Instituto de Medicina Molecular João Lobo Antunes

Master Project Proposal

Title: Mechanisms of MANF-mediated immune modulation in tissue repair

Synopsis:

Regenerative medicine is emerging as a strategy for tissue rejuvenation, holding the potential to improve human health by delaying age-related disease. Nevertheless, the efficacy of such therapeutic approaches is compromised by the inefficient repair capacity of old, degenerating tissues. Age-associated dysregulation of inflammatory signaling is an important roadblock for the success of regenerative therapies, and immune modulatory interventions that reestablish a regulated inflammatory response can be effective strategies to promote regenerative success in aging. Macrophages, as important integrators of inflammatory signaling and regulators of tissue homeostasis, are key candidates to mediate the effects of immune modulatory mechanisms during tissue repair.

The skeletal muscle has been extensively used as a model system to understand the age-related decline in tissue repair capacity, providing important insight into the role of macrophages in coordinating the inflammatory response during regeneration, and on the limitations imposed by chronic inflammation and the aged immune system to efficient muscle repair. However, we have an incomplete understanding of the cellular processes and molecular effectors that ensure the maintenance of a regulated inflammatory response during a repair event, and how their dysregulation contributes to the observed chronic activation of inflammatory signaling during aging. Highlighting the utility of macrophage-based strategies in regenerative medicine, recent studies have shown that interventions that harness the repair potential of macrophages can improve muscle regenerative capacity.

Our recent work uncovered an essential role for the immune modulator mesencephalic astrocyte-derived neurotrophic factor (MANF) in the skeletal muscle regenerative process. We found that MANF-deficiency leads to a dysregulated immune response during muscle repair and structural alterations in the macrophage population. We observed similar alterations in aged animals. We now aim to understand how MANF-mediated immune modulation controls macrophage function during tissue repair and how this mechanism is disrupted during aging.

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Bibliography:

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