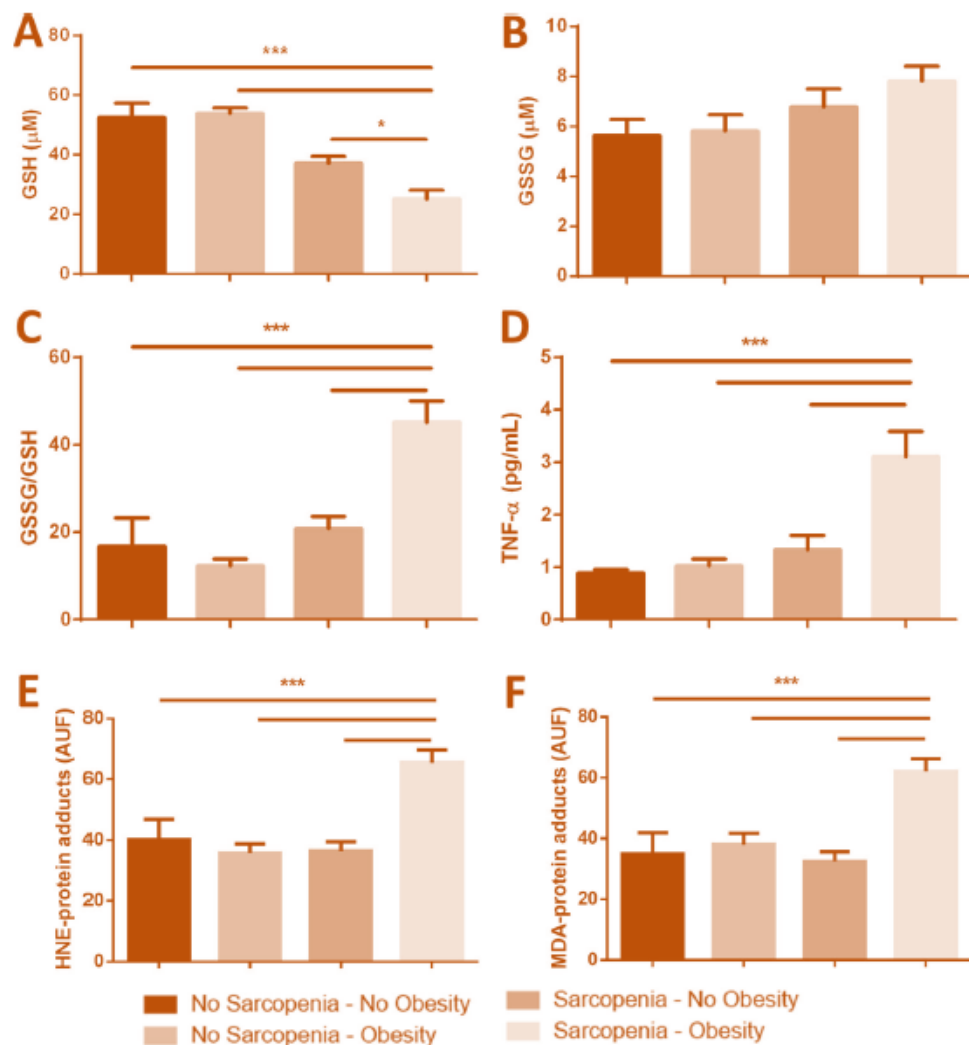
I marcatori circolanti di stress ossidativo sono aumentati nei pazienti sarcopenici

Bellanti F et al., Maturitas, 2018

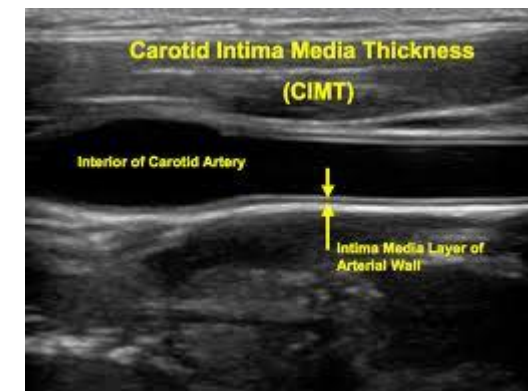




Questi marcatori sono particolarmente incrementati nell'obesità sarcopenica...

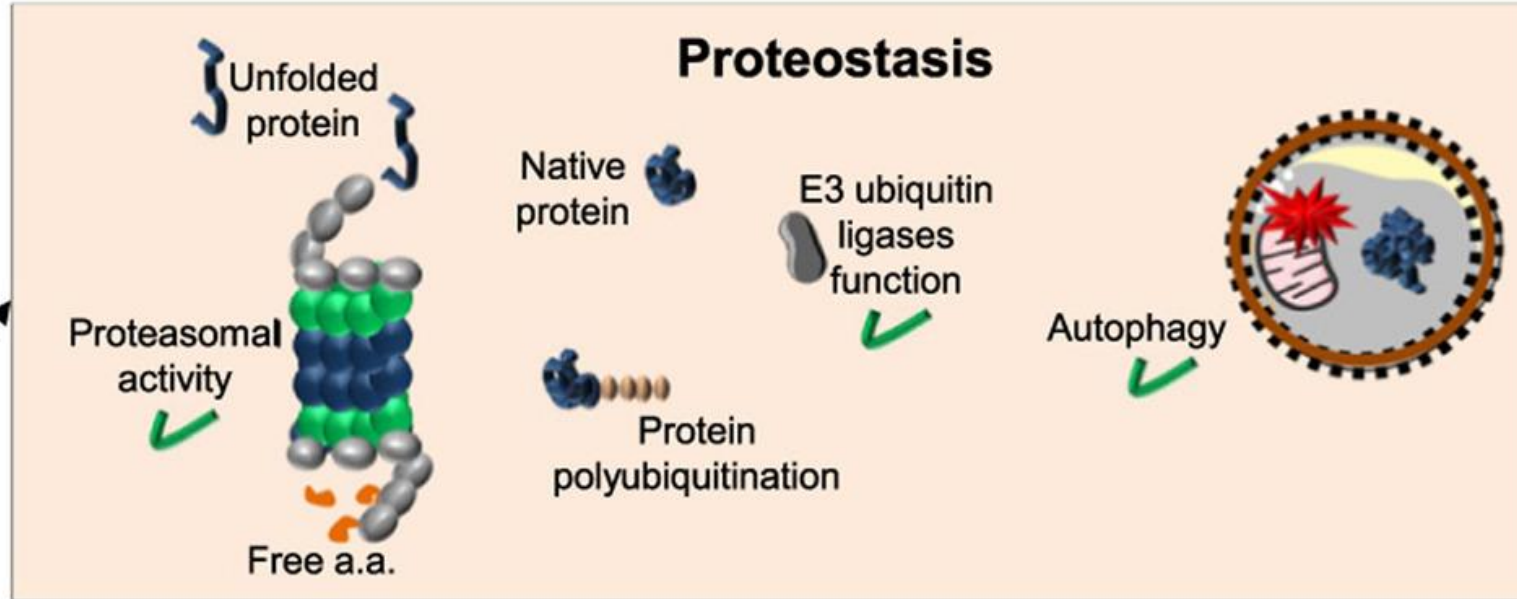
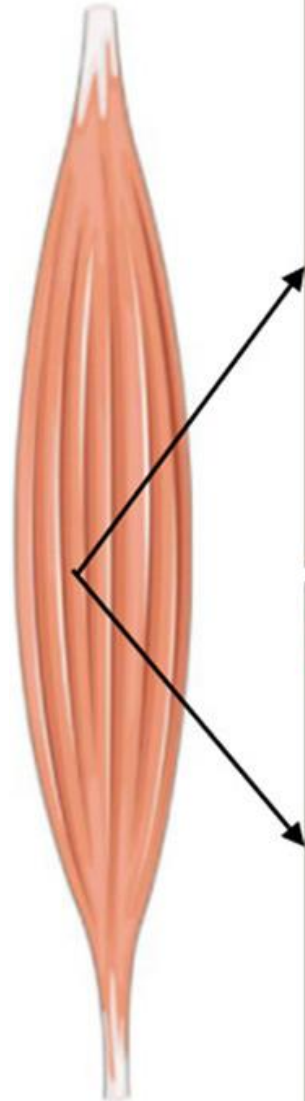


...e si associano ad alto rischio CV

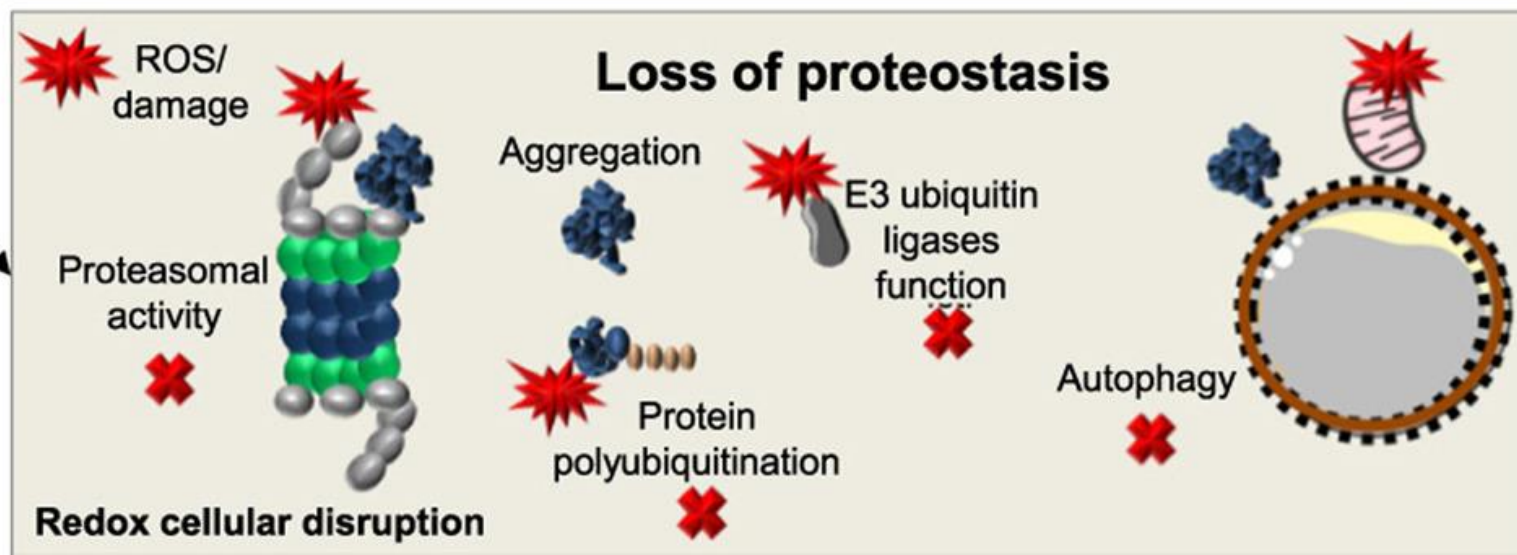


Redox changes lead to the loss of proteostasis and function in the skeletal muscle during aging

