Dualistic role of platelets in living donor liver transplantation: Are they harmful?

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Abstract

Platelets are anucleate fragments mainly involved in hemostasis and thrombosis, and there is emerging evidence that platelets have other nonhemostatic potentials in inflammation, angiogenesis, regeneration and ischemia/reperfusion injury (I/R injury), which are involved in the physiological and pathological processes during living donor liver transplantation (LDLT). LDLT is sometimes associated with impaired regeneration and severe I/R injury, leading to postoperative complications and decreased patient survival. Recent studies have suggested that perioperative thrombocytopenia is associated with poor graft regeneration and postoperative morbidity in the short and long term after LDLT. Although it is not fully understood whether thrombocytopenia is the cause or result, increasing platelet counts are frequently suggested to improve posttransplant outcomes in clinical studies. Based on rodent experiments, previous studies have identified that platelet-derived liver regeneration outweighed the associated risk of I/R injury after partial LT. Clinical strategies to increase perioperative platelet counts, such as thrombopoietin, thrombopoietin receptor agonist and platelet transfusion, may improve graft regeneration and survival after LDLT.

Key Words: Platelet; Liver transplantation; Regeneration; Ischemia/reperfusion injury; Kupffer cell; Oxidative stress

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Core Tip: Perioperative thrombocytopenia is considered to be associated with poor graft regeneration and postoperative morbidity in the short and long term after living donor liver transplantation (LDLT). This review presented recent evidence for the role of platelets in LDLT based on clinical and basic studies. Platelets have both beneficial and detrimental effects on liver grafts, with a generally positive role in liver regeneration and a potentially negative role in ischemia/reperfusion injury. As increasing perioperative platelet counts are suggested to improve graft regeneration and survival, “platelet therapy” may provide prophylactic or therapeutic strategies to enhance the beneficial effects of LDLT.

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INTRODUCTION

Living donor liver transplantation (LDLT) has been developed as an important option for patients with end-stage liver disease, particularly in the virtual absence of deceased donors. During LDLT, changes in the platelet count and platelet function may occur, and these alterations may lead to deterioration of hemostatic function[1]. Transient thrombocytopenia has been considered as a common phenomenon after LDLT[2]. It is characterized by an average reduction of 60% in platelet counts on postoperative day (POD) 3 and recovers to normal levels on POD 10 after LDLT[3]. The reduction in platelet number can be caused by hemodilution, immunologic reactions, decreased platelet production, or sequestration of platelets in the liver graft upon reperfusion[1]. Moreover, platelet function declines during LDLT, as it was demonstrated that a large number of degranulated platelets were detected in the sinusoids of the liver graft after reperfusion[4].

Recent studies have suggested that postoperative thrombocytopenia is not simply an academic observation but is associated with catastrophic events, such as postoperative bleeding, cerebral hemorrhage and infection, which eventually lead to poor graft regeneration, increased postoperative morbidity and decreased patient survival in the short and long term after LDLT[5]. However, the precise mechanism is unknown, and it is unclear whether increasing perioperative platelet counts could improve posttransplant outcomes. The aim of this article is to summarize and discuss the clinical and experimental evidence of the role of platelets in LDLT. We also referred to the potential beneficial and detrimental effects of “platelet therapy” in the form of thrombopoietin (TPO) receptor agonists that augment graft regeneration.

PLATELETS

Platelets are anucleate fragments of cytoplasm derived from megakaryocytes in the bone marrow[6]. The average life span of circulating platelets is approximately 9 d, and they are destroyed by phagocytosis in the spleen and liver[7]. The main function of platelets is to react to hemorrhage by clumping and initiating blood clots[8], which are regulated and kept in balance in hemostasis. However, multiple changes occur in patients with chronic liver disease and post transplantation (LT) conditions, including changes in prohemostatic and antihemostatic pathways, which may consequently lead to either bleeding diatheses or thrombotic disorders[9]. Clinical approaches to increase platelet levels are necessary to compensate for the increased blood loss and requirements for platelets. However, due to the fear of thrombosis and transfusion-related injury[5], the safety and strategies of increasing perioperative platelet counts are still under debate.

Apart from the well-known role of platelets in hemostasis, there is emerging evidence that platelets have other functions in inflammation, angiogenesis, immune response, wound healing, regeneration, and ischemia/reperfusion (I/R) injury[10-12]. Platelets contain three types of secretory granules: alpha granules, dense granules, and lysosomal granules. Each granule contains physiological substances such as platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), serotonin, epidermal growth factor (EGF), and transforming growth factor-β[13-16]. When platelets are activated in specific situations, these biologically active substances are released and may induce nonhemostatic processes. All these physiological or pathological processes are involved in the alterations that occur in patients undergoing LDLT.
**LIVER I/R INJURY**

I/R injury is tissue damage induced when the blood supply returns to tissue after a period of ischemia or hypoxia. It is an important cause of liver damage during hepatectomy and LT, which consequently induces graft dysfunction after surgery[29]. During the ischemic period, the absence of oxygen creates a condition in which inflammation and oxidative damage accumulate in the tissue under oxidative stress, which results in deregulation of the phenotype of all liver cellular components[29].

LSECs, which are essential in controlling vascular homeostasis and toxicant clearance, are especially vulnerable to I/R injury[30]. It was described that I/R injury could induce membrane discontinuation, vacuolization, and cell shape rounding in LSECs[31]. Concomitant with the deregulation of LSECs, the lack of oxygen and energy during the ischemic period produces edema in KCs, and biomolecules, such as damage-associated molecular patterns or pathogen-associated molecular patterns, can be released by neighboring hepatic cells to activate KCs[32]. Activated KCs can initiate the inflammatory response by

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**LIVER REGENERATION**

Liver regeneration is mainly mediated by the proliferation of hepatocytes. In addition, nonparenchymal cells such as Kupffer cells (KCs), liver sinusoidal endothelial cells (LSECs), and hepatic stellate cells contribute to liver growth via their own proliferation and proliferation-stimulatory effects on hepatocytes[22]. Proliferation is generated when normally quiescent parenchymal cells and nonparenchymal cells undergo one or two rounds of replication to restore liver mass by a process of compensatory hyperplasia[23]. Liver regeneration is usually induced under two conditions: trauma or surgical resection-induced tissue loss and toxins or virus-induced hepatocellular death[24]. Hepatic progenitor cells are liver stem cells with differentiation capacities that can be activated during hepatic stress or injury. According to the participation of hepatic progenitor cells, the origin of the cells compensating for liver mass could be different. The regenerative process after tissue loss is usually driven by some of the existing cells in the liver without activating the progenitor cell compartments. In contrast, when acute liver failure is induced by some toxins, such as galactosamine, intrahepatic progenitor cells can replicate and differentiate into different cell types, such as cholangiocytes, hepatocytes and epithelial cells, to compensate for impaired liver functions[25].

