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REVIEW ARTICLE

Platelet and liver regeneration after liver surgery

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Abstract
The success of liver surgery, including resection and transplantation, is largely dependent on the ability of the liver to regenerate. Despite substantial improvement in surgical techniques and perioperative care, one of the main concerns is post-hepatectomy liver failure and early allograft dysfunction, both of which are associated with impaired liver regeneration. Recent studies have demonstrated the positive role of platelets in promoting liver regeneration and protecting hepatocytes; however, the underlying mechanisms responsible for these effects are not fully understood. In this review, we updated the accumulated evidence of the role of platelets in promoting liver regeneration, with a focus on liver resection and liver transplantation. The goal of these studies was to support the clinical implementation of platelet agents, such as thrombopoietin receptor agonists, to augment liver regeneration after liver surgery. This "platelet therapy" may become a treatment choice for post-hepatectomy liver failure and early allograft dysfunction.

Keywords Platelets · Liver regeneration · Hepatectomy · Growth factors

Introduction

The functional capacity of the liver is to regenerate, which compensates for decreased hepatic volume and impaired function [1–3]. When the underlying liver function is low or the remnant liver volume is small in hepatic resection, or when graft liver volume is small in liver transplant, the liver regeneration will be insufficient to compensate, leading to post-hepatectomy liver failure (PHF) or early allograft dysfunction, being the major cause of morbidity and mortality [4–6]. Although the potential utility of vitamin E, prostaglandin E1, and N-acetylcysteine to boost postoperative liver regeneration has been reported, therapeutic strategies for hepatic insufficiency are not yet established [7–9].

Platelets are the smallest blood constituents and contain three types of granules: alpha granules, dense granules, and lysosomal granules [10, 11]. Each granule contains various growth factors such as hepatocyte growth factor (HGF), insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), and transforming growth factor alpha (TGF-α). The main physiological role for circulating platelets is hemostasis [12]. This process involves rapid adhesion of the platelets to the exposed endothelium of the vessels, followed by platelet aggregation, which culminates in the formation of platelet plugs sealing the injured vessel walls. In this process, platelet activation leads to exocytosis of granular substances, the release of newly synthesized mediators, and the discharge of membrane-bound transcellular signaling molecules.

Recent studies have demonstrated the different roles of platelets in wound healing, immune modulation, and cell proliferation [13–16]. Since the first report, in 1982, of the effect of platelets in inducing hepatocyte proliferation, a lot of evidence about platelets promoting liver regeneration has been presented in experimental and clinical studies [17–19]. Moreover, platelets have been found to have anti-fibrosis and anti-apoptosis effects on the liver [20–22]. However, the underlying mechanisms of these effects remain unclear. This review updates the evidence we have of the role of platelets in promoting liver regeneration, focusing on liver resection and liver transplantation. We also discuss the future perspective of "platelet therapy" in the form of thrombopoietin receptor agonists to augment liver regeneration.

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Liver regeneration and signal transductions

Hepatocytes account for 70% of the cells in the liver, with the remaining cells consisting of biliary epithelial cells, liver sinusoidal endothelial cells (LSEC), Kupffer cells, lymphocytes, and hepatic stellate cells. Liver regeneration occurs through the release and signaling of growth factors and cytokines such as HGF, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), VEGF, TGF-α, and epidermal growth factor (EGF) (Fig. 1) [23]. Each growth factor activates its downstream transcription cascade in hepatocytes, namely, TNF-α/nuclear factor-kappa B (NF-κB) [24, 25], IL-6/signal transducer and activator of transcription 3 (STAT3) [26], phosphatidylinositol-3-kinase (PI3 K)/Akt pathways [27], the HGF/HGF receptor (cMet) pathway [28], and extracellular signal-regulated kinase 1/2 (ERK1/2) [29]. Finally, cyclin-D1 is activated and the migration of cyclin-D1 to the nucleus initiates DNA synthesis of hepatocytes, leading to transition of the quiescent condition to the cell cycle [23, 30, 31]. HGF and EGF are considered direct mitogens, whereas TNF-α, IL-6, VEGF, and TGF-α are non-mitogenic cytokines, which orchestrate and optimize the timing and intensity of the intracellular signals essential for controlling hepatocyte proliferation and paracrine cell interactions [32]. Serotonin signaling is mediated through specific receptors, most of which are coupled with G-proteins [33]. G-proteins link the receptors to a variety of downstream pathways, including PI3 K/Akt pathways, mitogen-activated protein kinase pathways, and the STAT/Janus kinase pathway, and elicit cellular responses [33]. After 7 days, TGF-β produced by LSECs finally aborts the replicative stimuli acting on the hepatocytes [32].

