UNIVERSITÀ CATTOLICA del Sacro Cuore

SARCOPENIA OF AGING: FROM BENCH TO BEDSIDE

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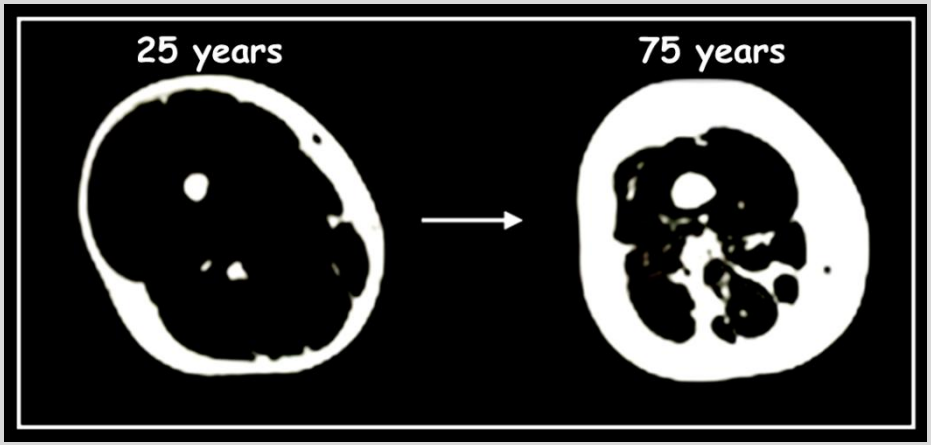
Age and Ageing 2010; **39:** 412–423
doi: 10.1093/ageing/afq034
Published electronically 13 April 2010

REPORT

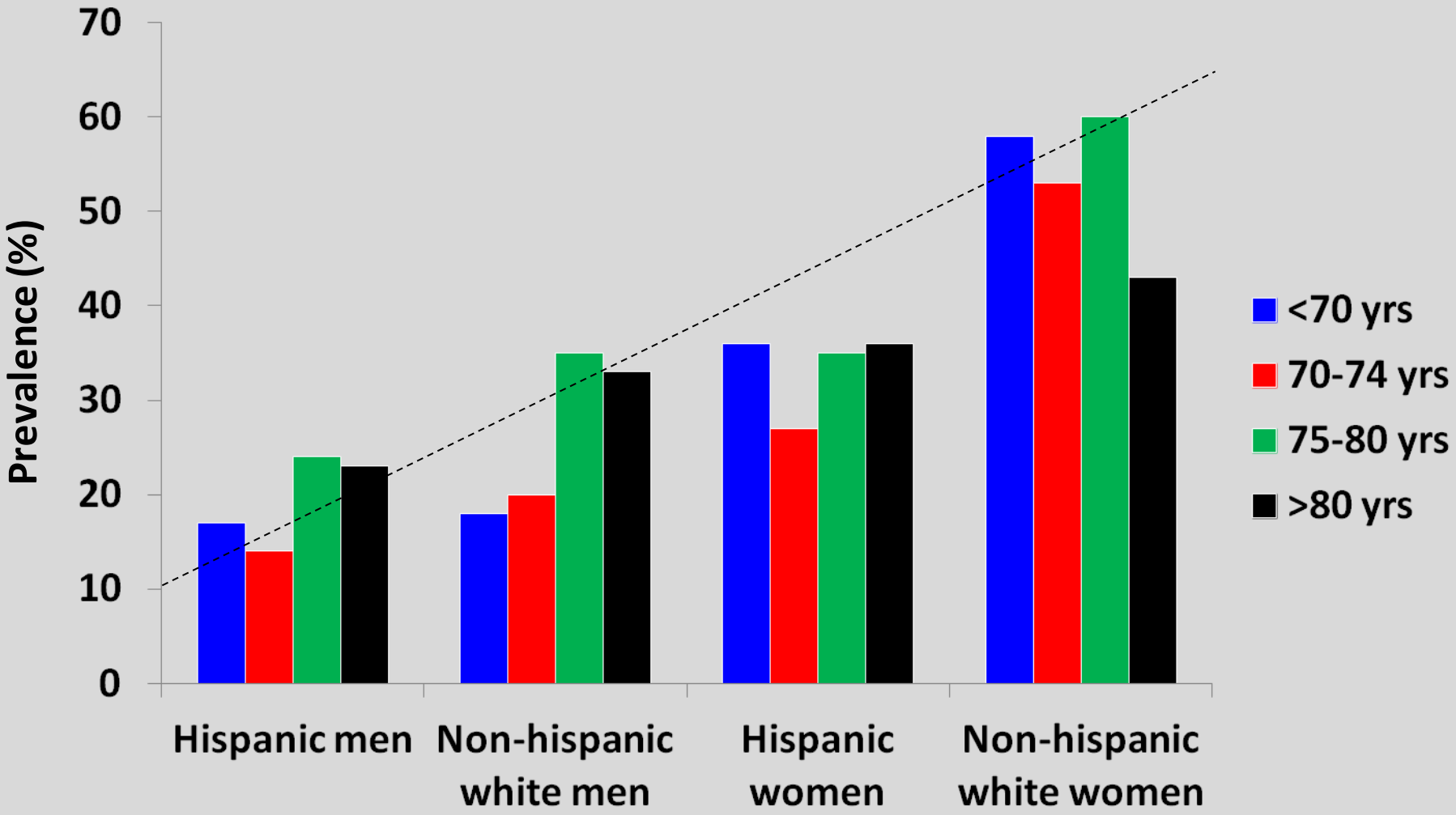
Sarcopenia: European consensus on definition and diagnosis

Report of the European Working Group on Sarcopenia in Older People
ALFONSO J. CRUZ-JENTOFT[1], JEAN PIERRE BAEYENS[2], JÜRGEN M. BAUER[3], YVES BOIRIE[4], TOMMY CEDERHOLM[5], FRANCESCO LANDI[6], FINBARR C. MARTIN[7], JEAN-PIERRE MICHEL[8], YVES ROLLAND[9], STÉPHANE M. SCHNEIDER[10], EVA TOPINKOVÁ[11], MAURITS VANDEWOUDE[12], MAURO ZAMBONI[13]

"Sarcopenia is a (geriatric) syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength (and/or function) with a risk of adverse outcomes such as physical disability, poor quality of life and death"



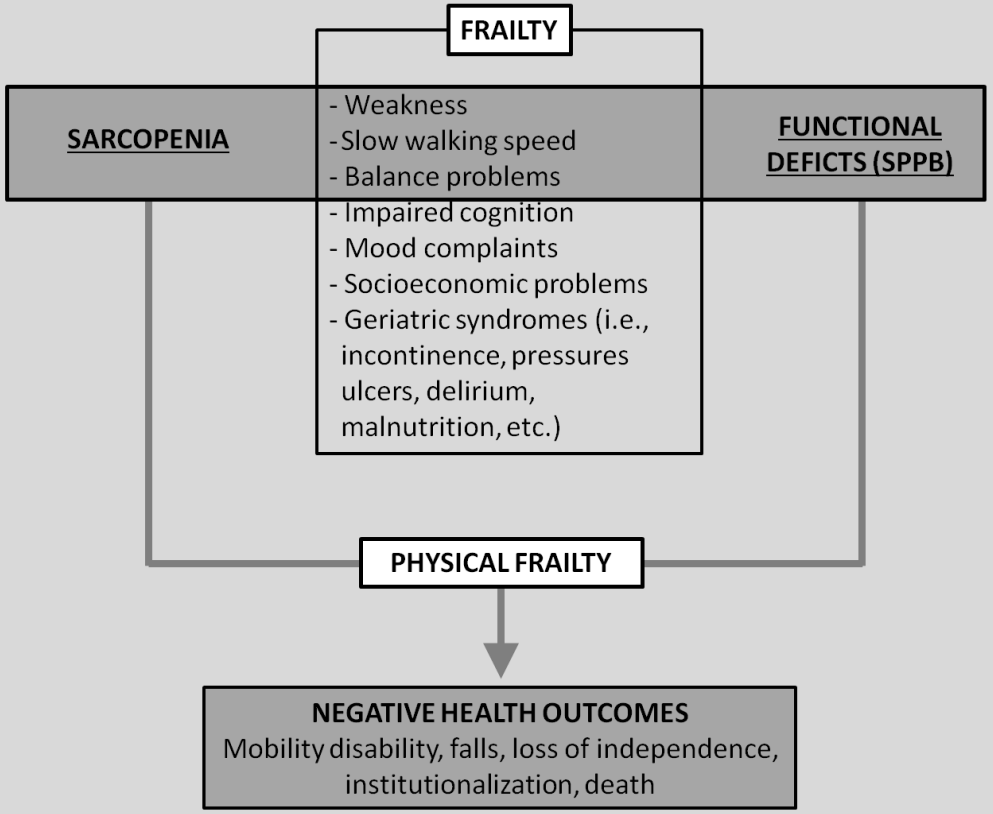
Prevalence of Sarcopenia (New Mexico Aging Process Study)



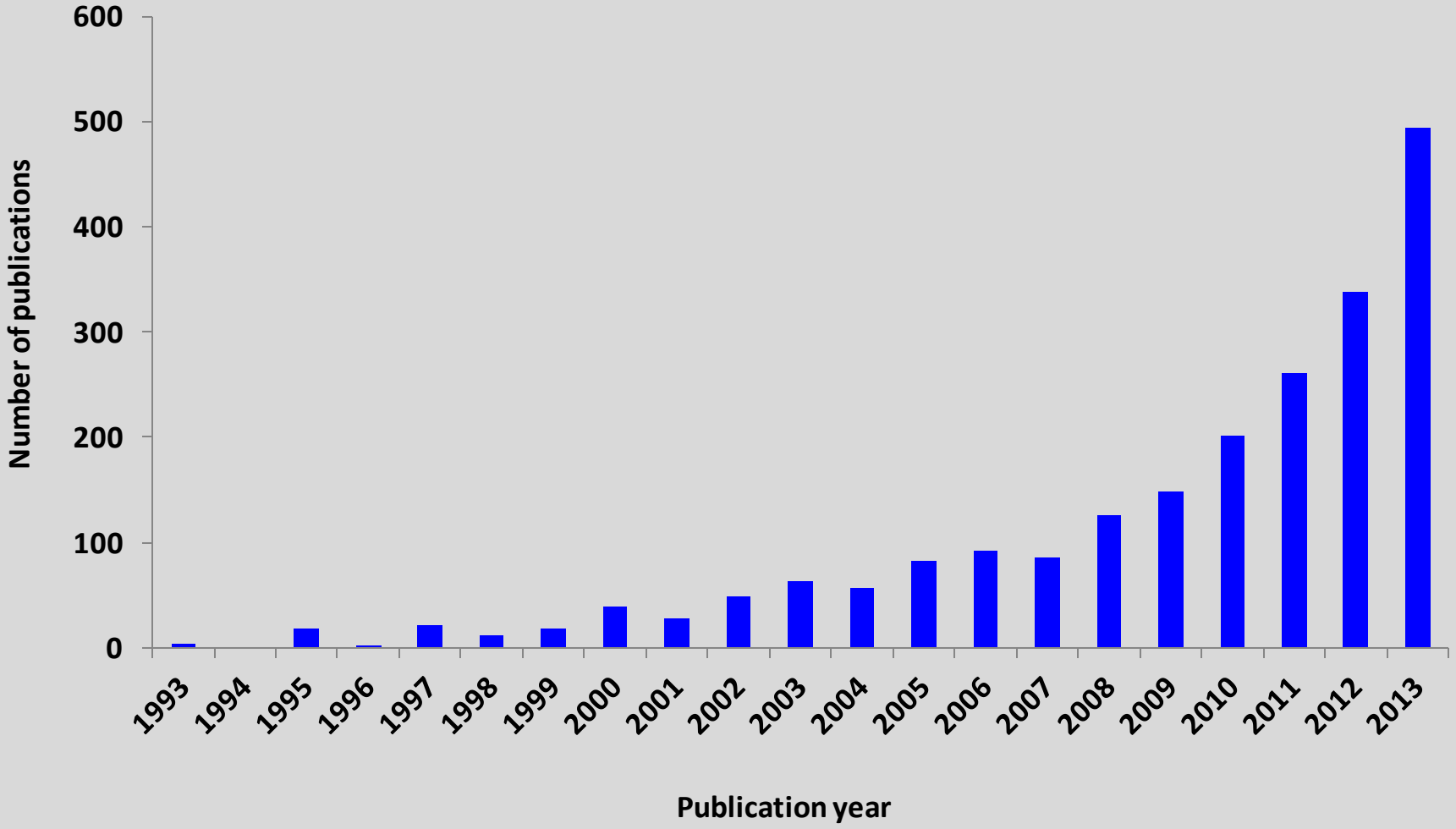
Baumgartner et al. Am J Epidemiol 1998

CLINICAL CORRELATES OF SARCOPENIA

- Great overlap with physical frailty (actually, a major cause of it!)
- ↑ risk of disability
- ↓ quality of life
- ↑ risk of institutionalization
- ↑ risk of mortality



SEARCH TERM: “SARCOPENIA” – 2,146 HITS (NOV. 27, 2013; SOURCE PUBMED)



Incomplete Knowledge on the Pathogenesis of Sarcopenia Hampers the Development of Effective Treatments

