Correlation of HGF and SDF-1 with peripheral mobilisation of CD133+/CD45+ bone marrow stem cells (BMSCs) after hepatectomy and chemotactic effects

C. Duhme¹, M. Wildner¹, M. Schmelzle², A. Krieg¹, G. Fürst³, K. Raba⁴, J.C. Fischer⁴, S. Topp¹, N.H. Stoecklein¹, W.T. Knoefel¹, J. Schulte am Esch¹

Abstract

Objectives:

Hematopoietic BMSCs are involved in hepatic regeneration after liver resection. We previously demonstrated peripheral mobilisation of CD133+/CD45+ hematopoietic BMSCs after extended forms of clinical hepatectomy. In this study we correlated peripheral CD133+/CD45+ cell mobilisation with the extent of resected liver volume and its regain, with paracrine factors participating in hepatic regeneration like hepatic growth factor (HGF), CXCL12 (SDF-1) and alpha fetoprotein (AFP). Additionally the potential mobilising capacity of HGF and SDF-1 for these stem cells was analyzed.

Methods:

Peripheral progenitor mobilisation was investigated by FACS analyses in 30 hepatectomy patients. Exact extend of liver volume loss and regain by day 21 after hepatic resection was determined by CT scan volumetry. 20 patients with resection volume of less than 20% (group A; n=20) were compared to 10 patients with a resection extend of 30-67% (group B; n=10). HGF, SDF-1 and AFP levels in patient's serum were determined by ELISA technology. Mobilising capacity of HGF and SDF-1 for CD133+/CD45+ BMSCs was investigated in in-vitro Transwell Chemotaxis Assays (Boyden Chamber).

Results:

In group B we observed increased serum levels of HGF, SDF-1 in the first 6h and of AFP beyond 24h if compared to group A. Beyond an augmented peripheral mobilisation of CD133+/CD45+ cells from day 2 on in the large resection group, levels of early CD133+/CD45+ stem cell mobilisation correlated directly with the level of hepatic volume regain by day 21.

The mobilisation of CD133+/CD45+ cells on day 4 after extended liver resection in group B was directly correlated with the levels of AFP serum levels on day 6 after hepatectomy.

In in-vitro migration assays human BM derived CD133+ cells isolated by MACS showed a specific target-directed migration towards recombinant HGF and SDF-1 gradients in concentration-dependant manner.

The observed mobilising capacity of HGF and SDF-1 for CD133+/CD45+ BMSCs was partly dependent on the specific receptors c-Met and CXCR4.

Conclusions:

These data suggest HGF and SDF-1 to play a role for mobilisation of CD133+ stem cells from BM in the liver regenerative scenario subsequent to hepatic resection. The increase of AFP serum levels supports the activation of stem cells after extended liver resections since AFP is considered to be a marker of "stemness" in hepatic regeneration.

Whether peripheral mobilisation of CD133+ BMSCs that correlates with levels of liver regeneration after hepatectomy results in integration of those cells in intra-hepatic stem cell compartments, as possibly suggested here by AFP expression data, needs to be further explored.