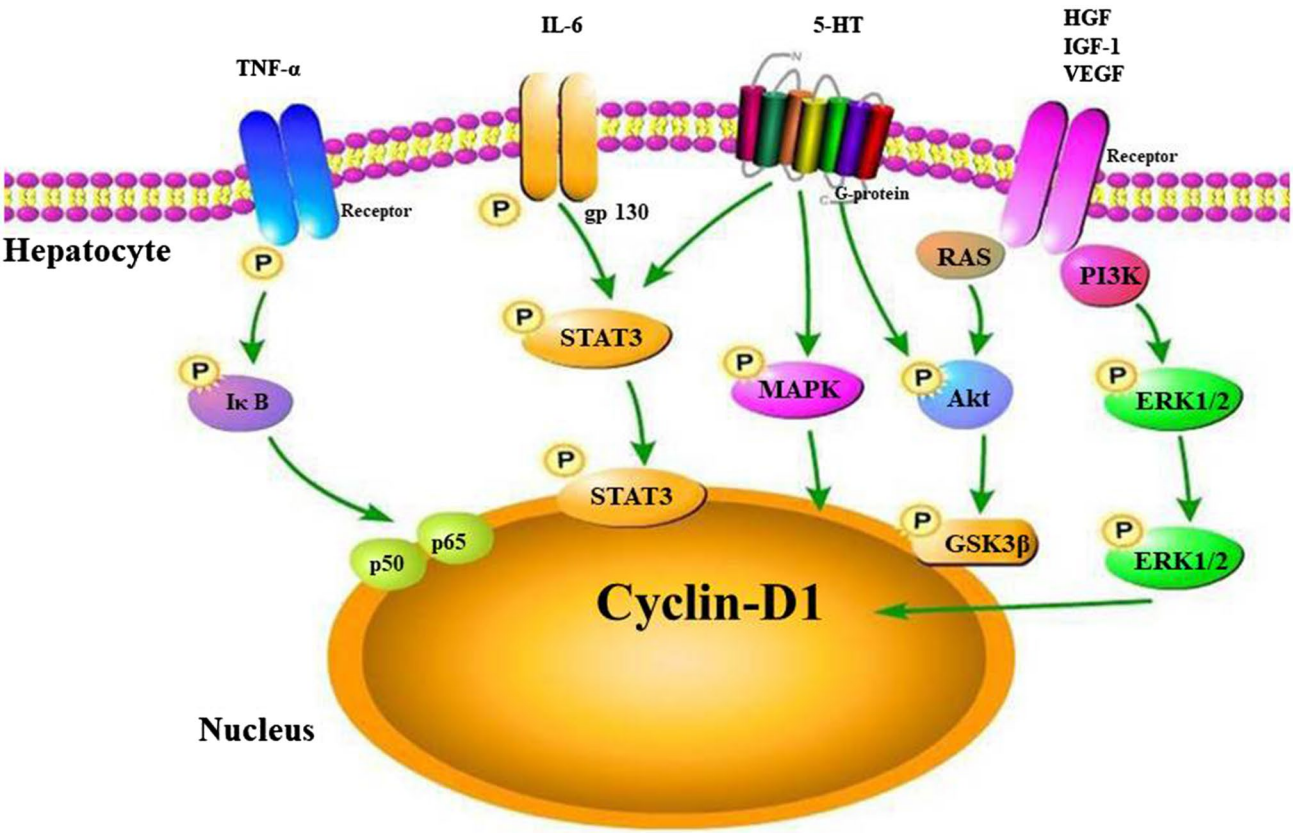

Fig. 1 Major signal transductions in hepatocyte proliferations. Hepatocyte proliferation is carried out by intercellular signaling in parenchymal and nonparenchymal cells though growth factors and cytokines. Each growth factor activates its downstream transcription cascade in hepatocytes, namely, TNF-α/nuclear factor-kappa B, IL-6/signal transducer and activator of transcription 3 (STAT3), phosphatidylinositol-3-kinase (PI3 K)/Akt pathways, HGF/HGF receptor pathway, and extracellular signal-regulated kinase 1/2 (ERK1/2) pathways. Finally, cyclin-D1 is activated, and the migration of cyclin-D1 to the nucleus initiates DNA synthesis of hepatocytes with transition of the quiescent condition to the cell cycle. Serotonin signaling is mediated through specific receptors, coupled with G-proteins. G-proteins link the receptors to PI3 K/Akt pathways, mitogen-activated protein kinase (MAPK) pathways, and the STAT/Janus kinase pathway, and elicit cellular responses

Evidence from basic studies

In the mid-1970s, researchers succeeded in inducing DNA synthesis in primary cultured hepatocytes [34–36]. In 1982, Strain et al. studied "platelet-derived" growth factors and found that hepatocytes initiate DNA synthesis after adding animal serum, but that the removal of blood platelets attenuated the activity of normal serum by over 50% [37]. In 1984, Nakamura et al. purified HGF from rat platelets, which had a strong stimulatory effect on hepatic DNA synthesis [38]. They reported that transient thrombocytopenia after hepatectomy had disrupted hepatic regeneration, being compatible with the early dynamics of HGF. Based on this result, they considered HGF to be the main inducer of liver