

fluorescent protein (Fluc⁺-GFP⁺). PAD model was constructed by unilateral femoral artery ligation. Male syngeneic BALB/c nude mice (n=90) were randomised into 3 groups receiving the following: (1) sham-operation+phosphate-buffered saline (PBS); (2) PAD+PBS; (3) PAD+ADSCs (1×10⁷, intramuscular injection). Long-term fate of ADSCs in vivo was monitored by bioluminescence imaging (BLI), and bioluminescence tomography with micro-CT (BLT/micro-CT), further validated by immunofluorescence staining. Hindlimb perfusion and angiogenesis were measured by in vivo laser Doppler perfusion imaging (LDPI) and micro-CT angiography, which were confirmed by vascular casting with scanning electron microscopy (SEM), immunohistochemistry and functional scores. Therapeutic signal pathways and angiogenic cytokines was assessed by Western blot and ELISA.

Results A short-lived survival (~5 weeks) of post-transplant ADSCs within the ischaemic hindlimb was longitudinally followed by noninvasive BLI/BLT/micro-CT, which enabled quantitative 3-dimensional (3D) imaging for the cells' location and kinetics in vivo. ADSCs could improve the blood perfusion recovery, ambulatory function and prognosis of the ischaemic hindlimb by inducing angiogenesis. ADSCs didn't incorporate into host microvasculature network, but were associated with an activation of vascular endothelial growth factor (VEGF), VEGF receptor 2 (VEGFR2), the mammalian target of rapamycin (mTOR) and Akt. Inhibition of VEGF, mTOR or Akt could suppress ADSCs-stimulated perfusion restoration.

Conclusions In vivo 3D multimodality imaging facilitates tracking the functional survival of transplanted ADSCs in PAD model. ADSCs may amplify the pro-angiogenic signal partly via VEGF/mTOR/Akt pathway and improve hindlimb ischaemia.

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ADIPOSE-DERIVED STROMAL CELLS AMPLIFY THE ANGIOGENIC SIGNAL VIA VEGF/MTOR/AKT PATHWAY IN THE MURINE PERIPHERAL ARTERIAL DISEASE MODEL: AN IN VIVO 3D MULTIMODALITY IMAGING STUDY

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Objectives Adipose-derived stromal cells (ADSCs) transplantation has been demonstrated a promising therapy for peripheral arterial disease (PAD). However, the underlying mechanism of ADSCs' potential efficacy remains uncertain. The current study aimed to investigate the long-term outcome and therapeutic behaviour of engrafted ADSCs in a murine PAD model by multimodality molecular imaging.

Methods ADSCs were isolated from C57BL/6 transgenic mice that constitutively express dual-reporter firefly luciferase and green