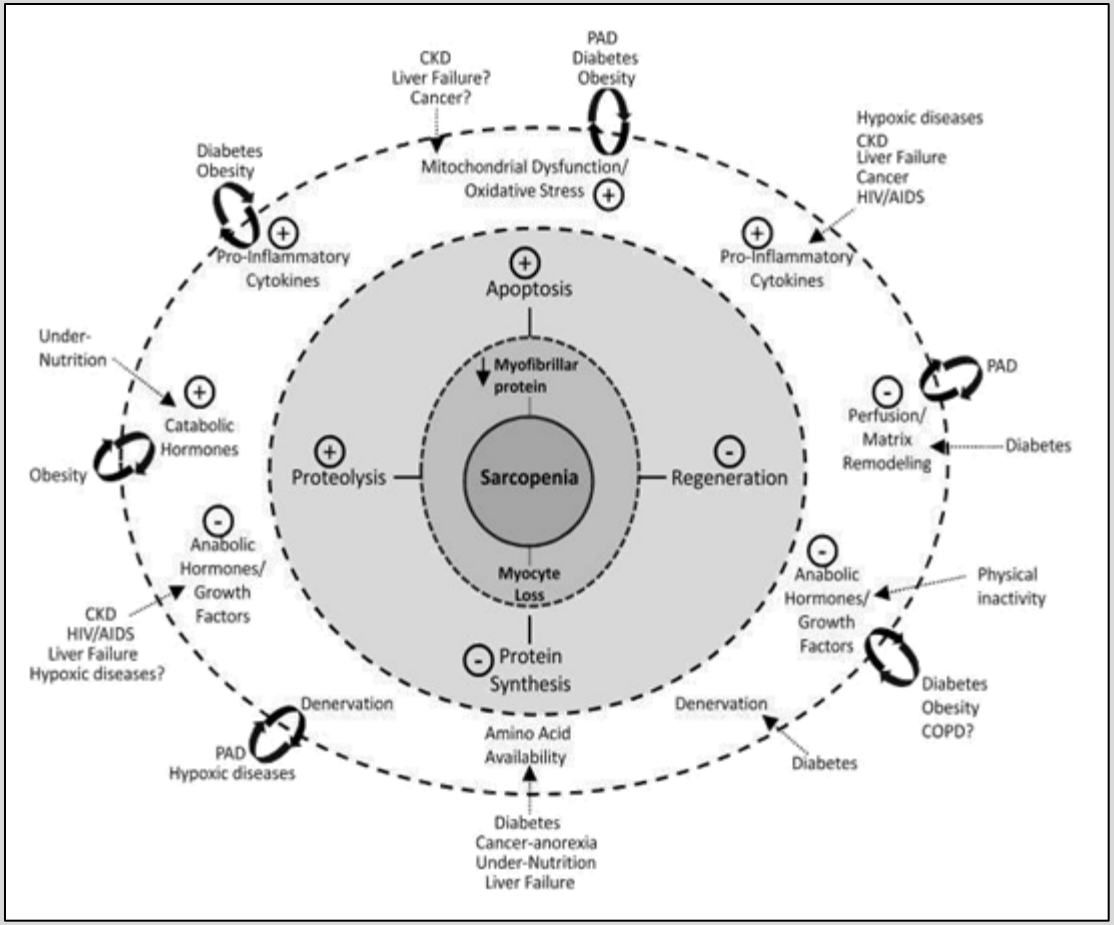
- No pharmacological treatment exists that is able to definitely halt the progression of sarcopenia.
- No pharmacological remedies are available to prevent the onset of age-related muscle wasting.

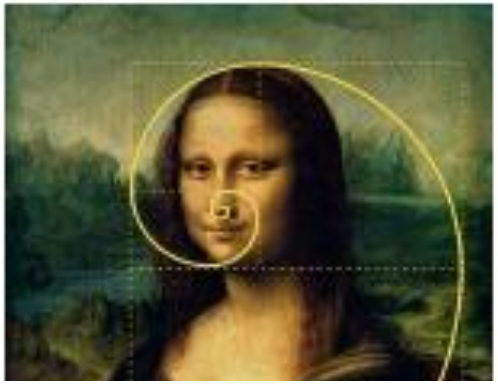
Ageing Research Reviews

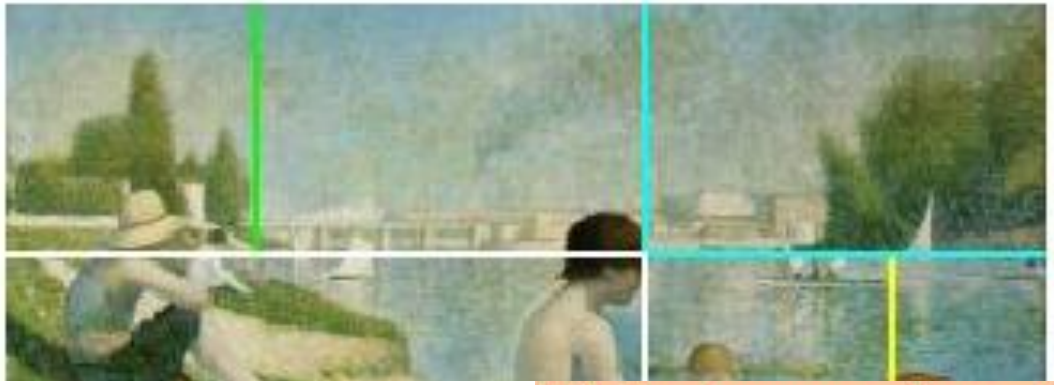
Review

Models of accelerated sarcopenia: Critical pieces for solving the puzzle of age-related muscle atrophy

Thomas W. Buford*, Stephen D. Anton, Andrew R. Judge, Emanuele Marzetti, Stephanie E. Wohlgemuth, Christy S. Carter, Christiaan Leeuwenburgh, Marco Pahor, Todd M. Manini*







The Journal of Frailty & Aging©
Volume 1, Number 3, 2012

JFA THE JOURNAL OF FRAILTY & AGING

IMAGING, FUNCTIONAL AND BIOLOGICAL MARKERS FOR SARCOPENIA: THE PURSUIT OF THE GOLDEN RATIO

E. MARZETTI

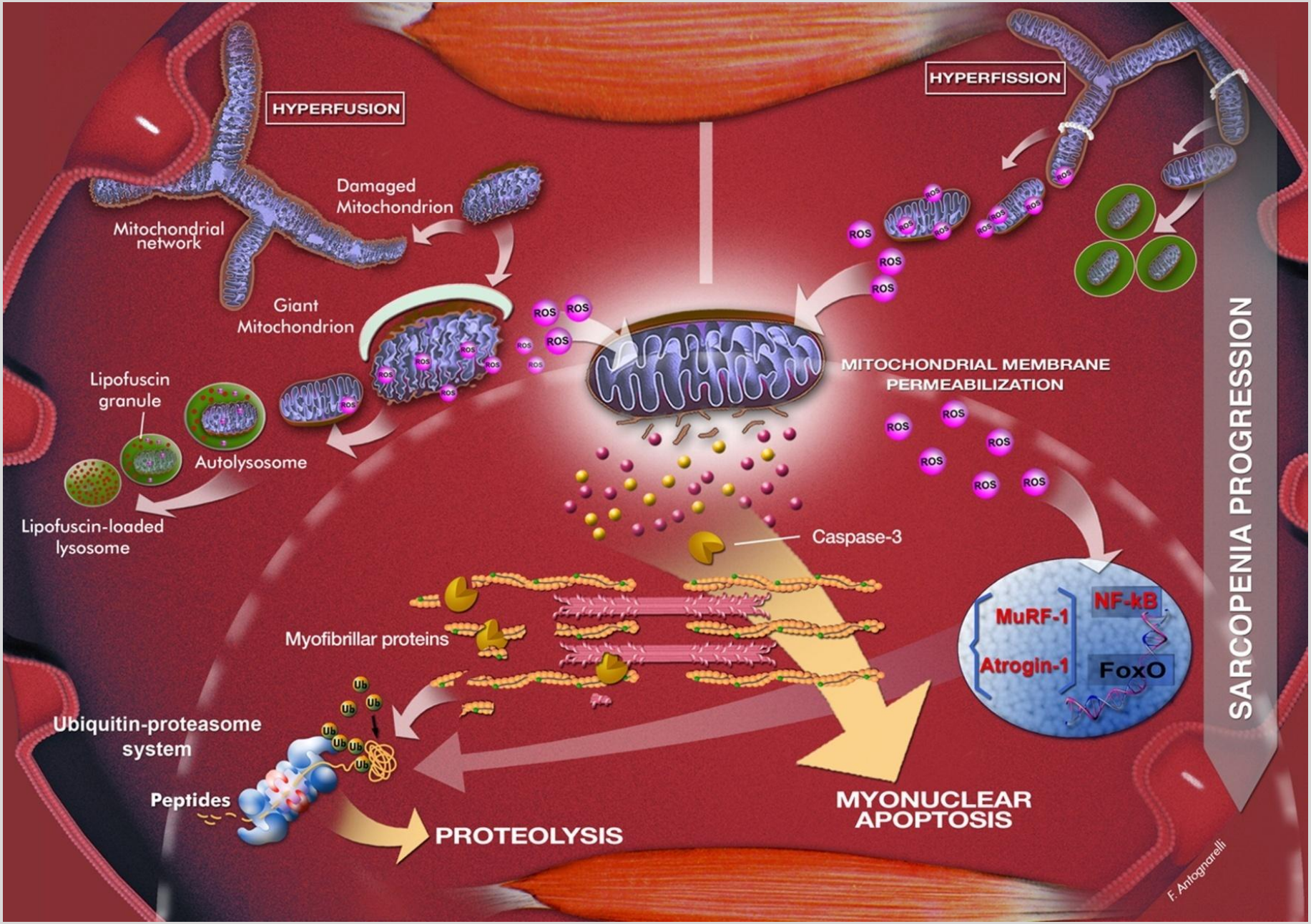
J Appl Physiol 113: 677–679, 2012;
doi:10.1152/japplphysiol.00304.2012.

VIEWPOINT

Muscle atrophy is not always sarcopenia

Russell T. Hepple
Department of Kinesiology, Department of Medicine, McGill University, Montreal, Canada

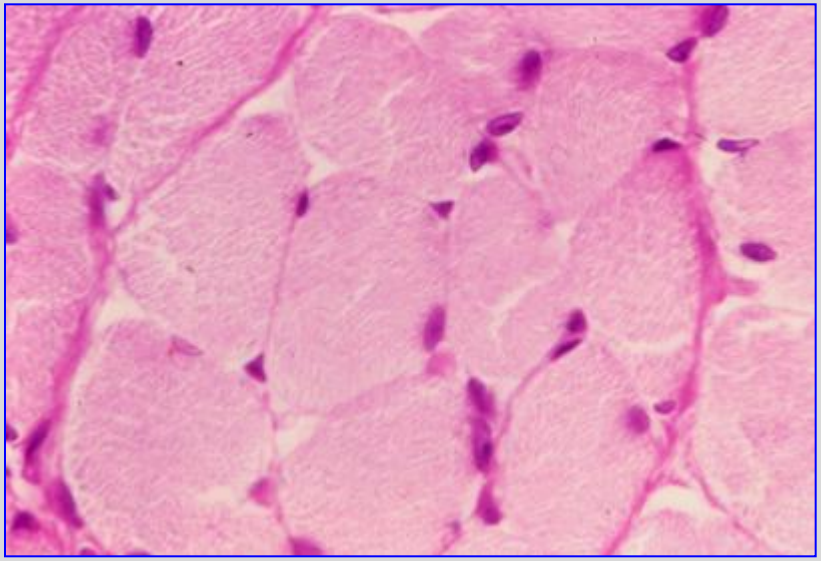
"(…) awareness of distinct features of sarcopenia should be more rigorously used in both human and animal model based studies pursuing the mechanisms of sarcopenia and its successful treatment. For example, many reports make the claim that a given intervention (e.g., resistance exercise, nutrient supplementation) is attenuating or reversing sarcopenia without determining if the intervention is impacting the morphological traits that represent aging's 'smoking gun(s)'. **Without such evidence, how will we really know whether we have affected the mechanisms causing sarcopenia per se, versus inducing compensatory hypertrophy only in the remaining healthy fibers?**"

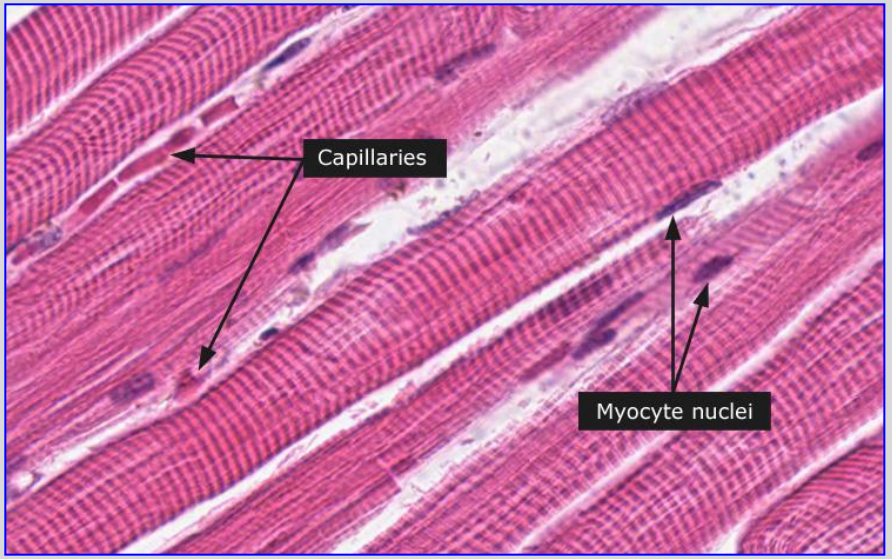


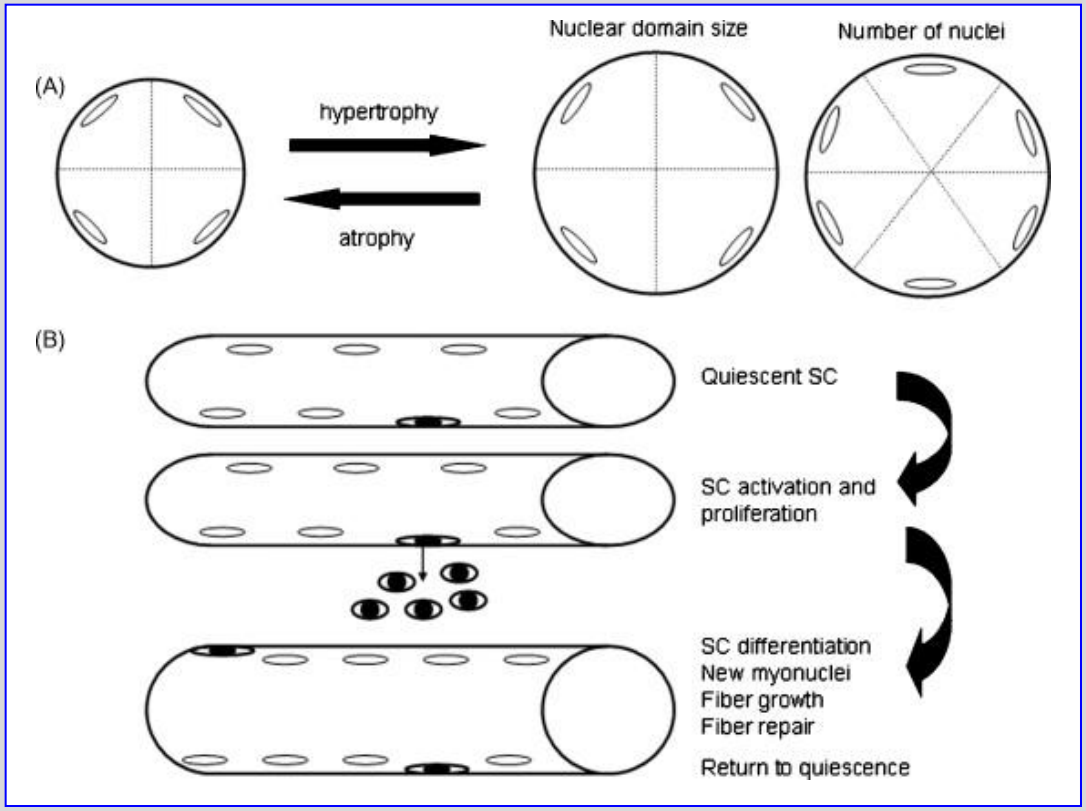
Marzetti et al. Int J Biochem Cell Biol 2013

Major Challenges in the Study of the Pathogenesis of Sarcopenia

- Skeletal muscle boasts unique morphological and physiological features.
- Multiple mechanisms are likely to be simultaneously involved in pathogenesis of sarcopenia.
- Sarcopenia develops over decades and pathogenetic processes may not necessarily be the same during its course.

