An exosome marker-enriched fibro/adipogenic progenitors (FAPs) population promotes muscle regeneration

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INTRODUCTION: Muscle interstitial fibro/adipogenic progenitors (FAPs) are non-myogenic, mesenchymal progenitors that play an important role in maintaining muscle extracellular matrix (ECM) and regulating other muscle progenitor cells, including satellite cells (SCs). FAPs actively communicate with SC and other cells, including immune cells during muscle regeneration. Though the detailed mechanisms are not fully illuminated, evidence suggests that this interaction may be mediated through extracellular vesicles (EVs), particularly exosomes [1,2]. Exosomes are nano-sized membrane EVs that are secreted by almost all cell types. Exosomes carry transmembrane markers from the tetraspanin family of proteins, including, CD63, CD81, and CD9. In this study, we isolated a subpopulation of FAP with high expression level of exosome marker of CD81 and tested their role in promoting muscle regeneration in a mouse volumetric muscle loss (VML) model. We hypothesize that CD81+ FAPs promote muscle regeneration after VML.

METHODS: Human FAPs (hFAPs) were isolated from hamstring muscle from patients undergoing anterior cruciate ligament (ACL) reconstruction. Muscles were minced and further digested with collagenase. FAPs were isolated through Fluorescence-activated Cell Sorting (FACS) with their surface markers of CD39-/CD45-/CD31-/ITGA7-/PDGFRα+. CD81+ hFAP were further separated from the FAP pool with their surface marker of CD81. Unilateral volumetric muscle loss (VML) injury was created in NGS immunodeficient mice (n=13) with a defect of full thickness of muscle with a 4mm in diameter punch at proximal one third of tibialis anterior (TA) muscle. CD81+ hFAPs were then transplanted to muscle defect (1×10^6 cell in 10μl HyA/CD31 minced and further digested with collagenase. FAPs were isolated through extracellular vehicles (EVs), particularly exosomes [1,2]. Though the detailed mechanisms are not fully illuminated, evidence suggests that this interaction may be mediated through exosomes. Exosomes carry and transfer a variety of cell-signaling molecules including protein and RNA [1]. Myoblast and myotube-derived EVs carry growth factors and miRNAs (MyoMirs) that may be involved in promoting myogenesis [2,3]. Future work is needed to define the role of CD81+ FAP-derived exosomes in muscle regeneration.

SIGNIFICANCE: Exosome marker-enriched FAPs may be used as a cellular source for treating volumetric muscle loss and other muscle injuries.


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