Review

Eur Surg (2015) 47:312–318
DOI 10.1007/s10353-015-0352-6

european surgery
ACA Acta Chirurgica Austriaca

The role of platelets and portal venous pressure fluctuations in postoperative liver regeneration

P. Starlinger · A. Assinger · T. Gruenberger · C. Brostjan

Received: 4 September 2015 / Accepted: 10 September 2015 / Published online: 23 September 2015

Summary
Background The most relevant factor predicting morbidity and mortality after liver resection is the ability of the remnant liver to regenerate. In line with extensive experimental research, we were recently able to demonstrate that serotonin and thrombospondin-1, two factors abundantly stored in platelets, are closely associated with liver regeneration of patients after liver resection.

Methods Within this review, we summarized existing evidence regarding the relevance of platelets in liver regeneration.

Results We illustrated a potential interaction of platelet activation and its relation to portal venous pressure during the process of liver regeneration.

Conclusions We are able to explore possible effects of specific granule release as a key regulator to allow for platelet-induced liver regeneration. As a second objective, we discussed postoperative portal venous pressure as a potential mechanism and initiating effect in postoperative platelet activation during liver regeneration which may offer new therapeutic targets to promote postoperative liver regeneration.

P. Starlinger, MD, PhD (✉) · C. Brostjan
Department of Surgery,
Medical University of Vienna, General Hospital,
Waehringer Guertel 18-20,
1090 Vienna, Austria
e-mail: patrick.starlinger@meduniwien.ac.at

A. Assinger
Center of Physiology and Pharmacology,
Medical University of Vienna,
Vienna, Austria

T. Gruenberger
Department of Surgery I, Rudolfstiftung Hospital,
Vienna, Austria

Keywords Liver regeneration · Platelets · Platelet activation · Alpha-granula · Portal venous pressure

Liver regeneration in the clinical setting

With its unique regenerative capacity and the potential of simultaneously maintaining vital organ specific functions, the liver is one of the most intriguing organs of the human body. Liver resection is considered as the only curative treatment option for several neoplastic entities of the liver [1, 2]. Accordingly, partial hepatectomies are performed for eligible patients based on the resection of all radiologically as well as macroscopically detectable tumor while preserving at least 20–25 % of healthy total liver volume [3, 4]. Despite substantial improvements in surgical techniques and perioperative care, postoperative morbidity and mortality remain an important concern after liver resection [5, 6]. The most significant factor determining morbidity and mortality following partial hepatectomy is the ability of the remnant liver to regenerate. To date, no efficient treatment option for patients suffering from postoperative liver failure exists. Accordingly, understanding the process of liver regeneration, to identify potential therapeutic targets, is of utmost importance. Although basic research has put forward several highly promising target molecules, only a few have been validated in the clinical setting [7–10].

A tightly regulated interplay of different stimuli

Although the process of liver regeneration requires a complex interplay of various factors, it follows a controlled pattern and can be divided into a total of three different phases: the initiation/priming phase, followed by the proliferation, and ultimately the termination phase [11, 12]. Diverse priming factors, growth factors,

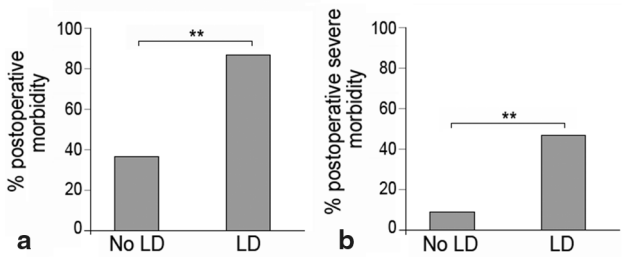

Fig. 1 Postoperative delayed liver regeneration is associated with increased postoperative morbidity. A total of 134 patients were evaluated for postoperative liver dysfunction using the ISGLS criteria to reflect delayed postoperative liver regeneration [65]. These groups were then compared for the incidence of postoperative morbidity **a** and severe morbidity **b** according to Dindo et al. [66] (severe morbidity = grade III–V)

comitogens, and their suppressors are associated with these stages and are overlapping in their mode of action, allowing a continuous progression of liver regeneration. The process of regeneration starts immediately after liver resection and lasts for about 8–15 days and initial changes can be observed already 5 min after surgery [12]. During this tightly regulated process, hepatocytes enter one first round of replication (leading to 60 % of hepatocytes). Another second round of DNA synthesis is entered by a smaller proportion of hepatocytes ultimately establishing the original liver mass. Apoptosis of hepatocytes marks the termination of liver regeneration, presumably to an overshooting of the regenerative response [12, 13]. Hepatocytes are the first cell population to enter the process of regeneration, followed by nonparenchymal cells of the liver and cells of the biliary tract [14]. While liver mass is be restored quickly, lobular reorganization seems to take place for several weeks after surgery [15].