Due to the central role of the liver in body homeostasis, intensive research was conducted to identify factors that might contribute to hepatic growth and regeneration. The essential circuitry required for liver regeneration encompasses three types of pathways, namely, cytokine, growth factor, and metabolic pathways that link liver function with cell growth and proliferation. Tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) are important cytokines involved in liver regeneration, as it was reported that both liver mRNA and serum levels of TNF-α and IL-6 stimulated liver regeneration after hepatectomy[26]. The elevations in TNF-α and IL-6 lead to the activation of the transcription factors nuclear factor kappa B (NF-κB) and signal transducer and activator of transcription 3 (STAT3), which consequently increase the expression levels of cyclin D1 and trigger cellular proliferation[27]. In addition, growth factors, such as HGF, EGF, IGF-1 and PDGF, play essential roles in driving cell cycle progression during liver regeneration[28]. With the release of growth factors, numerous intracellular signaling pathways are activated to regulate liver regeneration.

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**LDLT**

LT is one of the most definitive choices for patients with end-stage liver disease and acute liver failure, and LDLT has been recognized as an important option for patients, particularly small pediatric patients and adults who are disadvantaged by the current deceased donor allocation system[17,18]. The feasibility of LDLT is based on the regenerative capacity of the liver, the evolution of surgical techniques in splitting the liver, and the widespread shortage of deceased liver grafts. In the LDLT procedure, a part of the healthy liver is surgically resected from a living person and transplanted to a recipient immediately after the recipient’s diseased liver is removed[18]. After LDLT, the liver graft undergoes two different processes, namely, liver regeneration and I/R injury[18]. In liver regeneration, the remnant partial liver graft has to rapidly grow to meet the demands of the recipient’s reduced metabolic and synthetic capacities[19]. At the same time, reactive oxygen species (ROS) and inflammatory factors are generated, leading to various responses related to I/R injury[20].

LDLT is sometimes associated with impaired regeneration and severe I/R injury in the liver graft, resulting in small-for-size syndrome (SFSS). SFSS is usually induced by size mismatching between donors and recipients and is characterized by synthetic dysfunction, elevated aminotransferases, and prolonged cholestasis[21]. The increased transaminitis and cholestasis may be attenuated with supportive care and time after LDLT, but sometimes irreversible damage, such as hypoglycemia, cholestasis, encephalopathy, renal failure and acidosis, may occur, which could be critical for recipients[21]. Thus, strategies to improve graft conditions are essential in clinical practice.
releasing ROS and proinflammatory cytokines, including TNF-α, interleukin-1, interferon-α and interleukin-12[33].

I/R injury is associated with two forms of cell death, namely, apoptosis and necroptosis. Apoptosis is a form of programmed cell death that is characterized by a series of cellular alterations, such as DNA breaks, plasma membrane blebbing, cell shrinkage and chromatin condensation[34]. Most of the biochemical and morphological changes in cells are mediated by a subset of the caspase family. Necroptosis, which is a programmed form of necrosis, occurs from extracellular signals or intracellular cues and involves the process of cellular swelling, plasma membrane rupture, and the release of proinflammatory molecules[35]. In the process of apoptosis, TNF-α leads to the activation of initiator caspases such as caspase-8 and caspase-10. These caspases cleave and activate downstream effector caspases, including caspase-3 and caspase-7, which promote the release of pro-apoptotic molecules to execute apoptosis[34]. Necroptosis is also typically driven in response to the engagement of TNF-α. Activation of the TNF receptor facilitates receptor-interacting protein kinase (RIPK) 1 to assemble with RIPK3 and concomitantly phosphorylates mixed lineage kinase domain-like (MLKL), which is a crucial downstream effector protein of necroptosis. The phosphorylation of MLKL induces plasma membrane permeabilization and the release of cell damage-associated molecular patterns, which results in cell destruction[36]. Overall, TNF-α serves as a central regulator in the process of apoptosis and necroptosis during hepatic I/R injury.

EVIDENCE FROM CLINICAL STUDIES

Platelets and partial hepatectomy
Hepatectomy is the surgical resection of the liver mainly performed for the treatment of primary or metastatic hepatic malignancies. This technique is conducted based on the regeneration capacity of the liver. Although surgical techniques and perioperative management have been substantially improved in recent years, partial hepatectomy is still associated with a high postoperative mortality rate of 1% to 5%[37]. Perioperative thrombocytopenia has been recognized as a common phenomenon during liver resection. It was reported that platelet counts drop immediately after surgery with a nadir on POD 2–3 and return to normal levels by POD 14[38]. The potential reasons concerning preoperative thrombocytopenia may be decreased platelet production, hemodilution, splenic sequestration, medications, or infections[2], but the precise mechanism remains unclear.

Recently, the association of the perioperative platelet count with posthepatectomy liver failure and mortality has been investigated. By conducting retrospective studies, several researchers stated that a low postoperative platelet count was associated with poor recovery and worse outcomes after liver surgery[37,39]. Takahashi et al[40] reported that a greater than 40% decrease in the platelet count was an independent risk factor for delayed liver function recovery after partial hepatectomy. They observed that the platelet count in the delayed recovery group returned to preoperative levels significantly later than that in the adequate recovery group, which indicated that the extra platelets were consumed to compensate for the delayed recovery, resulting in delayed restoration of the platelet counts in the delayed recovery group[40]. In addition, several other parameters regarding perioperative platelet counts, such as the platelet-to-lymphocyte ratio, alkaline phosphatase-to-platelet ratio index, aspartate aminotransferase to platelet count ratio index, and fibrosis-4 index, were reported to be effective criteria for predicting poor surgical outcomes after partial hepatectomy[5]. Although the underlying mechanisms are not fully understood, these reports indicated that increasing the perioperative platelet count may improve the outcomes after partial hepatectomy.

Platelets and deceased donor liver transplantation
The total number of deceased donor liver transplantation (DDLT) has dramatically increased with innovations in both immune suppression and surgical techniques. Posttransplant thrombocytopenia has been recognized as a common phenomenon since the prevalence of DDLT began to increase[1]. In 1968, it was first reported that an acute drop in platelet count to less than 10 × 10^9/μL was observed on POD 3 in some patients undergoing DDLT[1]. By using 111In-labeled platelets, researchers found that transplant recipients had a delayed recovery of platelet counts after DDLT[41]. Subsequent studies have demonstrated that retransplantation, low preoperative platelet counts, massive intraoperative platelet transfusions, and poor general preoperative conditions were factors associated with posttransplant thrombocytopenia[42]. However, they did not pay attention to the meaning of posttransplant thrombocytopenia in DDLT.

The first report clarifying the relationship between thrombocytopenia and DDLT was presented in 1992, when McCaughan et al[43] conducted an analysis of a large cohort of 541 DDLT patients and identified that the decreased counts after DDLT were an independent risk factor for graft survival. Since then, several consecutive studies have been reported to demonstrate perioperative thrombocytopenia as a negative factor for grafts and patient survival in the short and long term after DDLT[42,44,45]. In 2014, Lesurtel et al[9] suggested the 60-5 criteria in which a platelet count of < 60 × 10^9/μL on POD 5 was an independent risk factor associated with severe postoperative complications, early graft failure, and
patient mortality in the short term after DDLT.

