DLK1 from fibroadipogenic cells prevents fatty muscle degeneration in humans

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INTRODUCTION: Fibroadipogenic progenitor cells (FAPs) are stem cells within skeletal muscle that both maintain healthy muscle in homeostasis and also drive degeneration during chronic injury by promoting adipogenesis and fibrosis. To uncover how these stem cells switch from a pro-regenerative to pro-degenerative role we performed experiments on human FAPs from healthy and injured muscles, focusing on rotator cuff tears. We then elucidate the role of Delta-Like Non-Canonical Notch Ligand-1 (DLK1) in prevention of fatty muscle degeneration.

METHODS: We performed single-cell mRNA sequencing of over 24,000 human FAPs from healthy and injured muscle. This robust dataset contained 14 unique samples, including 6 patients with paired injured rotator cuff muscle and healthy deltoid samples. We combined this transcriptomic data with full spectrum flow cytometry to identify distinct FAP subpopulations. In vitro culture experiments and in vivo xenotransplant experiments were performed in mice treated with control vs. DLK1 protein.

RESULTS: We identified distinct FAP subpopulations with progenitor, adipogenic, or fibrogenic signatures. Injury severity increases adipogenic commitment of FAP subpopulations and is driven by the downregulation of DLK1. Both DLK1 mRNA and protein are decreased in chronically degenerated muscle compared to healthy controls. Treatment of FAPs with DLK1 reduced adipogenesis by over 50% in vitro. In a xenotransplant model of human FAPs, treatment with DLK1 after injury results in 5-fold less fatty infiltration in vivo.

DISCUSSION AND CONCLUSION: Injury severity increases adipogenic commitment of FAPs and is driven by the downregulation of DLK1. Treatment of FAPs both in vitro and in vivo with DLK1 reduced adipogenesis and fatty infiltration, suggesting that during injury, reduced DLK1 within a subpopulation of FAPs may drive degeneration. Our findings that tissue degeneration is driven by the regulation of specific stem cell populations within the larger stem cell pool presents opportunities for development of targeted therapies.