Several different molecules have now been identified to affect liver regeneration and studies showed that blockage of a single molecule generally only delays liver regeneration [16]. Ultimately, liver regeneration is completed even if apparently central mediators are blocked [16]. Indeed, downstream effects are highly redundant between distinct effector molecules, so that blocking of a single component can be compensated by another. However, this delay in regeneration is not without clinical relevance. Indeed, partial postoperative liver dysfunction, caused by delayed liver regeneration, is associated with an increased incidence of postoperative morbidity as we have also observed in our patients (Fig. 1). However, only a few of these patients go into complete liver failure, which is fatal and currently untreatable. Thus, an in-depth understanding of the molecular processes involved in liver regeneration of patients undergoing liver resection is essential for an improvement of current therapeutical interventions. Animal models give important hints for a better understanding of liver pathophysiology but may not completely reflect the human situation. Rodent knock-out models often represent with altered liver histology and long-term adaptation to specific genetic alterations that might substantially affect liver regeneration [16]. With respect to the inevitable differences between rodent models and humans, we placed our focus on prospective translational clinical trials to evaluate the relevance of basic research findings in the human setting.

Platelets and liver regeneration

Several factors have been identified to affect liver regeneration [12, 17]. Among those, hepatocyte growth factor, vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), thrombospondin-1 (TSP-1), serotonin (5-HT) and transforming growth factor β (TGF-β) have been described to regulate the complex process of liver function recovery [17]. More recently, animal studies have shown that platelets are able to modulate liver regeneration [18–21]. Platelet inhibition by the $P2Y_{12}$ inhibitor, clopidogrel, has previously been shown to prevent hepatocyte proliferation after 70 % partial hepatectomy in mice, emphasizing a critical role of platelets in liver regeneration [21]. Accordingly, in platelet-depleted mice liver regeneration is severely suppressed [19–22]. In contrast, thrombopoietin (TPO) induced thrombocytosis was found to promote liver regeneration after partial hepatectomy [18, 20]. Even direct application of platelet-rich plasma via the portal vein seems to accelerate postoperative liver regeneration [23]. All these experimental data document the beneficial effect of platelets in postoperative liver regeneration. Of note, also clinical studies suggest that platelets affect postoperative liver regeneration. In particular, preoperative platelet counts have been identified as outcome predictors after liver resection [24, 25]. Moreover, Alkozai et al. [26] demonstrated that immediate postoperative low platelets, at the onset of liver regeneration, are independently associated with delayed liver function recovery. In line with the experimental data on TPO, we were able to document that patients who fail to increase circulating TPO levels after liver surgery suffer from a significantly increased risk of postoperative liver dysfunction [27]. Accordingly, several lines of evidence clearly suggest a central role of platelets in liver regeneration.

Indeed, platelets store most of the relevant factors for liver regeneration in their granules [28, 29]. Platelets contain three types of granula: α-, dense, and lysosomal granula. Accumulating evidence suggests that dense and α-granules exhibit distinct functions in liver regeneration and will therefore be discussed separately.

Dense granules

Several researchers aimed to identify the mechanism how platelets modify postoperative liver regeneration. Lesurtel et al. reported on the role of platelet-derived 5-HT in a mouse model. The majority of the body's 5-HT pool is generated in the enterochromaffin cells of the gastrointestinal tract from L–tryptophan through by

tryptophan hydroxylase activity. Apart from its relatively short half-life in the extracellular matrix, 5-HT is rapidly taken up and stored by platelets. Lesurtel et al. [21] used knockout mice, lacking the rate-limiting enzyme of 5-HT biosynthesis, to demonstrate that these mice fail to show adequate liver regeneration after partial hepatectomy. As a result, platelet-derived 5-HT has been postulated to be a relevant effector of platelets on hepatocyte growth and liver regeneration. Many experimental models have now verified that liver regeneration is affected by platelet-derived 5-HT and the interaction with its receptors [21, 30–35]. Of note, we were able to provide the first clinical evidence that intra platelet (IP) 5-HT may promote liver regeneration in humans [7]. Accordingly, patients with a reduced preoperative IP 5-HT pool, that may be released upon activation at the site of liver regeneration, were found to have an increased incidence of postoperative complications and more frequently suffered from post-operative liver dysfunction and delayed liver function recovery.