Skeletal muscle



Young - Healthy muscle

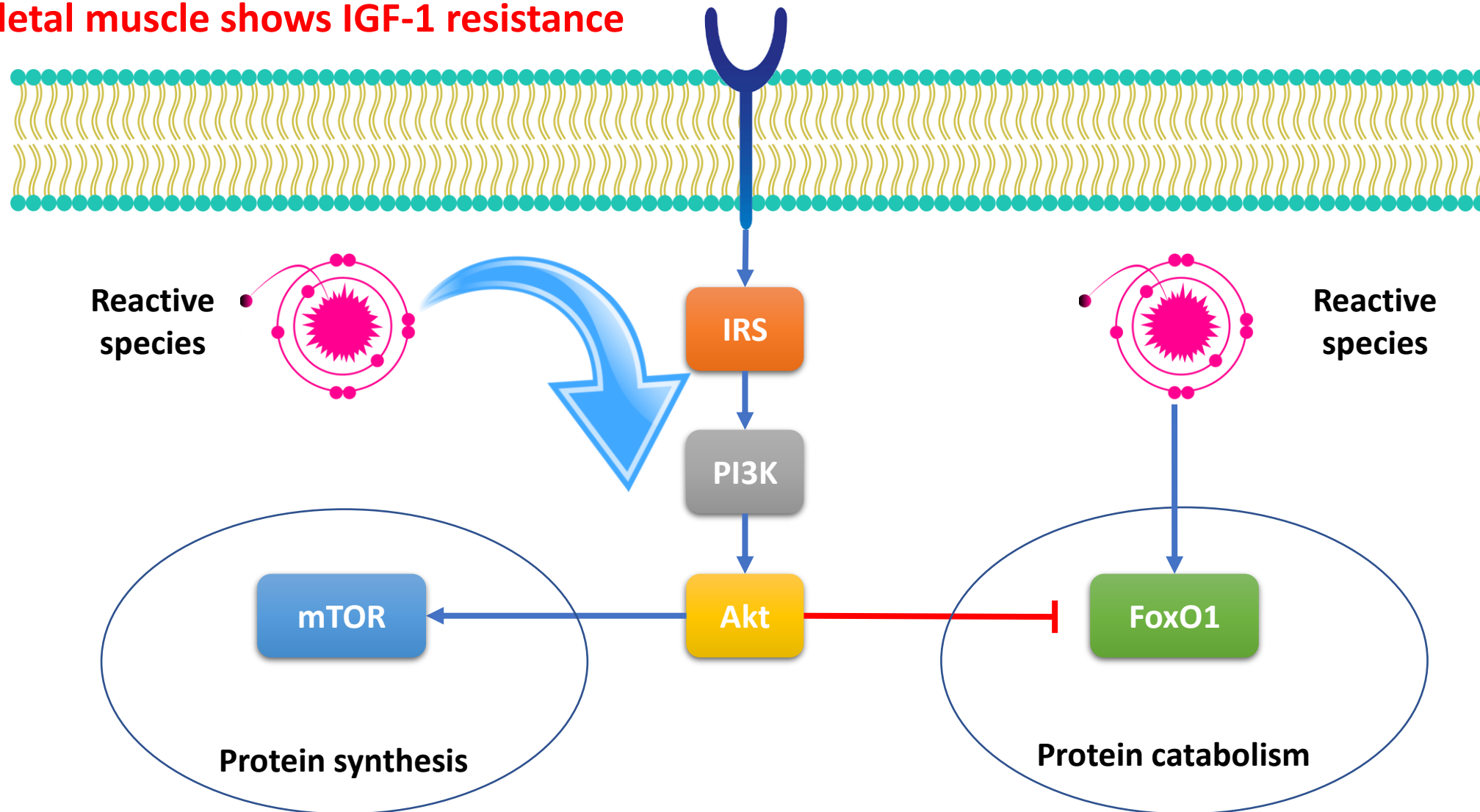


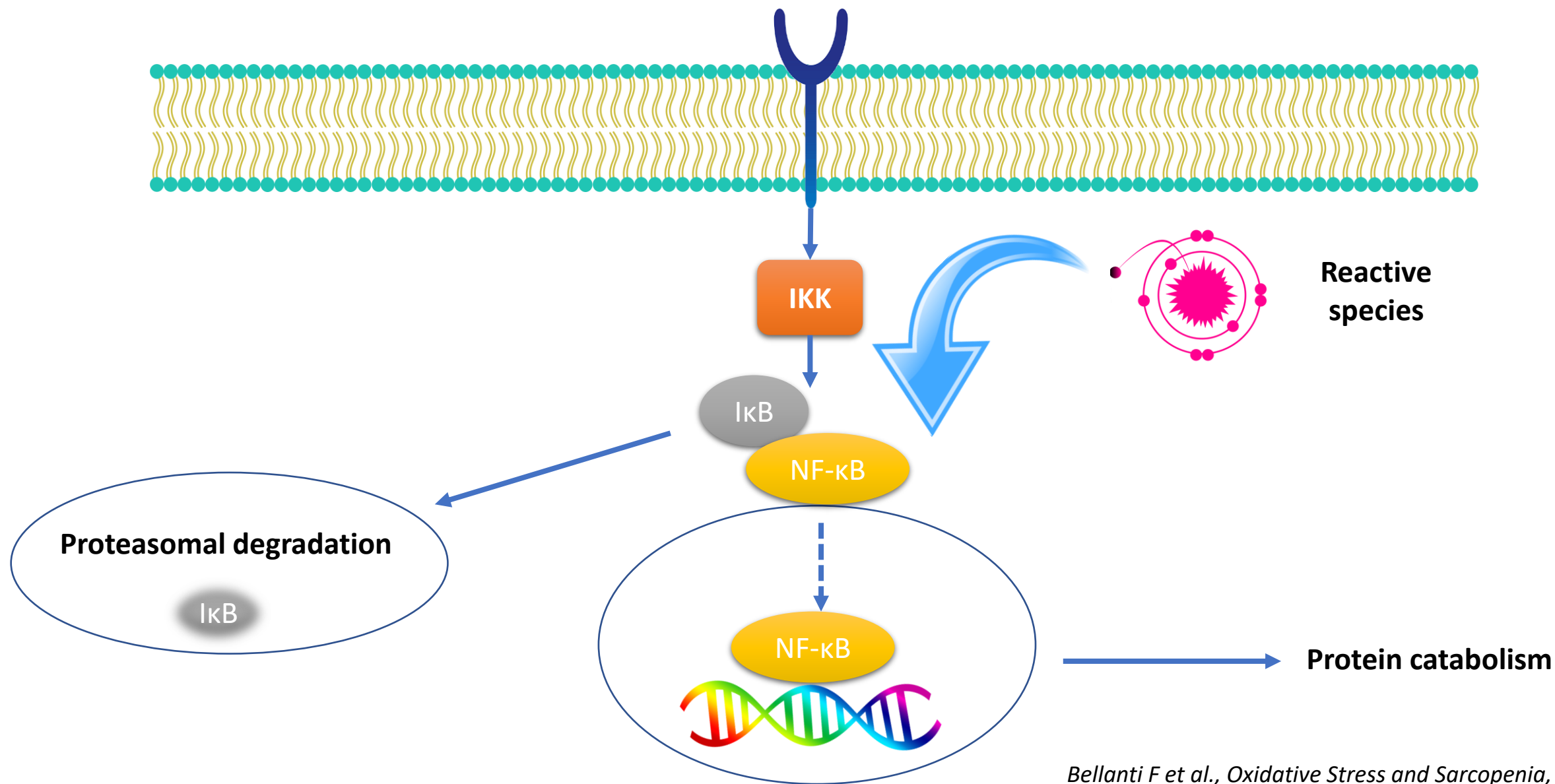
Old - Dysfunctional and sarcopenic muscle

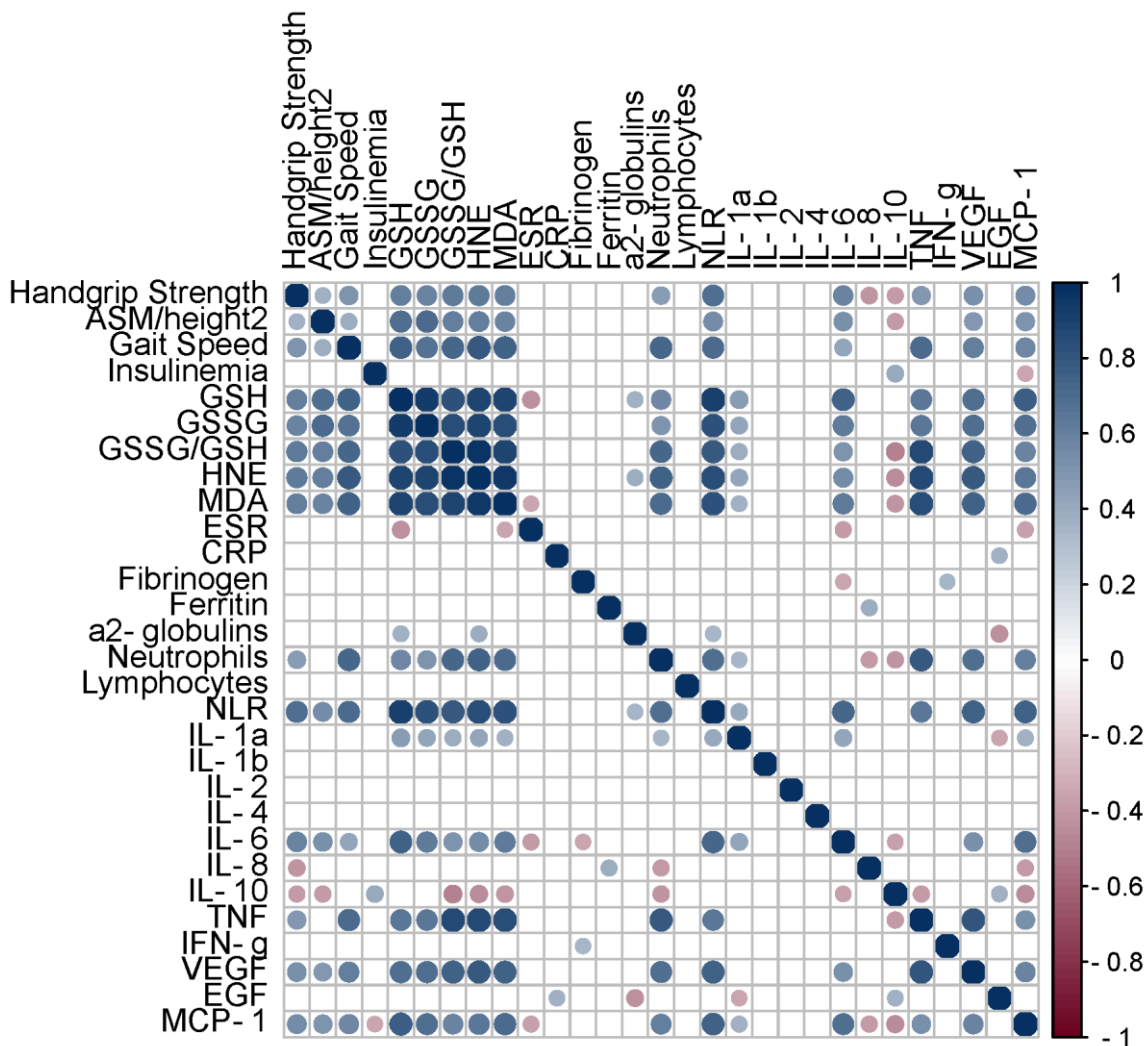




Aging skeletal muscle shows IGF-1 resistance







Nei pazienti sarcopenici, le alterazioni circolanti del bilancio redox si associano ai cambiamenti della risposta immunitaria innata



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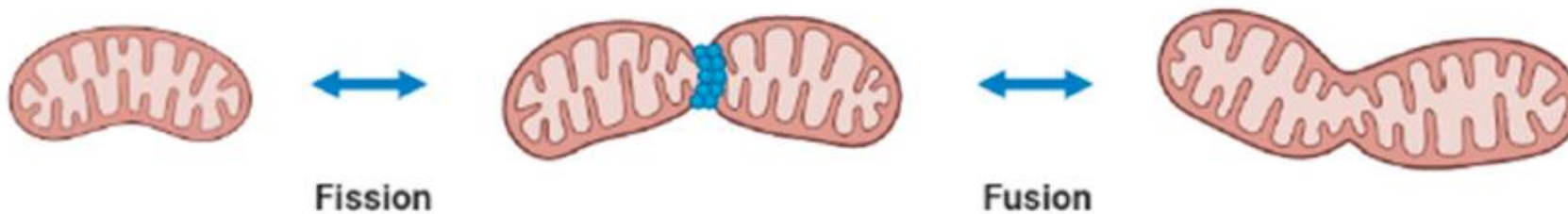
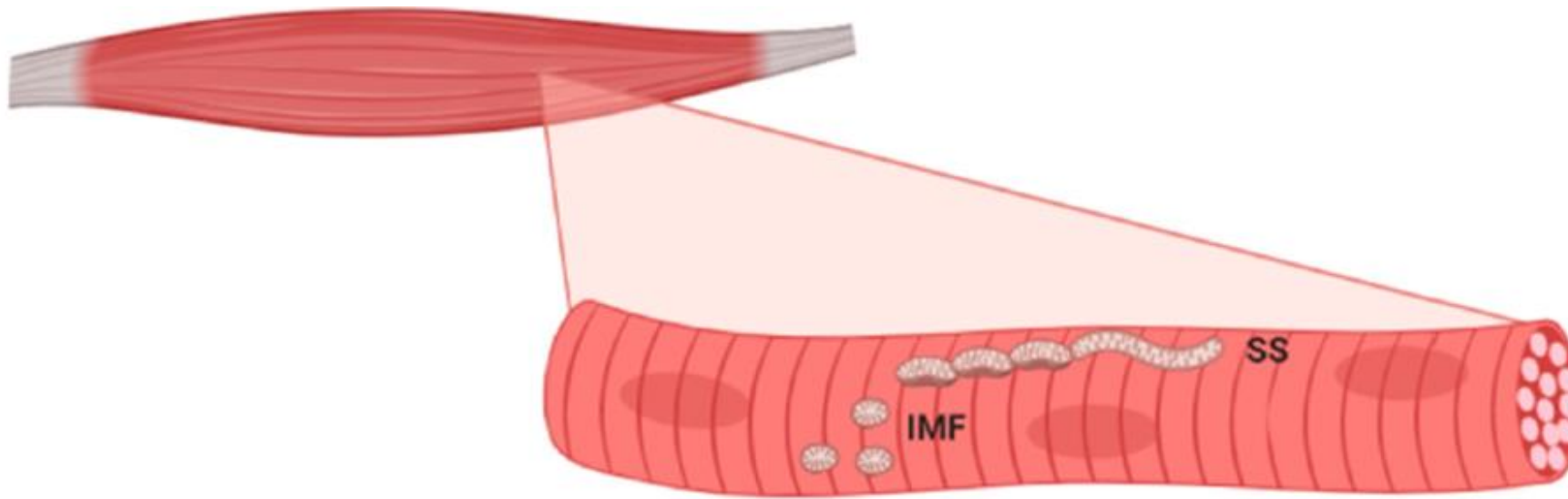
2 Alterazioni del bilancio redox nella sarcopenia

