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INTEGRIN LIGANDS ON HUMAN CARDIAC FIBROBLAST-SECRETED EXTRACELLULAR VESICLES INCREASE SARCOPLASMIC RETICULUM-DEPENDENCY OF HUMAN CARDIOMYOCYTE CALCIUM HANDLING

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Introduction: A key feature of adult cardiomyocytes (CMs) is Ca2+-induced Ca2+ release (CICR), mediating efficient excitation-contraction coupling. This is poorly utilised in developing CMs & impaired in disease. We have reviewed the importance of heterocellularity in disease modelling. Notably, cardiac fibroblasts regulate turnover of extracellular matrix (ECM) proteins that bind to CM integrins. Our group identified that cardiac fibroblasts improve calcium cycling efficiency by recruiting the sarcoplasmic reticulum (SR) but the role of integrin's and fibroblast-secreted extracellular vesicles (EVs) has not yet been explored.

Hypothesis: Cardiac fibroblast-secreted EVs and integrin ligands signal between human fibroblasts and CMs.

Methods: Human induced pluripotent stem cell-derived CMs were treated with human cardiac fibroblast EVs or EV inhibitor GW4869. Alternatively, CMs were treated with integrin-binding RGDSGAITIGA (RGD_A) or RGDSGAITIGC (RGD_C). CM Ca2+ transients were monitored with Fluo4-AM.

Results: Fibroblast contact shortens CM Ca2+ transient time to peak (A) and increase rate of decay (B); the latter due to increased sarcoplasmic reticulum (SR) Ca2+ uptake, which is attenuated by GW4869 (C and D). Fibroblast EVs abbreviate time to peak compared to serum-free control and fibroblast-naïve (E). RGD_A and RGD_C abbreviate Ca2+ transients (G) and change CMs to a more rod-like morphology (H and I). Size exclusion chromatography (SEC) fractions (J) with CD63-expressing EVs (fractions 8-12) (K) contain fibronectin, a prominent integrin-binding protein (L).

Conclusion: Fibroblast EVs increase CICR efficiency due to increased SR contribution to Ca2+ regulation. Integrin ligands mimicking ECM proteins also abbreviate Ca2+ transients. This increase in decay efficiency is due to increased SR Ca2+ reuptake rate to closer reflect healthy adult CMs. We suggest that fibroblast-secreted EVs and integrin ligands-receptor interactions are modalities by which fibroblasts modulate CM structure and function in health and may be important in disease.

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