regeneration after partial hepatectomy [39]. In this era, some other growth factors such as early pregnancy factor [40], platelet-derived growth factor [41], and TGF-β [42] were identified as platelet-derived regulators for liver regeneration. In 2006, Lesurtel et al. indicated platelet-derived serotonin-mediated liver regeneration in mice [43]. A year later, Ohkohchi et al. reported finding that liver regeneration was accelerated under the thrombocytotic condition induced by thrombopoietin administration in rodents [44]. They observed that platelets accumulated immediately post-hepatectomy and some platelets translocated in the space of Disse and had direct contact with hepatocytes. This positive effect on liver regeneration was also reported after platelet transfusion. Matsuo et al. transfused platelet-rich plasma (PRP) into rats after 70% partial hepatectomy and observed that the PRP infusion increased the liver/body weight ratio and the Ki-67 labeling index 24 h after hepatectomy [45].

Apart from the 70% hepatectomy model, Myronovych et al. and Lopez et al. separately evaluated the role of platelets in overall survival after 90% partial hepatectomy, which was a fatal model for mice. They reported a higher survival rate of mice with high platelet counts after hepatectomy, and concluded that platelets enhanced survival through a protective effect on hepatocytes [46, 47]. Hisakura et al. investigated the protective effect of thrombocytosis on the liver after extended hepatectomy in pigs and found that cholestasis, ballooning, and necrosis in the liver were attenuated in the thrombocytotic condition [48].

Mechanisms of platelets as a promoter of liver regeneration

How do platelets accumulate in the liver?