Although clinical studies have identified that postoperative thrombocytopoenia deteriorates graft and patient survival after DDLT\[9\], thrombocytosis has not been proven to be a positive factor for DDLT. Some studies stated that a higher preoperative platelet count was associated with I/R injury and arterial thrombosis in DDLT\[46,47\]. As a result, it is difficult to perform prospective trials by increasing perioperative platelet counts.

**Platelets and LDLT**

LDLT is different from DDLT in that the partial liver graft needs to regenerate under the condition of I/R injury\[18\]. Transient thrombocytopoenia has been regarded as an independent risk factor for LDLT. Several separate authors stated that a low postoperative count had a higher chance of developing early allograft dysfunction and was a strong predictor of postoperative complications in recipients undergoing LDLT\[3,48\]. It was demonstrated that an immediate posttransplant platelet count of $< 68 \times 10^9/\mu L$ or a platelet count of $< 30 \times 10^9/\mu L$ on POD 3 was an independent risk factor for major postoperative complications and was associated with early graft dysfunctions\[3,48\]. Takahashi et al\[19\] reported that a platelet count of $< 60 \times 10^9/\mu L$ on POD 5 was independently associated with the incidence of postoperative morbidity in the mid-term after LDLT and was especially related to small-for-size syndrome such as ascites and infection.

Increasing perioperative platelet counts has been considered to be positively associated with LDLT. Kim et al\[49\] performed a retrospective study in a population of 87 recipients with LDLT and reported that the number of platelets transfused was significantly associated with graft regeneration. Moreover, some consecutive studies were conducted to provide further evidence regarding the benefits and risks of platelet transfusion. They described that platelet transfusion enhanced graft regeneration in recipients after LDLT without increasing morbidity and mortality rates\[50,51\].

Living donor hepatectomy is sometimes associated with postoperative complications, leading to posthepatectomy liver failure. Previous studies reported that the morbidity rates in liver donors ranged from 8.3% to 78.3%\[52,53\]. The remnant liver volume ratio, which was recommended to exceed the minimum of 30% to 35% for donor safety\[54\], is closely related to postoperative morbidity such as liver failure, and platelets have been highlighted as playing an important role in this condition. Yoshino et al\[55\] retrospectively collected data from 254 donors undergoing LDLT and showed that a lower preoperative platelet count was an independent risk factor for postoperative complications, such as bile leakage, subphrenic effusion, infectious ascites, postoperative anemia, and liver failure, after living donor hepatectomy. Emond et al\[56\] demonstrated that even in healthy donors, the fluctuation of platelet count within the normal range was negatively associated with potential portal hypertension and subclinical liver dysfunction, indicating that platelet count might serve as a surrogate marker to predict potential liver failure in healthy donors.

Although postoperative thrombocytopoenia after LDLT was associated with low graft regeneration, it is unclear whether postoperative thrombocytopoenia is the “cause” of low graft regeneration or just a “result” that appears as an unfavorable postoperative condition of the patients. As posttransplant thrombocytopoenia was reported to be associated with LDLT, clinical studies concerning this field are necessary. However, due to the fear of thrombosis and other complications, strategies to increase platelet counts are difficult to implement in clinical practice. Thus, basic studies explaining the precise mechanism of platelets in liver regeneration, I/R injury and LT are warranted.

**EVIDENCE FROM BASIC STUDIES**

**The role of platelets in liver regeneration**

Platelets are considered to stimulate liver regeneration, as they can secrete physiological substances such as IGF-1 and HGF\[57\], which play important roles during liver regeneration\[22\]. In addition, platelet-derived serotonin was demonstrated to be an inducer of liver regeneration, as it was reported that the liver failed to regenerate after partial hepatectomy in mice lacking intraplatelet serotonin\[11\].

Previous studies revealed that platelets accumulated in the liver after hepatectomy with a 2-fold increase compared with prehepatectomy levels\[58\], and electron microscopy showed that platelets translocated from the sinusoidal space into the space of Disse and directly contacted hepatocytes\[59\]. It was shown that marked changes in proliferation-related signaling pathways and mitosis occurred after changing the platelet levels in mice after hepatectomy\[59\]. These results suggest that platelets accumulate in the liver after hepatectomy and may provide signals for rapid hepatocyte proliferation.

It was suggested that direct contact between platelets and hepatocytes contributed to liver regeneration. When recruited in the liver, platelets translocate from the liver sinusoids to the space of Disse and trigger the release of soluble mediators from platelets such as HGF, IGF-1, serotonin and VEGF, which leads to hepatocyte proliferation\[60\]. LSECs and KCs were also reported to interact with platelets to stimulate liver regeneration. It was identified that platelets induced the release of IL-6 from LSECs through direct contact with LSECs\[61\]. On the other hand, platelets could attach to KCs, and the hepatic expression of TNF-α and IL-6, which are predominantly produced by KCs, increased in response.
to the interaction between platelets and KCs[62]. Due to the secretion and stimulation capacities of platelets, researchers found that the TNF-α/NF-κB, IL-6/STAT3, and phosphatidylinositol 3-kinase (PI3K)/Akt pathways are the three major cascades in which platelets exert their effects during the process of liver regeneration[62]. The pathways are associated with the transition of quiescent hepatocytes to the cell cycle and progression beyond the restriction point in G1 phase of the cycle[22], which finally stimulates hepatocyte proliferation.

In addition, platelet-derived messenger RNA was considered to have an impact on liver regeneration. By coculturing platelets with hepatocytes, it was found that platelets accumulated in the perinuclear region of hepatocytes, and messenger RNA from platelets was transferred throughout the hepatocyte cytoskeleton[63]. This result suggested that platelets were internalized into hepatocytes and transferred proliferation-related messenger RNA and stimulated hepatocyte proliferation[63].

Overall, basic studies have identified that platelet-derived liver regeneration occurs through four different mechanisms: (1) direct effects on hepatocytes; (2) cooperative effects with LSECs; (3) collaborative effects with KCs; and (4) the transfer of messenger RNA to hepatocytes (Figure 1).

The role of platelets in I/R injury

There is emerging evidence that platelets have pathological functions in hepatic I/R injury. Cywes et al[12] used a perfusion model to study the contribution of platelets to I/R injury. They isolated the rat liver and perfused the liver ex vivo with Krebs-Henseleit solution containing platelets. They speculated that the degree of platelet adherence to LSECs was related to hepatic injury in perfused rat livers[12], and the number of apoptotic LSECs increased by 6-fold in isolated liver perfused with platelets. These reports indicated that platelets are directly responsible for hepatic injury and contribute to the development of apoptosis in LSECs after reperfusion. Adhesion molecules such as selectins and integrins, which are expressed on platelets and LSECs, are thought to mediate the interaction between platelets and LSECs and result in liver damage[10].

