Instituto de Medicina Molecular João Lobo Antunes

Master Project Proposal

Title: Rejuvenating Strategies for Stem Cell-Based Therapies in the Aged Skeletal Muscle

Synopsis: A central goal of the regenerative medicine field is the development of interventions that restore or rejuvenate tissues using replacement cells derived from stem or progenitor cells. This approach requires a good understanding of the limitations imposed by the aging tissue environment, as well as intrinsic limitations of the progenitor cells, to the process of tissue repair (*1*). An important change in tissue environment that develops with aging is a state of low-grade chronic inflammation, now considered a major roadblock to effective tissue regeneration. The identification of new systemic regulators of inflammation involved in the aging process, partially responsible for the improvement in regenerative capacity in old mice after heterochronic parabiosis, could provide a path to enhance stem cell-based therapies effect in old organs (*2*).

Skeletal muscle is a paradigmatic model to study tissue regeneration. Changes in local and systemic cues can affect muscle regenerative capacity in old mice, and intrinsic limitations of muscle stem cells (MuSCs) impair regeneration at later stages of the aging process (*3, 4*). This combination of factors makes the skeletal muscle also an excellent model to test systemic rejuvenating interventions in old animals and explore how alterations in tissue environment drive the process of stem cell aging.

We recently identified the stress responsive protein MANF (Mesencephalic Astrocyte-derived Neurotrophic Factor) as a regulator of organismal aging. Mouse models of reduced MANF levels develop signs of chronic sterile inflammation, accompanied by accelerated aging phenotypes. Using heterochronic parabiosis experiments, along with genetic and pharmacologic interventions, we showed that MANF is an effective therapy to reverse several hallmarks of aging (*5*). In proof of principal studies carried out by our team, using the retina as a test case, we showed that MANF supplementation is an effective intervention to improve the success of cell replacement therapies (*6, 7*). However, how MANF signaling affects muscle regeneration remains unknown.

In this project we will use our unique models of MANF loss of function to mimic an age-related inflammatory condition to investigate its consequences for muscle regeneration, and to isolate the role of age-related inflammation as a driver of MuSC dysfunction. Finally we will test benefits of MANF therapy and MuSC transplants as strategies to improve regenerative capacity of the old skeletal muscle.

The master project will involve characterization of immune cell profiles, regenerative defects and stem cell function in MANF loss of function models in the skeletal muscle following injury.

Supervisor: *Pedro Sousa-Victor, Aging and Tissue Repair Lab, psvictor@medicina.ulisboa.pt*
Co-Supervisor: *Joana Neves, Aging and Tissue Repair Lab, joana.neves@medicina.ulisboa.pt*
Webpage of the group

Bibliography:

1. J. Neves, P. Sousa-Victor, H. Jasper, Rejuvenating Strategies for Stem Cell-Based Therapies in Aging. *Cell stem cell* **20**, 161 (Feb 2, 2017).

2. J. Neves, P. Sousa-Victor, Regulation of inflammation as an anti-aging intervention. *The FEBS journal* **287**, 43 (Jan, 2020).
3. P. Munoz-Canoves, J. Neves, P. Sousa-Victor, Understanding muscle regenerative decline with aging: new approaches to bring back youthfulness to aged stem cells. *The FEBS journal* **287**, 406 (Feb, 2020).
4. P. Sousa-Victor *et al.*, Geriatric muscle stem cells switch reversible quiescence into senescence. *Nature* **506**, 316 (Feb 20, 2014).
5. P. Sousa-Victor *et al.*, MANF regulates metabolic and immune homeostasis in ageing and protects against liver damage. *Nature metabolism* **1**, 276 (Feb, 2019).
6. J. Neves *et al.*, Immune modulation by MANF promotes tissue repair and regenerative success in the retina. *Science* **353**, aaf3646 (Jul 1, 2016).
7. J. Neves *et al.*, MANF delivery improves retinal homeostasis and cell replacement therapies in ageing mice. *Exp Gerontol* **134**, 110893 (Feb 28, 2020).