Alpha granules

Besides dense granules, which contain small molecules including 5-HT, α-granules, which contain larger molecules, are of major interest for liver regeneration, as they contain several important regulatory factors such as VEGF or TSP-1. While dense granules are the first to be discharged upon activation, the release of α-granules has been discussed controversially within the past few years. In 2008, Italiano et al. [36] reported that angiogenic factors are stored in different α-granule populations and can be specifically released in response to distinct stimuli. In particular, protease activating receptor 1 (PAR-1) activation caused a release of pro-angiogenic factors (such as VEGF), while PAR-4 stimulation induced anti-angiogenic factor secretion (such as TSP-1). While some studies failed to confirm this particular mechanism [37, 38], other studies support the possibility that α-granules differ in their composition as they observed agonist-specific release of distinct granules [39, 40]. The specific release of α-granule content is of major importance during the process of liver regeneration as α-granules contain regulatory factors with opposing function. In particular, while VEGF is a well-established promotor of liver regeneration [41–44], TSP-1 has recently been shown to represent a negative regulator of liver regeneration after partial hepatectomy [45]. TSP-1 is a homotrimeric glycoprotein with well-known functions in hemostasis and angiogenesis [46–48]. In adult tissue, TSP-1 is primarily released at sites of tissue remodeling where it acts in the pericellular space to regulate cell proliferation and extracellular matrix remodeling [49]. Hayashi et al. [45] reported that TSP-1 suppresses liver regeneration by the activation of latent TGF-β1. Based on a mouse model of partial hepatectomy, they were able to demonstrate that TSP-1 was induced as an immediate early gene in the initial response to liver resection. Moreover, they were recently able to demonstrate that a leucine-serine-lysine-leucine peptide, that inhibits TSP-1 mediated TGF-β activation, promoted liver regeneration in mice after partial hepatectomy, suggesting potential clinical applicability [50]. In line with these results, we were recently able to provide the first clinical evidence for TSP-1 as a relevant suppressor of liver regeneration after partial hepatectomy [10]. Patients with elevated TSP-1 levels, on the first postoperative day (the onset of liver regeneration), were found to suffer from an increased incidence of postoperative liver dysfunction and poor postoperative clinical outcome, as a reflection of reduced postoperative liver regeneration. Importantly, we were able to confirm these observations and the predictive marker potential of TSP-1 in an independent prospective validation cohort [9].

Considering the opposing roles of VEGF and TSP-1 in liver regeneration, a differential release of granule-stored mediators via specific activation of platelets would enable a distinct regulation of liver regeneration by platelets. However, proof that the selective α-granule release does indeed occur in vivo is still missing. Moreover, potential mechanisms on how differential α-granule release could be mediated have to be further defined.

Portal hemodynamics in liver regeneration

Under physiological conditions, the liver is supplied with arterial as well as venous blood. After partial hepatectomy the highly regulated arterial blood flow remains unchanged, while changes in the venous blood flow occur and are highly dependent on the volume of the remaining liver tissue as well as the architecture of the liver as determined by fibrosis/cirrhosis or steatosis [16]. This increase in portal venous pressure is associated with the activation of a variety of signaling pathways within the liver that contribute to liver regeneration [16]. Accordingly, portal blood flow has been proposed to act as one of the major inducers of liver regeneration after hepatectomy. However, excessive increase in portal venous pressure, as observed after major liver resection or in severely diseased livers impairs liver regeneration and can result in postoperative liver dysfunction or even liver failure [51]. In this context, Asencio et al. [52] postulated that the development of postoperative liver failure is not per se determined by the mass of the liver remnant, but is rather determined by the hemodynamic parameters of the hepatic circulation. Summarizing growing experimental as well as clinical evidence they suggest that not only the absolute amount of remaining liver tissue, the so-called “small for size” aspect, but rather the postoperative portal venous flow, a “small for flow” syndrome, seems to be critical in liver regeneration [52]. Indeed, portal hypertension has been found to be associated with several morphological changes within hepatic ultrastructure with a pronounced effect on the sinusoidal endothelial cell lining [53, 54]. These observations are of major clinical importance as there are several options to interact with portal venous pressure, while the therapeu-