KCs are considered to act in synergy with platelets in the mechanism of I/R injury, as activated KCs release a large amount of both proinflammatory and anti-inflammatory mediators, such as TNF-α, IL-6, interleukin-10 and interleukin-13, which aggravate liver injury[64]. Electron microscopy showed platelets attached to KCs in the early period after hepatic ischemia[65]. It was demonstrated that platelet-related I/R injury after hepatic reperfusion was mainly characterized by the activation of KCs, which potentially release proinflammatory cytokines and generate ROS[66].

ROS, which contribute to inflammatory responses in I/R injury[67], are pivotally related to platelets. First, oxidases or proinflammatory molecules located in platelets are able to produce ROS[68]. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is considered to be the most relevant source of ROS in platelets. Patients with a hereditary deficiency of NADPH oxidase had an almost complete loss of platelet-related ROS production[69]. Xanthine oxidase is another potential source of ROS[70], but its precise relationship with platelet physiology is still unclear. In addition, platelet proinflammatory molecules, such as P-selectin and CD40 ligand, are demonstrated to be associated with intraplatelet ROS generation[71]. Second, ROS formation is functionally associated with platelet activation. It has been reported that catalase, which can reduce the cytosolic concentration of hydrogen peroxide, inhibits platelet aggregation[72]. Moreover, the inhibition of NADPH oxidase by chemical inhibitors, such as diphenyleneiodonium and apocynin, was observed to be related to the suppression of platelet activation[73].

In contrast, platelets have been demonstrated to indirectly inhibit I/R injury. Oberkofler et al[74] reported that the platelet-serotonin-VEGF-interleukin 10/matrix metalloproteinase 8 axis mediated the protective effects of preconditioning on I/R injury in mice. Additionally, it was reported that inductive nitric oxide synthase, an aggravating enzyme for I/R injury[75], was inhibited in macrophages after coculture with platelets under lipopolysaccharide-induced inflammatory conditions[76].

Although the role of platelets in hepatic I/R injury is controversial, it is supposed that platelets could directly aggravate hepatic I/R injury in three ways: (1) adhesion to LSECs; (2) cooperative effects with KCs; and (3) platelet-derived ROS formation (Figure 2).

The role of platelets in partial LT

Platelets are suggested to be positively associated with LDLT in that partial liver grafts require postoperative liver regeneration under I/R injury[77]. This is compatible with previous studies that proved that platelets stimulate liver regeneration after hepatectomy in animal models[59]. Although the positive role of higher perioperative platelet counts has been suggested, the precise mechanisms clarifying how platelets interact with other cells under I/R conditions were reported recently. Liang et al[61] reported that TPO-induced preoperative thrombocytosis contributed to a better outcome in a rat model of partial LT. In this study, platelets stimulated liver regeneration after partial LT via several proliferation-related cytokines and pathways. I/R injury was not aggravated, as shown by unchanged levels of aggravating parameters such as ROS, apoptosis or necrosis. They further used a critical model of 20% partial LT and identified that thrombocytosis could prolong the survival rate in rats. This research explained that thrombocytopenia is not a “result” but a “cause” of postoperative complications.
Platelets translocate into the space of Disse and release insulin-like growth factor-1, hepatocyte growth factor, and vascular endothelial growth factor. The direct contact of platelets with liver sinusoidal endothelial cells (LSECs) results in the excretion of interleukin-6 (IL-6) from LSECs. In addition, the attachment of platelets activates Kupffer cells (KCs) and enhances the release of tumor necrosis factor-alpha and IL-6 from KCs to promote liver regeneration. Moreover, platelets are internalized into hepatocytes and trigger the functional transfer of messenger RNA stored in platelets, which stimulates hepatocyte proliferation.

KCs: Kupffer cells; LSECs: Liver sinusoidal endothelial cells; IGF-1: Insulin-like growth factor-1; HGF: Hepatocyte growth factor; VEGF: Vascular endothelial growth factor; LSECs: Liver sinusoidal endothelial cells; IL-6: Interleukin-6; KCs: Kupffer cells; TNF-α: Tumor necrosis factor-alpha.

Liver sinusoidal endothelial cells (LSECs) express selectins and integrins to stimulate the interaction between platelets and LSECs, and platelets result in the excretion of interleukin-6 (IL-6) from LSECs. The generation of tumor necrosis factor-alpha, IL-6 and reactive oxygen species (ROS) from KCs is elevated after the cooperative effect between platelets and KCs. Furthermore, platelets can produce ROS independently and consequently aggravate ischemia/reperfusion injury.

KCs: Kupffer cells; LSECs: Liver sinusoidal endothelial cells; IL-6: Interleukin-6; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; IGF-1: Insulin-like growth factor-1; HGF: Hepatocyte growth factor; VEGF: Vascular endothelial growth factor; LSECs: Liver sinusoidal endothelial cells; IL-6: Interleukin-6; KCs: Kupffer cells; TNF-α: Tumor necrosis factor-alpha; ROS: Reactive oxygen species; I/R injury: Ischemia/reperfusion injury.

The most ambiguous factor concerning platelets and partial LT is TNF-α, which is a pleiotropic cytokine possessing two opposite effects on hepatocytes, namely, promoting proliferation and inducing apoptosis. TNF-α binds to its receptor and activates signaling pathways such as the NF-κB pathway and cyclin protein families to stimulate cellular proliferation[78]. On the other hand, TNF-α can induce apoptosis through caspase cascades[78]. The Akt signaling pathway, which could be activated by IGF-1 [59], was reported to suppress TNF-α-mediated apoptosis through NF-κB activation[78,79]. It was supposed that the elevated secretion of IGF-1 under thrombocytosis enhanced the phosphorylation of Akt and NF-κB and consequently prevented liver grafts from undergoing apoptosis[61]. However, direct evidence proving the interaction between the Akt pathway and IGF-1 or TNF-α was not provided in previous studies. Partial transplantation models using Akt agonists or inhibitors are necessary to clarify the precise mechanisms (Figure 3).

PERSPECTIVES FOR PLATELET THERAPY

Platelet transfusion and TPO receptor agonists are some alternatives to increase perioperative platelet levels in the clinical setting. Platelet transfusion in LT has been controversial, as prophylactic platelet transfusion was reported to have a prothrombotic effect in patients with liver disease[80]. On the other
Figure 3 Platelets, liver regeneration and ischemia/reperfusion injury after partial liver transplantation. After accumulating in the liver graft, platelets excrete hepatocyte growth factor (HGF) and insulin-like growth factor-1 (IGF-1) and collaborate with KCs to increase the release of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). As a result, the serum levels of HGF, IGF-1, IL-6 and TNF-α increase under thrombocytosis, which consequently induces the phosphorylation of the ERK, Akt, STAT3 and nuclear factor-kappa B signaling pathways to promote liver regeneration (Cyclin D1). On the other hand, platelets do not aggravate in ischemia/reperfusion injury. The phosphorylated Akt pathway inhibits TNF-α-induced apoptosis and necrosis in the liver graft. KCs: Kupffer cells; HGF: Hepatocyte growth factor; IL-6: Interleukin-6; IGF-1: Insulin-like growth factor-1; TNF-α: Tumor necrosis factor-alpha; HGFR: HGF receptor; IGF1R: IGF-1 receptor; gp130: Glycoprotein 130; TNFR1: Tumor necrosis factor receptor; ERK: Extracellular signal-regulated kinase; STAT3: Signal transducer and activator of transcription 3; NF-κB: Nuclear factor-kappa B; Caspase: Cysteinyl aspartate specific proteinase; I/R injury: Ischemia/reperfusion injury.