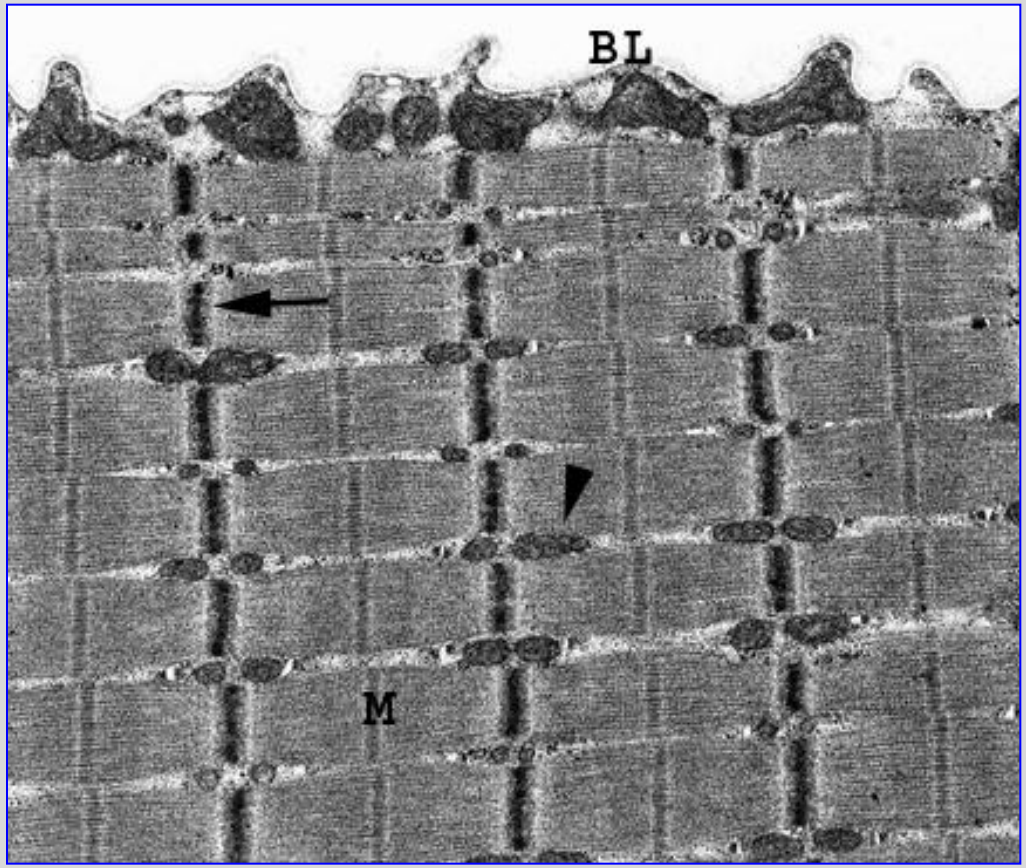






Snijders et al. Ageing Res Rev 2009

Two mitochondrial subpopulation in skeletal myocytes: Subsarcolemmal and Intermyofibrillar Mitochondria

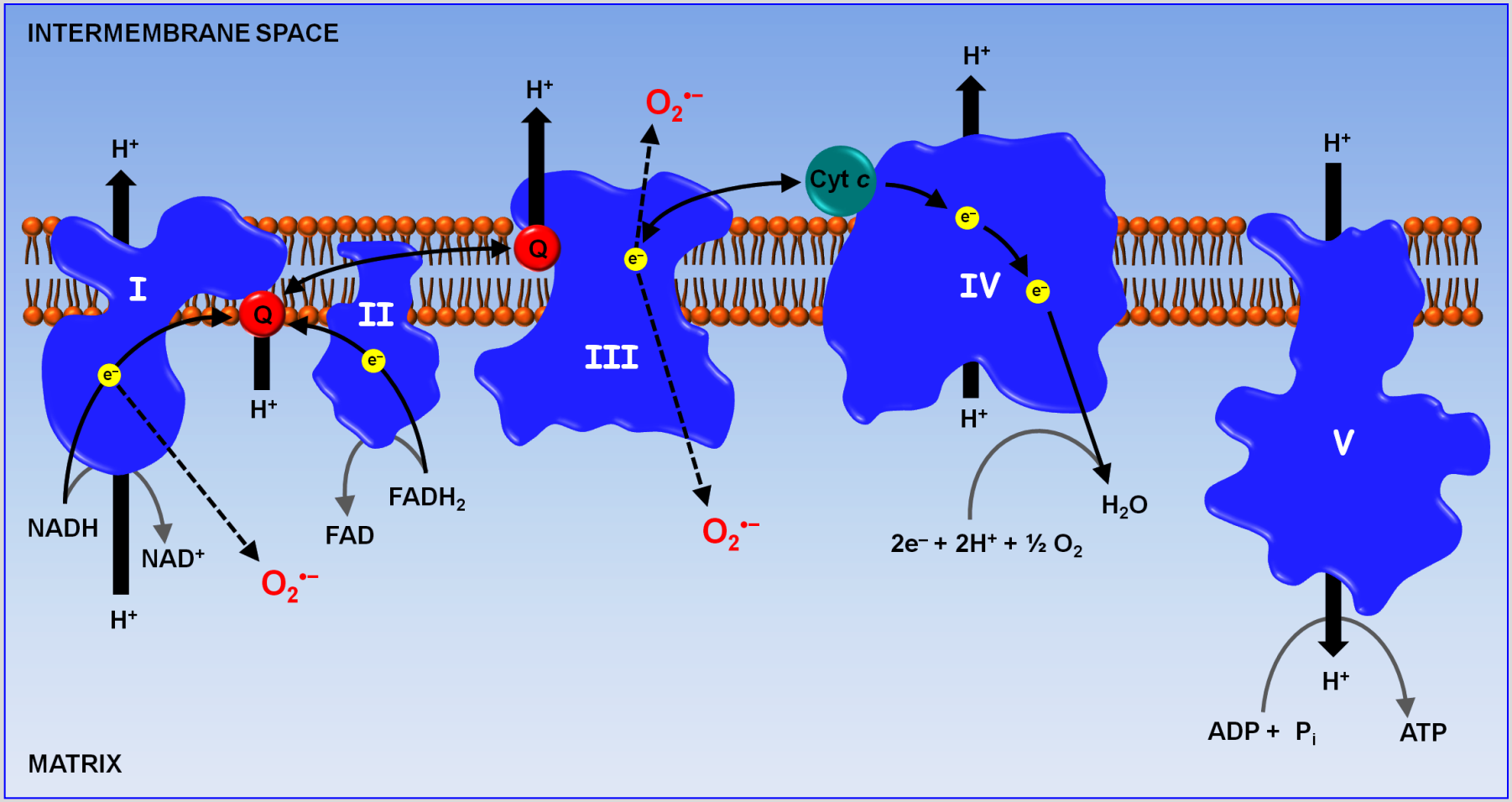


SSM *vs.* IFM

- Specific bioenergetic properties.
- Distinct repertoire of enzymatic and non-enzymatic antioxidant defenses.
- Different rates of fragmentation and autophagic degradation.
- Diverse susceptibility towards apoptotic stimuli.

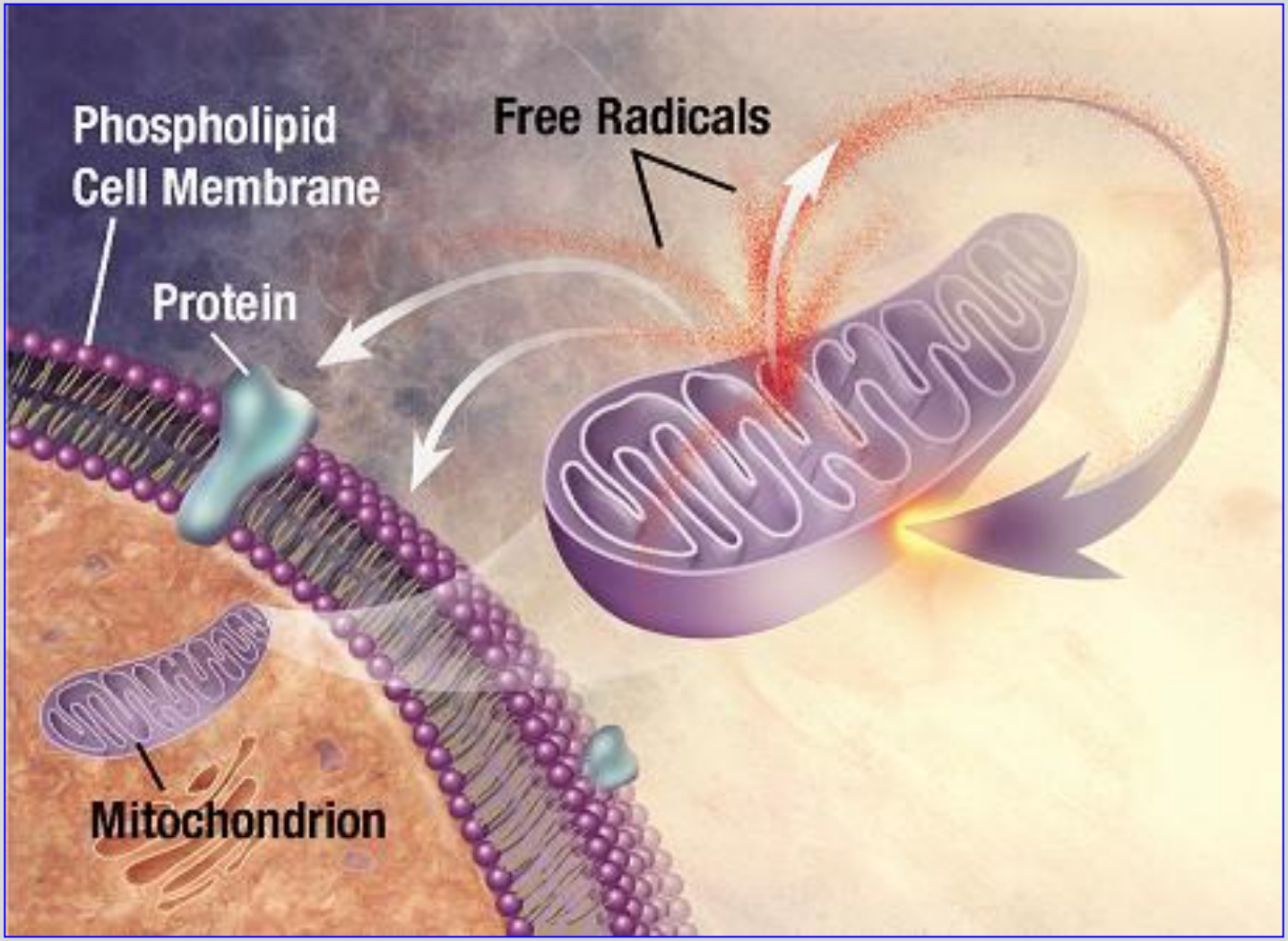
IFM and SSM may play distinct roles in the pathogenesis of sarcopenia

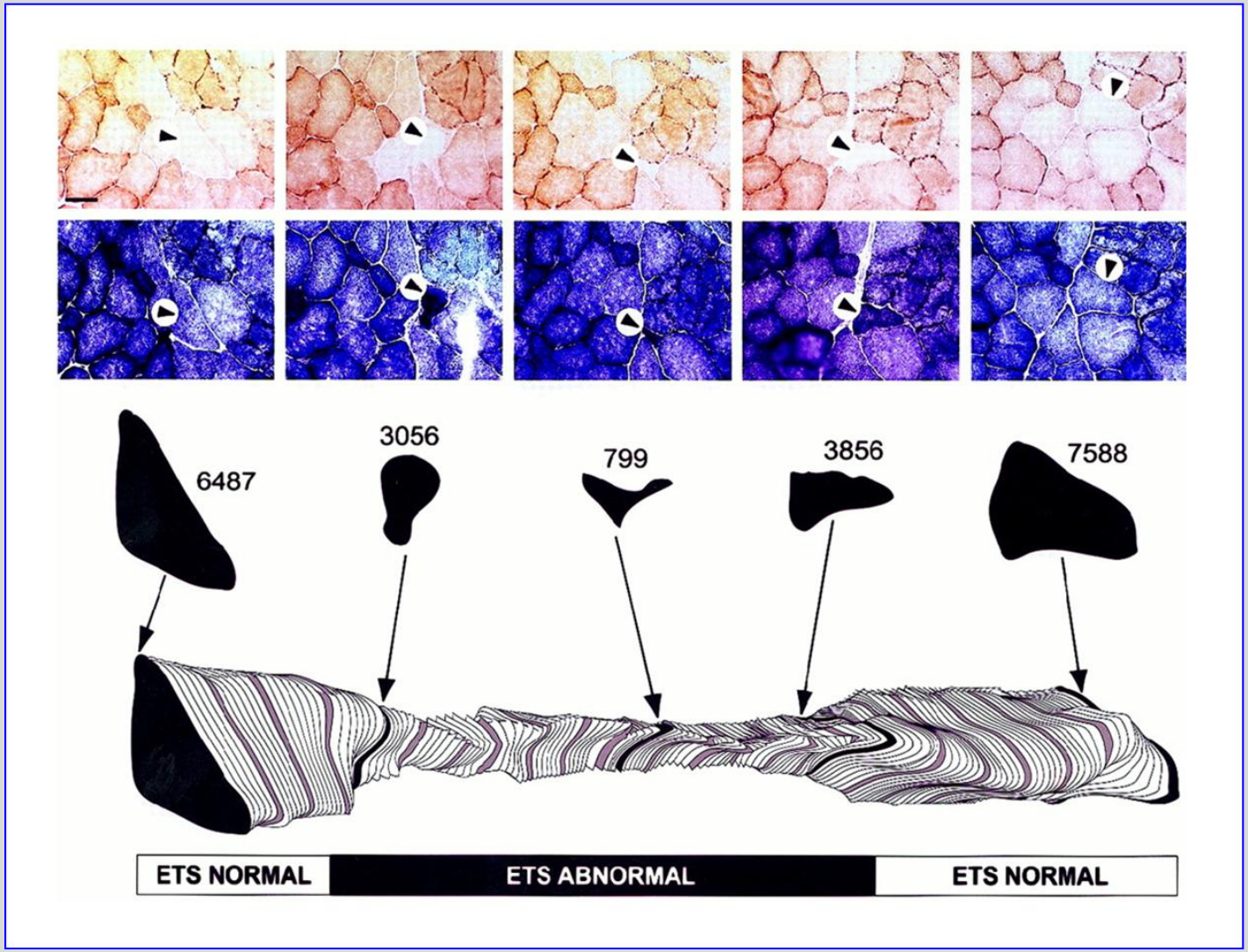
MITOCHONDRIA: CELLULAR POWERHOUSES AND SOURCES OF OXIDANTS



Marzetti et al. Diet and Aging: Role in Prevention of Muscle Mass Loss. Academic Press 2012