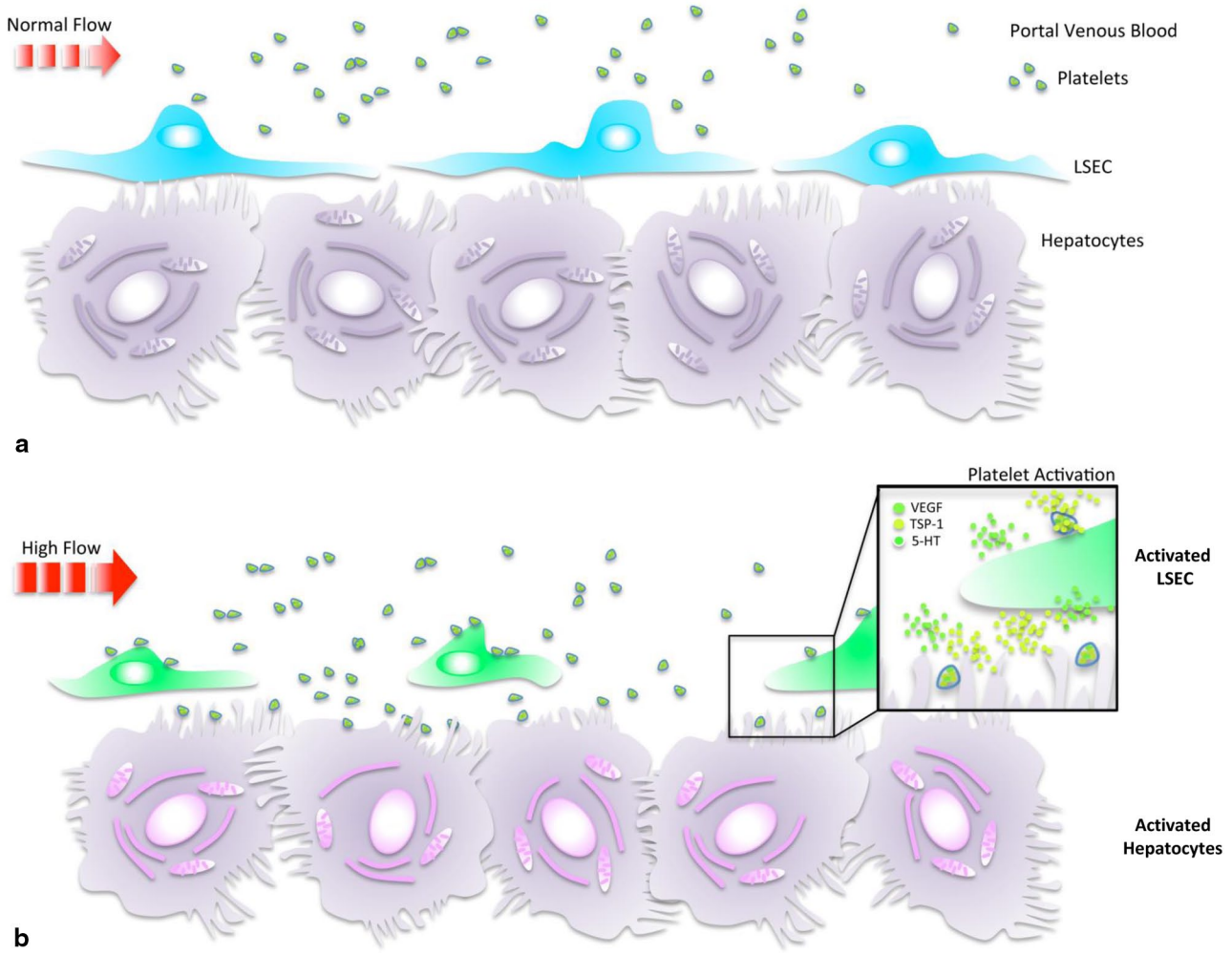

Fig. 2 Possible relation between portal venous pressure and platelet activation. **a** The intrahepatic microcirculation under normal conditions with an intact liver sinusoidal endothelial cells lining and no substantial platelet extravasation into the space of Disse. **b** Potential changes after partial hepatectomy with a disruption of the endothelial cell lining and platelet adhesion to liver cells resulting in the local release of platelet-stored growth factors, which in turn modulates liver regeneration

tic options for postoperative liver failure are currently very limited. In particular, Fahrner et al. [55] were able to document that the application of terlipressin, a vasoconstrictor with primary effects on the splanchnic vasculature and the ability to decrease hepatic blood flow, was able to accelerate postoperative liver regeneration in a mouse model. In particular, one of the most relevant beneficial effects of terlipressin seemed to be a reduction in the disruption of hepatic sinusoids. Furthermore, the beneficial effects seemed to be even more pronounced in steatotic mouse livers. Importantly, these experimental results are currently evaluated in a therapeutic intervention trial in patients undergoing major liver resection (ClinicalTrials.gov Identifier: NCT01921985).