CONCLUSION

This review presented accumulated evidence for the role of platelets in LT, especially LDLT, based on clinical and basic studies. Platelets have both beneficial and detrimental effects on liver grafts, with generally positive roles in liver regeneration and potentially negative roles in I/R injury. Clinical and basic studies have broadened our horizons about altering platelet counts in patients undergoing LDLT, and “platelet therapy” may provide prophylactic or therapeutic strategies to enhance the beneficial
effects on LDLT.

**FOOTNOTES**

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**REFERENCES**

1. Hutchison DE, Genton E, Porter KA, Daloze PM, Huguet C, Brettschneider L, Groth CG, Starzl TE. Platelet changes following clinical and experimental hepatic homotransplantation. *Arch Surg* 1968; 97: 27-33 [PMID: 4232038 DOI: 10.1001/archsurg.1968.01340010057003]

2. Amygdalos I, Cizginy Z, Bednarsh J, Boecker J, Santana DAM, Meister FA, von der Massen J, Liu WJ, Smad P, Neumann UP, Lurje G. Low Postoperative Platelet Counts Are Associated with Major Morbidity and Inferior Survival in Adult Recipients of Orthotopic Liver Transplantation. *J Gastrointest Surg* 2020; 24: 1996-2007 [PMID: 31388889 DOI: 10.1007/s11605-019-04337-3]

3. Pamecha V, Mahansaria SS, Kumar S, Bharathiy KG, Sasatkar SV, Sinha PK, Kumar N, Kumar V. Association of thrombocytopenia with outcome following adult living donor liver transplantation. *Transpl Int* 2016; 29: 1126-1135 [PMID: 27429066 DOI: 10.1111/tci.12819]

4. Himmelreich G, Hundi K, Isenberg C, Bechstein WO, Neuhaus P, Riess H. Thrombocytopenia and platelet dysfunction in orthotopic liver transplantation. *Semin Thromb Hemost* 1993; 19: 209-212 [PMID: 8362249 DOI: 10.1055/s-2007-994027]

5. Takahashi K, Liang C, Oda T, Ohkohchi N. Platelet and liver regeneration after liver surgery. *Surg Today* 2020; 50: 974-983 [PMID: 31720801 DOI: 10.1007/s00595-019-01890-x]

6. Machlus KR, Thon NJ, Italiano JE Jr. Interpreting the developmental dance of the megakaryocyte: a review of the cellular and molecular processes mediating platelet formation. *Br J Haematol* 2014; 165: 227-236 [PMID: 24499183 DOI: 10.1111/bjh.12758]

7. Holmsen H. Platelet metabolism and activation. *Semin Hematol* 1985; 22: 219-240 [PMID: 2994234]

8. Laki K. Our ancient heritage in blood clotting and some of its consequences. *Ann N Y Acad Sci* 1972; 202: 297-307 [PMID: 4508929 DOI: 10.1111/j.1749-6632.1972.tb16342.x]

9. Li Q, Wang Y, Ma T, Ren F, Mu F, Wu R, Lv Y, Wang B. Preoperative platelet count predicts posttransplant portal vein complications in orthotopic liver transplantation: a propensity score analysis. *BMC Gastroenterol* 2021; 21: 1 [PMID: 33407176 DOI: 10.1186/s12876-020-01553-z]

10. Sindram D, Porte RJ, Hoffman MR, Bentley RC, Clavien PA. Platelets induce sinusoidal endothelial cell apoptosis upon reperfusion of the cold ischemic rat liver. *Gastroenterology* 2000; 118: 183-191 [PMID: 10611167 DOI: 10.1016/s0016-5085(00)70427-6]

11. Lesurtel M, Graf R, Aleil B, Walther DJ, Tian Y, Jochum W, Gachet C, Badir M, Clavien PA. Platelet-derived serotonin mediates liver regeneration. *Science* 2006; 312: 104-107 [PMID: 16601191 DOI: 10.1126/science.1123842]

12. Cywes R, Packham MA, Tietze L, Sanabria JR, Harvey PR, Phillips MJ, Strasberg SM. Role of platelets in hepatic allograft preservation injury in the rat. *Hepatology* 1993; 18: 635-647 [PMID: 8359805]

13. Suzuki H, Yamazaki H, Tanoue K. Immunocytochemical aspects of platelet membrane glycoproteins and adhesive proteins during activation. *Prog Histochem Cytochem* 1996; 30: 1-106 [PMID: 8824844 DOI: 10.1016/s0079-6336(96)80009-9]

14. Blair P, Faumenhardt R. Platelet alpha-granules: basic biology and clinical correlates. *Blood Rev* 2009; 23: 177-189 [PMID: 19450911 DOI: 10.1016/j.brh.2009.04.001]

15. McNicol A, Israels SJ. Platelet dense granules: structure, function and implications for haemostasis. *Thromb Res* 1999; 95: 1-18 [PMID: 10403682 DOI: 10.1016/s0049-3848(99)0015-8]

16. Polasek J. Platelet secretory granules or secretory lysosomes? *Platelets* 2005; 16: 500-501 [PMID: 16287618 DOI: 10.1080/09537100500169926]
March 7, 2022 | Volume 28 | Issue 9 | WJG | https://www.wjgnet.com

17 Meirelles Júnior RF, Salvagallo P, Rezende MB, Evangelista AS, Guardia BD, Matiolo CE, Neves DB, Pandullo FL, Felga GE, Alves JA, Curvelo LA, Diaz LG, Rusti MB, Viveiros Mde M, Almeida MD, Pedroso PT, Rocco RA, Meira Filho SP. Liver transplantation: history, outcomes and perspectives. Einstein (Sao Paulo) 2015; 13: 149-152 [PMID: 25993082 DOI: 10.1590/S1679-4508201500030164]

18 Florman S, Miller CM. Live donor liver transplantation. Liver Transpl 2006; 12: 499-510 [PMID: 16553528 DOI: 10.1002/lt.20754]

19 Takahashi K, Nagai S, Collins KM, Safwan M, Rizzari MD, Schnickel GT, Yoshida A, Abouljoud MS. Factors associated with low graft regeneration in the early phase after living donor liver transplantation. Clin Transplant 2019; 33: e13690 [PMID: 31400136 DOI: 10.1111/ctr.13690]

