PROJECT

Supervisor:	Prof. Patrizia Rovere Querini
Title:	Metabolic exhaustion and adaptive remodeling in sarcopenic obesity: from pathophysiology to pharmacological targeting
Curriculum:	Cell and Molecular Biology
Link to the personal page of the University or relevant hospital site website:	https://www.unisr.it/docenti/r/roverequerini-patrizia

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Sarcopenia is a leading cause of disability in aging and obesity. Individuals with comparable adiposity levels may exhibit marked metabolic and functional heterogeneity, suggesting that intrinsic molecular drivers, rather than obesity alone, determine sarcopenia susceptibility. Our laboratory has recently demonstrated, in a two-hit mouse model of sarcopenic obesity (aging + high-fat diet), that sarcopenia associates with skeletal muscle "metabolic exhaustion" — a time-independent molecular signature identified through Multi-Omics Factor Analysis. In this model, mitochondria emerge as a central node linking lipid metabolism to contractile function. The causal mechanisms connecting mitochondrial dysfunction to muscle strength loss remain to be elucidated. Whether pharmacological targeting of mitochondrial function can promote adaptive muscular remodeling also remains unexplored.

Rationale and hypothesis

We hypothesize that muscle strength loss in obesity and aging is driven by mitochondrial dysfunction characterized by "metabolic exhaustion", and that pharmacological treatments modulating mitochondrial function (including novel incretin-based therapies) can promote adaptive remodeling preserving muscle function.

Objectives and specific aims

1. Characterization of mitochondrial and contractile dysfunction in the diet-induced mouse model of sarcopenic obesity.

2. Development of a cellular model to identify mechanisms linking metabolic exhaustion to contractile dysfunction.

3. Identification of circulating translational biomarkers and validation using human samples.

4. Evaluation (in vivo and in vitro) of potential drugs modulating mitochondrial function, including incretin-based therapies.

Expected outcomes

1. Identification of a causal mechanism linking mitochondrial dysfunction to muscle strength loss.

2. Discovery of potential therapeutic targets of sarcopenic obesity.

Skills that the student should acquire (max. 600 characters including spaces):

The doctoral student will acquire expertise in mitochondrial biology (respirometry, membrane potential, ROS quantification), murine and cellular models of sarcopenic obesity, skeletal muscle functional assessment (grip strength, treadmill test, ex vivo contractility), and preclinical study design with clinical applicability. Training will also include advanced bioinformatics, scientific writing, and presentation skills.

References (max. 15)

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12. Zuo, X., Zhao, R., Wu, M., Wang, Y., Wang, S., Tang, K., Wang, Y., Chen, J., Yan, X., Cao, Y., et al. (2025). Multi-omic profiling of sarcopenia identifies disrupted branched-chain amino acid catabolism as a causal mechanism and therapeutic target. Nat. Aging 5, 419–436. https://doi.org/10.1038/s43587-024-00797-8.
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