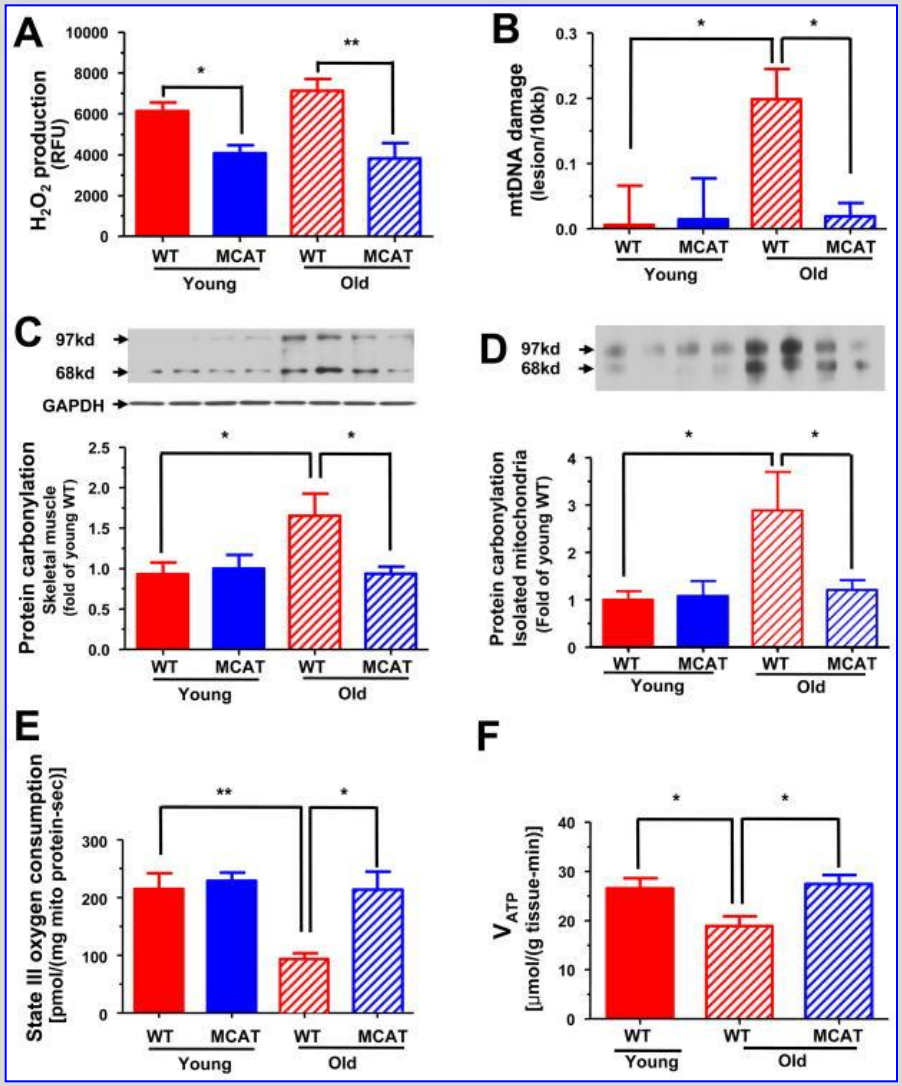
The Mitochondrial Free Radical Theory of Aging

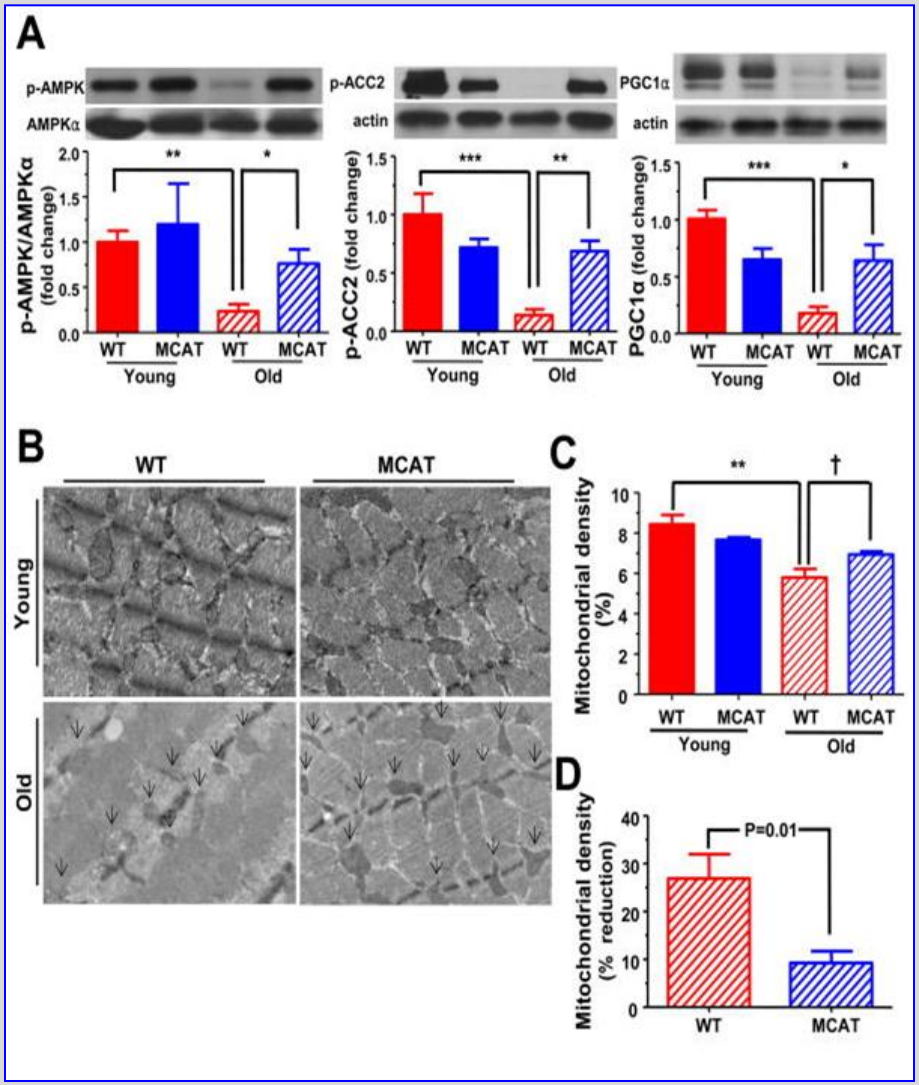




Electron transport system abnormalities co-localize with segmental atrophy in a fiber from a 38-month-old rat rectus femoris muscle.

Wanagat et al. FASEB J 2001

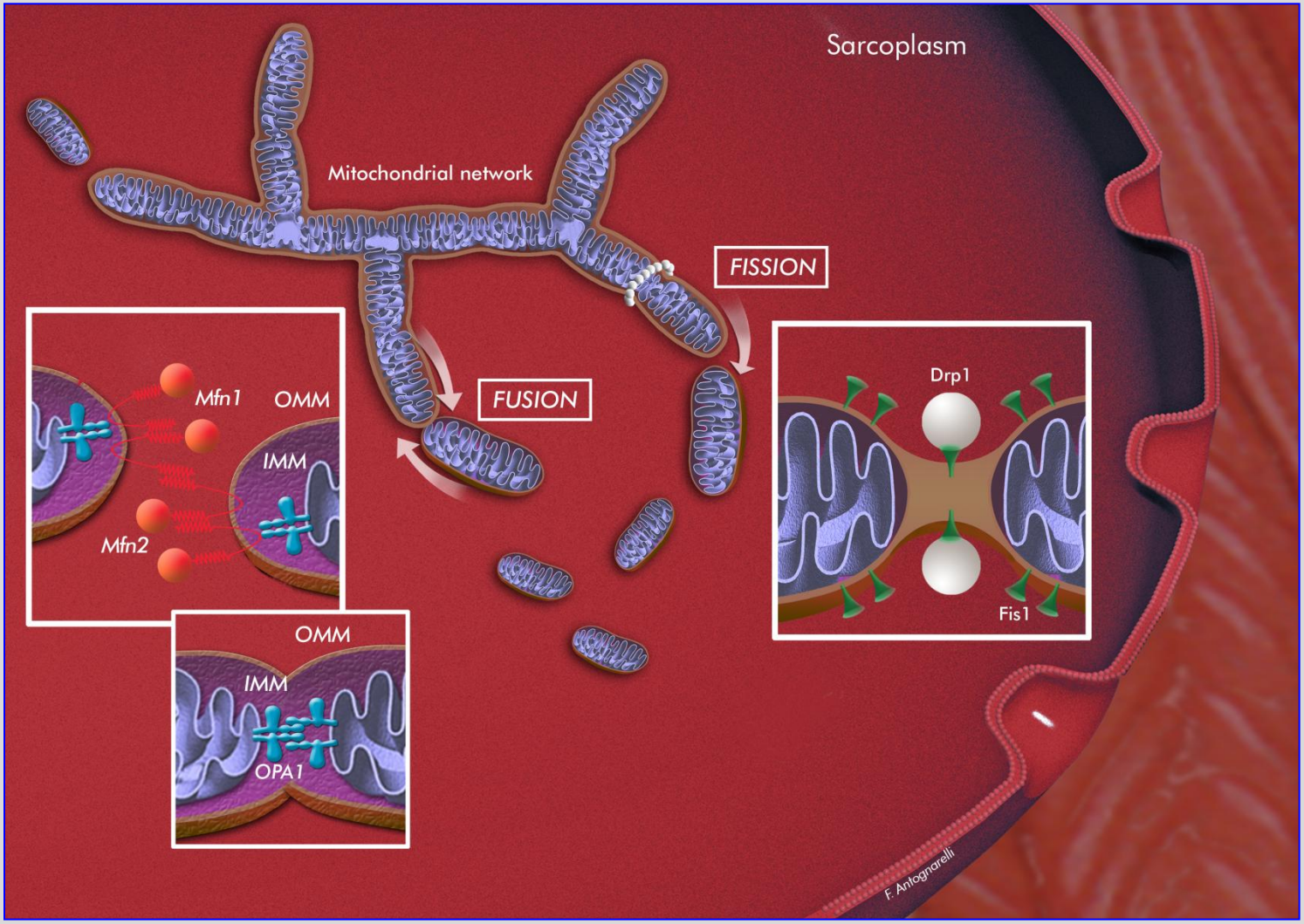




Overexpression of human catalase targeted to the mitochondrial matrix (mCAT) reduces H_2O_2 production, mtDNA damage, and whole tissue and mitochondrial protein carbonyls, while improving mitochondrial bioenergetics and mitochondrial density in skeletal muscle of old mice.

Lee et al. Cell Metab 2010

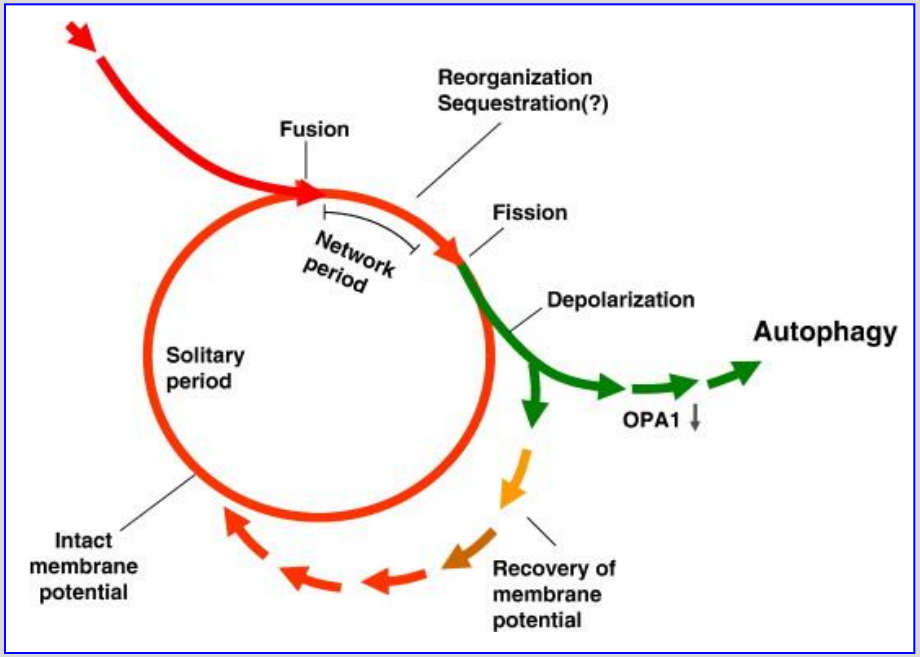
Mitochondria Are Organized in a Dynamic Network: Is the MFRTA still Valid?



