To the Editor:

The most significant factor determining morbidity and mortality following hepatectomy is the ability of the remnant liver to regenerate. In this context, Hayashi et al. [1] recently reported on a previously unknown role of thrombospondin-1 (TSP-1) in liver regeneration (LR). During tissue remodeling, TSP-1 is released into the pericellular space to regulate cell survival and extracellular matrix remodeling [2]. A major TSP-1 function is the conversion of latent TGF-β1 (transforming growth factor-beta 1) to its active form [3]. Based on a mouse model of partial hepatectomy, Hayashi et al. [1] demonstrated that TSP-1 was rapidly released in response to liver resection and triggered TGF-β1 signaling, which promoted the proliferation of hepatocytes as a mechanism to inhibit the proliferative hepatic response [4–5]. Accordingly, knockdown of TSP-1 expression resulted in a significant reduction of TGF-β1 signaling, which was deduced to determine the high-risk group for postoperative liver dysfunction. We are now able to present the first clinical data, which support the relevance of TSP-1 in LR based on a cohort of metastasized colorectal cancer (mCRC) patients undergoing hepatic resection of liver metastases.

A total of 66 mCRC patients without preexisting liver disease were included. Blood was retrieved before surgery (pre OP) and on day 1 (POD1) or days 5–8 (POD5) after liver resection, and plasma was prepared with an optimized method [6–7]. Samples were assayed by ELISA for human TSP-1 (R&D Systems, Minneapolis, MN, USA) and TGF-β1 (eBioscience, San Diego, CA, USA). For statistical analysis, non-parametric tests (Mann–Whitney U test, Wilcoxon test and Spearman correlation) and the Fisher exact test were applied.

A significant increase in TSP-1 (Fig. 1A) and TGF-β1 was observed on POD1 (p = 0.007 and p = 0.006, respectively), which dropped moderately until POD5 (p = 0.016 and p = 0.397). Circulating TSP-1 and TGF-β1 showed a highly significant correlation (k = 0.736, p < 0.001). To further investigate whether a high postoperative release of TSP-1 or TGF-β1 was associated with delayed LR, we assessed the incidence of postoperative liver dysfunction (LD), based on the previously defined “50–50 criteria” [8], with a prothrombin time (PT) <50% and a serum bilirubin (SB) level >50 μmol/L (>2.9 mg/dl). Our classification referred to measurements of any day within the first postoperative week to identify patients with delayed postoperative hepatic recovery. TSP-1 concentrations were significantly elevated (Fig. 1B) in patients with LD (median TSP-1 for LD: 98.8 ng/ml; no LD: 44.6 ng/ml, p = 0.003). Comparably, circulating TGF-β1 tended to be increased in individuals with LD (median TGF-β1 for LD: 2266 pg/ml; no LD: 1726 pg/ml, but the difference was not statistically significant (p = 0.102). Of note, our analyses were restricted to total TGF-β1 in patient blood since activated TGF-β1 was below ELISA detection limit. This may explain the lack of association between TGF-β1 levels and postoperative LD.

To further characterize the potential of TSP-1 to predict postoperative LD, a ROC analysis was performed (Fig. 1C), revealing a significant predictive value of circulating TSP-1 on POD1 (AUC: 0.870; p = 0.003). A cut-off level of 100 ng/ml TSP-1 on POD1 was deduced to determine the high-risk group for postoperative LD with 95% specificity. No statistically significant difference in age and sex distribution or the site of primary tumor, type of hepatic resection and preoperative liver function parameters was observed between the TSP-1high individuals (>100 ng/ml TSP-1) and patients with lower circulating TSP-1 levels on POD1.

When biochemical markers of postoperative liver function were compared between these groups, the TSP-1high patients showed a significant elevation in SB (Fig. 1D) and γ-glutamyl-transferase (p < 0.001; p = 0.011). Prothrombin time (Fig. 1E) was found to be significantly decreased in TSP-1high patients (p < 0.001). A trend towards elevated alanine and aspartate...
Aminotransferase levels was found in TSP-1<sup>high</sup> patients but did not reach statistical significance (p = 0.125 and p = 0.092).

We further assessed the clinical performance of TSP-1<sup>high</sup> individuals in terms of morbidity and hospital stay. Only 4 patients suffered from severe morbidity of grade III, IV or V according to Dindo et al. [9], which limits the conclusions of the statistical analysis. However, TSP-1 levels were significantly elevated in patients with severe complications (p = 0.016) and we found a substantial increase of postoperative severe morbidity from 4% to 33% in the TSP-1<sup>high</sup> subgroup (p = 0.053). With respect to hospital stay, a highly significant correlation of TSP-1 levels on POD1 with days of postoperative hospitalization was observed (k = 0.488; p < 0.001). In accordance, TSP-1<sup>high</sup> patients required a doubled median hospitalization time of 16.5 days as compared to 8 days for the remaining patients to recover from hepatectomy (p = 0.011).

In conclusion, these are the first clinical data confirming that TSP-1 negatively correlates with liver regeneration in humans, which warrants validation in large-scale studies. TSP-1 may prove a helpful clinical marker to predict LD on the first postoperative day and to identify high-risk patients for potential complications and suitable interventions.

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Conflict of interest

The authors who have taken part in this study declare that they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

References


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