20 Inci I, Arni S, Iskender I, Citak N, Rodriguez JM, Weisskopf M, Opitz I, Weder W, Frauenfelder T, Kraft MP, Spahn DR. Functional, Metabolic and Morphologic Results of Ex Vivo Donor Lung Perfusion with a Perfluorocarbon-Based Oxygen Carrier Nanoemulsion in a Large Animal Transplantation Model. Cells. 2020; 9 [PMID: 33218154 DOI: 10.3390/cells9121501]

21 Tucker ON, Heaton N. The 'small for size' liver syndrome. Crit Opin Crit Care 2005; 11: 150-155 [PMID: 15758596 DOI: 10.1097/01.ccc.0000157580.11117.45]

22 Malik R, Seldin C, Hodgson H. The role of non-parenchymal cells in liver growth. Semin Cell Dev Biol 2002; 13: 425-431 [PMID: 12468243 DOI: 10.1016/s1084-9521(02)003101]

23 Mao SA, Glorioso JM, Nyberg SL. Liver regeneration. Transl Res 2014; 163: 352-362 [PMID: 24495569 DOI: 10.1016/j.trsl.2014.01.005]

24 Ibrahim S, Weiss TS. Augmenter of liver regeneration: Essential for growth and beyond. Cytokine Growth Factor Rev 2019; 45: 65-80 [PMID: 30579845 DOI: 10.1016/j.cytogfr.2018.12.003]

25 Fausto N. Liver regeneration and repair: hepatocytes, progenitor cells, and stem cells. Hepatology 2004; 39: 1477-1487 [PMID: 15185236 DOI: 10.1002/hep.20214]

26 Isai M, Cui X, Kitamura H, Saito M, Shimazu T. Increased secretion of tumour necrosis factor and interleukin 6 from isolated, perfused liver of rats after partial hepatectomy. Cytokine 2001; 13: 60-64 [PMID: 11145844 DOI: 10.1006/cyto.2000.0797]

27 Cressman DE, Diamond RH, Taub R. Rapid activation of the Stat3 transcription complex in liver regeneration. Hepatology 1995; 21: 1443-1449 [PMID: 7737651]

28 Michalopoulos GK, Khan Z. Liver regeneration, growth factors, and amphiregulin. Gastroenterology 2005; 128: 503-506 [PMID: 15685562 DOI: 10.1053/j.gastro.2004.12.039]

29 Hirao H, Nakamura K, Kupiec-Weglinski JW. Liver ischaemia-reperfusion injury: a new understanding of the role of innate immunity. Nat Rev Gastroenterol Hepatol 2021 [PMID: 34837066 DOI: 10.1038/s41575-021-00549-8]

30 Wisse E. An ultrastructural characterization of the endothelial cell in the rat liver sinusoid under normal and various experimental conditions, as a contribution to the distinction between endothelial and Kupffer cells. J Ultrastruct Res 1972; 38: 528-562 [PMID: 4335119 DOI: 10.1016/0022-5320(72)90089-5]

31 Caldwell-Kenkel JC, Thurman RG, Lemasters JJ. Selective loss of nonparenchymal cell viability after cold ischemic storage of rat livers. Transplantation 1988; 45: 834-837 [PMID: 3283269]

32 Vollmar B, Glasz J, Leiderer R, Post S, Menger MD. Hepatic microcirculatory perfusion failure is a determinant of liver dysfunction in warm ischemia-reperfusion. Am J Pathol 1994; 145: 1421-1431 [PMID: 7992845]

33 Baidya R, Crawford DHG, Gautheron J, Wang H, Bride K. Necroptosis in Hepatotoxicot I-Ischaemia-Reperfusion Injury. Int J Mol Sci 2020; 21 [PMID: 32824744 DOI: 10.3390/ijms21169311]

34 Gan I, Jiang J, Lian D, Huang X, Fuhrmann B, Liu W, Haig A, Jevnikar AM, Zhang ZX. Mitochondrial permeability regulates cardiac endothelial cell necroptosis and cardiac allograft rejection. Am J Transplant 2019; 19: 686-698 [PMID: 30205351 DOI: 10.1111/ajt.15112]

35 Pasparakis M, Vandenabeele P. Necroptosis and its role in inflammation. Nature 2015; 517: 311-320 [PMID: 25592536 DOI: 10.1038/nature14191]

36 Festjens N, Vanden Berghe T, Vandenabeele P. Necrosis, a well-orchestrated form of cell demise: signalling cascades, important mediators and concomitant immune response. Biochim Biophys Acta 2006; 1757: 1371-1387 [PMID: 16950166 DOI: 10.1016/j.bbagcbio.2006.06.014]

37 Alkozai EM, Nijsten MW, de Jong KP, de Boer MT, Peeters PM, Slooff MJ, Porte RJ, Lisman T. Immediate postoperative low platelet count is associated with delayed liver function recovery after partial liver resecion. Ann Surg 2010; 250: 301-306 [PMID: 19779326 DOI: 10.1097/SLA.0b013e3181b76557]

38 Kim SJ, Na GH, Choi HJ, You Y, Kim DG. Effect of donor right hepatectomy on splenic volume and platelet count for living donor liver transplantation. J Gastrointest Surg 2013; 17: 1576-1583 [PMID: 23838878 DOI: 10.1007/s11605-013-2219-0]

39 Marqis GA, Amini N, Buettnner S, Besharati S, Kim Y, Sobhani F, Kamel IR, Pawlik TM. Impact of early postoperative platelet count on volumetric liver gain and perioperative outcomes after major liver resecion. Br J Surg 2016; 103: 899-907 [PMID: 26691709 DOI: 10.1002/bjs.10120]

40 Takahashi K, Kurosawa T, Oshiro Y, Fukunaga K, Sakashita S, Ohkohchi N. Postoperative Decrease in Platelet Counts Is Associated with Delayed Liver Function Recovery and Complications after Partial Hepatectomy. Tohoku J Exp Med 2016; 239: 47-55 [PMID: 27181573 DOI: 10.1620/jem.239.47]

41 Plevak DM, Halm GA, Forstrom LA, Dewanjee MK, O'Connor MK, Moore SB, Krom RA, Rettke SR. Thrombocytopenia after liver transplantation. Transplant Proc 1988; 20: 630-633 [PMID: 3279654]

42 Ben Hamida C, Lauzet JY, Rézaiguia-Delclaux S, Duvooux C, Cherqui D, Duvaldestin P, Stéphan F. Effect of severe thrombocytopenia on patient outcome after liver transplantation. Intensive Care Med 2003; 29: 756-762 [PMID: 12677370 DOI: 10.1007/s00134-003-1727-x]

43 McCaughan GW, Herkes R, Powers B, Rickard K, Gallagher ND, Thompson JF, Shiel AG. Thrombocytopenia post liver transplantation. Correlations with pre-operative platelet count, blood transfusion requirements, allograft function and outcome. J Hepatol 1992; 16: 16-22 [PMID: 1484150 DOI: 10.1016/1688-8824(92)80089-3]
Chatzipetrou MA, Tsaroucha AK, Weppler D, Pappas PA, Kenyon NS, Nery JR, Khan MF, Kato T, Pinna AD, O'Brien C, Viciana A, Ricordi C, Tzakis AG. Thrombocytopenia after liver transplantation. *Transplantation* 1999; 67: 702-706 [PMID: 10065625 DOI: 10.1097/00007890-199903150-00010]