Calvani et al. Biol Chem 2013

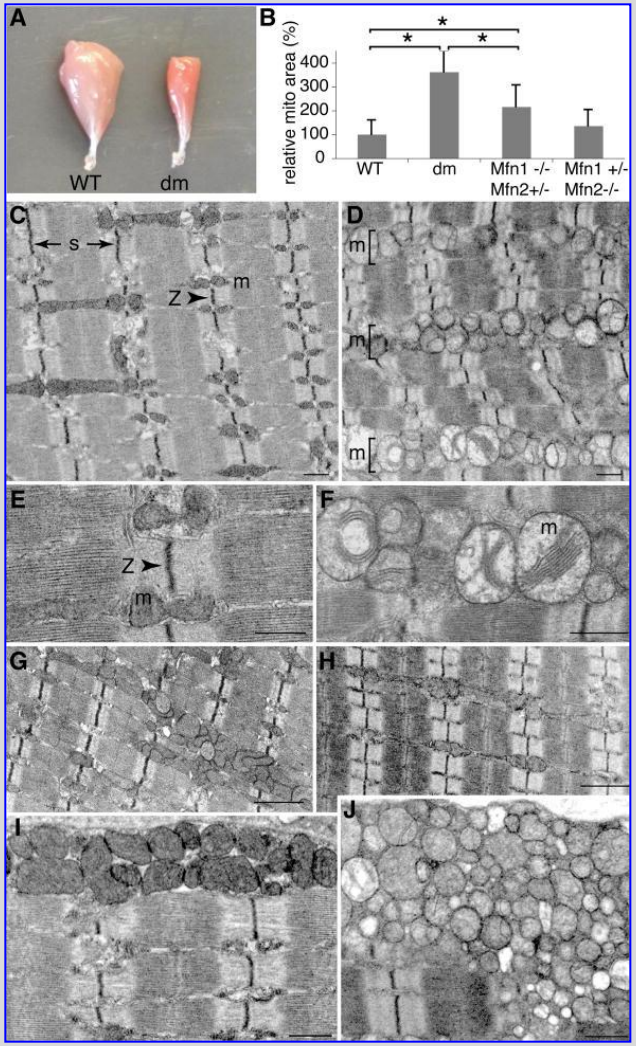
Fusion and Fission: Remodeling the Mitochondrial Network for Quality Control

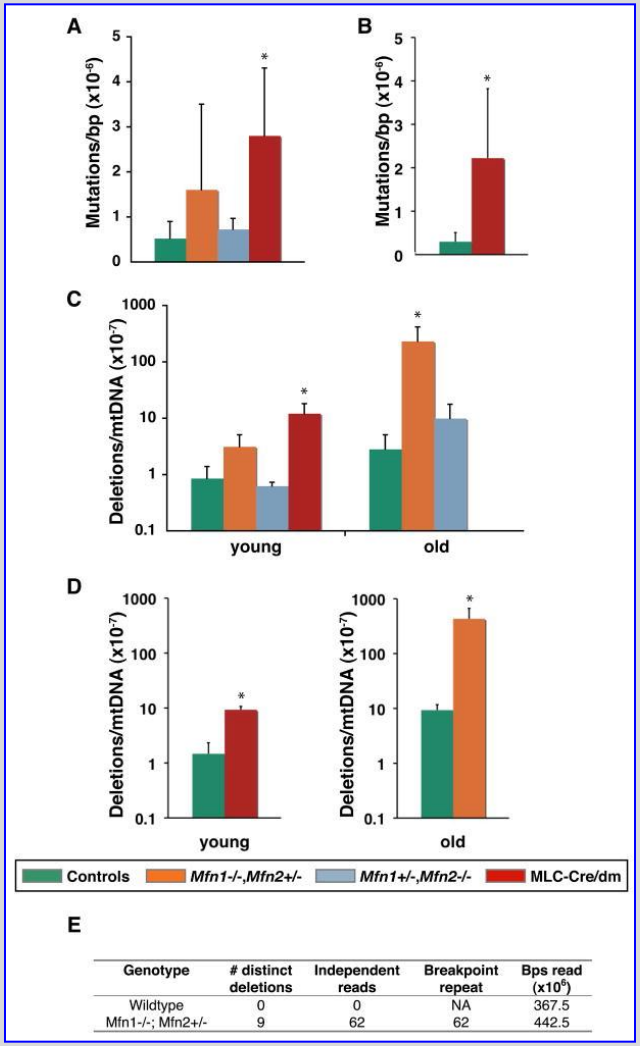
- Fusion of isolated mitochondria results in the formation of a network, which enables mitochondria to mix their contents, redistribute metabolites, proteins and mtDNA, and prevent the local accumulation of abnormal mitochondria.
- Fission segregates components of the mitochondrial network that are irreversibly damaged or unnecessary, allowing for their autophagic removal.



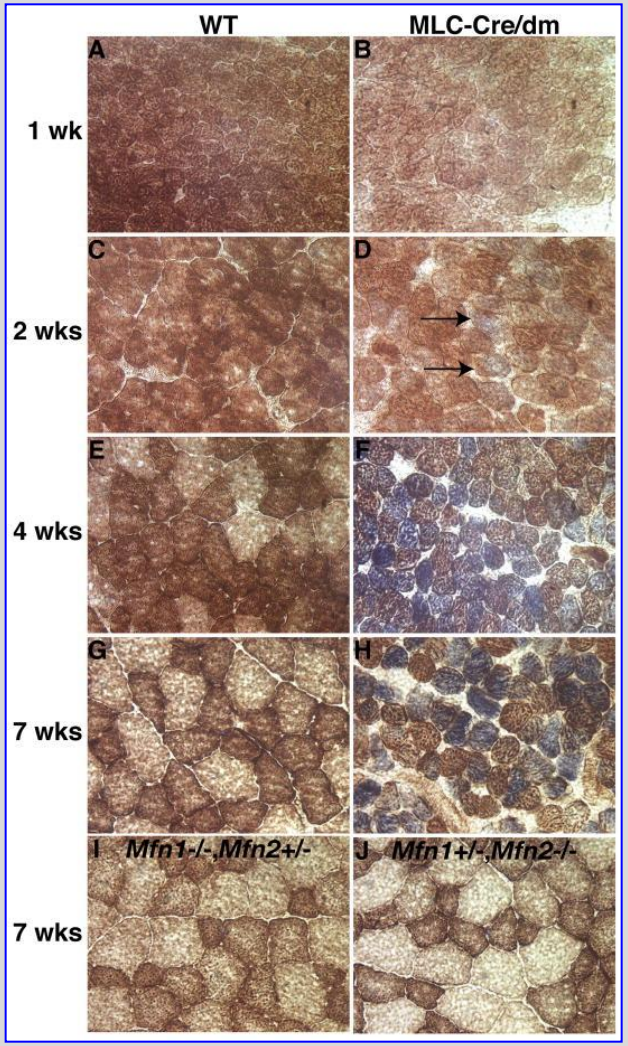
Twig et al. Biochim Biophys Acta 2008

Disruption of Mitochondrial Fusion Reduces Mitochondrial Function and Induces Muscle Atrophy



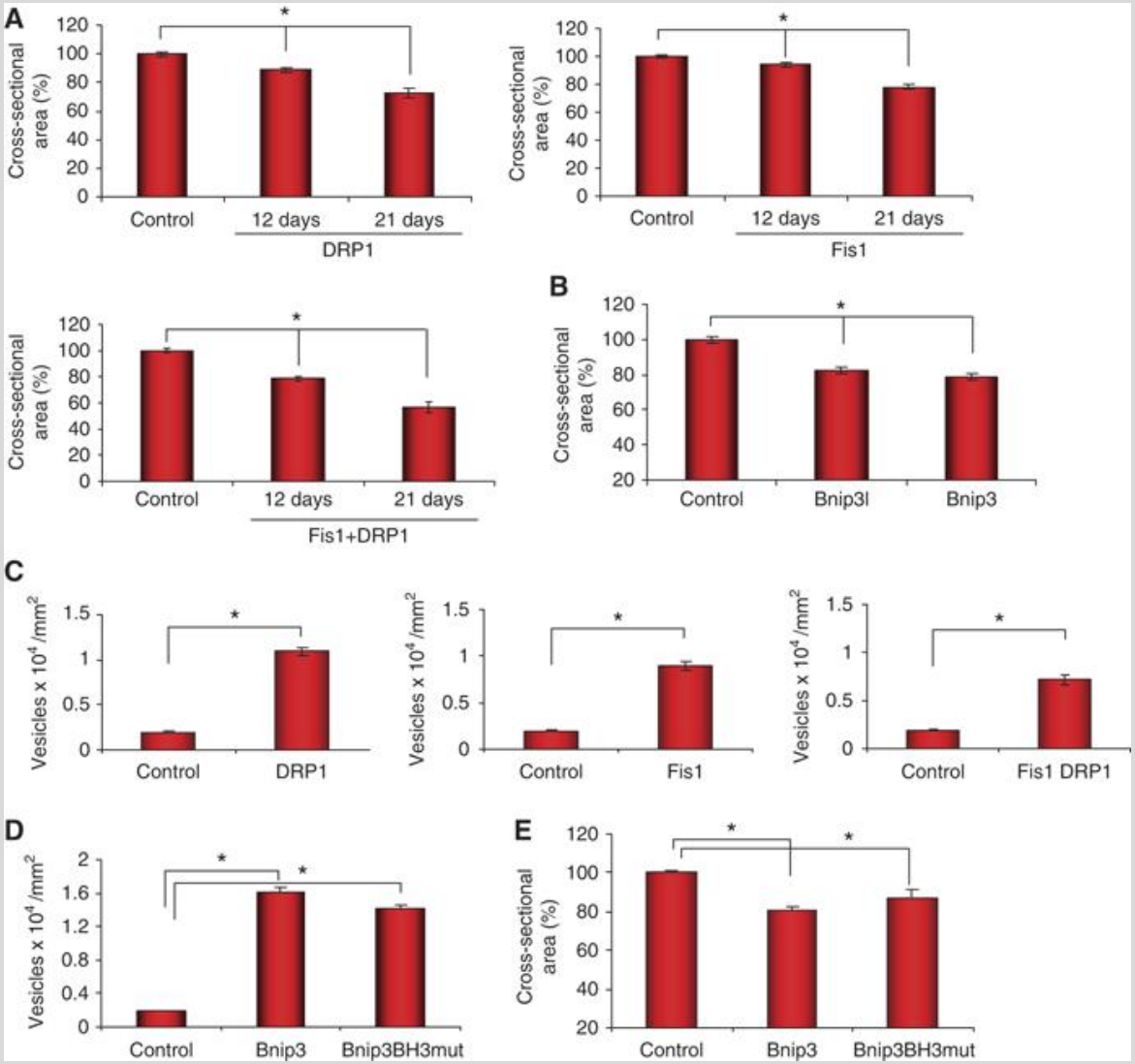


Genotype	# distinct deletions	Independent reads	Breakpoint repeat	Bps read ($x10^6$)
Wildtype	0	0	NA	367.5
Mfn1-/-; Mfn2+/-	9	62	62	442.5



