Instituto de Medicina Molecular João Lobo Antunes

Master Project Proposal

Title: Immune regulation of skeletal muscle metabolic health and exercise response in aging

Synopsis:

Aging stands alone as the major risk factor for metabolic diseases. Work in the past decade has revealed a close relationship between these metabolic disorders and increased inflammation at the whole organism level. Although studies exploring how organ specific immune populations are altered during metabolic dysfunction have been mostly focused on the adipose tissue, recent work point to a potential role of resident immune populations in the regulation of the skeletal muscle (SkM) metabolic health.

The SkM is a central organ in the regulation of metabolic homeostasis and exercise-based interventions that improve SkM health and are critical for the prevention and treatment of metabolic diseases. However, the capacity of the SkM to respond to exercise is itself altered during aging. A better understanding of the drivers of metabolic dysfunction and poor exercise responsiveness in the aged SkM is fundamental to broaden the targets available for the treatment of metabolic disease in aging.

Our recent work described how immune changes underlie a decline in the repair capacity of the aged SkM. Here, we hypothesize that age-related alterations in the local immune environment are a cause of deterioration in SkM's metabolic health and impaired exercise responsiveness. In this project, we will detail how immune cell populations and signals change in the SkM during aging in mice and humans, and show how specific immune changes in isolation are sufficient to drive metabolic dysfunction and reduced capacity to grow in response to mechanical overload. Using this knowledge as basis, we aim to design and test new interventions directed at the aged SkM, showing, as proof-of-principle, that immune modulatory strategies in the SkM are a viable therapeutic solution to improve insulin sensitivity and exercise responsiveness in the elderly population.

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