Chang FY, Singh N, Gayowski T, Wagener MM, Mietzner SM, Stout JE, Marino IR. Thrombocytopenia in liver transplant recipients: predictors, impact on fungal infections, and role of endogenous thrombopoietin. *Transplantation* 2006; 70: 70-75 [PMID: 16653383 DOI: 10.1097/00007890-200601010-00014]

Gwiasda J, Schrem H, Klemmnaier J, Kalkenborn A. Identifying independent risk factors for graft loss after primary liver transplantation. *Langenbecks Arch Surg* 2017; 402: 757-766 [PMID: 28573420 DOI: 10.1002/rar.2215-1594.5]

Zahrf Elder F, Roll GR, Derosas C, Rao R, Khan MS, Gunson BK, Hodson J, Mergenthal H, Ferraz-Neto BH, Isaac J, Muiesan P, Mizen DA, Iqbal A, Perera MT. Preoperative Thromboelastography as a Sensitive Tool Predicting Those at Risk of Developing Early Hepatic Artery Thrombosis After Adult Liver Transplantation. *Transplantation* 2016; 100: 2382-2390 [PMID: 27790186 DOI: 10.1097/tp.0000000000001395]

Li L, Wang H, Yang J, Jiang L, Wang W, Yan L, Wen T, Li B, Xu M. Immediate Postoperative Low Platelet Counts After Living Donor Liver Transplantation Predict Early Allograft Dysfunction. *Blood* 2015; 125: 1052-1058 [PMID: 2591125 DOI: 10.1182/blood-2015-01-6464-x]

Han S, Park HW, Song JH, Gwak MS, Lee WJ, Kim G, Lee SK, Ko JS. Association Between Intraoperative Platelet Transfusion and Early Graft Regeneration in Living Donor Liver Transplantation. *Ann Surg* 2016; 264: 1065-1072 [DOI: 26720430 DOI: 10.1097/sla.0000000000001526]

Han S, Ko JS, Gwak MS, Kim GS. Association of Platelet Count and Platelet Transfusion With Serotonin Level During Living Donor Liver Transplantation: Possible Connection to Graft Regeneration. *Transplant Proc* 2018; 50: 1104-1107 [PMID: 29731075 DOI: 10.1016/j.transproceed.2018.02.035]

Lei J, Yan L, Wang W. Donor safety in living donor liver transplantation: a single-center analysis of 300 cases. *PLoS One* 2013; 8: e61769 [PMID: 23637904 DOI: 10.1371/journal.pone.0061769]

Kim SH, Kim YK. Improving outcomes of living-donor right hepatectomy. *Br J Surg* 2013; 100: 528-534 [PMID: 23220858 DOI: 10.1002/bjs.9022]

Miller CM, Durand F, Heimbach JK, Kim-Schluger L, Lee SG, Lerut J, Quintini C, Pomfret EA. The International Liver Transplant Society Guideline on Living Liver Donation. *Transplantation* 2016; 100: 1238-1243 [PMID: 27120453 DOI: 10.1097/TP.0000000000001247]

Yoshino K, Taura K, Ikeno Y, Okuda Y, Nishio T, Yamamoto G, Seo S, Yagi S, Hata K, Kado T, Okajima H, Uemoto S. Low Preoperative Platelet Count Predicts Risk of Subclinical Posthepatectomy Liver Failure in Right Lobe Donors for Liver Transplantation. *Liver Transpl* 2018; 24: 1178-1185 [PMID: 29679437 DOI: 10.1002/lt.25181]

Kim PT, Testa G. Living donor liver transplantation in the USA. *Hepatobiliary Surg Nutr* 2016; 5: 133-140 [PMID: 27115007 DOI: 10.3978/j.issn.2304-3881.2015.06.01]

Rendu F, Brohard-Bohn B. The platelet release reaction: granules' constituents, secretion and functions. *Platelets* 2001; 12: 261-273 [PMID: 11487378 DOI: 10.1080/095371020020061870]

De Ruuder M, Diti A, Stärkel P, Leclercq IA. Critical Role of LSEC in Post-Hepatectomy Liver Regeneration and Failure. *J Mol Biol Sci* 2021; 22: [PMID: 34360818 DOI: 10.3390/jims22150855]

Murata S, Ohkohchi N, Matsuo R, Ikeda O, Myronovich A, Hoshi R. Platelets promote liver regeneration in early period after hepatectomy in mice. *World J Surg* 2007; 31: 808-816 [PMID: 17354025 DOI: 10.1007/s00268-006-0772-3]

Han S. Possible roles of platelets in liver transplantation: regeneration and cancer recurrence. *Anesth Pain Med (Seoul)* 2021; 16: 225-231 [PMID: 34352964 DOI: 10.17085/apm.21063]

Liang C, Takahashi K, Furuya K, Oda T, Ohkohchi N. Platelets Stimulate Liver Regeneration in a Rat Model of Partial Liver Regeneration. *Liver Transpl* 2021; 27: 719-734 [PMID: 33277780 DOI: 10.1002/lt.29562]

Takahashi K, Murata S, Ohkohchi N. Novel therapy for liver regeneration by increasing the number of platelets. *Surg Today* 2013; 43: 1081-1087 [PMID: 23180116 DOI: 10.1007/s00595-012-0418-z]

Kirschbaum M, Karimian G, Adelmeijer J, Giepmans BN, Porte RJ, Lisman T. Horizontal RNA transfer mediates platelet-cell communication. *Hepatology* 2012; 55: 1316-1323 [PMID: 22770576 DOI: 10.1002/hep.24830]

Rah DK, Min HJ, Kim YK, Cheon YW. Effect of Platelet-Rich Plasma on Ischemia-Reperfusion Injury in a Skin Flap Model. *Int J Mol Sci* 2017; 18: 829-839 [PMID: 28824320 DOI: 10.3390/ijms20151125]

Kalogeris T, Baines CP, Krenz M, Korthuis RJ. Characteristics of platelet release. *Comm Physiol* 2016; 7: 113-170 [PMID: 28135002 DOI: 10.1002/cphy.c160006]

Ide T, Tsutsui H, Kinugawa S, Utsuni H, Kang D, Hattori N, Uchiha K, Arimura K, Egashira K, Takeshita A. Mitochondrial electron transport complex I is a potential source of oxygen free radicals in the failing myocardium. *Circ Res* 1999; 85: 357-363 [PMID: 10455064 DOI: 10.1161/01.res.85.4.357]

Pignatelli P, Pulcini FM, Lenti L, Gazzaniga PP, Violif F. Hydrogen peroxide is involved in collagen-induced platelet activation. *Blood* 1998; 91: 484-490 [PMID: 9427701]