Platelets accumulate in the liver immediately after liver resection and liver transplantation [49] and slow down their flow with rolling and adhering inside the sinusoids [45]. The mechanism for platelet accumulation in the liver is still not clear. Two reports propose the following potential mechanisms. First, Takahashi et al. reported that platelets attached to the Kupffer cells in the liver sinusoidal space after partial hepatectomy, not seen without hepatectomy [50]. This hypothesis of Kupffer cell involvement is supported by some basic studies in the field of liver transplantation. Sindram et al. also reported that the reperfusion of rat livers preserved for 24 h at a cold temperature resulted in the rapid sequestration of platelets in the liver graft and platelet adherence to the sinusoidal lining, which induced apoptosis of the LSECs in concert with activated Kupffer cells [51]. Porte et al. also reported that thrombocytopenia started immediately after reperfusion and that the sequestration of platelets was observed as platelets accumulated in the sinusoids and were phagocytized by Kupffer cells [52]. On the other hand, Krischbaum et al. indicated that platelet accumulation was absent in the presence of the antibody to von Willebrand factor (VWF), suggesting that VWF released from LSECs mediates platelet accumulation at the liver [49]. Starlinger et al. presented the first evidence in humans that the von VWF antigen, released from LSECs, was required for adequate platelet accumulation and subsequent liver regeneration [53]. They speculated that a decrease in the VWF antigen released from LSECs under morbid conditions could diminish liver regeneration by hindering platelet accumulation.

How do platelets induce liver regeneration when they contain both accelerative and suppressive factors for regeneration?

Platelets contain accelerative and suppressive factors for liver regeneration, both of which are released in the remnant liver. This is one of the mysteries in the platelet-mediated regenerative process. Starlinger et al. investigated the pattern of circulating alpha-granule molecules in platelets during liver regeneration in patients who underwent partial hepatectomy. They focused on VEGF as a pro-regenerative factor and thrombospondin-1 (TSP-1) as a negative regenerative factor, both of which exist in alpha-granule molecules. They found patients with worse postoperative outcomes had an unfavorable alpha-granule molecule profile, namely, high TSP-1 and low VEGF, suggesting selective growth factor release from platelets in the liver during the liver regeneration process [54].

How do platelets induce hepatocyte proliferation after hepatectomy?

Previous studies have disclosed four different mechanisms for platelet-mediated liver regeneration (Fig. 2).