3 Compromissione muscolare e mitocondri

4 Medicina mitocondriale per la sarcopenia



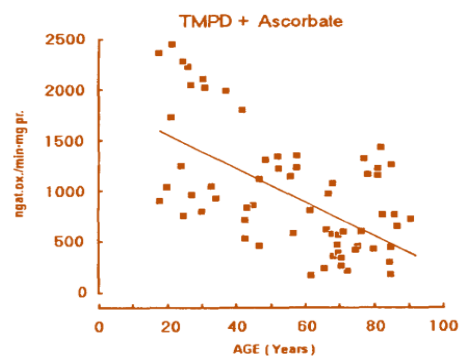
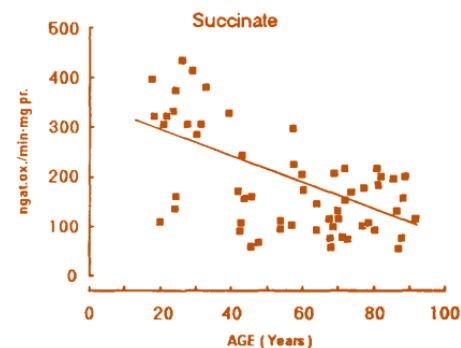
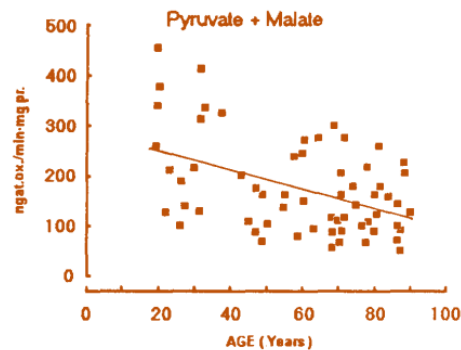
IL NETWORK MITOCONDRIALE NEL MUSCOLO SCHELETRICO





La funzione
mitocondriale nel
muscolo
scheletrico si
riduce durante
l'invecchiamento

Consumo di ossigeno



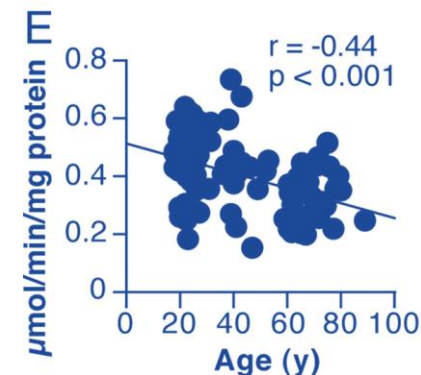
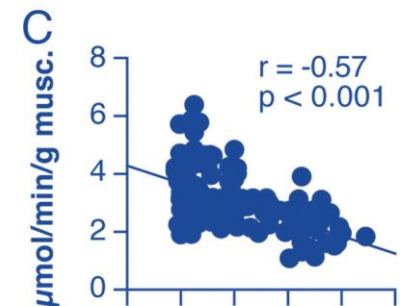
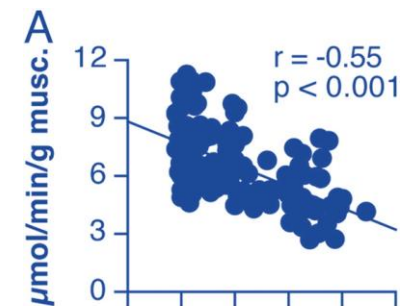
Boffoli D et al., BBA, 1994

Compl. I

PPKM

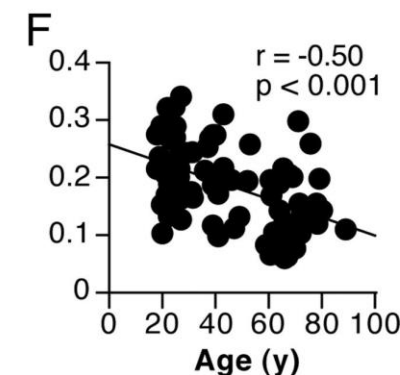
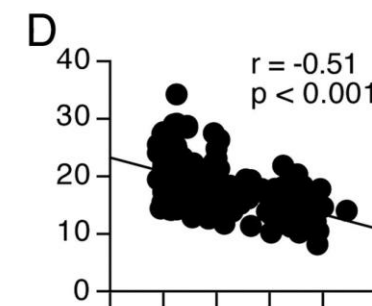
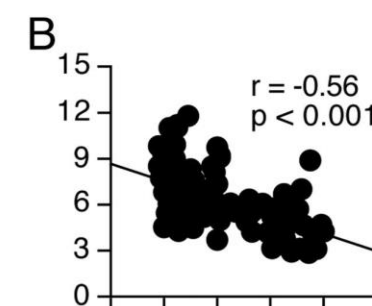
Compl. II

Sintesi di ATP

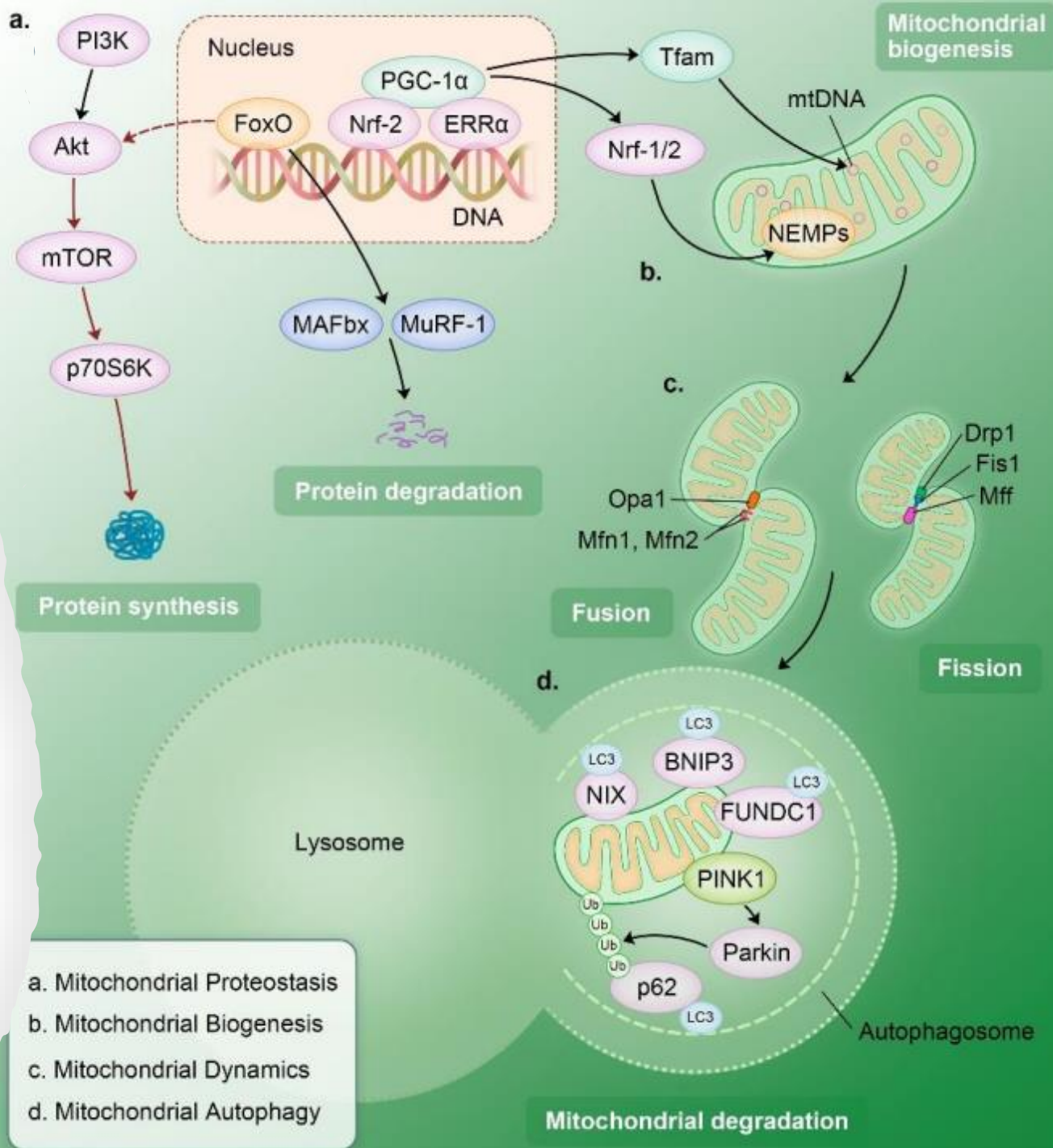


Short KR et al., Proc Natl Acad Sci, 2005

Attività della CS



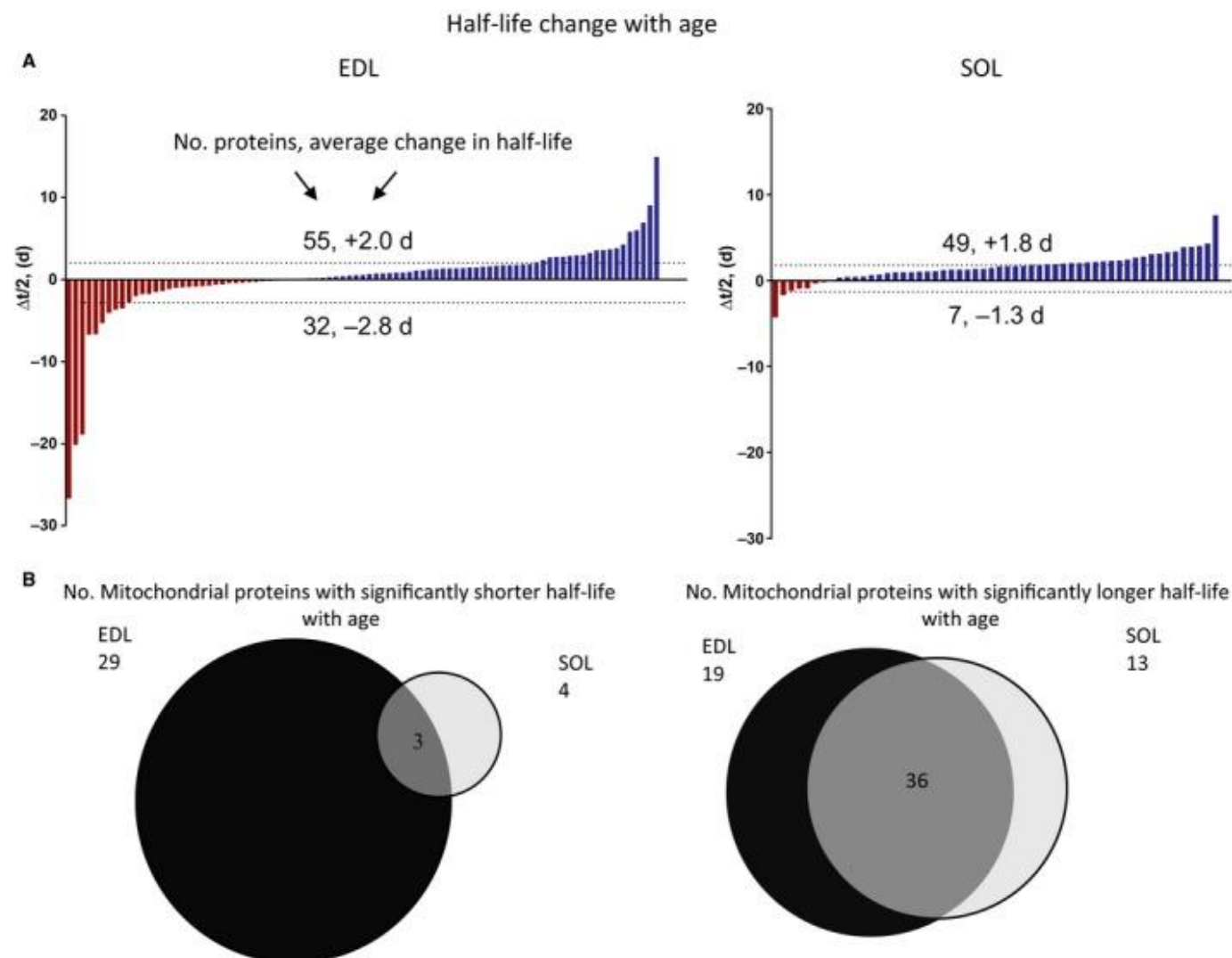
“Mitochondrial quality control”