While there is extensive evidence for the role of portal venous pressure in liver regeneration, [56] the simple increase of portal flow itself is not sufficient to induce liver regeneration [57]. In particular, Mortensen et al. [57] demonstrated that an increase in portal flow by an aorto-portal shunt did not induce liver regeneration as seen after partial hepatectomy, suggesting a substantial contribution of other, potentially humoral factors to the regenerative process .

Potential links between platelets and portal venous pressure

As an isolated increase of portal pressure is not sufficient to induce liver regeneration [57], other circulating factors, affected by the changes in hemodynamics after liver resection, seem to be of crucial relevance. In this context, platelets, loaded with regulatory factors, could be central players that sense and respond to fluctuations of portal venous pressure thereby translating changes in blood flow dynamics to molecular signals for liver cells. Indeed, Schlegel et al. [58] recently proposed that circulating growth factors are more important in liver regeneration than the increase in portal venous pressure itself. Of note, the investigators were able to demonstrate that

the simple injection of plasma derived from mice with accelerated liver regeneration was vital and sufficient to promote liver regeneration in mice undergoing singular portal vein embolization without liver resection. As platelets represent one of the major sources for hepatotrophic growth factors and are also sensitive for changes in blood flow dynamics and one of the first cells to arrive within the liver after resection, it is reasonable to speculate that they contribute to accelerating liver regeneration in response to elevated portal pressure. The sudden increase in venous pressure after liver resection exposes the liver to excessive hemodynamic forces, which greatly affects liver sinusoidal endothelial cells (LSEC). Disruption of the fenestrations of the LSEC layer shortly after hepatectomy seems to be of central relevance as it allows rapid accumulation of platelets within the liver sinusoids [20, 59–61]. Moreover, endothelial cell damage, caused by an increase in portal venous pressure, has been shown to promote platelet adhesion and activation [62, 63]. Platelets directly interact with LSEC thereby modifying hepatocyte proliferation [64]. Accordingly, several experimental reports support the hypothesis that postoperative changes in intrahepatic hemodynamics result in postoperative platelet activation thereby promoting liver regeneration, as summarized in Fig. 2.

Summary

Several experimental as well as clinical studies have indisputably demonstrated that platelets play a critical role in postoperative liver regeneration. However, the exact mechanism of specific postoperative platelet activation remains to be elucidated. Postoperative portal venous pressure seems to be a likely candidate to mediate postoperative platelet activation and thereby affect liver regeneration via the release of platelet-stored factors. By exploring the connections between postoperative platelet activation and postoperative portal venous pressure in the clinical setting, we might be able to identify therapeutic targets to improve clinical care of patients after liver resection.

Conflict of interest No conflict of interest.