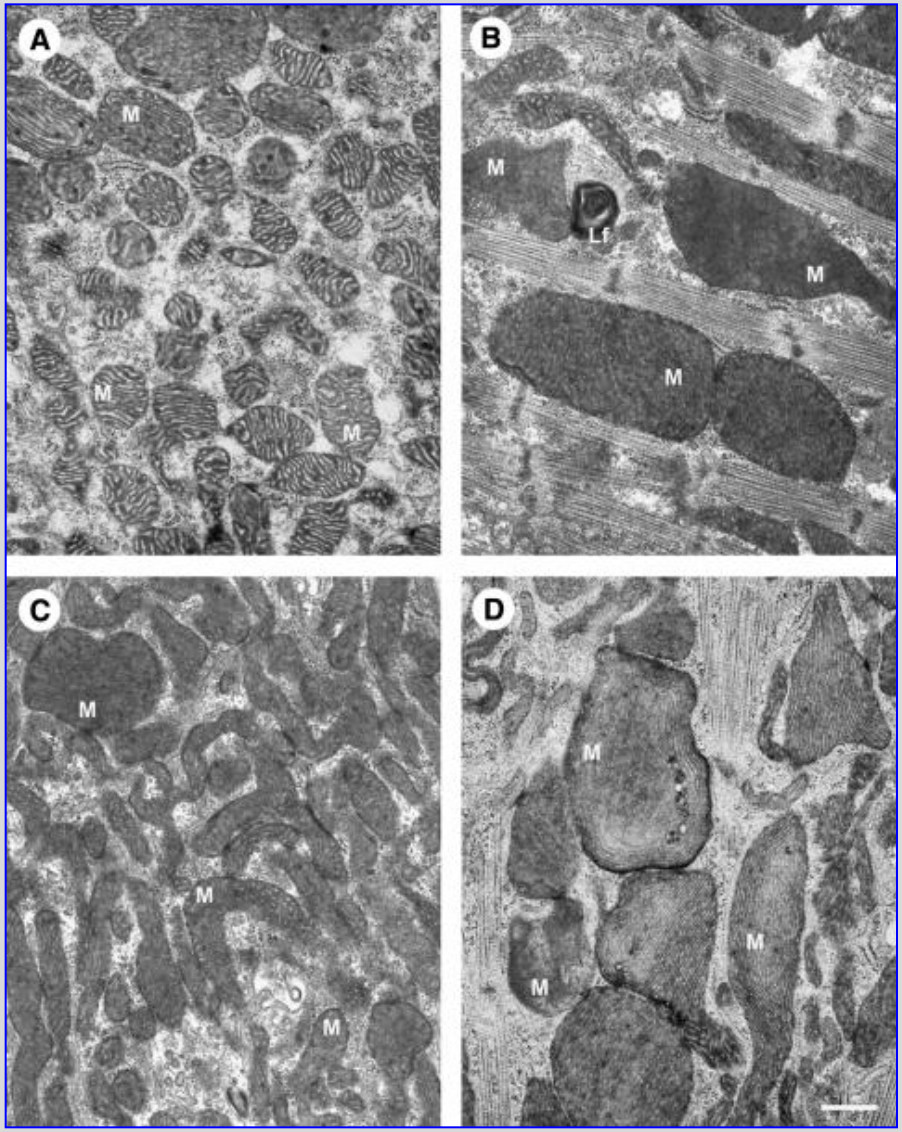
Chen et al. Cell 2010

Activation of Mitochondrial Fission is Sufficient to Induce Muscle Atrophy



Romanello et al. EMBO J 2010

Mitochondrial Morphology Is Altered in Old Myocytes



Young

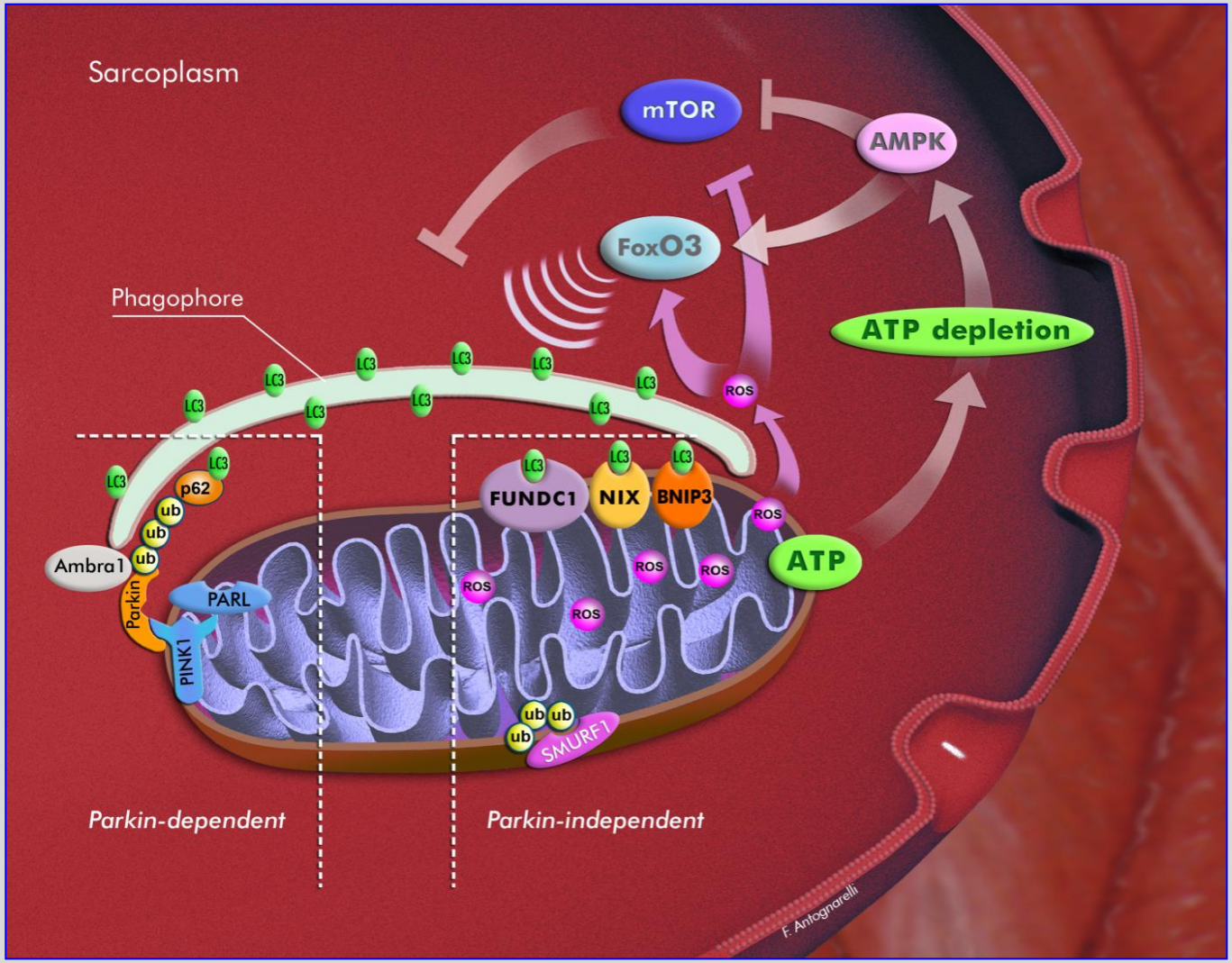
Old

Terman et al. Antioxid Redox Signal 2010

Mitochondrial Dynamics Are Altered in the Aged Muscle

- Fusion rates may be heightened in aging skeletal myocytes to withstand the increasing load of mtDNA mutations.
- This would allow preserving cell viability until a critical threshold of pathogenic mtDNA is breached and the degree of mitochondrial interconnection becomes incompatible with the efficient autophagic removal of damaged mitochondria.
- Excessive mitochondrial interconnection hampers the segregation of damaged mitochondria by fission and subsequent disposal by autophagy.
- The concomitant inefficiency of mitochondriogenesis aggravates mitochondrial dyshomeostasis.

Selective Mitochondrial Autophagy: The Final Effector of Mitochondrial Quality Control



Calvani et al. Biol Chem 2013

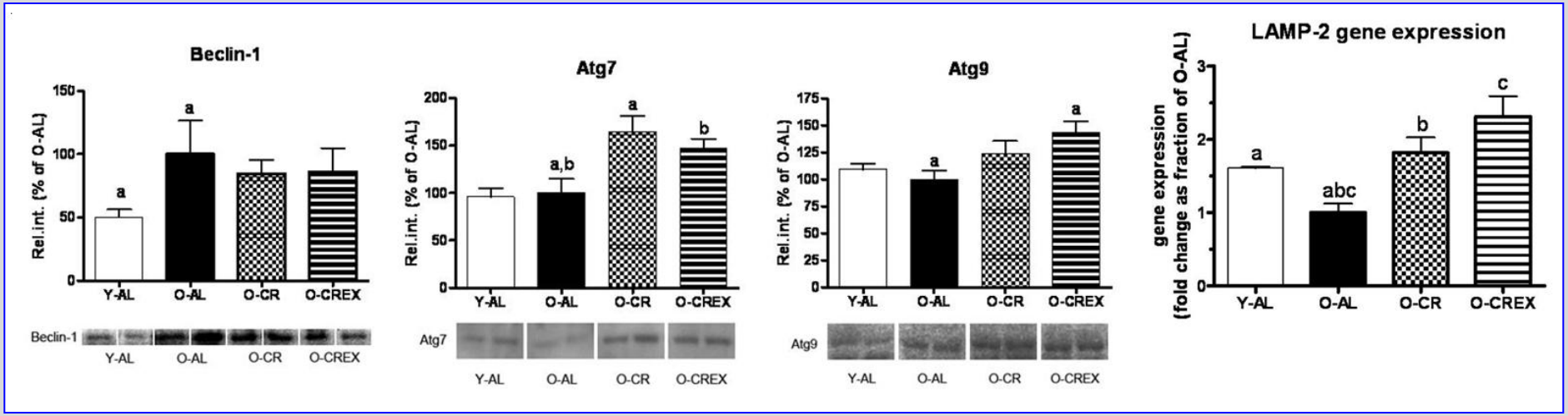
Contents lists available at ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero

Skeletal muscle autophagy and apoptosis during aging: Effects of calorie restriction and life-long exercise

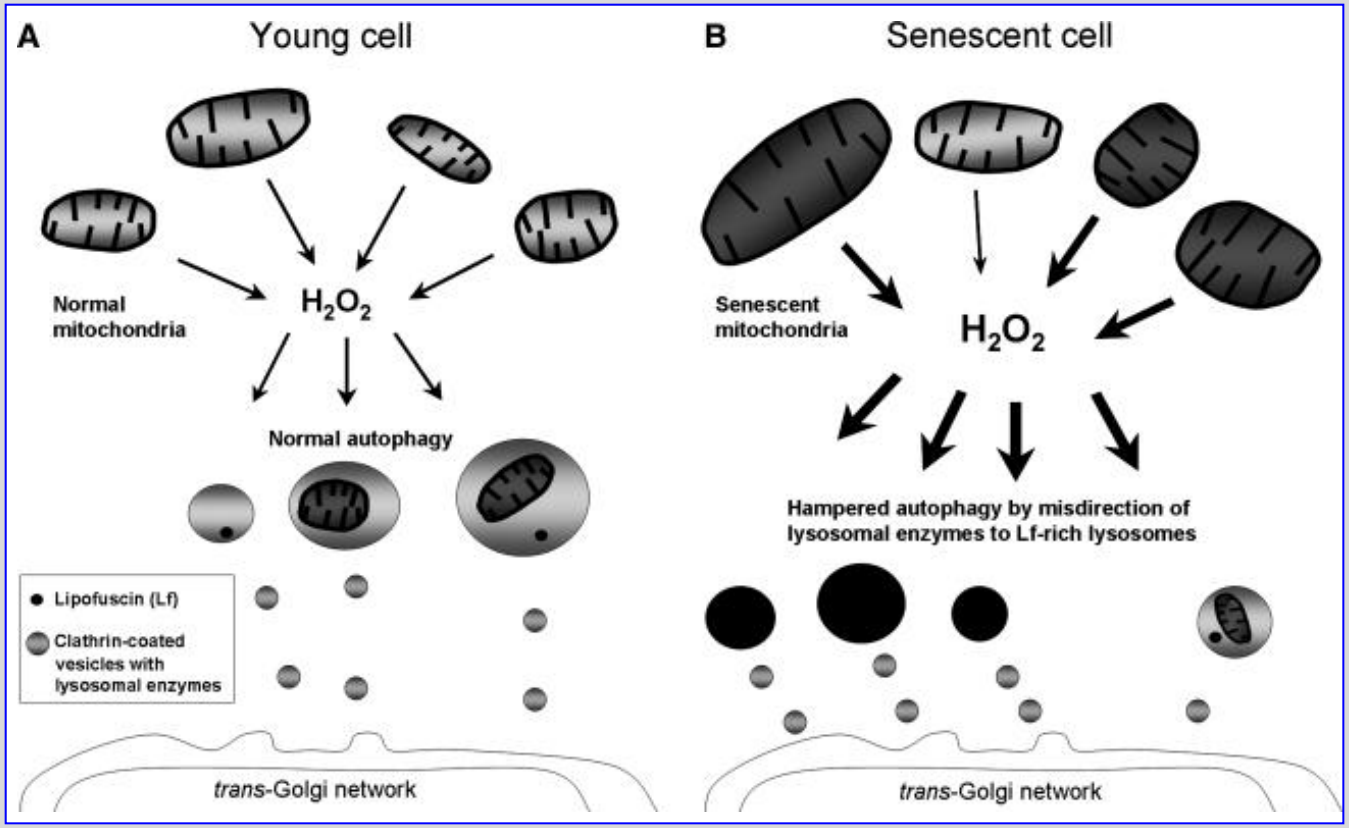
Stephanie Eva Wohlgemuth [a,*], Arnold Young Seo [a], Emanuele Marzetti [a,b], Hazel Anne Lees [a], Christiaan Leeuwenburgh [a]

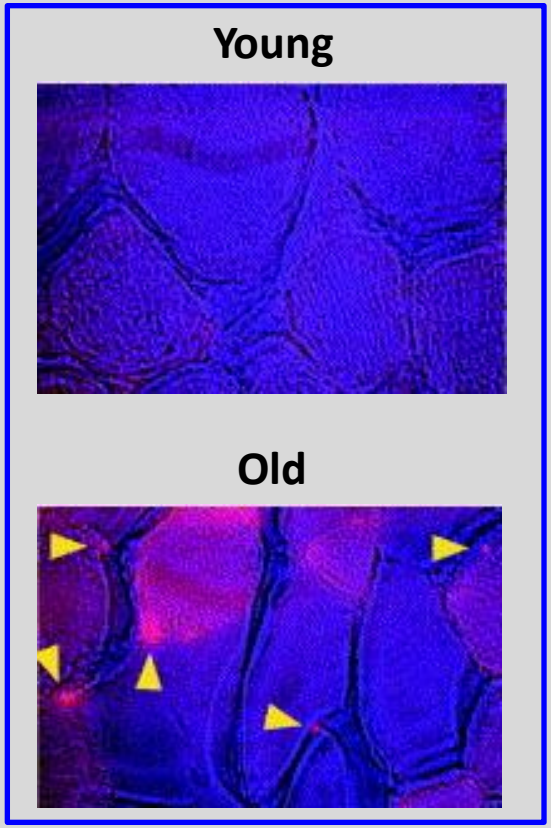


AUTOPHAGIC MARKERS ARE ALTERED IN MUSCLES OF OLD RATS AND RESTORED BY CALORIE RESTRICTION AND EXERCISE

Wohlgemuth et al. Exp Gerontol 2010

Imperfect Autophagy in Old Myocytes: the Garbage Catastrophe Theory of Aging





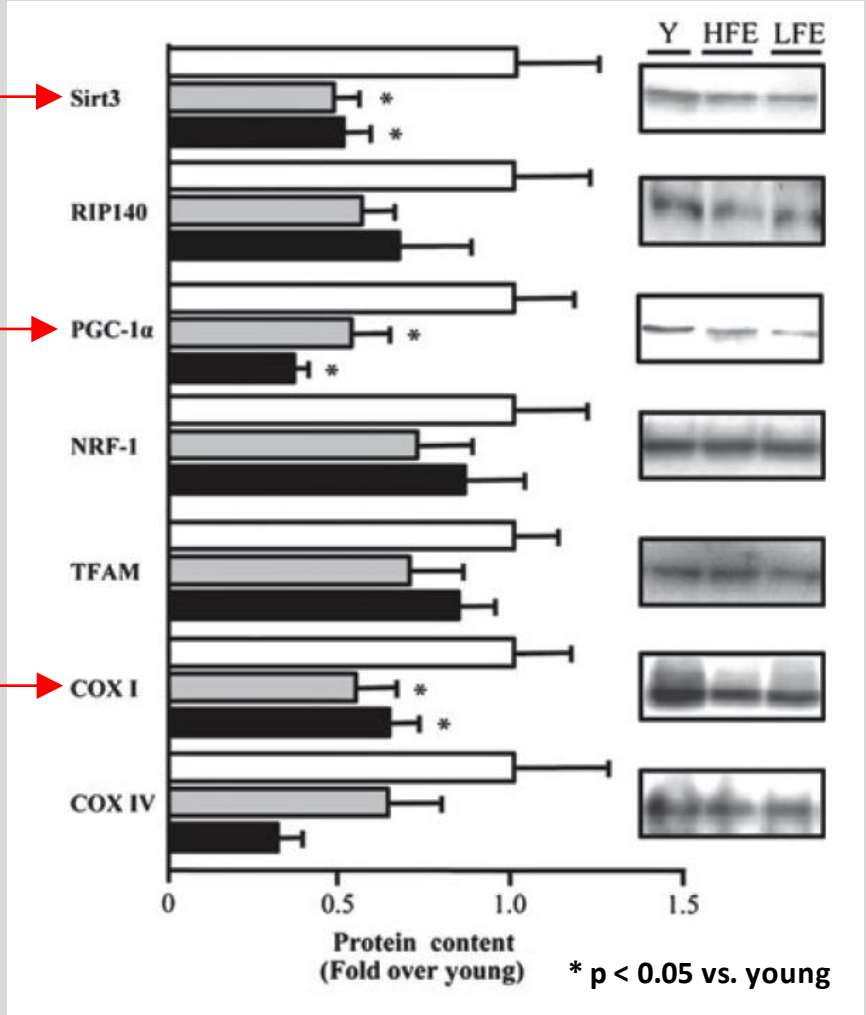
Terman et al. Antioxid Redox Signal 2010