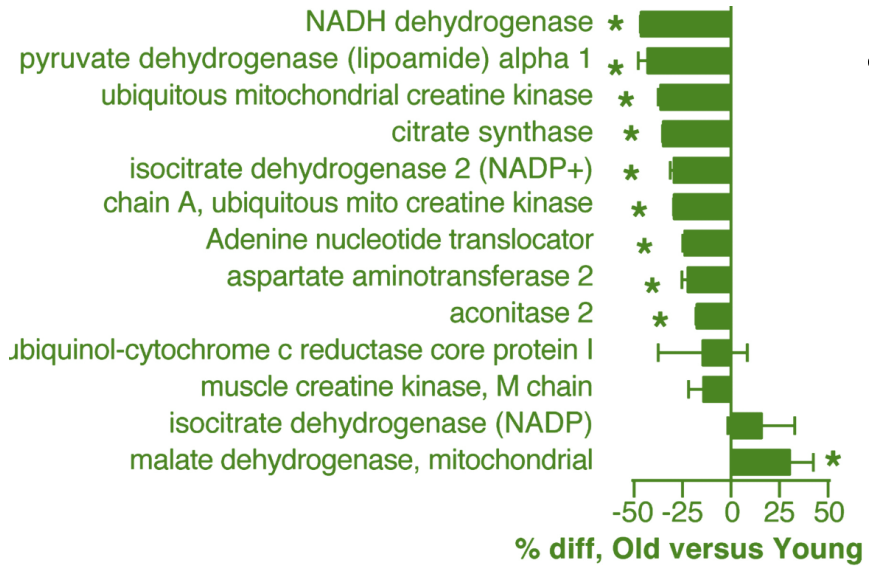
Sarcopenia e **proteostasi** mitocondriale

L'emivita delle proteine
mitocondriali si modifica
nell'invecchiamento e
dipende dal tipo di
muscolo scheletrico

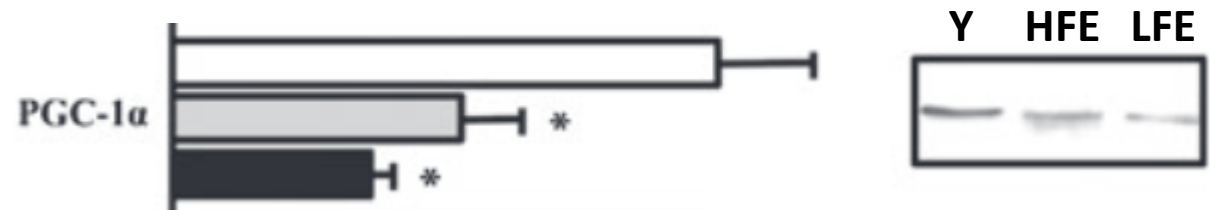




Proteine mitocondriali

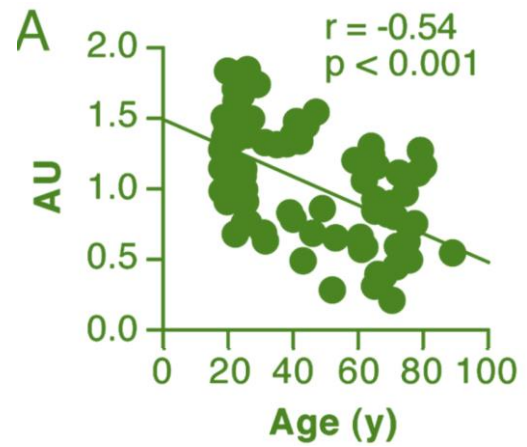


Sarcopenia e **biogenesi** mitocondriale



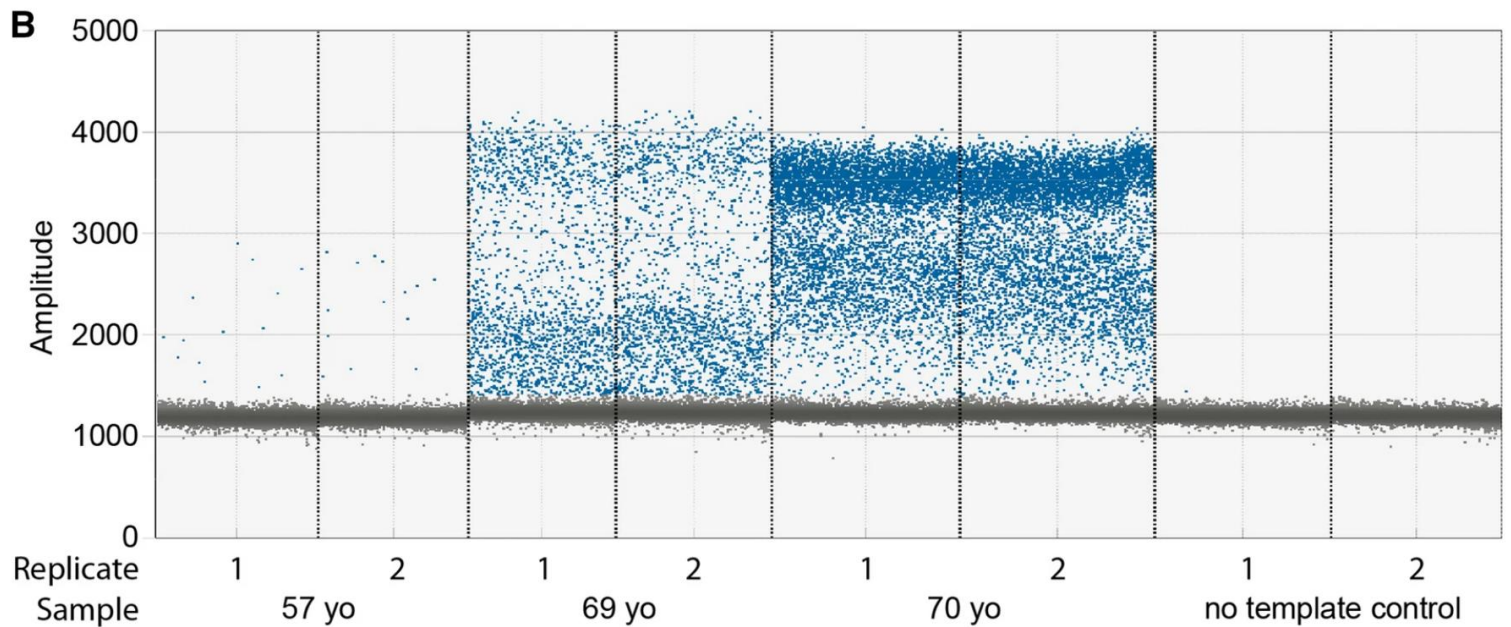
Joseph AM et al., *Aging Cell*, 2012

Contenuto in mtDNA



Short KR et al., *Proc Natl Acad Sci*, 2005

Delezioni/mutazioni del DNA mitocondriale



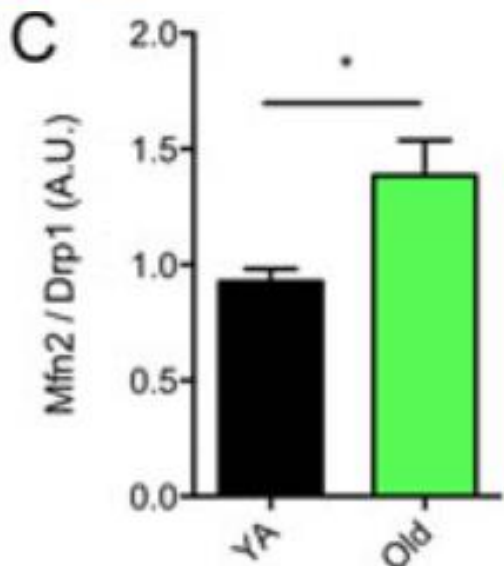
Herbst A et al., *Aging Clin Exp Res*, 2020



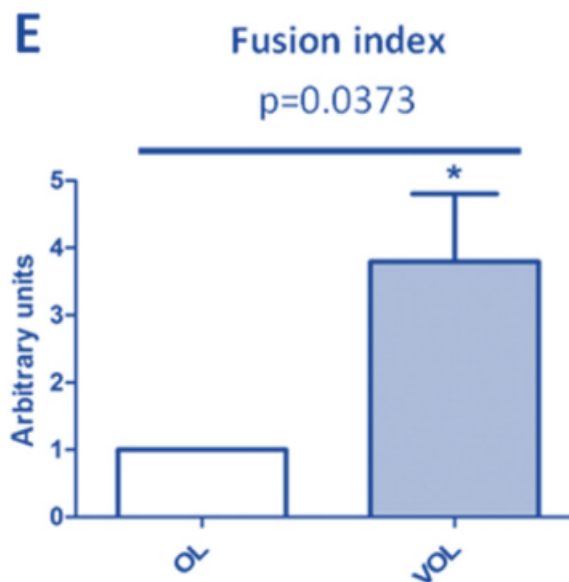
Sarcopenia e **dinamica** mitocondriale



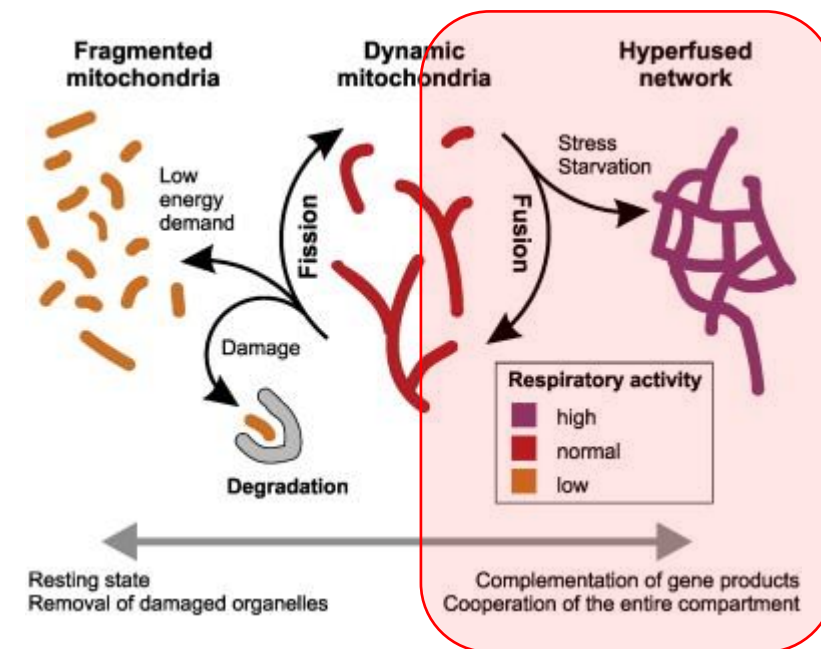
I mitocondri si allungano e si ramificano nel muscolo scheletrico dei topi e dei pazienti sarcopenici