References

1. Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M. Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. Br J Cancer. 2006;94(7):982–99.
2. Van Cutsem E, Nordlinger B, Adam R, Kohne CH, Pozzo C, Poston G, et al. Towards a pan-European consensus on the treatment of patients with colorectal liver metastases. Eur J Cancer. 2006;42(14):2212–21.
3. Kopetz S, Chang GJ, Overman MJ, Eng C, Sargent DJ, Larson DW, et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol. 2009;27(22):3677–83.
4. Abdalla EK, Adam R, Bilchik AJ, Jaeck D, Vauthey JN, Mahvi D. Improving resectability of hepatic colorectal metastases: expert consensus statement. Ann Surg Oncol. 2006;13(10):1271–80.
5. Wei AC, Tung-Ping Poon R, Fan ST, Wong J. Risk factors for perioperative morbidity and mortality after extended hepatectomy for hepatocellular carcinoma. Br J Surg. 2003;90(1):33–41.
6. Mullen JT, Ribero D, Reddy SK, Donadon M, Zorzi D, Gautam S, et al. Hepatic insufficiency and mortality in 1,059 noncirrhotic patients undergoing major hepatectomy. J Am Coll Surg. 2007;204(5):854–62.
7. Starlinger P, Assinger A, Haegele S, Wanek D, Zikeli S, Schauer D, et al. Evidence for serotonin as a relevant inducer of liver regeneration after liver resection in humans. Hepatology. 2014;60(1):257–66.
8. Starlinger P, Brostjan C, Gruenberger T. Evidence for serotonin as an inducer of liver regeneration in humans—further investigations. Hepatology. 2015;62(3):984. doi:10.1002/hep.27672.
9. Starlinger P, Haegele S, Wanek D, Zikeli S, Schauer D, Alidzanovic L, et al. Plasma thrombospondin 1 as a predictor of postoperative liver dysfunction. Br J Surg. 2015;102(7):826–36.
10. Starlinger P, Schauer D, Alidzanovic L, Zikeli S, Gebhardt K, Luf F, et al. Clinical evidence for thrombospondin-1 as a relevant suppressor of liver regeneration. J Hepatol. 2013;58(5):1053–4.
11. Fausto N, Campbell JS, Riehle KJ. Liver regeneration. Hepatology. 2006;43(2 Suppl 1):S45–53.
12. Michalopoulos GK. Liver regeneration. J Cell Physiol. 2007;213(2):286–300.
13. Sakamoto T, Liu Z, Murase N, Ezure T, Yokomuro S, Poli V, et al. Mitosis and apoptosis in the liver of interleukin-6-deficient mice after partial hepatectomy. Hepatology. 1999;29(2):403–11.
14. Yin C, Evason KJ, Asahina K, Stainier DY. Hepatic stellate cells in liver development, regeneration, and cancer. J Clin Invest. 2013;123(5):1902–10.
15. Wagenaar GT, Chamuleau RA, Pool CW, de Haan JG, Maas MA, Korfage HA, et al. Distribution and activity of glutamine synthase and carbamoylphosphate synthase upon enlargement of the liver lobule by repeated partial hepatectomies. J Hepatol. 1993;17(3):397–407.
16. Michalopoulos GK. Liver regeneration after partial hepatectomy: critical analysis of mechanistic dilemmas. Am J Pathol. 2010;176(1):2–13.
17. Clavien PA. Liver regeneration: a spotlight on the novel role of platelets and serotonin. Swiss Med Wkly. 2008;138(25–26):361–70.
18. Murata S, Matsuo R, Ikeda O, Myronovych A, Watanabe M, Hisakura K, et al. Platelets promote liver regeneration under conditions of Kupffer cell depletion after hepatectomy in mice. World J Surg. 2008;32(6):1088–96.
19. Tomikawa M, Hashizume M, Highashi H, Ohta M, Sugimachi K. The role of the spleen, platelets, and plasma hepatocyte growth factor activity on hepatic regeneration in rats. J Am Coll Surg. 1996;182(1):12–6.
20. Murata S, Ohkohchi N, Matsuo R, Ikeda O, Myronovych A, Hoshi R. Platelets promote liver regeneration in early period after hepatectomy in mice. World J Surg. 2007;31(4):808–16.
21. Lesurtel M, Graf R, Aleil B, Walther DJ, Tian Y, Jochum W, et al. Platelet-derived serotonin mediates liver regeneration. Science. 2006;312(5770):104–7.
22. Myronovych A, Murata S, Chiba M, Matsuo R, Ikeda O, Watanabe M, et al. Role of platelets on liver regeneration after 90 % hepatectomy in mice. J Hepatol. 2008;49(3):363–72.