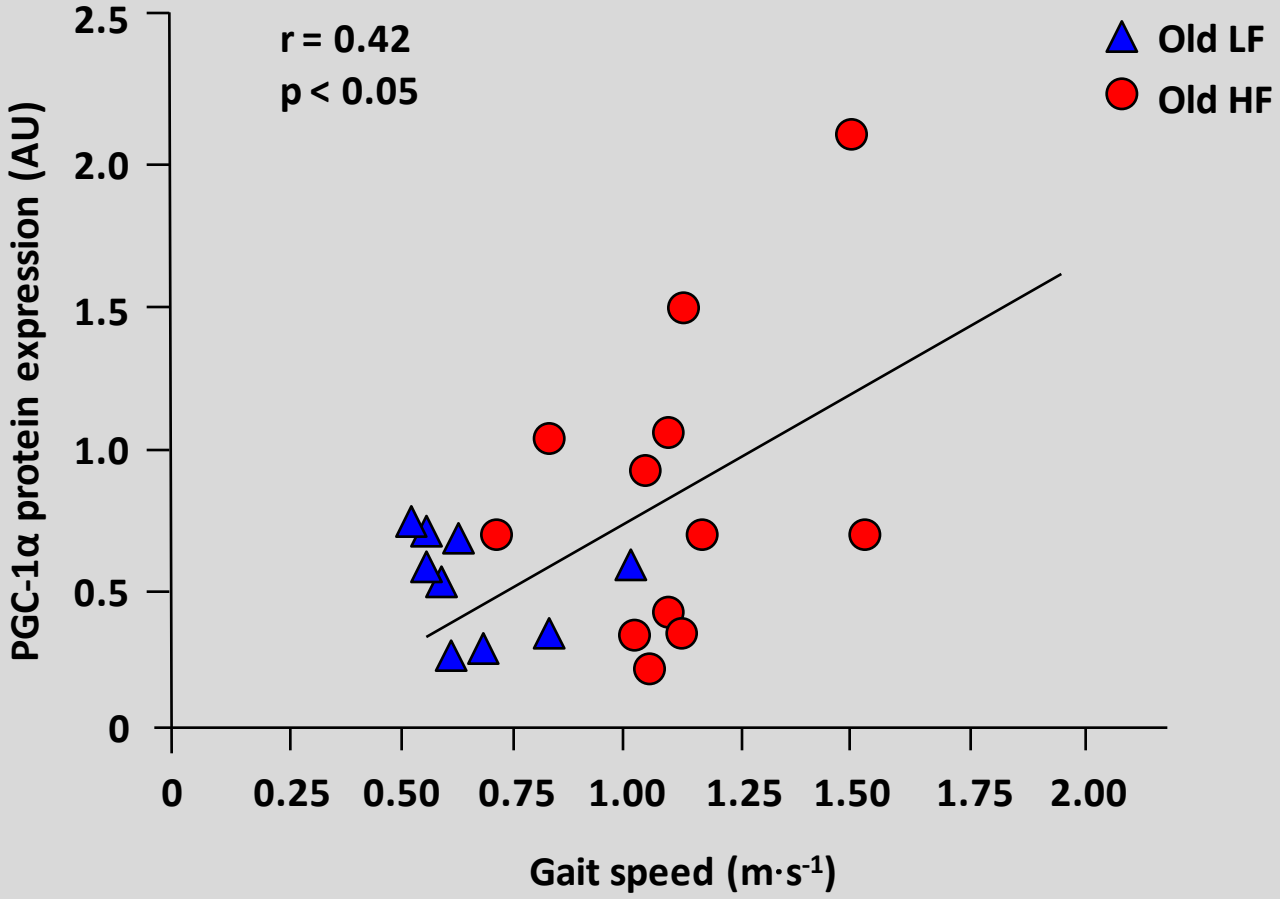
Kishi et al. Exp Gerontol 2003

Aging Cell (2012) **11,** pp801–809

The impact of aging on mitochondrial function and biogenesis pathways in skeletal muscle of sedentary high- and low-functioning elderly individuals

Anna-Maria Joseph,[1] Peter J. Adhihetty,[2] Thomas W. Buford,[1] Stephanie E. Wohlgemuth,[1] Hazel A. Lees,[1] Linda M.-D. Nguyen,[2] Juan M. Aranda,[3] Bhanu D. Sandesara,[1] Marco Pahor,[1] Todd M. Manini,[1] Emanuele Marzetti[1,4] and Christiaan Leeuwenburgh[1]





Joseph et al. Aging Cell 2012

Contents lists available at ScienceDirect

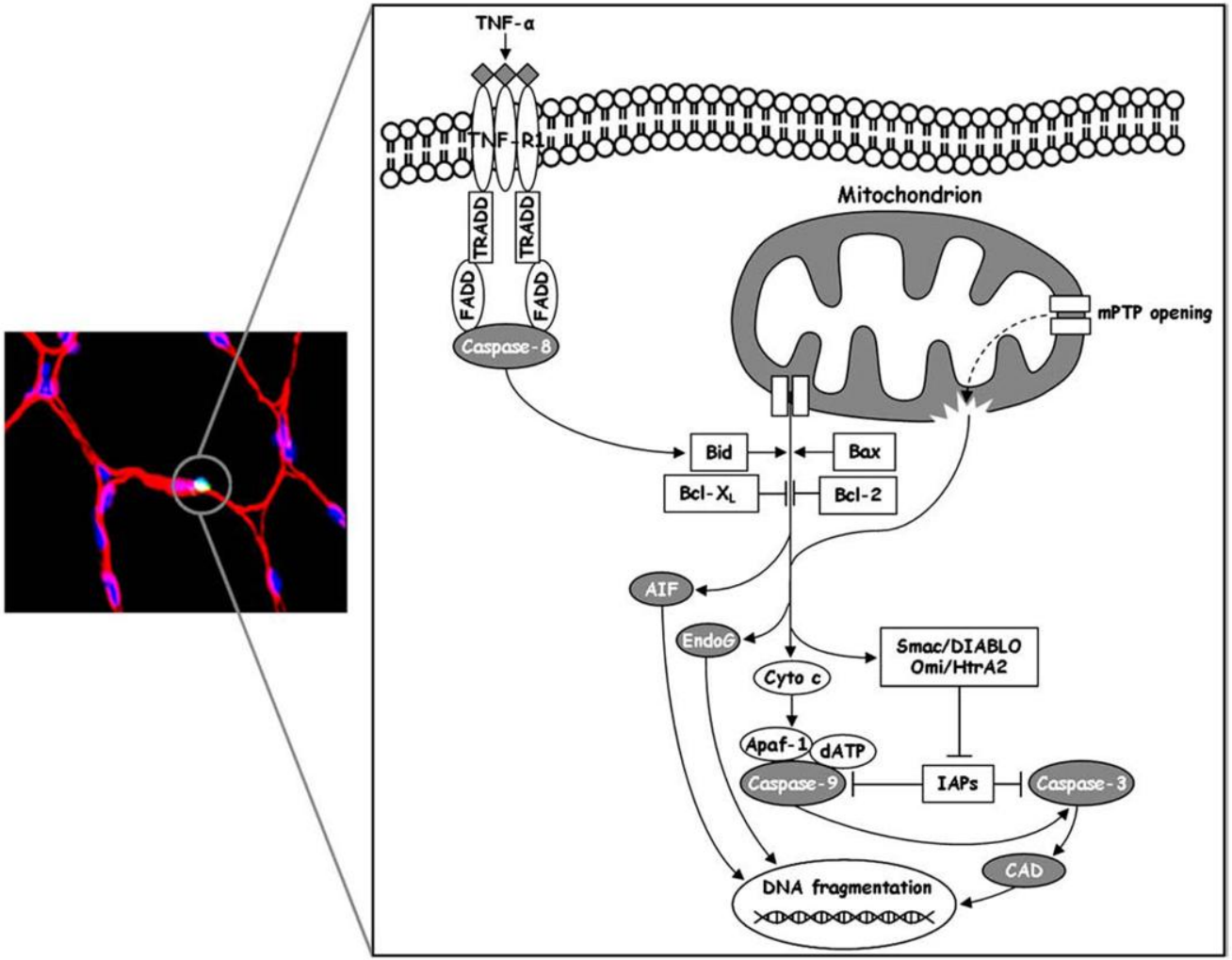
Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbagen

Review

Mitochondrial death effectors: Relevance to sarcopenia and disuse muscle atrophy

Emanuele Marzetti [a,b,*], Judy C.Y. Hwang [a], Hazel A. Lees [a], Stephanie E. Wohlgemuth [a], Esther E. Dupont-Versteegden [c], Christy S. Carter [a], Roberto Bernabei [b], Christiaan Leeuwenburgh [a,*]



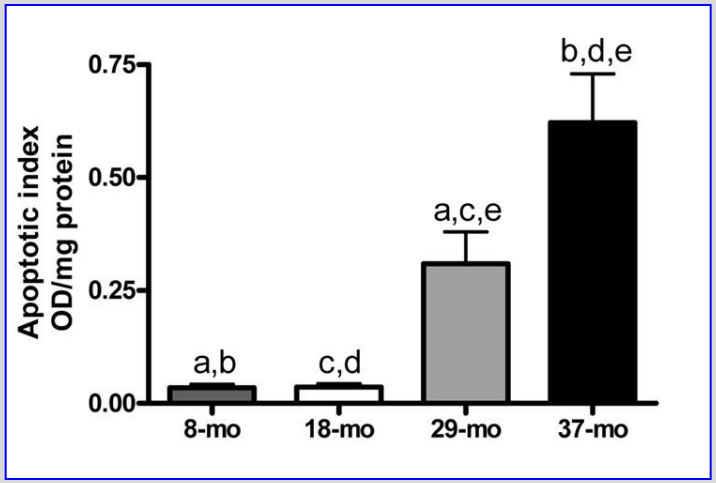
Contents lists available at ScienceDirect

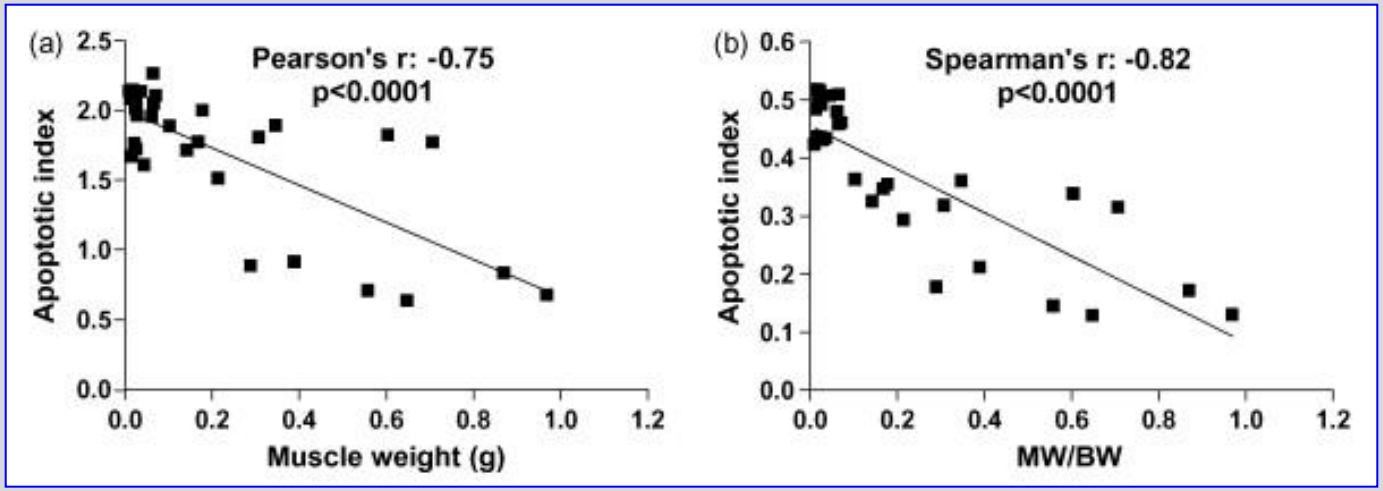
Mechanisms of Ageing and Development

journal homepage: www.elsevier.com/locate/mechagedev

Age-related activation of mitochondrial caspase-independent apoptotic signaling in rat gastrocnemius muscle

Emanuele Marzetti [a,b,*], Stephanie Eva Wohlgemuth [a], Hazel Anne Lees [a], Hae-Young Chung [c], Silvia Giovannini [a,b], Christiaan Leeuwenburgh [a,**]