Leduc-Gaudet JP et al., *Oncotarget*, 2015



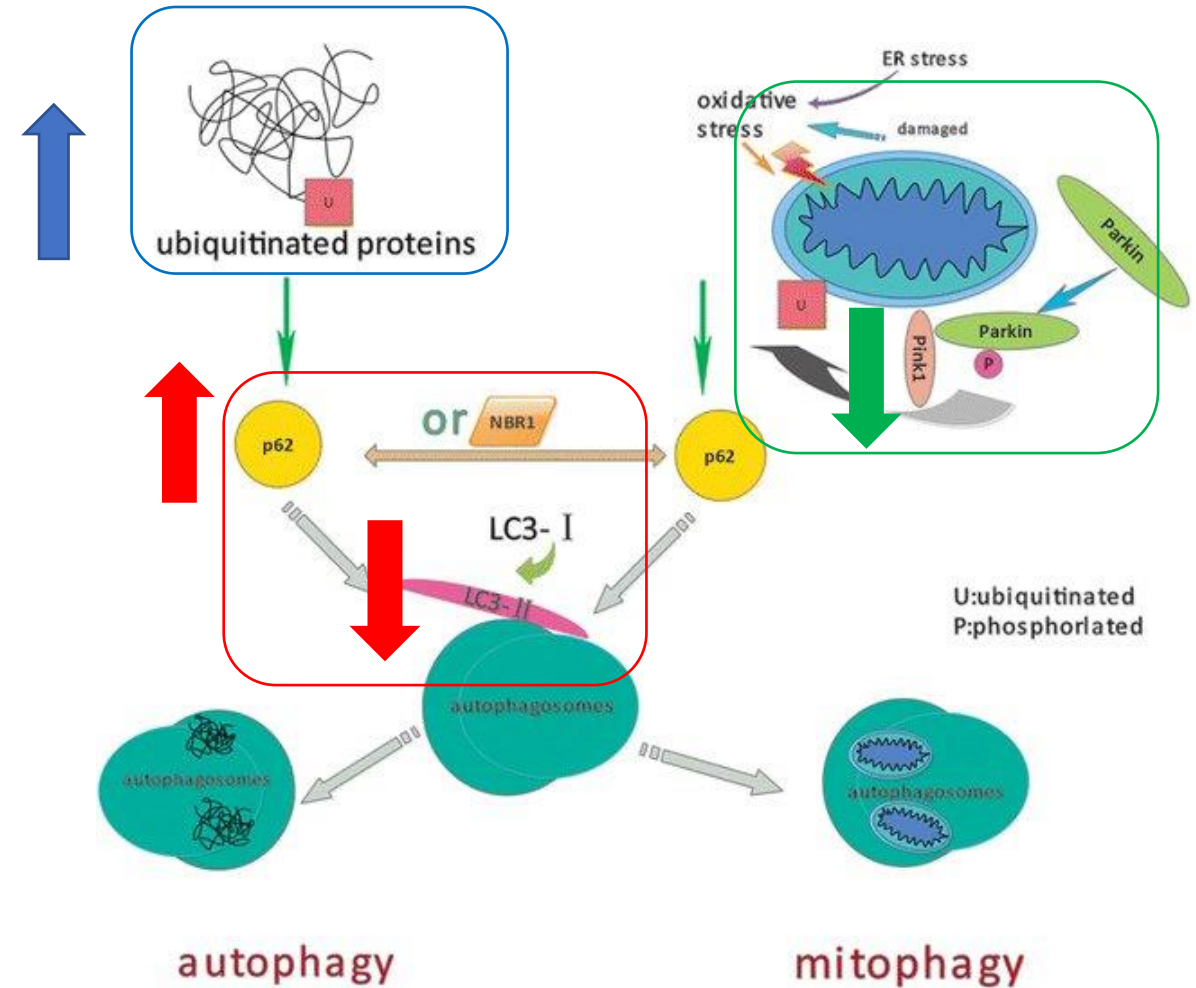
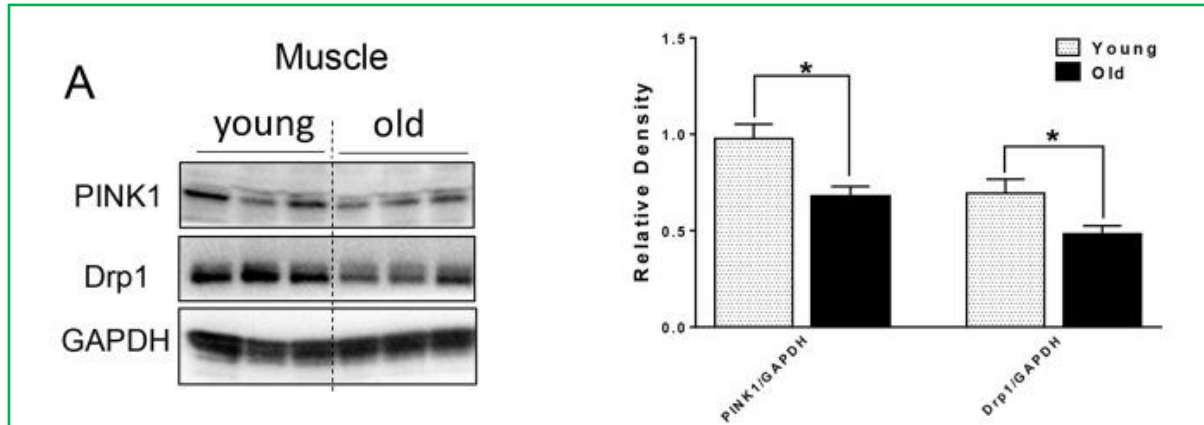
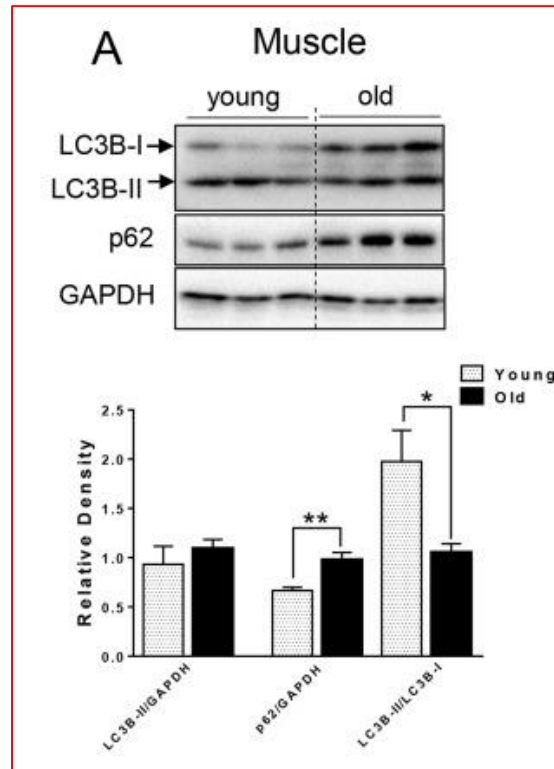
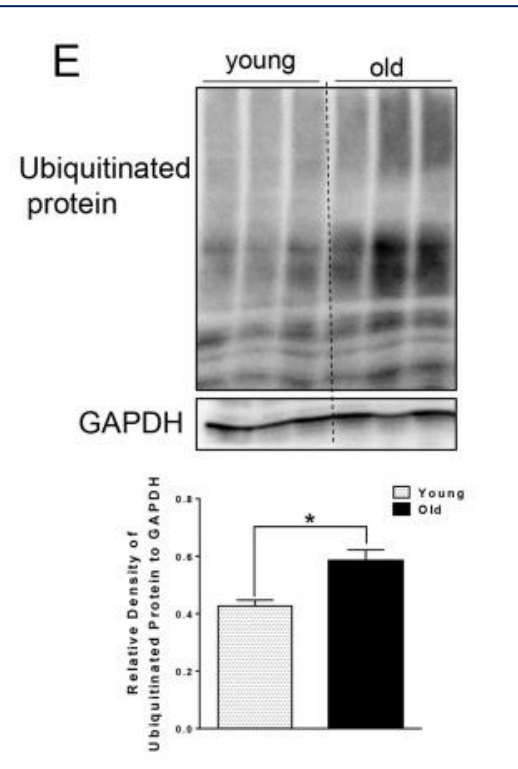
Picca A et al., *Exp Gerontol*, 2017

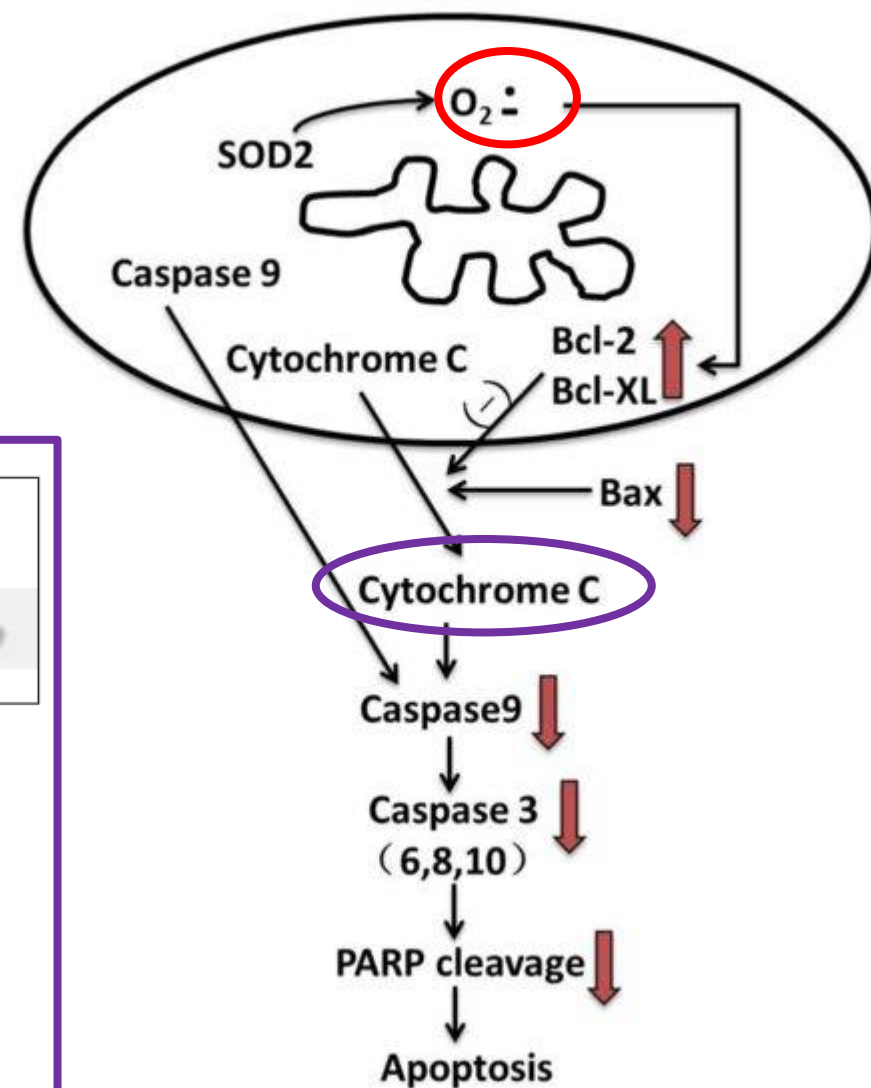
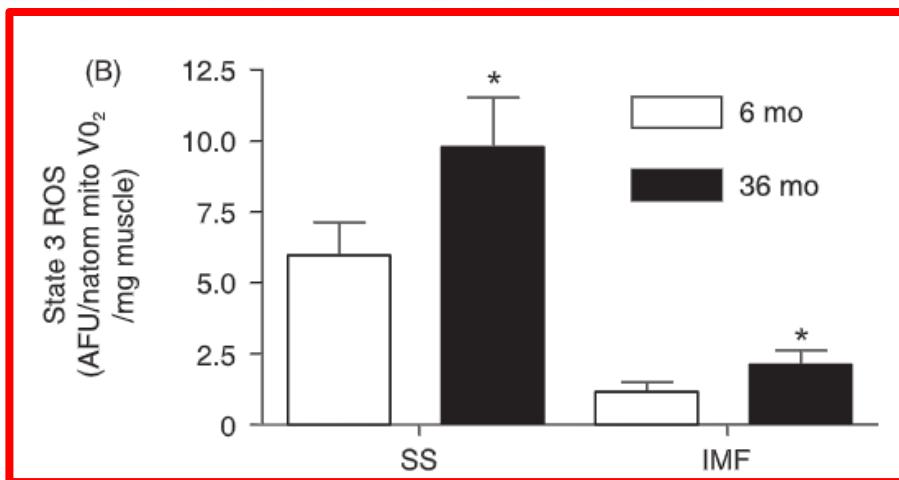


**Risposta compensatoria
inefficace ad uno stress lieve?**

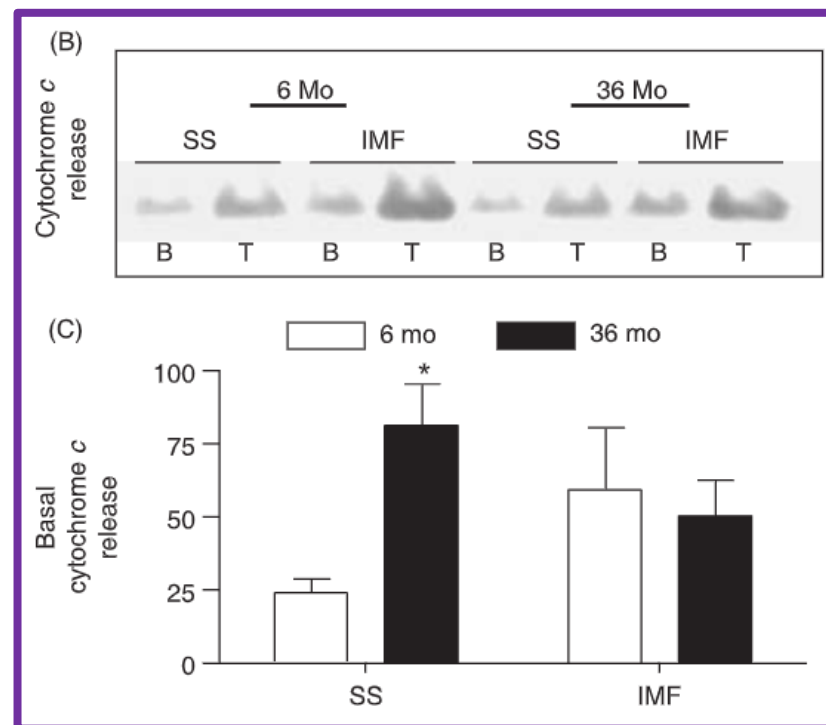


Sarcopenia e **autofagia** mitocondriale





Sarcopenia e
apoptosi
mitocondrio-
dipendente





AGENDA

1 Sarcopenia: un'insidia di salute pubblica

2 Alterazioni del bilancio redox nella sarcopenia

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4 Medicina mitocondriale per la sarcopenia