23. Matsuo R, Nakano Y, Ohkohchi N. Platelet administration via the portal vein promotes liver regeneration in rats after 70 % hepatectomy. Ann Surg. 2011;253(4):759–63.
24. Kaneko K, Shirai Y, Wakai T, Yokoyama N, Akazawa K, Hatakeyama K. Low preoperative platelet counts predict a high mortality after partial hepatectomy in patients with hepatocellular carcinoma. World J Gastroenterol. 2005;11(37):5888–92.
25. Soubrane O, Brouquet A, Zalinski S, Terris B, Brezault C, Mallet V, et al. Predicting high grade lesions of sinusoidal obstruction syndrome related to oxaliplatin-based chemotherapy for colorectal liver metastases: correlation with post-hepatectomy outcome. Ann Surg. 2010;251(3):454–60.
26. Alkozai EM, Nijsten MW, de Jong KP, de Boer MT, Peeters PM, Slooff MJ, et al. Immediate postoperative low platelet count is associated with delayed liver function recovery after partial liver resection. Ann Surg. 2010;251(2):300–6.
27. Haegele S, Offensperger F, Pereyra D, Lahner E, Assinger A, Fleischmann E, et al. Deficiency in thrombopoietin induction after liver surgery is associated with postoperative liver dysfunction. PloS One. 2015;10(1):e0116985.
28. Jain S, Harris J, Ware J. Platelets: linking hemostasis and cancer. Arterioscler Thromb Vasc Biol. 2010;30(12):2362–7.
29. Starlinger P, Alidzanovic L, Schauer D, Brugger P, Sommerfeldt S, Kuehrer I, et al. Platelet-stored angiogenesis factors: clinical monitoring is prone to artifacts. Dis Markers. 2011;31(2):55–65.
30. Balasubramanian S, Paulose CS. Induction of DNA synthesis in primary cultures of rat hepatocytes by serotonin: possible involvement of serotonin S2 receptor. Hepatology. 1998;27(1):62–6.
31. Sulaiman P, Joseph B, Kaimal SB, Paulose CS. Decreased hepatic 5-HT1A receptors during liver regeneration and neoplasia in rats. Neurochem Res. 2008;33(3):444–9.
32. Nagao Y, Akahoshi T, Kamori M, Uehara H, Hashimoto N, Kinjo N, et al. Liver regeneration is promoted by increasing serotonin content in rat liver with secondary biliary cirrhosis. Hepatol Res. 2011;41(8):784–94.
33. Papadimas GK, Tzirogiannis KN, Panoutsopoulos GI, Demonakou MD, Skaltsas SD, Hereti RI, et al. Effect of serotonin receptor 2 blockage on liver regeneration after partial hepatectomy in the rat liver. Liver Int. 2006;26(3):352–61.
34. Liu Y, Zhang ZY. Serotonin receptor agonist quipazine promotes proliferation and apoptosis of human hepatocyte strain of L-02 strain. Hepatobiliary Pancreat Dis Int. 2009;8(3):278–81.
35. Tian Y, Graf R, El-Badry AM, Lesurtel M, Furrer K, Moritz W, et al. Activation of serotonin receptor-2B rescues small-for-size liver graft failure in mice. Hepatology. 2011;53(1):253–62.
36. Italiano JE Jr, Richardson JL, Patel-Hett S, Battinelli E, Zaslavsky A, Short S, et al. Angiogenesis is regulated by a novel mechanism: pro- and antiangiogenic proteins are organized into separate platelet alpha granules and differentially released. Blood. 2008;111(3):1227–33.
37. Kamykowski J, Carlton P, Sehgal S, Storrie B. Quantitative immunofluorescence mapping reveals little functional coclustering of proteins within platelet alpha-granules. Blood. 2011;118(5):1370–3.
38. Jonnalagadda D, Izu LT, Whiteheart SW. Platelet secretion is kinetically heterogeneous in an agonist-responsive manner. Blood. 2012;120(26):5209–16.
39. Battinelli EM, Markens BA, Italiano JE Jr. Release of angiogenesis regulatory proteins from platelet alpha granules: modulation of physiologic and pathologic angiogenesis. Blood. 2011;118(5):1359–69.
40. Chatterjee M, Huang Z, Zhang W, Jiang L, Hultenby K, Zhu L, et al. Distinct platelet packaging, release, and surface expression of proangiogenic and antiangiogenic factors on different platelet stimuli. Blood. 2011;117(14):3907–11.
41. Furrer K, Rickenbacher A, Tian Y, Jochum W, Bittermann AG, Kach A, et al. Serotonin reverts age-related capillarization and failure of regeneration in the liver through a VEGF-dependent pathway. Proc Natl Acad Sci USA. 2011;108(7):2945–50.
42. Bockhorn M, Goralski M, Prokofiev D, Dammann P, Grunewald P, Trippler M, et al. VEGF is important for early liver regeneration after partial hepatectomy. J Surg Res. 2007;138(2):291–9.
43. Oe H, Kaido T, Mori A, Onodera H, Imamura M. Hepatocyte growth factor as well as vascular endothelial growth factor gene induction effectively promotes liver regeneration after hepatectomy in Solt-Farber rats. Hepatogastroenterology. 2005;52(65):1393–7.
44. Taniguchi E, Sakisaka S, Matsuo K, Tanikawa K, Sata M. Expression and role of vascular endothelial growth factor in liver regeneration after partial hepatectomy in rats. J Histochem Cytochem. 2001;49(1):121–30.
45. Hayashi H, Sakai K, Baba H, Sakai T. Thrombospondin-1 is a novel negative regulator of liver regeneration after partial hepatectomy through transforming growth factor-beta1 activation in mice. Hepatology. 2012;55(5):1562–73.
46. Bonnefoy A, Moura R, Hoylaerts MF. The evolving role of thrombospondin-1 in hemostasis and vascular biology. Cell Mol Life Sci. 2008;65(5):713–27.
47. Starlinger P, Moll HP, Assinger A, Nemeth C, Hoetzenecker K, Gruenberger B, et al. Thrombospondin-1: a unique marker to identify in vitro platelet activation when monitoring in vivo processes. J Thromb Haemost. 2010;8(8):1809–19.
48. Kazerounian S, Yee KO, Lawler J Thrombospondins in cancer. Cell Mol Life Sci. 2008;65(5):700–12.
49. Adams JC, Bentley AA, Kvansakul M, Hatherley D, Hohenester E. Extracellular matrix retention of thrombospondin 1 is controlled by its conserved C-terminal region. J Cell Sci. 2008;121(Pt 6):784–95.
50. Kuroki H, Hayashi H, Nakagawa S, Sakamoto K, Higashi T, Nitta H, et al. Effect of LSKL peptide on thrombospondin 1-mediated transforming growth factor beta signal activation and liver regeneration after hepatectomy in an experimental model. Br J Surg. 2015;102(7):813–25.
51. Li J, Liang L, Ma T, Yu X, Chen W, Xu G, et al. Sinusoidal microcirculatory changes after small-for-size liver transplantation in rats. Transpl Int. 2010;23(9):924–33.
52. Asencio JM, Vaquero J, Olmedilla L, Garcia Sabrido JL. "Small-for-flow" syndrome: shifting the "size" paradigm. Med Hypotheses. 2013;80(5):573–7.
53. May D, Djonov V, Zamir G, Bala M, Safadi R, Sklair-Levy M, et al. A transgenic model for conditional induction and rescue of portal hypertension reveals a role of VEGF-mediated regulation of sinusoidal fenestrations. PloS One. 2011;6(7):e21478.
54. Morsiani E, Aleotti A, Ricci D. Haemodynamic and ultrastructural observations on the rat liver after two-thirds partial hepatectomy. J Anat. 1998;192(Pt 4):507–15.
55. Fahrner R, Patsenker E, de Gottardi A, Stickel F, Montani M, Stroka D, et al. Elevated liver regeneration in response to pharmacological reduction of elevated portal venous pressure by terlipressin after partial hepatectomy. Transplantation. 2014;97(9):892–900.
56. Abshagen K, Eipel C, Vollmar B. A critical appraisal of the hemodynamic signal driving liver regeneration. Langenbecks Arch Surg. 2012;397(4):579–90.

