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Human adventitial pericytes secrete bioactive factors exerting distinct biological effects on cardiac cells: hints for cardiac repair

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Background: Pericytes are attracting much attention as potential candidates for successful cell therapy of myocardial ischaemia. Intramyocardially delivered adventitial pericytes (APCs) secrete paracrine factors which stimulate angiogenesis and recruitment of cardiac stromal cells, reduce fibrosis and promote cardiomyocyte proliferation and viability. However, factors responsible for these biological effects have not been elucidated yet.

Purpose: To exploit the components of APC secretome exerting a biological effect on cardiac cells with the aim to discover new druggable targets with potential therapeutic activity.

Methods and results: APCs were derived from saphenous veins of adult patients (n=13, 68 ± 11 yrs, all with coronary artery disease - CAD). The APC-conditioned medium (CM) stimulated the proliferation of human iPS-derived cardiomyocytes compared with unconditioned medium (UCM) (EdU incorporation, 1.3-fold increases, P=0.004). Stimulation with APC-CM increased the number of mitotic figures in cardiomyocytes (Aurora B, 1.5-fold increases compared to UCM, P=0.002). Furthermore, APC-CM abrogated the hypoxia-induced apoptosis in cardiomyocytes (2-fold increase in Caspase 3/7 activity in hypoxic cells exposed to UCM compared to normoxic cells, P=0.002). We also found that APC-CM stimulates the migration of human cardiac stromal cells (CSCs) obtained from healthy donors (n=6, 54 ± 11 yrs) in both a transwell and scratch migration assays (n=6, P<0.01 and P<0.05 vs UCM respectively). Interestingly, APC-CM activated also the migration of HUVECs (n=6, P<0.01 vs UCM) but did not attract fibroblasts. Next, we aimed to identify the biologically active components of the APC-CM. Depletion of exosomes and heat and RNase treatments did not abolish the pro-migratory action of the APC-CM, while this was abrogated by Proteinase K. Fractionation of the APC-CM based on the MW indicated that the bioactive peptides have MW > 30KDa. The pro-migratory fractions of the APC-CM obtained from size exclusion chromatography underwent mass spectrometry analysis (n=3 APCs). This identified 14 proteins uniquely present in the pro-migratory fractions. The two most relevant candidates were SPARC and TGFBI, both confirmed by ELISA. Intriguingly, the recombinant SPARC and TGFBI failed to reproduce the biological effect of APC-CM on CSC migration, suggesting that the secreted proteins may carry unique post-translational modifications not found in synthetic peptides. Further analyses are being carried out to reveal the biological properties of the endogenous SPARC and TGFBI.

Conclusions: This study suggests a fascinating approach based on the use of the active component of the APC-CM as a surrogate of APC therapy. If the biological properties of the cellular proteins will be successfully reproduced in synthetic peptides *in vitro*, this innovative approach may extend the benefits of APC therapy to all those patients with CAD for whom cell therapy is not an available option.