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Reverse Sarcopenia

Ad oggi, l'esercizio resta l'unica terapia comprovata per la sarcopenia

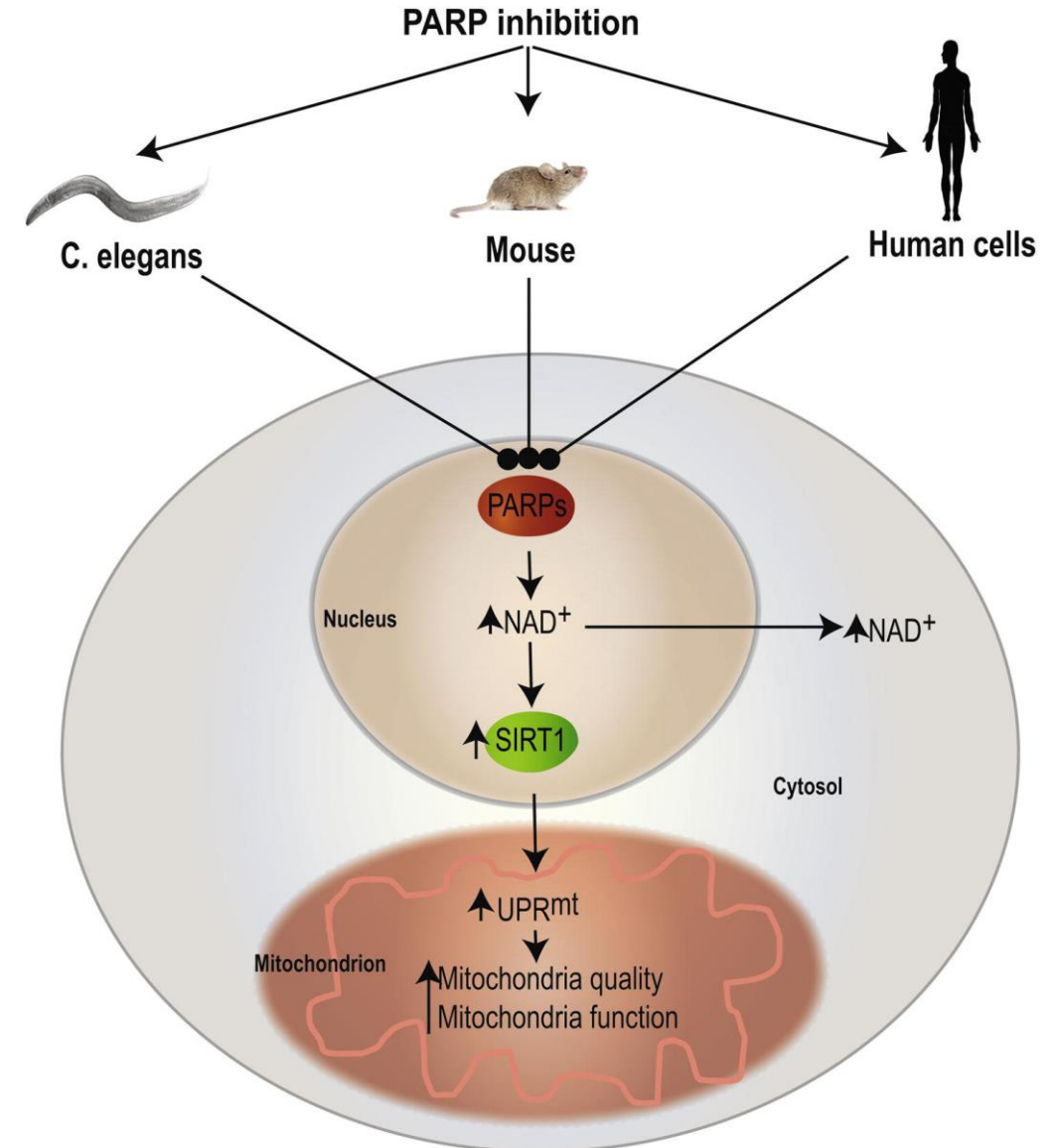
An Easy-to-Follow Program to Keep Muscles Strong and Youthful While Reducing Your Risk of Developing Dementia



Includes
100
Color Photos



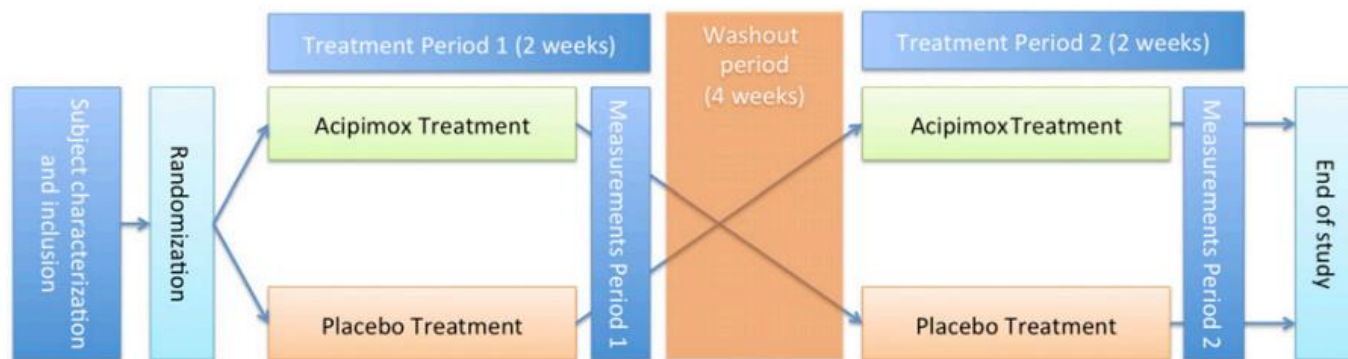
L'inibizione farmacologica della poli(ADP-ribosio) polimerasi migliora la funzione mitocondriale ed il fitness del muscolo scheletrico



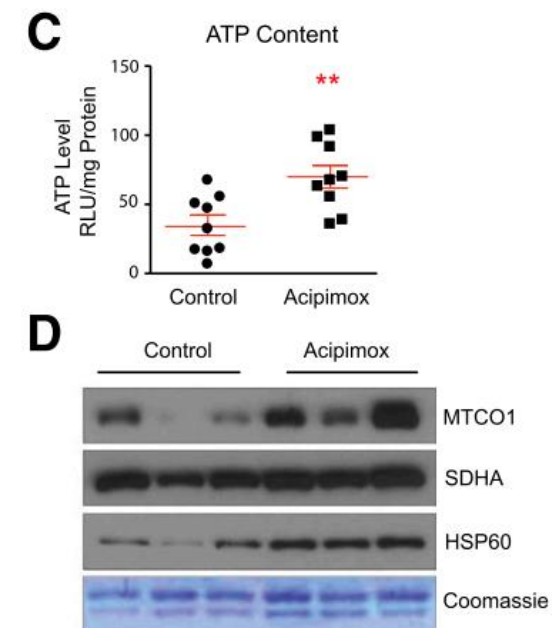


L'acipimox migliora la funzione mitocondriale nel muscolo scheletrico dell'uomo

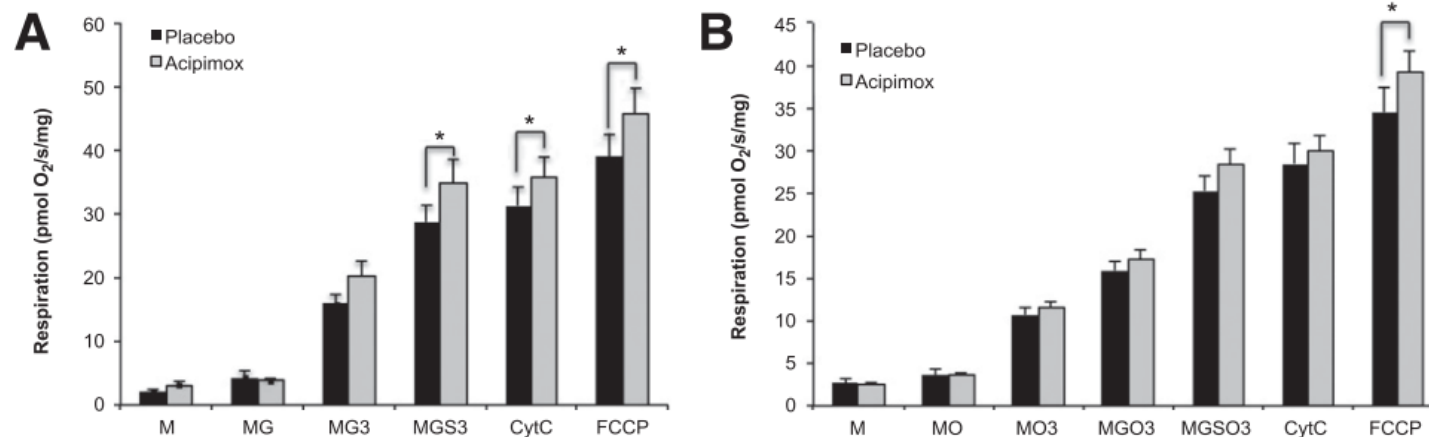
Disegno dello studio



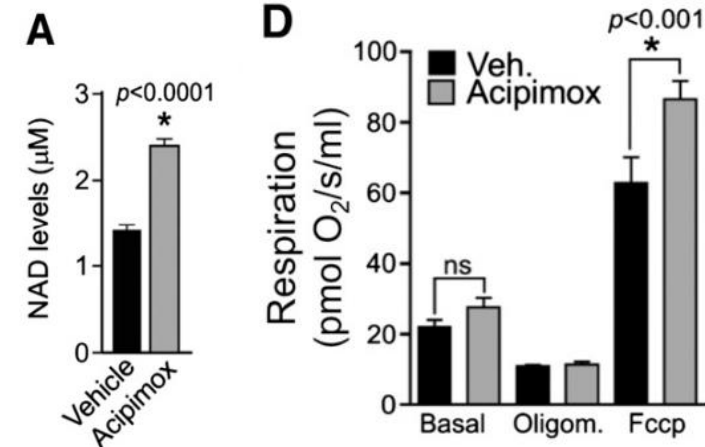
Biopsie muscolari



Fibre muscolari permeabilizzate



Cellule C2C12

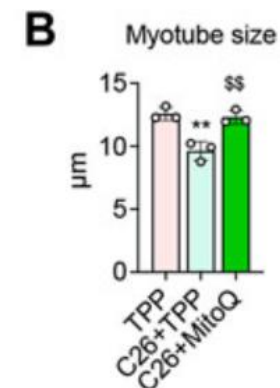
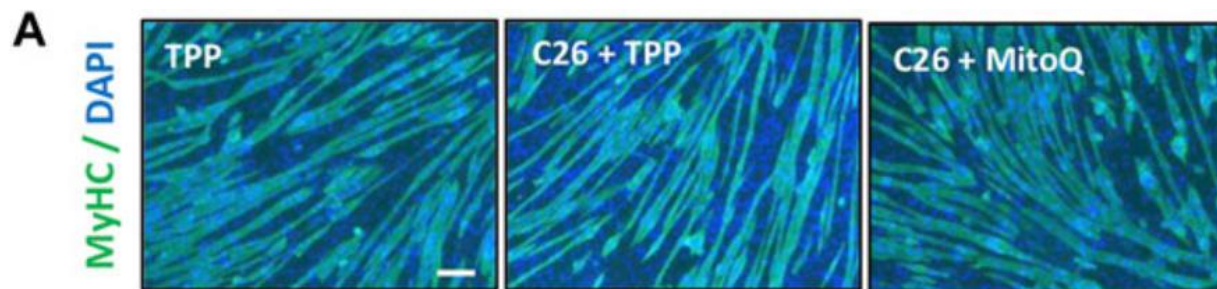




