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Cardiac pericytes can be pharmacologically redirected towards a smooth muscle phenotype to enhance the revascularisation of the ischemic heart

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Elisa Avolio, Rajesh Katare, Anita Thomas, Andrea Caporali, Daryl Schwenke, Marco Meloni, Massimo Caputo, Paolo Madeddu

Background: Pericytes (PC) are abundant cells that wrap around the whole vasculature of the heart. To date, it is not known if PC contribute to the maturation of new arterioles in the ischemic heart.

Purpose: we verified whether cardiac PC differentiate into contractile vascular smooth muscle cells (VSMC) *in vitro*, and if this potential can be pharmacologically induced to enhance the revascularisation of the heart post ischemia *in vivo*.

Methods and Results: PC were extracted from adult myocardial tissue, expanded *in vitro*, and characterised for antigenic profile and function. At baseline, PC do not express contractile VSMC antigens αSMA, CALP, SM22α, SM-MHC and Smoothelin B. We discovered that the inhibition of MEK1/2 activity and ERK1/2 signalling using the small molecule PD0325901 redirects the PC towards a VSMC phenotype. Contraction, calcium flux and migration assays confirmed that differentiated PC became stationary contractile cells, phenocopying control coronary artery SMC (CASMC). We further verified this finding using next-generation RNA-sequencing, which showed that differentiated PC expressed a cluster of contractile VSM transcripts similarly to control CASMC. Moreover, treated PC acquired a unique pro-angiogenic transcriptional profile, upregulating pro-angiogenic genes *LEP* and *PDGFB* while downregulating potent angiogenesis inhibitors *ANGPT2*, *TIE1* and *SERPINF1*. We also verified that human PC acquire contractile VSM markers when injected subcutaneously in mice. We next validated this innovative approach *in vivo*. Healthy C57BL6/J mice given the drug orally, for two weeks, showed an increase in the small arteriole density along with an improved myocardial perfusion, when compared with mice given vehicle. Last, administration of PD0325901 to mice with myocardial infarction improved left ventricular function and induced an increase in both capillary and arteriole density in the peri-infarct area, when compared with controls given vehicle. Improved revascularisation resulted in reducing infarct expansion in PD0325901-treated mice.

Conclusion: we propose a novel therapeutic approach based on MEK inhibition to promote the revascularisation of the infarcted heart reawakening the plasticity of resident PC. This approach could benefit the treatment of patients with coronary artery disease.