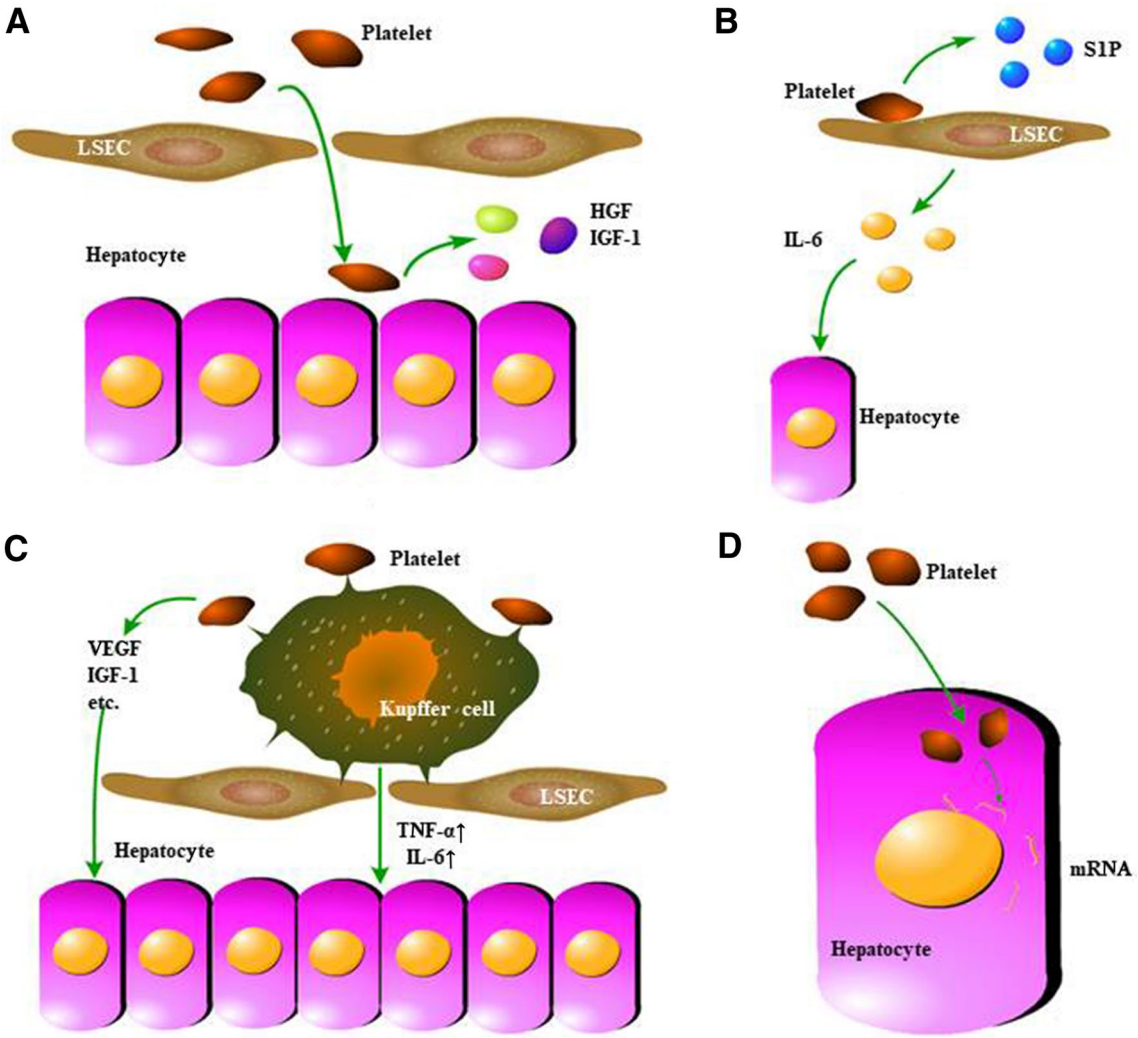

Fig. 2 Four different mechanisms of platelet-mediated liver regeneration. **a** Platelets translocate into the space of Disse and release IGF-1, HGF, and VEGF by direct contact with hepatocytes. **b** The direct contact of platelets with liver sinusoidal endothelial cells (LSECs) induces the release of sphingosine-1-phosphate from the platelets, resulting in the excretion of IL-6 from LSECs. **c** Kupffer cells activated after hepatectomy induce the accumulation and activation of platelets. Growth factors released from platelets and the enhanced release of TNF-α and IL-6 from Kupffer cells promote liver regeneration. **d** Platelet internalization by hepatocytes, followed by the functional transfer of messenger RNA stored in the platelets, stimulates hepatocyte proliferation

The direct effect of platelets

Under electron microscopy, Murata et al. observed that platelets translocated from the sinusoidal space into the space of Disse and had direct contact with hepatocytes [44]. To clarify the meaning of this direct contact, Matsuo et al. used co-culturing chamber systems, in which platelets and hepatocytes were separated by a permeable membrane [55]. It was revealed that direct contact between platelets and hepatocytes triggered the release of soluble mediators such as HGF, IGF-1, and VEGF, from the platelets, which led to hepatocyte proliferation.

The cooperative effect with LSECs

Kawasaki et al. studied the role of LSECs [56]. They identified that platelets induced the release of IL-6 from LSECs, which in turn accelerated DNA synthesis of the hepatocytes. The direct contact between platelets and LSECs was required for IL-6 excretion. They further clarified that sphingosine-1-phosphate, which is abundant in platelets, played an important role in IL-6 secretion.

The collaborative effect with Kupffer cells

Takahashi et al. observed that transfused platelets accumulated in the residual liver in the presence of activated Kupffer cells after 70% hepatectomy [50]. The hepatic expression of TNF-α and IL-6, predominantly produced by Kupffer cells [31, 57], increased in response to a platelet transfusion, indicating that the function of the Kupffer cells was enhanced by platelet transfusion.