Violif F, Pignatelli P. Platelet oxidative stress and thrombosis. *Thromb Res* 2012; 129: 378-381 [PMID: 22209450 DOI: 10.1016/j.thromres.2011.12.002]

Jin RC, Mahoney CE, Coleman Anderson L, Ottaviano F, Croce K, Leopold JA, Zhang YY, Tang SS, Handy DE, Loscalzo J. Glutathione peroxidase-3 deficiency promotes platelet-dependent thrombosis in vivo. *Circulation* 2011; 123: 1963-1973 [PMID: 21518981 DOI: 10.1161/CIRCULATIONAHA.11.000344]

Ghasemzadeh M, Hosseini E. Platelet granule release is associated with reactive oxygen species generation during platelet storage: A direct link between platelet pro-inflammatory and oxidation states. *Thromb Res* 2017; 156: 101-104 [PMID: 28623810 DOI: 10.1016/j.thromres.2017.06.016]
Del Principe D, Menichelli A, De Matteis W, Di Giulio S, Giordani M, Savini I, Agro AF. Hydrogen peroxide is an intermediate in the platelet activation cascade triggered by collagen, but not by thrombin. *Thromb Res* 1991; 62: 365-375 [PMID: 1896957 DOI: 10.1016/0049-3848(91)90010-i]

Pignatelli P, Carnevale R, Di Santo S, Bartimoccia S, Sanguigni V, Lenti L, Finocchi A, Mendoliechio L, Soresina AR, Pleban A, Violi F. Inherited human gp91phox deficiency is associated with impaired isoprostane formation and platelet dysfunction. *Arterioscler Thromb Vasc Biol* 2011; 31: 423-434 [PMID: 21071703 DOI: 10.1161/ATVBAHA.110.217885]

Oberkofler CE, Limani P, Jang JH, Rickenbacher A, Lehmann K, Raptis DA, Ungethuem U, Tian Y, Grabliauskaite K, Humar R, Graf R, Humar B, Clavien PA. Systemic protection through remote ischemic preconditioning is spread by platelet-dependent signaling in mice. *Hepatology* 2014; 60: 1409-1417 [PMID: 24700614 DOI: 10.1002/hep.27089]

Iwasaki J, Aify M, Blizelevs C, Klinge U, Weiskirchen R, Steitz J, Vogt M, Yagi S, Nagai K, Uemoto S, Tolba RH. The Impact of a Nitric Oxide Synthase Inhibitor (L-NAME) on Ischemia-Reperfusion Injury of Cholestatic Livers by Pringle Maneuver and Liver Resection after Bile Duct Ligation in Rats. *Int J Mol Sci* 2019; 20: [PMID: 31035686 DOI: 10.3390/jms20092114]

Renn TY, Kao YH, Wang CC, Burnouf T. Anti-inflammatory effects of platelet biomaterials in a macrophage cellular model. *Vox Sang* 2015; 109: 138-147 [PMID: 25899557 DOI: 10.1111/vox.12264]

Taki-Eldin A, Zhou L, Xie HY, Zheng SS. Liver regeneration after liver transplantation. *Eur Surg Res* 2012; 48: 139-153 [PMID: 22527292 DOI: 10.1159/000351564]

Jing ZT, Liu W, Xue CR, Wu SX, Chen WN, Lin XJ, Lin X. AKT activator SC79 protects hepatocytes from TNF-alpha-mediated apoptosis and alleviates d-Gal/LPS-induced liver injury. *Am J Physiol Gastrointest Liver Physiol* 2019; 316: G387-G396 [PMID: 30629471 DOI: 10.1152/ajpgi.00350.2018]

Valizadeh A, Majdminia M, Samadi-Kafli H, Yousefi M, Yousefi B. The roles of signaling pathways in liver repair and regeneration. *J Cell Physiol* 2019 [PMID: 30770551 DOI: 10.1002/jcp.28336]

von Mejlenfeldt FA, van den Boom BP, Adelmeijer J, Veldt BJ. Management of Thrombocytopenia in Chronic Liver Disease: Focus on platelet transfusion and platelet transfusion have a prothrombotic effect in patients with liver disease. *J Thromb Haemost* 2021; 19: 664-676 [PMID: 32219597 DOI: 10.1111/htj.15185]

Howard JE, Perkins HA. The natural history of alloimmunization to platelets. *Transfusion* 1978; 18: 496-503 [PMID: 684804 DOI: 10.1046/j.1537-2995.1978.18478251250.x]

Pereboom IT, de Boer MT, Haagsma EB, Hendriks HG, Lisman T, Porte RJ. Platelet transfusion during liver transplantation is associated with increased postoperative mortality due to acute lung injury. *Anesth Analg* 2009; 108: 1083-1091 [PMID: 19299765 DOI: 10.1213/ane.0b013e3181948a59]

Furuchi Y, Takeuchi H, Yoshimasu Y, Kasai Y, Abe M, Itoi T. Thrombopoietin receptor agonist is more effective than platelet transfusion for chronic liver disease with thrombocytopenia, shown by propensity score matching. *Hepatol Res* 2020; 50: 1062-1070 [PMID: 32510789 DOI: 10.1111/hepr.13530]

Maan R, de Knecht RJ, Veldt BJ. Management of Thrombocytopenia in Chronic Liver Disease: Focus on Pharmacotherapeutic Strategies. *Drugs* 2015; 75: 1981-1992 [PMID: 26501978 DOI: 10.1007/s40265-015-0480-0]

Cheloff AZ, Al-Samkari H. Avatrombopag for the treatment of immune thrombocytopenia and thrombocytopenia of chronic liver disease. *J Blood Med* 2019; 10: 313-321 [PMID: 31565009 DOI: 10.2147/JBM.S191790]

Ramadori P, Klag T, Malek NP, Heikenwalder M. Platelets in chronic liver disease, from bench to bedside. *JHEP Rep* 2019; 1: 448-459 [PMID: 32039397 DOI: 10.1016/j.jhepr.2019.10.001]

Leung T, Lokan J, Turner P, Smith C. Reversible bone marrow reticulin fibrosis as a side effect of romiplostim therapy for the treatment of chronic refractory immune thrombocytopenia. *Pathology* 2011; 43: 520-522 [PMID: 21753725 DOI: 10.1097/PAT.0b013e328348fece]

Terrault N, Chen YC, Izumi N, Kayali Z, Mitruit P, Tak WY, Allen LF, Hassanein T. Avatrombopag Before Procedures Reduces Need for Platelet Transfusion in Patients With Chronic Liver Disease and Thrombocytopenia. *Gastroenterology* 2018; 155: 705-718 [PMID: 29778606 DOI: 10.1053/j.gastro.2018.05.025]

Sakamaki A, Watanabe T, Abe S, Kamimura K, Tsuchiya A, Takamura M, Kawai H, Yamagiwa S, Terai S. Lusutrombopag increases hematocrit in a compensated liver cirrhosis patient. *Clin J Gastroenterol* 2017; 10: 261-264 [PMID: 28324272 DOI: 10.1007/s12328-017-0735-2]
