ELSEVIER

Stem Cell Factor Levels Do Increase in Patients Subsequent to Hepatectomy With the Extent of Parenchymal Loss

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BONE MARROW stem cells (BMSCs) have been demonstrated to participate in liver regeneration.[1–3] However, the mechanisms by which BMSCs promote liver regeneration are still controversial. Some authors favor that BMSCs show fusion with local hepatocytes. Other groups have demonstrated that BMSCs transdifferentiate into hepatocytes without evidence of cell fusion.[4,5] There is increasing evidence that stromal-derived factor 1 (SDF-1), hepatocyte growth factor (HGF), and stem cell factor (SCF) are involved in liver regeneration after hepatic injury.[6] SCF and HGF have been shown to participate in the mobilization and migration of BMSCs to the liver following hepatic injury.[6] Increased serum levels of HGF have been observed after right hepatectomy for living-related liver donation in healthy individuals.[7] After liver injury, levels of HGF are associated with homing of $CD34^+$ stem cells by increasing progenitor motility.[6] SCF is a known ligand to its corresponding receptor c-*kit* with the potential to boost liver cell proliferation. After 70% hepatectomy, Ren et al[8] demonstrated an initial decrease in hepatic SCF levels, and in contrast a significant increase in serum SCF levels in a murine model of partial hepatectomy. Blocking of SCF inhibited hepatocyte proliferation after partial hepatectomy and hepatocyte proliferation is restored subsequent to replacement of SCF in genetically SCF-deficient mice after partial hepatectomy.[8] The aim of this study was to investigate patient serum expression of SCF, SDF-1, and HGF in the early course after hepatectomy to gain insight into the role of growth factors in liver regeneration. Furthermore, we evaluated the influence of the extent of liver resection on levels and kinetics of serum growth factors.

PATIENTS AND METHODS

Sixteen consecutive patients with malignant tumor masses scheduled for hepatectomy were enrolled in this study. Following informed consent, serum samples were drawn prior to as well as at the time of completion of the resection (0, 3, 6, 12, 24, and 48 hours after operation). The samples were immediately stored at −20°C. Serum levels of HGF, SDF-1, and SCF were determined utilizing enzyme-linked immunosorbent assays (ELISA, Huamn Quantikine ELISA Kit, R&D Systems, Mineapolis, Minn). According to the extent of hepatectomy and parenchymal loss, patients were divided into three groups: group I patients, a nonanatomic resection with a maximal parenchymal loss of <2 hepatic segments; group II, resection of 3 to 4 segments; and group III, 5 to 6 resected segments (Table 1). Statistical analysis was performed utilizing SPSS 11.0 (SPSS, Germany) to correlate blood levels of HGF, SCF, or SDF-1 with extent of hepatectomy using paired Student *t*-tests. A P value <.05 was considered to indicate statistical significance.

Table 1. Patient Groups and Characteristics

Parenchymal Loss	Group I (<2 Segments)	Group II (3–4 segments)	Group III (5–6 segments)
Patients (*n*)	4	5	7
Gender (W/M)	0/4	3/2	2/5
Age	64.8 ± 7.8	64.2 ± 11.1	69.9 ± 7.3
Duration of operation (min)	216.5 ± 146.5	363.3 ± 188.2	385.6 ± 120.7
Duration of hospital stay (d)	10 ± 3.5	26.8 ± 14.2	22.7 ± 14.0

RESULTS

The mean age of 11 male and 5 female patients was 66.8 ± 8.6 years with no significant difference between all three groups (Table 1). The reasons for hepatectomy were hepatocellular carcinomas (HCC, $n = 5$), hepatic metastases from colorectal carcinomas ($n = 4$), gastrointestinal stromal tumor (GIST, $n = 3$), carcinoma of the esophagogastric junction ($n = 2$), neurendocrine carcinoma ($n = 1$), or primary cholangiocellular carcinoma (CCC; $n = 2$). The mean duration of the operation was 334.5 ± 154.8 minutes, ranging from 55 to 605 minutes. All patients remained for 20.4 ± 13.2 days in hospital. Group I resections were characterized by a shorter duration of operative time and hospital stay.

Mean preoperative HGF serum level in group I was 1010 ± 510.4 pg/mL; in group II 1571 ± 707.1 pg/mL; and in group III, 927.2 ± 313.9 pg/mL (P = NS). HGF demonstrated independence of the extent of resection and paren-

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chymal loss with a peak at 24 hours (Fig 1A). In group I, SDF-1 demonstrated a mean preoperative serum level of 2422.4 ± 513.5 pg/mL; in group II, 2920.3 ± 919.6 pg/mL; and in group III, 2026.4 ± 547 pg/mL (P = NS). In contrast to HGF, the SDF-1 level was marked by a declining trend at 6 hours after resection, reaching preoperative levels at 48 h after hepatectomy without significant differences among the groups (Fig 1B).