RNA transfer to hepatocytes

Krischbaum et al. co-cultured platelets and platelet-like particles (PLPs) with hepatocytes in vitro, and found that platelets and PLP were internalized to the hepatocytes and accumulated at the perinuclear region within 1 h of culture [58]. Then, they tagged messenger RNA of PLPs using green fluorescent protein (GFP). Co-culturing of hepatocytes with PLP resulted in GFP expression throughout the hepatocyte cytoskeleton, implying translation of the PLP-derived messenger RNA by hepatocytes. They speculated that platelets stimulate hepatocyte proliferation via a mechanism dependent on platelet internalization by hepatocytes, followed by the functional transfer of messenger RNA stored in the platelets.

Which growth factor or cytokine promotes liver regeneration?

Lesurtel et al. discovered that platelet-derived serotonin was an inducer of liver regeneration by showing the failure of liver regeneration after partial hepatectomy in tryptophan hydroxylase-1 knockout mice, lacking intra-platelet serotonin. They reported that antagonists of serotonin receptors inhibited liver regeneration in normal mice [43]. On the other hand, Matsuo et al. reported that when mitogenic fractions were obtained from the platelet extracts by gel exclusion chromatography, the fractions were rich in HGF and IGF-1, and lacked serotonin [55]. Matondo et al. also reported that despite the marked reduction of intra-platelet serotonin levels in their transgenic rats lacking the serotonin transporter, efficient liver regeneration occurred [59]. Starlinger et al. found that platelet-derived serotonin was an inducer of liver regeneration in humans [60]; however, there are opposing opinions about serotonin as the most important promotive chemokine for liver regeneration [61]. The process and underlying mechanisms of platelet-mediated liver regeneration is complicated, and many intra-platelet chemokines, including serotonin, HGF, IGF-1, and other growth factors, seem to be involved.

Evidence from clinical studies

Liver resection

The role of platelets in liver resection differs depending on background liver function. Extensive liver fibrosis and portal hypertension result in poor liver function and low perioperative platelet counts. Thus, it is necessary to discuss the role of platelets in hepatocellular carcinoma (HCC), where fibrosis is extensive, and in metastatic liver tumors, where fibrosis is limited, separately.

Liver resection for HCC and perioperative thrombocytopenia

Thrombocytopenia is a well-known indicator of portal hypertension, which is a direct cause of most of the complications of liver cirrhosis along with gastroesophageal varices, ascites, and encephalopathy. The association of thrombocytopenia and post-hepatectomy morbidity has been discussed since the early 2000s. Clinical studies on a limited number of patients found that "preoperative" thrombocytopenia was a risk factor for postoperative morbidity, hospital mortality, and HCC recurrence [62–67]. Some meta-analyses evaluated the "perioperative" platelet counts and postoperative outcomes after liver resection for HCC [68, 69]. Mehrabi et al. performed meta-analyses of 13 studies, with a total of 5260 patients, and reported that patients with a "preoperative" platelet count $< 150 \times 10^3$/ul had higher incidence of PHF and mortality, especially those with a platelet count $< 100 \times 10^3$/ul, with an odds ratio (OR) of 4.65 and 6.35 for PHF and mortality, respectively [69]. According to an analysis by Pang et al., of 33 studies including 5545 patients, patients with "preoperative" thrombocytopenia (platelet count $< 100 \times 10^3$/ul) tended to have poor overall and disease-free survival, and HCC recurrence [70]. Several other parameters using "preoperative" platelet counts, such as the platelet-to-lymphocyte ratio, alkaline phosphatase-to-platelet ratio index, aspartate aminotransferase/platelet count ratio index, and FIB-4 index, were reportedly effective for predicting postoperative complications and survival after hepatectomy [71–75]. This stands to reason considering that "preoperative" thrombocytopenia is caused by splenic sequestration secondary to liver fibrosis and portal hypertension, and portal hypertension is likely to be worse in the smaller remnant liver after hepatectomy. These patients would have a higher risk of PHF because of their poor background liver function, complicating short-term postoperative outcomes. Moreover, because of the higher grade of liver fibrosis, these patients have a higher risk of HCC

recurrence, which would impact mid- and long-term survival [76, 77]. On the other hand, Wang et al., reported that in their cohort of 565 patients, a low immediate "postoperative" platelet count ($< 100 \times 10^3$/ul), rather than a low "preoperative" platelet count, was related to a significantly higher incidence of grade III–IV complications, PHF, and mortality [78]. Although the underlying mechanisms were not clarified, these authors suggested the necessity of increasing platelet counts by platelet transfusion, or the administration of thrombopoietin or serotonin to prevent hepatic insufficiency.

