Project Title: Deciphering the cellular mechanisms of disuse-induced muscle atrophy

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Hosting Lab: - Skeletal Muscle Plasticity

Background

Skeletal muscle is a highly plastic tissue that undergoes profound structural, functional and molecular remodelling in response to physical inactivity and mechanical unloading. Disuse-induced muscle atrophy is a major biomedical challenge, relevant to prolonged immobilisation, bed rest, ageing and spaceflight. Despite extensive research, the mechanisms that initiate and sustain muscle wasting remain only partially understood, and effective strategies to prevent or reverse disuse-induced muscle loss are still limited.

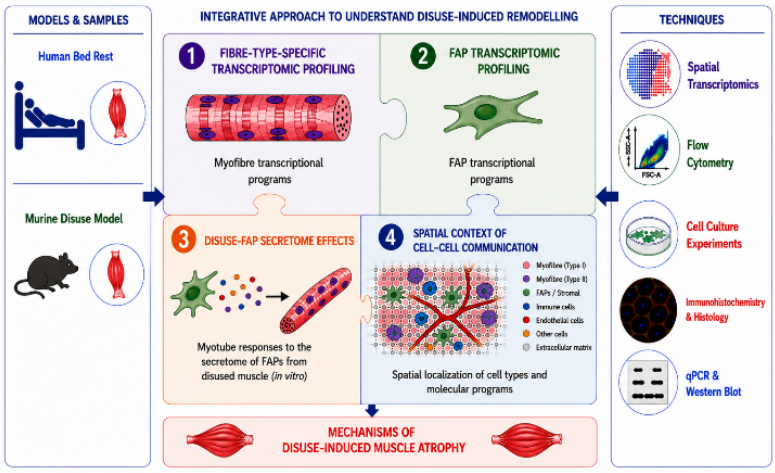
Skeletal muscle is increasingly recognised as a multicellular ecosystem in which myofibres interact with a complex network of resident mononuclear cells, including fibro-adipogenic progenitors (FAPs), immune cells, endothelial cells, pericytes, and Schwann/glial cells. These cells play essential roles not only in regeneration but also in maintaining tissue homeostasis [1]. Among these, FAPs have emerged as key regulators of muscle adaptation. Initially described as bipotent progenitors supporting either regeneration or fibro-adipogenic degeneration [2-3], FAPs are now recognized as a heterogeneous and dynamic population that coordinates intercellular communication within muscle. However, how distinct muscle fibre types transcriptionally reprogramme in response to disuse, and how these fibre-specific adaptations influence or reflect remodelling of the surrounding cellular niche, remains poorly understood.

Aims

By leveraging available skeletal muscle samples from human bed-rest studies and preclinical murine models of disuse, the project will pursue the following aims:

Aim 1. To define the effects of mechanical unloading on skeletal muscle by mapping fibre-type-specific structural and transcriptional changes together with the remodelling of the muscle microenvironment.

Aim 2. To characterize unloading-induced changes in FAPs and determine how these changes affect their communication with muscle cells and contribute to muscle atrophy.



Techniques: The project will employ a combination of complementary approaches, including spatial transcriptomics, real-time PCR, western blotting, immunohistochemistry, flow cytometry and cell culture experiments.

[1] Farup J, Madaro L, Puri PL, Mikkelsen UR. Interactions between muscle stem cells, mesenchymal-derived cells and immune cells in muscle homeostasis, regeneration and disease. Cell Death Dis. 2015 Jul 23;6(7):e1830. doi: 10.1038/cddis.2015.198.
[2] Joe AW, Yi L, Natarajan A, Le Grand F, So L, Wang J, Rudnicki MA, Rossi FM. Muscle injury activates resident fibro/adipogenic progenitors that facilitate myogenesis. Nat Cell Biol. 2010 Feb;12(2):153-63. doi: 10.1038/ncb2015.
[3] Uezumi A, Fukada S, Yamamoto N, Takeda S, Tsuchida K. Mesenchymal progenitors distinct from satellite cells contribute to ectopic fat cell formation in skeletal muscle. Nat Cell Biol. 2010 Feb;12(2):143-52. doi: 10.1038/ncb2014.