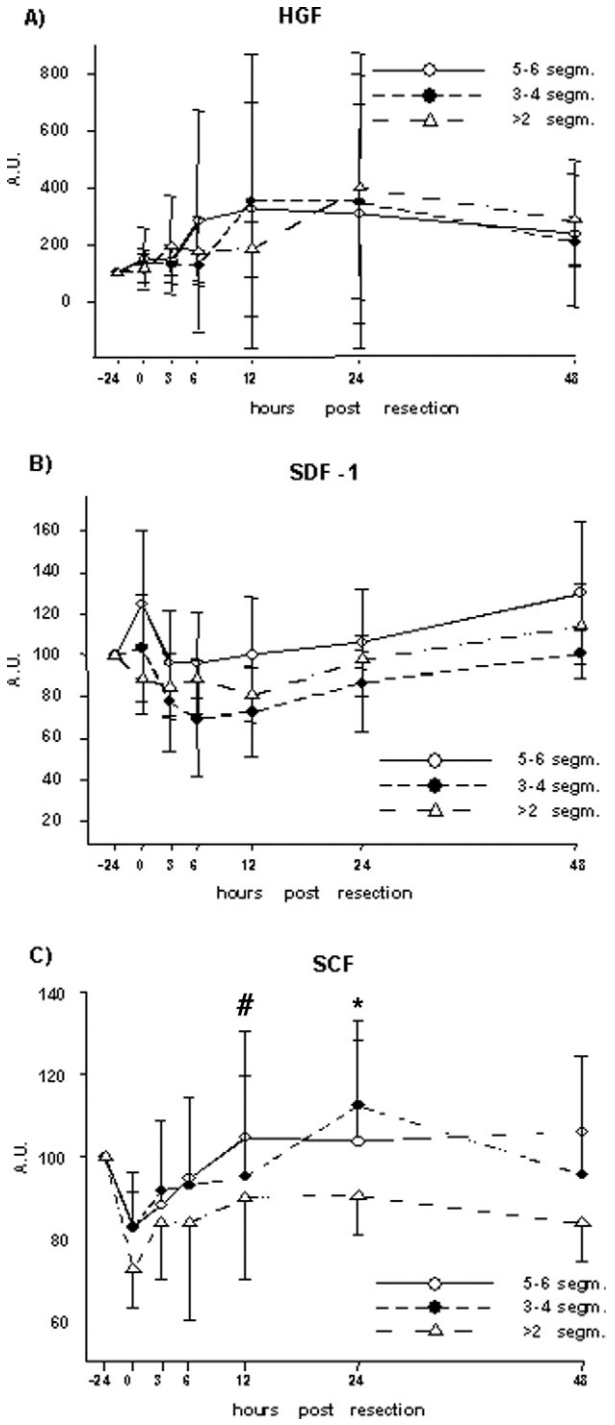

Fig 1. Serum levels of HGF. Data are expressed as arbitrary units (AU) in percent of prehepatectomy levels, which was determined as 100%. (C) A significant increase of mean serum SCF levels could be observed in group II (*) (P = .02) and group III (#) (P = .046).

In group II, the preoperative mean serum SCF level of 847.2 ± 241.4 pg/mL showed a significant (P = .02) increase from 81.3% of the prehepatectomy level to 112.4% by 24 hours (Fig 1B). This course could also be observed in an attenuated form from 82.8% of prehepatectomy levels to 104.6% by 12 hours (P = .046) in group III. In contrast, in patients with a parenchymal loss of <2 segments (group I), SCF serum levels remained significantly below prehepatectomy values (P = .04) during the observation period. However, SCF demonstrated a significant decline toward time of completion of resection, which we designated as time point 0 hours.

DISCUSSION

SCF demonstrated significantly increased serum levels after extended in contrast to smaller degrees of hepatectomy. These data suggested an important role for SCF in the regeneration of remnant liver tissue, especially subsequent to extensive loss of hepatic volume. SCF, therefore, might be crucial for postoperative reconstitution of liver volume and, consequently, liver function.

Irrespective of the extent of liver resection, we observed a rise in HGF serum levels with a maximum at 24 hours postoperatively. Consistent with previous studies, the levels of HGF in our study population showed no relation to the resected liver volume.[9,10] Surprisingly, for SDF-1, which has been demonstrated to be involved in liver regeneration,[6] the trend declined by 6 hours reaching preoperative levels by 48 hours. SDF-1, which has been shown to be increased in plasma in autoimmune and viral diseases, might not play a major role in liver regeneration after hepatectomy.[11]

In summary, we observed an elevation of serum SCF after hepatectomy, which showed a significant correlation with the extent of liver resection.

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