Platelets as a promoter of liver regeneration

In 2010, Alkozai et al. found that a low postoperative platelet count immediately after hepatectomy was an independent predictor of delayed postoperative liver function recovery and associated with an increased risk of postoperative mortality [79]. This is important because they assessed platelet function in patients with normal liver function, which allowed the assessment of "pure" platelet function for liver regeneration. However, this study was limited by the fact that they evaluated liver regeneration from indirect findings by blood tests; namely, the serum bilirubin level and the prothrombin time. Margonis et al. assessed liver regeneration directly by CT volumetric analysis and found that the relative increase in liver volume within 2 months after hepatectomy was considerably lower in the low platelet group [80].

Thrombocytopenia occurs after partial hepatectomy. The platelet count drops immediately after surgery with the nadir occurring on postoperative day (POD) 2–3. It then increases to exceed the pretransplant levels by POD 14 [81]. Takahashi et al. reported that a greater than 40% decrease in the platelet count after partial hepatectomy was an independent risk factor for delayed liver function recovery and postoperative morbidity [82]. They indicated that the platelet count returned to preoperative levels significantly earlier in the adequate liver function recovery group than in the delayed liver function recovery group and speculated that more platelets were consumed to promote liver regeneration in the delayed liver function recovery group, resulting in delayed restoration of the peripheral platelet counts.

Starlinger et al. presented the first evidence in humans that platelet-derived serotonin was a critical inducer of liver regeneration [60]. Although the number of patients enrolled in their study was small, they identified that a low preoperative intra-platelet serotonin level was associated with a higher incidence of postoperative liver dysfunction and morbidity after partial hepatectomy. They also found a higher incidence of postoperative liver dysfunction after liver resection in patients receiving selective serotonin reuptake inhibitors, which are known to reduce intra-platelet serotonin levels. Yoshizumi et al. supported their theory, showing that the intra-platelet serotonin concentrations in living donors with a larger hepatectomized cohort were lower than those in living donors with a smaller hepatectomized cohort [83]. There are some opposing opinions and criticisms against these theories. Alkozai et al. reported that they could not find any changes in serotonin levels in platelets in the early postoperative period between a major hepatectomized group and a control group [61]. In this study, the serotonin concentration was identical in samples taken from the portal vein and hepatic vein before and after hepatectomy. Padickakudy et al. reported that patients with high intra-platelet serotonin levels had a higher incidence of disease recurrence 6 and 12 months postoperatively, but lower incidences of PHF, perioperative morbidity, and severe mortality [84]. They suggested a bivalent role of intra-platelet serotonin for liver resection.

Liver transplantation

Liver transplantation is the treatment of choice for patients with end-stage liver disease and HCC within the Milan criteria. Transient thrombocytopenia, a common phenomenon after liver transplantation, is characterized by a decreasing platelet count following transplantation, with a nadir on POD 3–5 and recovery between PODs 7 and 14 [85, 86]. Thrombocytopenia has been associated with poor graft regeneration and poor postoperative short- and long-term outcomes [87–89].

DDLT

Post-transplant thrombocytopenia has been recognized since the advent of liver transplantation [86], but its meaning was not discussed until the 90s. The first report on the relationship between thrombocytopenia and liver transplantation was by McCaugan et al., in 1992, who found that a 63% decrease in the platelet count after DDLT became a risk for graft survival in their cohort of 541 patients [90]. Several reports have been published since demonstrating perioperative thrombocytopenia as the risk for allograft dysfunction, rejection, fungal infection, biliary stricture, and graft survival [89, 91–95]. Two recent studies focused on platelet counts specifically on POD 5. The authors found separately that low platelet counts on POD 5 were related to short-term and long-term graft and patient survival (cutoff value of 60×10^3/ul and 72.5×10^3/ul, respectively) [87, 88]. Other studies have demonstrated the deleterious impact of perioperative high platelet counts on postoperative outcomes after DDLT, such as deteriorating ischemia–reperfusion injury and early hepatic arterial thrombosis [96, 97]. It was suggested that platelets accumulate in the LSECs after graft ischemia and release inflammatory mediators, resulting in apoptosis and the necrosis of hepatocytes [96]. High pretransplant platelet counts caused a hypercoagulable state, which increased thromboembolic events after DDLT [97].

