RestorAGING - A novel role for PGE2 signalling in promoting aged neuromuscular junctions reinnervation and counteracting sarcopenia

Aging is characterised by a progressive decline in muscle mass and force, potentially resulting in the insurgence of sarcopenia. Sarcopenic patients are at an increased risk of falls and fractures, with a concordant decrease in mobility and personal independence. Evidence suggests that key determinants of sarcopenia insurgence are muscle denervation, failure of its reinnervation and degeneration of neuromuscular junctions (NMJ), representing the connection between the nerve and the muscle and essential for muscle function. This MSCA project will inform our understanding on the interplay between prostaglandin signalling and the NMJ in the onset and treatment of sarcopenia. Prostaglandin E2 (PGE2) stimulates tissue regeneration. Its levels are reduced in aged human and mice skeletal muscles due to increased activity of its degrading enzyme 15- prostaglandin dehydrogenase (15-PGDH). Inhibition of 15-PGDH in aged rodents restores PGE2 concentrations to youthful levels, increasing muscle mass, strength and endurance. However, the mechanisms underlying how 15-PGDH/PGE2 modulation exerts these effects are not well understood. Here, I will show how PGE2 impacts NMJ integrity in mice, establishing if restoration of its signalling restores NMJs innervation progressively lost in aging. My final aim is to determine whether boosting PGE2 levels via 15-PGDH inhibition represents a viable therapeutic strategy to treat sarcopenia. To confirm the relevance of the dysregulated 15-PGDH/PGE2 axis in determining NMJ alterations in humans, I will perform single nuclei RNASeq and spatial proteomics (CODEX) on muscle samples of young and aged healthy, pre-sarcopenic and sarcopenic individuals. I will integrate the molecular data with in-vivo muscle morphology and function, (1) to reveal whether 15- PGDH expression, activity and localization is different in sarcopenic muscle and correlates with any in-vivo parameter and (2) to generate a macro-to-micro atlas of human aging and sarcopenia.

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