57. Mortensen KE, Conley LN, Nygaard I, Sorenesen P, Mortensen E, Bendixen C, et al. Increased sinusoidal flow is not the primary stimulus to liver regeneration. Comp Hepatol. 2010;9:2.
58. Schlegel A, Lesurtel M, Melloul E, Limani P, Tschuor C, Graf R, et al. ALPPS: from human to mice highlighting accelerated and novel mechanisms of liver regeneration. Ann Surg. 2014;260(5):839–46.
59. Wack KE, Ross MA, Zegarra V, Sysko LR, Watkins SC, Stolz DB. Sinusoidal ultrastructure evaluated during the revascularization of regenerating rat liver. Hepatology. 2001;33(2):363–78.
60. Braet F, Wisse E. Structural and functional aspects of liver sinusoidal endothelial cell fenestrae: a review. Comp Hepatol. 2002;1(1):1.
61. Lalor PF, Herbert J, Bicknell R, Adams DH. Hepatic sinusoidal endothelium avidly binds platelets in an integrin-dependent manner, leading to platelet and endothelial activation and leukocyte recruitment. Am J Physiol Gastrointest Liver Physiol. 2013;304(5):G469–78.
62. Gracia-Sancho J, Maeso-Diaz R, Fernandez-Iglesias A, Navarro-Zornoza M, Bosch J. New cellular and molecular targets for the treatment of portal hypertension. Hepatol Int. 2015;9(2):183–91.
63. Croner RS, Hoerer E, Kulu Y, Hackert T, Gebhard MM, Herfarth C, et al. Hepatic platelet and leukocyte adherence during endotoxemia. Crit Care. 2006;10(1):R15.
64. Kawasaki T, Murata S, Takahashi K, Nozaki R, Ohshiro Y, Ikeda N, et al. Activation of human liver sinusoidal endothelial cell by human platelets induces hepatocyte proliferation. J Hepatol. 2010;53(4):648–54.
65. Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery. 2011;149(5):713–24.
66. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205–13.