LDLT

In LDLT, partial liver grafts need rapid regeneration to meet the functional demand of the recipient; otherwise, liver failure will occur [98]. On the other hand, platelets are thought to act in concert with activated Kupffer cells and leukocytes, which may be the core mechanisms for ischemia–reperfusion injury [98]. Two separate papers from Korea reported that platelet transfusion was positively associated with graft regeneration after LDLT [99, 100]. Several other reports have identified that a low postoperative count after liver transplant was correlated with early allograft dysfunction and severe complications [94, 95, 101]. Takahashi et al. reported recently that the incidence of postoperative morbidity in the mid-term post-LDLT, especially related to small-for-size syndrome such as ascites and infection, was significantly higher in the low platelet group than in the high platelet group [102]. The authors assessed the graft regeneration rate using CT volumetry on POD 7 and found that a platelet count $< 60 \times 10^3/\mu l$ on POD 5 was an independent risk factor for low graft regeneration after LDLT.

Future perspectives

Thrombopoietin receptor agonists [103–105], artificial platelets [106–108], and freeze-dried platelets [109–111] are being developed and utilized in the clinical setting and could become a choice for "platelet therapy". Maruyama et al. reported that platelet transfusion once a week for 12 weeks improved serum albumin, cholinesterase, and hyaluronic levels in patients with chronic liver disease and cirrhosis, suggesting the possibility of using platelet transfusion as a treatment choice for liver fibrosis [112]. On the other hand, platelet transfusion has several potential problems such as platelet transfusion refractoriness secondary to anti-platelet antibodies, anaphylaxis reaction, and transfusion-related lung injury, any of which critically harm the patient [113, 114]. Thrombopoietin receptor agonists are currently the main focus for the development of pharmaceutical treatment options for thrombocytopenia [115]. Eltrombopag is an oral thrombopoietin receptor agonist approved for patients with chronic immune thrombocytopenia. Afdhal et al. reported that eltrombopag 75 mg, administered once daily for 14 days, raised platelet counts and significantly reduced the proportion of patients requiring a platelet transfusion related to an invasive procedure [116]. Kurokawa et al. also reported that eltrombopag induced a significant increase in platelet counts with stable liver function in patients with chronic liver disease [117], and noted an anti-tumor effect on HCC [118]. However, this agent has limitations, as serious side effects such as hepatic decompression and thromboembolic events have been reported. Moreover, there is a delay of several days between eltrombopag administration and an increase in the platelet count, compromising eligibility for emergency liver surgery such as DDLT. Recently, other thrombopoietin receptor analogues such as avatrombopag and romiplostim are being explored. Avatrombopag was recently licensed in the US for liver procedures based on a large randomized placebo-controlled trial [119]. It proved effective and safe even at high doses and no data have suggested hepatotoxicity or an increase in thromboembolic or bleeding events, and no rebound thrombocytopenia. Avatrombopag is promising and might be the most suitable agent for "platelet therapy".

Conclusion

This review presents accumulated evidence of the positive impact of platelets on liver regeneration. Animal experiments have disclosed objective evidence of platelets promoting liver regeneration and its potential mechanisms. Subsequent clinical studies show that a high perioperative platelet count is beneficial for short- and long-term outcomes after liver resection and liver transplantation. We anticipate that "platelet therapy" will add to prophylactic or therapeutic strategies for the surgical challenges in liver resection and liver transplantation.

Compliance with ethical standards

Conflict of interest We have no conflicts of interest or funding to disclose.

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