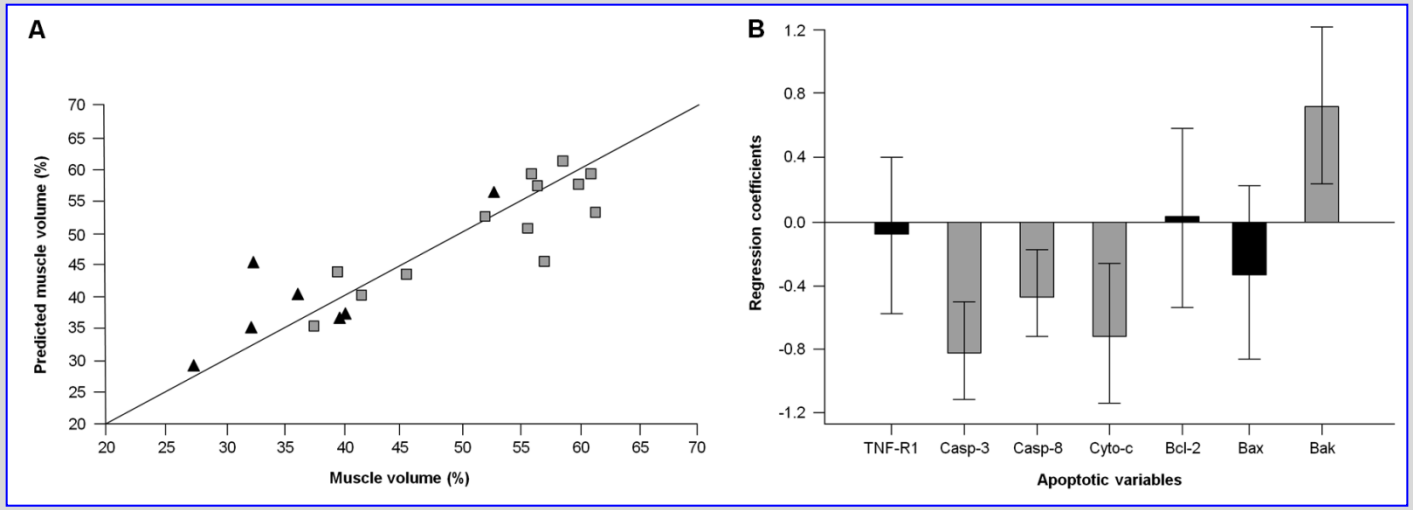


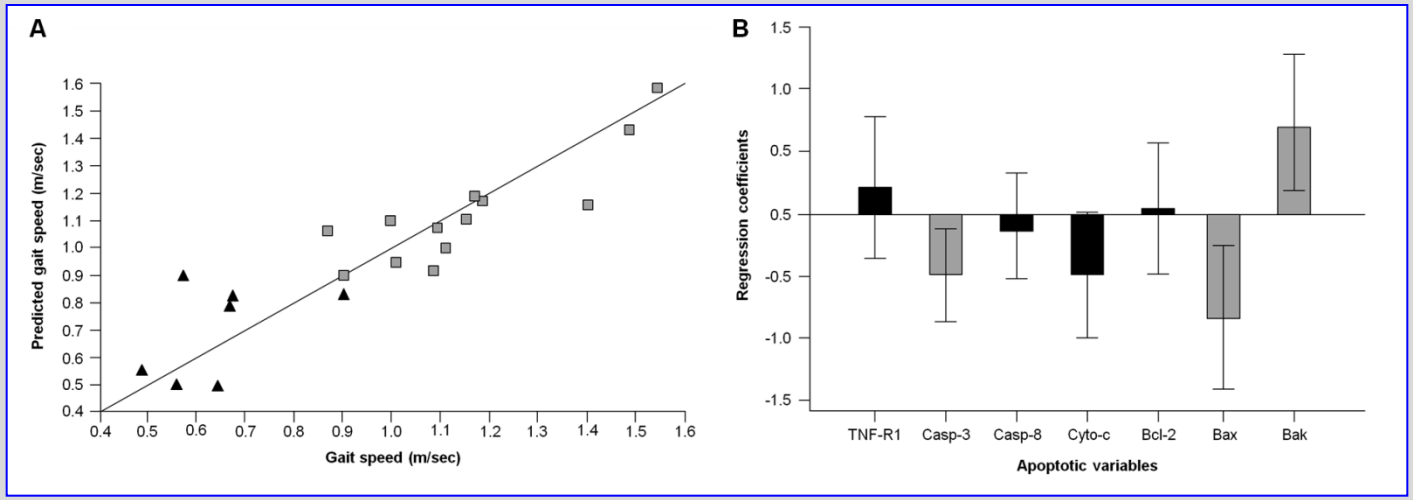
OPEN ACCESS Freely available online

PLoS one

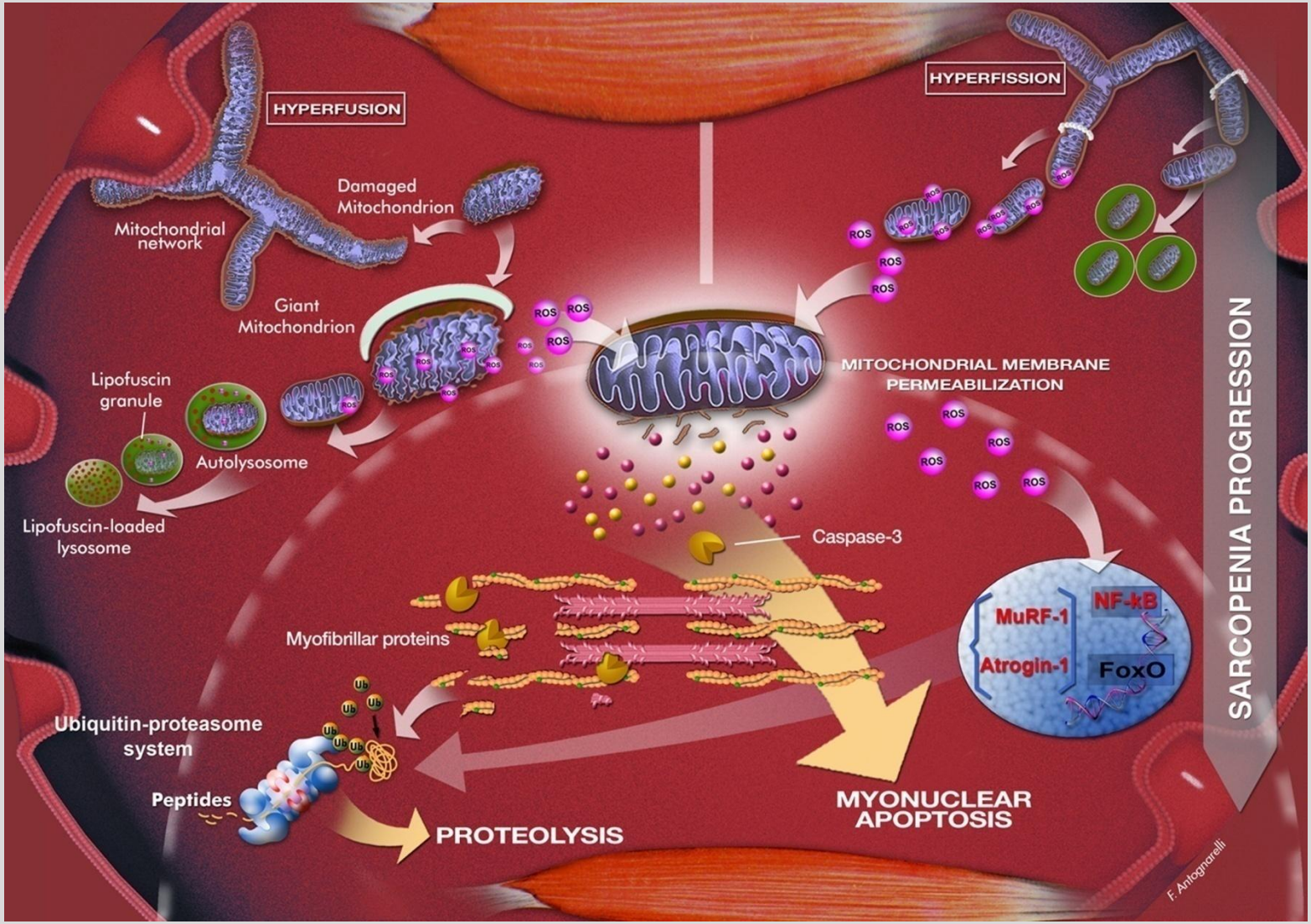
Skeletal Muscle Apoptotic Signaling Predicts Thigh Muscle Volume and Gait Speed in Community-Dwelling Older Persons: An Exploratory Study

Emanuele Marzetti[1,2]*, Hazel A. Lees[1], Todd M. Manini[1], Thomas W. Buford[1], Juan M. Aranda Jr.[3], Riccardo Calvani[4,5], Giorgio Capuani[6], Michael Marsiske[7], Donovan J. Lott[8], Krista Vandenborne[8], Roberto Bernabei[5], Marco Pahor[1], Christiaan Leeuwenburgh[1]*, Stephanie E. Wohlgemuth[1]





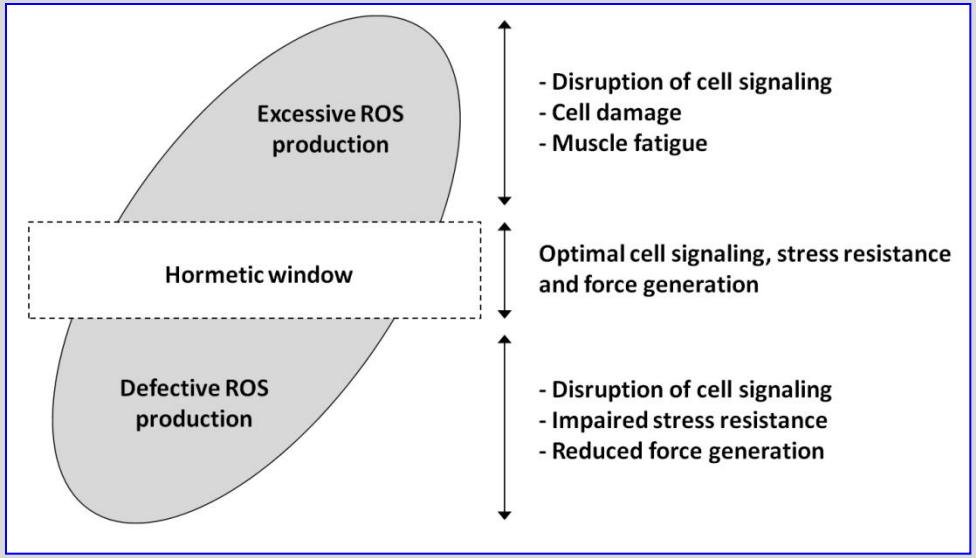
Integrated Mitochondrial Pathways in Muscle Atrophy: A Proposed Refinement of the MFRTA



Marzetti et al. Int J Biochem Cell Biol 2013

Challenges of Targeting Mitochondria to Treat Sarcopenia

- Just like most biological processes, the previously described mitochondrial pathways are not on/off phenomena, but proceed along a *continuum* with an optimal window of functioning, flanked by (detrimental) defective and excessive levels of operation.
- Antioxidant supplementation is a paradigmatic example of how a simplistic way of tackling a complex issue produces unpredictable outcomes.



Proposed effects of varying levels of ROS on skeletal myocyte homeostasis.

Calvani et al. J Frailty Aging 2013

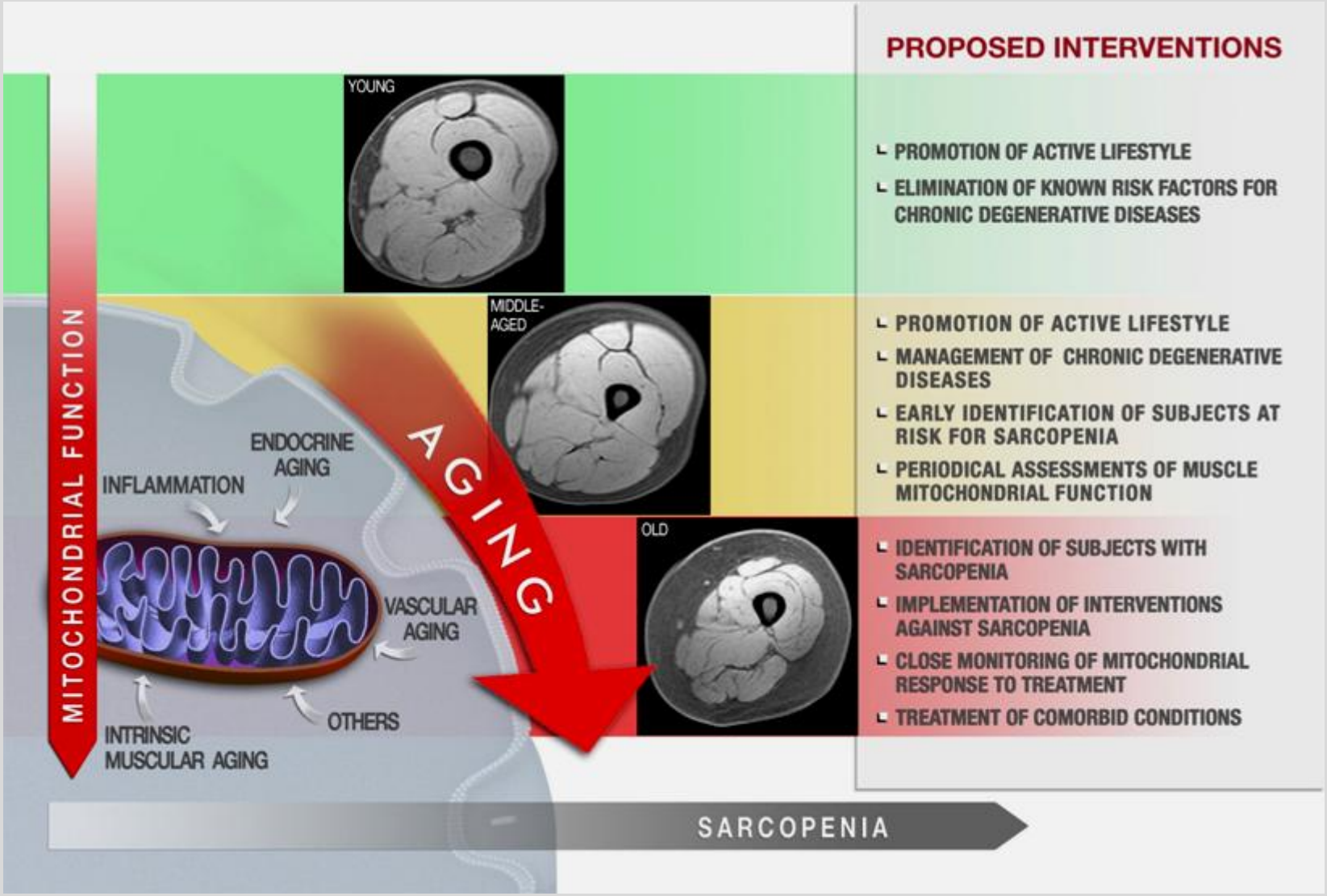
Challenges of Targeting Mitochondria to Treat Sarcopenia

- While an excessive apoptotic activation may promote muscle atrophy, the indiscriminate abolition of apoptosis could result in the persistence of dysfunctional nuclei or damaged contractile elements.
- Unchecked stimulation of autophagy could lead to autophagic cell death, while its abolition would abrogate the housekeeping function of this pathway.
- Excessive mitochondrial biogenesis is maladaptive unless it is compensated by adequate upregulation of mitophagy.
- **No reliable biomarkers are presently available to assess muscle mitochondrial function and track its changes over time or in response to an intervention.**

Challenges of Targeting Mitochondria to Treat Sarcopenia

- Another important aspect to take into account is the pleiotropic function of nearly all mediators of the mitochondrial pathways described.
- Targeting a single molecule might therefore impact multiple processes.
- Manipulation of one pathway could elicit compensatory effects, impeding a clear distinction between primary and secondary outcomes and cause-effect relationships.

Hypothetical Progression of Mitochondrial Dysfunction During the Development Sarcopenia and Possible Windows for Interventions



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