GW23-e1909

SYNERGISTIC ADIPOSE-DERIVED STROMAL CELLS AND SARPOGRELATE RECOVER THE IMPAIRED ANGIOGENESIS AND INFLAMMATION MODULATORY FUNCTION IN AGED HINDLIMB ISCHAEMIA MICE

doi:10.1136/heartjnl-2012-302920c.6

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Objectives The elderly is susceptible and vulnerable to peripheral arterial disease (PAD) due to higher prevalence, worse prognosis and fewer therapeutic options than the younger. This study aims to investigate the significance and mechanism of combined murine adipose-derived stromal cells (mADSCs) and sarpogrelate treatment for aged hindlimb ischaemia mice.

Methods mADSCs (1.0×10^7) constitutively express enhanced green fluorescent protein or firefly luciferase reporter were engrafted into aged Vegfr2-luc transgenic mice or FVB/N mice with unilateral femoral artery ligation respectively, which further administrated with sarpogrelate. Multimodality noninvasive imaging and histological approaches were employed to monitor mADSCs' survival and therapeutic efficacy for hindlimb ischaemia restoration. Therapeutic signal targets and cytokines were assessed by Western blot and ELISA.

Results The aged Vegfr2-luc mice showed a decreased expression and activation of VEGFR2, and lower level of VEGF and pro/anti-

inflammatory cytokines within ischaemic hindlimb than the younger, resulting in impaired angiogenic capacity and incompensation for ischaemia. Although mADSCs could modulate inflammation-induced angiogenesis and yield pro-angiogenic and anti-apoptotic effect partly via VEGF/VEGFR2/mTOR/STAT3 in vivo, they had abbreviated lives post transplantation. Sarpogrelate treatment together with mADSCs could further upregulate mTOR/STAT3 signal and attenuate pro-inflammatory IL-1beta/TNF-α/IFN-gamma expression, which ultimately facilitated mADSCs' survival and therapeutic efficacy in vivo. Sarpogrelate also prevented mADSCs from apoptosis over hypoxia/reoxygenation via mTOR/STAT3 in vitro.

Conclusions This study firstly demonstrates the in vivo kinetics of VEGFR2 expression as biomarker for evaluating cell-directed therapeutic angiogenesis in the elderly. mADSCs and sarpogrelate synergistically restore the impaired angiogenesis and inflammation modulatory function in aged hindlimb ischaemia mice, which may translate into promising strategy for the elderly PAD patient.