Mesenchymal stromal cells form vascular tubes when placed in fibrin sealant and accelerate wound healing in vivo.

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Abstract:

Non-healing, chronic wounds are a growing public health problem and may stem from insufficient angiogenesis in affected sites. Here, we have developed a fibrin formulation that allows adipose-derived mesenchymal stromal cells (ADSCs) to form tubular structures invitro. The tubular structures express markers of endothelium, including CD31 and VE-Cadherin, as well as the pericyte marker NG2. The ability for the MSCs to form tubular structures within the fibrin gels was directly dependent on the stoichiometric ratios of thrombin and fibrinogen and the resulting gel concentration, as well as on the presence of bFGF. Fibrin gel formulations that varied in stiffness were tested. ADSCs that are embedded in a stiff fibrin formulation express VE-cadherin and CD31 as shown by PCR, FACS and immunostaining. Confocal imaging analysis demonstrated that tubular structures formed, containing visible lumens, in the stiff fibrin gels invitro. There was also a difference in the amounts of bFGF secreted by ADSCs grown in the stiffer gels as compared to softer gels. Additionally, hAT-MSCs gave rise to perfusable vessels that were VE-cadherin positive after subcutaneous injection into mice, whereas the softer fibrin formulation containing ADSCs did not. The application of ADSCs delivered in the stiff fibrin gels allowed for the wounds to heal more quickly, as assessed by wound size, amount of granulation tissue and collagen content. Interestingly, following 5 days of healing, the ADSCs remained within the fibrin gel and did not integrate into the granulation tissue of healing wounds invivo. These data show that ADSCs are able to form tubular structures within fibrin gels, and may also contribute to faster wound healing, as

compared with no treatment or to wounds treated with fibrin gels devoid of ADSCs.