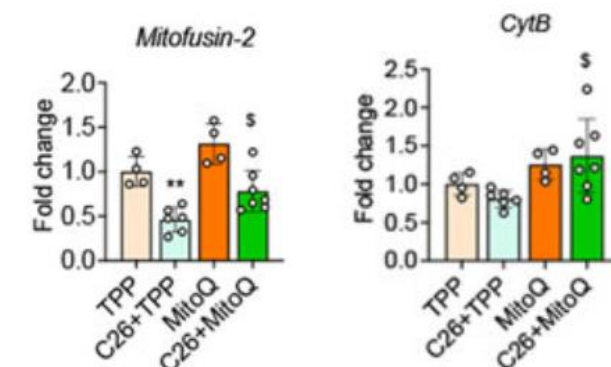
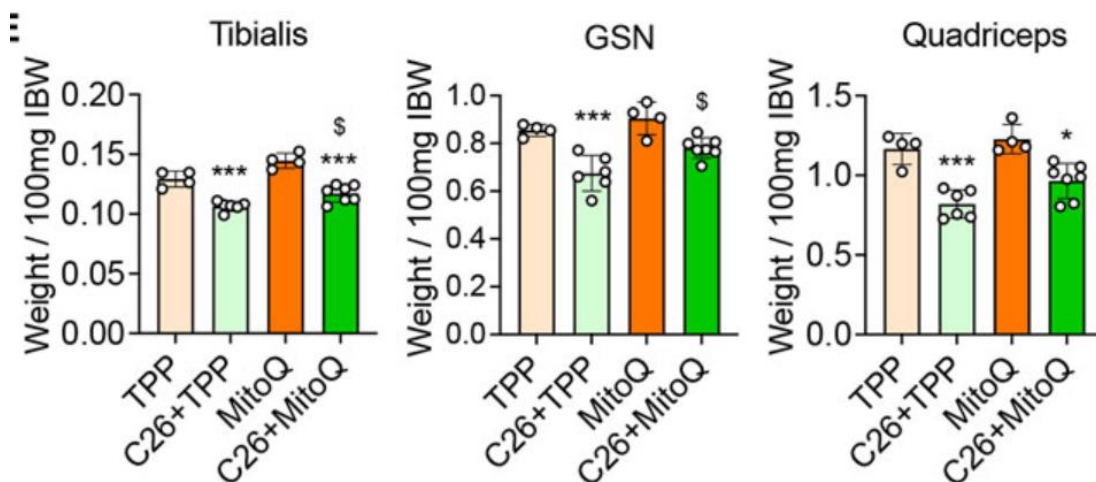
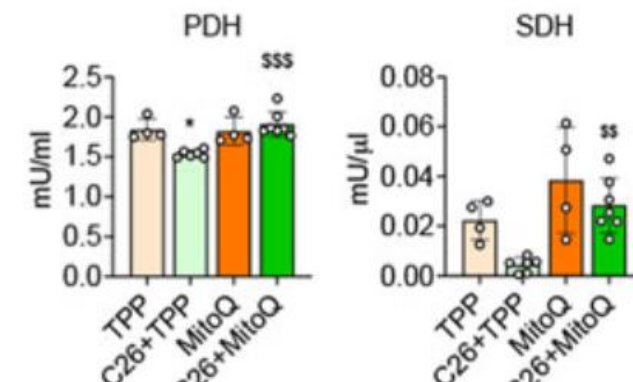
Il MitoQ migliora l'atrofia, la debolezza e la funzione mitocondriale nei muscoli di topi C26



Dimensioni e forza muscolari



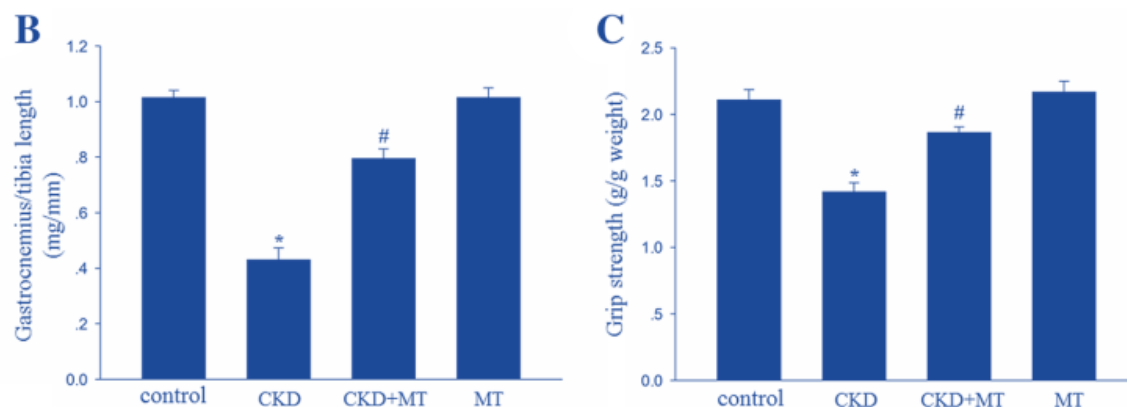
Funzione e omeostasi mitocondriale



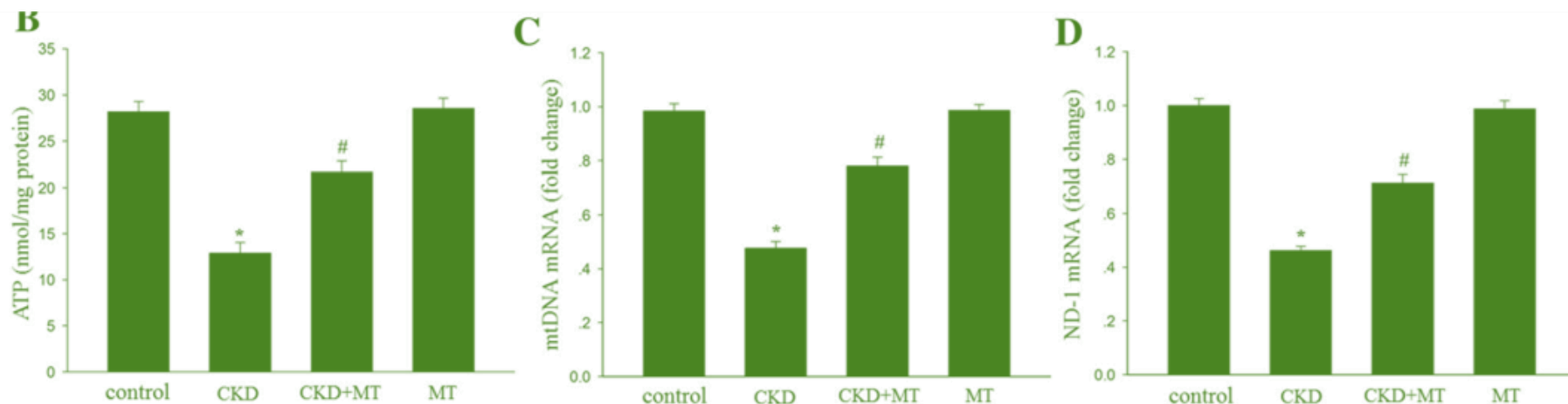
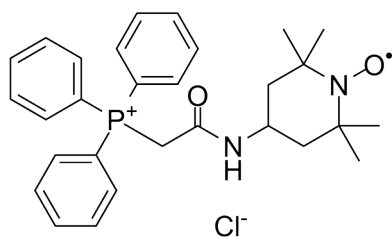
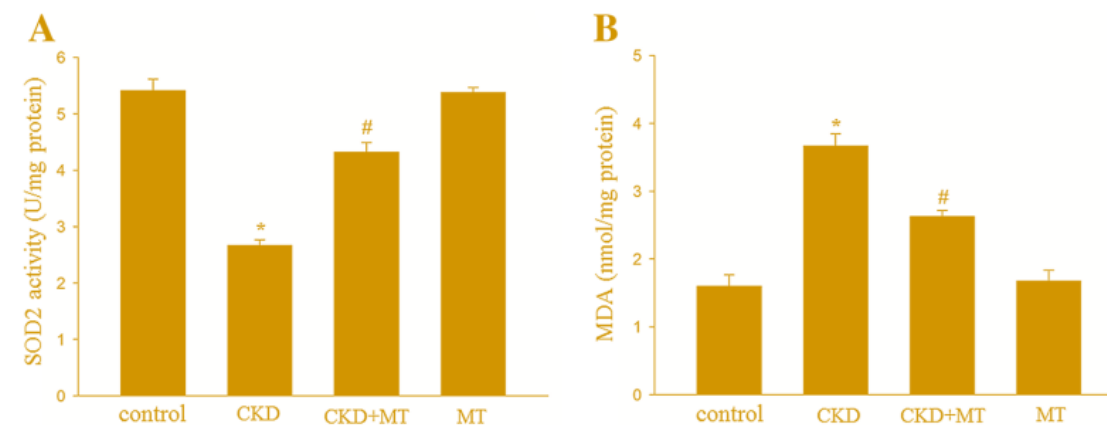


Il Mito-TEMPO previene l'atrofia muscolare in un modello di uremia, migliorando la funzione mitocondriale

Massa e forza muscolare

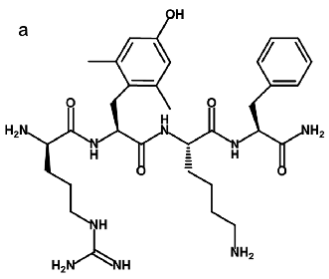


Bilancio redox

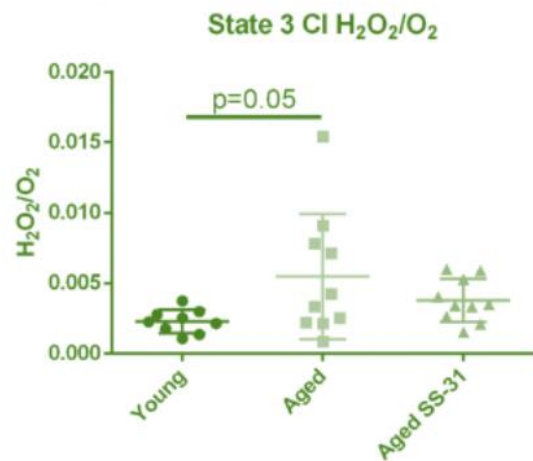
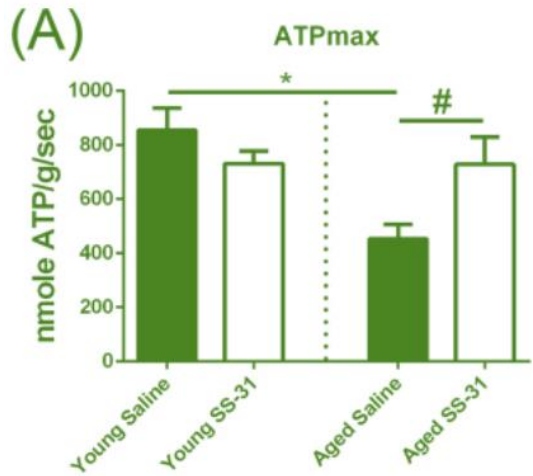


Omeostasi mitocondriale

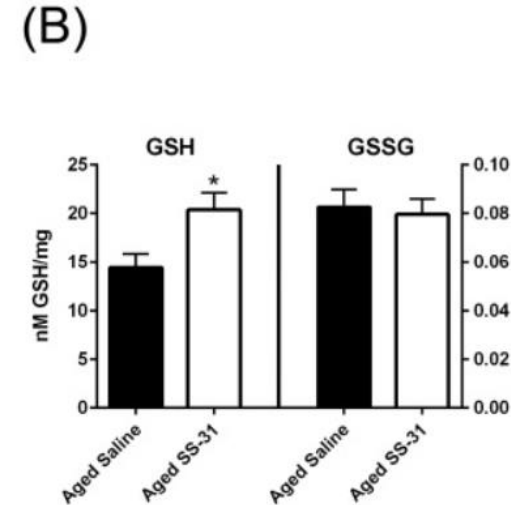
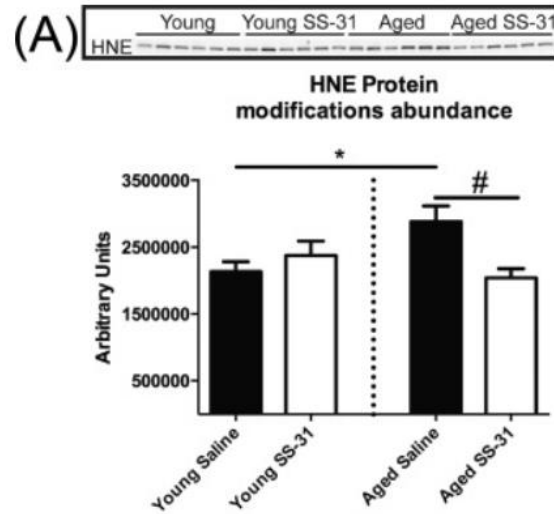
SS-31 contrasta lo stress ossidativo età-correlato e migliora la performance muscolare



