Mesenchymal stromal cells mitigate liver damage after extended resection in the pig by modulating thrombospondin-1/TGF-β

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Autoren

Sandra Nickel Sebastian Vlaic Madlen Christ Kristin Schubert Reinhard Henschler Franziska Tautenhahn Caroline Burger Hagen Kühne Silvio Erler Andreas Roth Christiane Wild Janine Brach **Seddik Hammad** Claudia Gittel Manja Baunack Undine Lange Johannes Broschewitz Peggy Stock Isabella Metelmann Michael Bartels Uta-Carolin Pietsch Sebastian Krämer Uwe Eichfeld Martin von Bergen **Steven Dooley** Hans-Michael Tautenhahn Bruno Christ

Abstract

Post-surgery liver failure is a serious complication for patients after extended partial hepatectomies (ePHx). Previously, we demonstrated in the pig model that transplantation of mesenchymal stromal cells (MSC) improved circulatory maintenance and supported multi-organ functions after 70% liver resection. Mechanisms behind the beneficial MSC effects remained unknown. Here we performed 70% liver resection in pigs with and without MSC treatment, and animals were monitored for 24 h post surgery. Gene expression profiles were determined in the lung and liver. Bioinformatics analysis predicted organ-independent MSC targets, importantly a role for thrombospondin-1 linked to transforming growth factor-β (TGF-β) and downstream signaling towards providing epithelial plasticity and epithelial-mesenchymal transition (EMT). This prediction was supported histologically and mechanistically, the latter with primary hepatocyte cell cultures. MSC attenuated the surgery-induced increase of tissue damage, of thrombospondin-1 and TGF-β, as well as of epithelial plasticity in both the liver and lung. This suggests that MSC ameliorated surgery-induced hepatocellular stress and EMT, thus supporting epithelial integrity and facilitating regeneration. MSC-derived soluble factor(s) did not directly interfere with intracellular TGF-β signaling, but inhibited thrombospondin-1 secretion from thrombocytes and non-parenchymal liver cells, therewith obviously reducing the availability of active TGF-β.