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MTORC1 AND MTORC2 PLAY DIFFERENT ROLES IN THE FUNCTIONAL SURVIVAL OF TRANSPLANTED ADIPOSE-DERIVED STROMAL CELLS IN HINDLIMB ISCHAEMIA MICE VIA REGULATING INFLAMMATION IN VIVO

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Objectives Poor cell survival severely limits the benefits from stem cell therapy for peripheral arterial disease (PAD). In this study, we investigated the role of mammalian target of rapamycin (mTOR) in survival and therapeutic function of engrafted murine adipose-derived stromal cells (mADSCs) in murine PAD model.

Methods mADSCs (1.0×10^7) were isolated from dual-reporter firefly luciferase and green fluorescent protein positive ($Fluc^+$-GFP^+) trangenic mice, intramuscularly implanted into the hindlimb of C57BL/6 mice with femoral artery ligation, and followed by noninvasive bioluminescence imaging (BLI). Ex vivo Fluc assay and immunofluorescence analysis were employed to validate in vivo BLI. Protein expression and cell apoptosis were determined by Western blot/ELISA and TUNEL assay.

Results Even though grafted mADSCs yielded anti-apoptotic effect by modulating pro-/anti-inflammatory cytokines expression (IL-1β, TNF-α, IL-6, IL-10) in which mTOR signalling pathway participated, in vivo bioluminescence imaging longitudinally tracked a progressive death of mADSCs within post-transplant 4 weeks in the murine ischaemic hindlimb. Selectively inhibiting mTOR complex 1 (mTORC1) could attenuate pro-inflammatory IL-1β/TNF-α production by rapamycin treatment together with mADSCs, which ultimately promoted mADSCs' viability and anti-apoptotic efficacy in vivo. In contrast, dual mTORC1/mTORC2 blockade using PP242 aggravated IL-1β/TNF-α level and suppressed

anti-inflammatory IL-10/IL-6 expression, which exerted deleterious effects on mADSCs' survival and anti-apoptotic benefit.

Conclusions mTORC1 and mTORC2 may play different roles in regulating inflammation, which involves mADSCs' functional survival in ischaemic hindlimb. These findings uncover that mTOR may evolve into a candidate within mechanism-driven approach to facilitate the availability of cell-based PAD therapy.