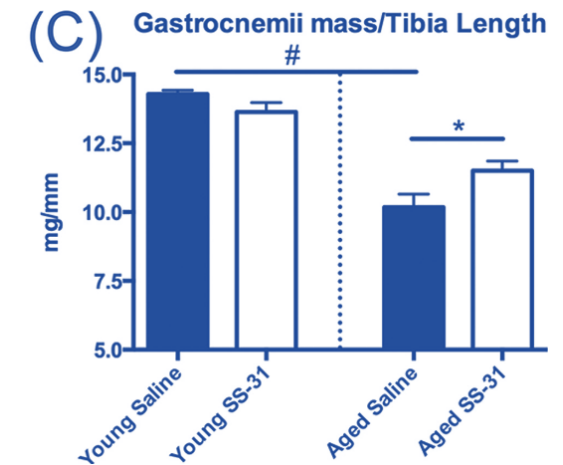
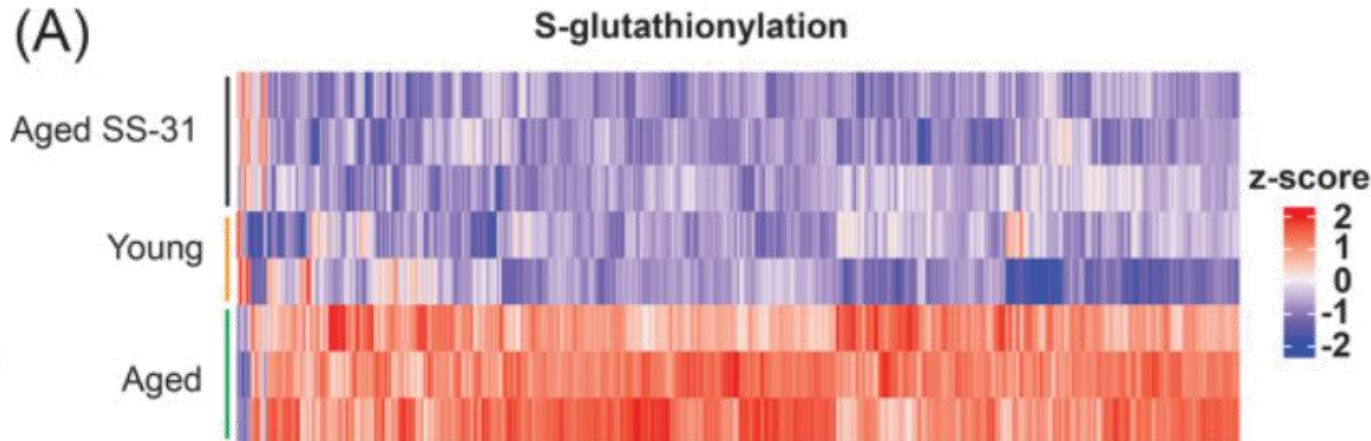
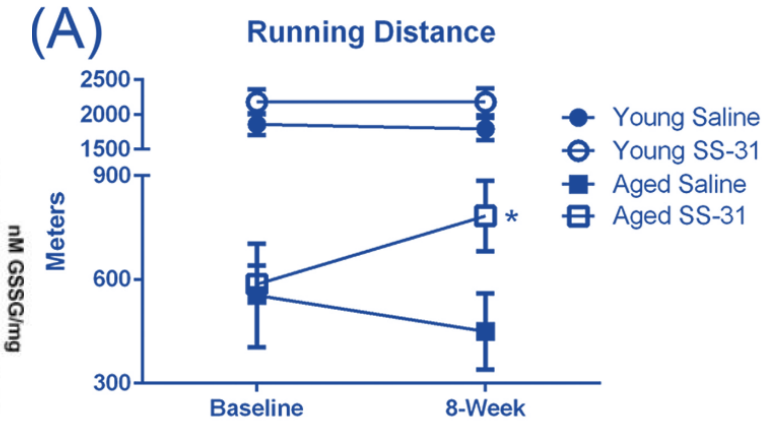
Funzione mitocondriale



Omeostasi redox



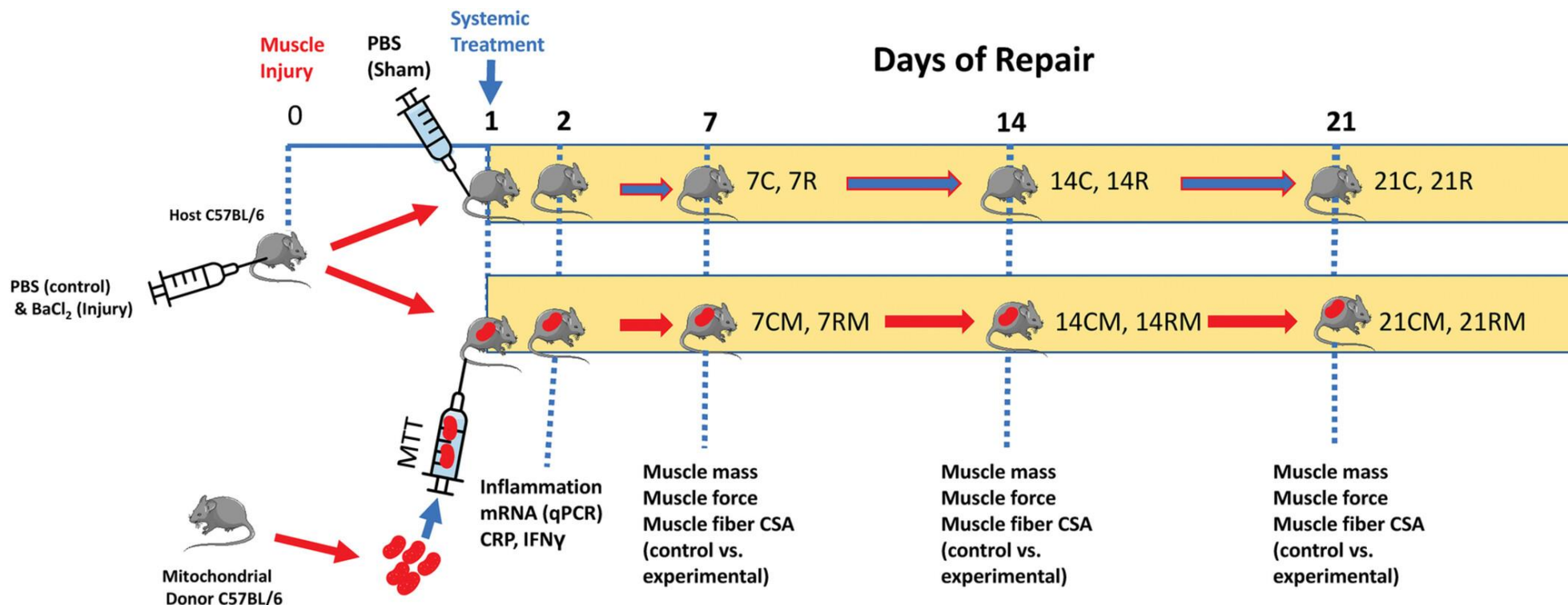
Forza e massa muscolare





Il trapianto mitocondriale ripristina il danno al muscolo scheletrico

Study protocol

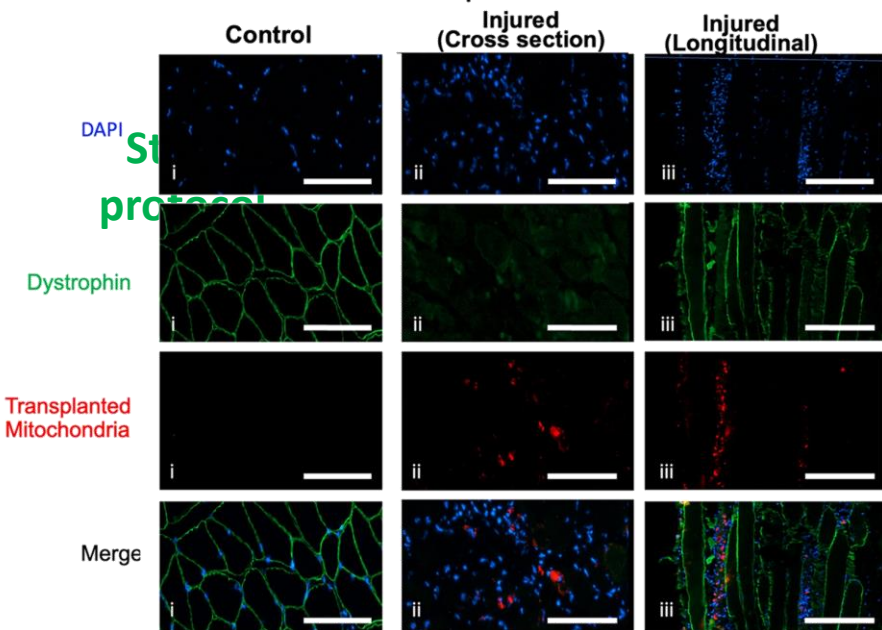




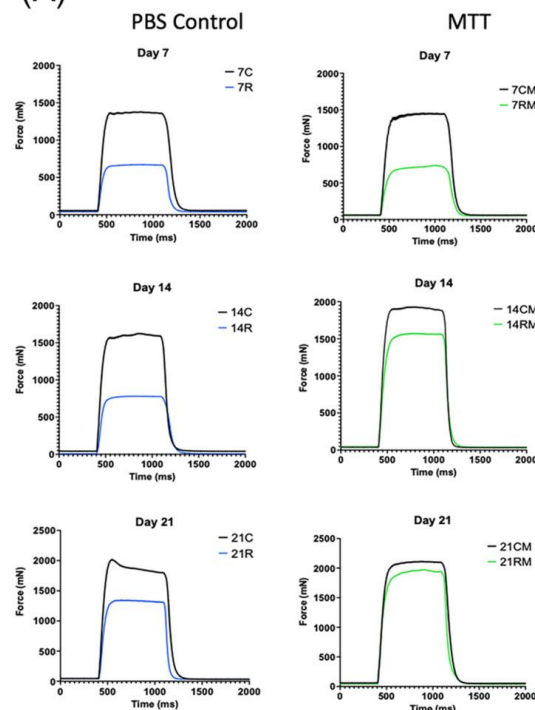
Il trapianto mitocondriale ripristina il danno al muscolo scheletrico

In situ Muscle force and Muscle Mass

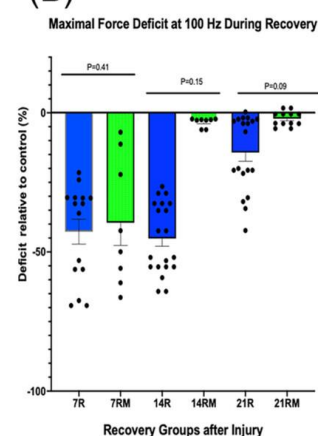
Mitochondria uptake in muscle- *in vivo*



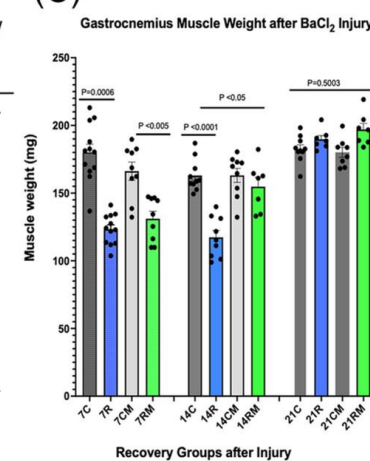
(A)



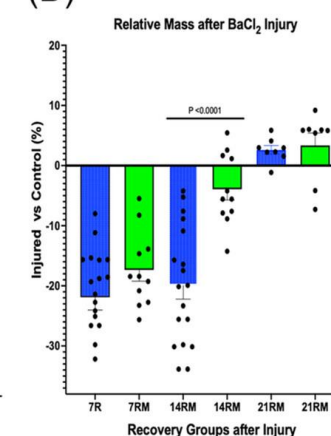
(B)

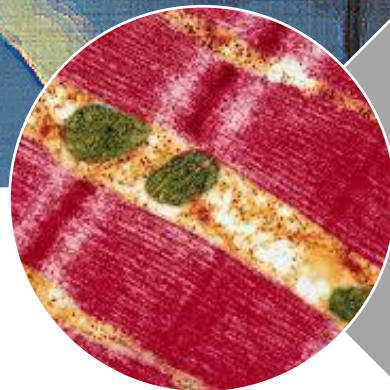


(C)

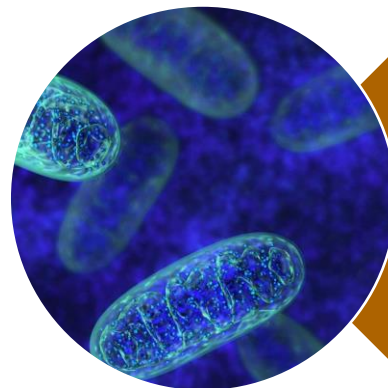


(D)





Le alterazioni del bilancio redox e dell'omeostasi mitocondriale sono alla base dello sviluppo di sarcopenia



Entrambi questi fattori possono essere selettivamente modulati da farmaci d'avanguardia



Studi preliminari che considerano i mitocondri muscolari come bersaglio terapeutico spianeranno la strada a futuri trial clinici