Instituto de Medicina Molecular João Lobo Antunes

Master Project Proposal

Title: Immune regulation of Stem Cell Aging

Synopsis:

The consequences of aging on human health are broadly apparent, yet the causes and drivers of the aging process are just beginning to be understood. Adult stem cells are major regulators of organismal homeostasis, sustaining tissue renewal and repair throughout life. However, knowledge regarding what drives stem cell aging and how this contributes to tissue deterioration is just starting to emerge. Our lab aims to understand the process of stem cell aging, with the goal of developing new therapeutic solutions to slow degenerative changes in organs and design stem cell-based therapies for age-related diseases.

The skeletal muscle is a paradigmatic model to study age-related loss of repair capacity. Skeletal muscle regeneration is sustained by a population of adult resident stem cells, termed muscle stem cells (MuSCs). During ageing, muscle regenerative capacity is lost due to MuSC impaired activity. Aged MuSCs present multiple functional defects, including an increased propensity to convert into alternative cellular lineages. Some environmental drivers of impaired MuSC function have been defined in recent years. However, what drives MuSC alternative lineage commitment with age is still unknown. Yet, such divergence in cellular identity is likely to have a major impact on muscle functional decline with age.

The immune system, a central player in the regulation of skeletal muscle repair, is also affected by aging, with consequences for MuSC function. Ongoing studies in our lab uncovered defects in immune signaling in the aged regenerating muscle. We were able to recapitulate these age-related immune defects in mouse models of immune dysfunction. Importantly, we found that changes in immune signaling during the regenerative process were sufficient to cause impairments in MuSCs function and lineage commitment. This work led to the novel hypothesis that dysregulated immune signaling plays a central role in the loss of MuSC function and lineage identity in ageing. We propose to understand how immune dysfunction drives MuSC functional decline through a detailed characterization of age-related changes in immune populations and signaling events associated with muscle repair, and evaluation of the causal nature of those changes over MuSC intrinsic defects.

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Bibliography:

P. Sousa-Victor, L. Garcia-Prat, P. Munoz-Canoves, Control of satellite cell function in muscle regeneration and its disruption in ageing. *Nature Reviews Molecular Cell Biology* 23, 204 (Mar, 2022).