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MINIREVIEWS

Platelet therapy: A novel strategy for liver regeneration, anti-fibrosis, and anti-apoptosis

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Abstract

Platelets contain bio-physiological substances, including insulin-like growth factor-1, vascular endothelial growth factor, platelet-derived growth factor, hepatocyte growth factor, serotonin, transforming growth factor-β, adenosine diphosphate, adenosine tri-phosphate, and epidermal growth factor. Platelets have conventionally been considered to exacerbate the inflammatory response and liver injury. Recently, platelets were discovered to have a positive impact on the liver. In this review, we present experimental and clinical evidence indicating that platelets accelerate liver regeneration and have anti-fibrosis and anti-apoptosis activity, and we detail the mechanisms of action. Platelets accelerate liver regeneration by three different mechanisms: (1) a direct effect on hepatocytes, (2) a cooperative effect with liver sinusoidal endothelial cells, and (3) a collaborative effect with Kupffer cells. Platelets exert anti-fibrotic activity by deactivating hepatic stellate cells *via* the adenosine-cyclic adenosine 5′-monophosphate signaling pathway. Platelets prevent hepatocyte apoptosis by activating the Akt pathway and up-regulating Bcl-xL, which suppresses caspase-3 activation. Platelet therapy with thrombopoietin, thrombopoietin receptor agonists, and platelet transfusion has the advantages of convenience and cost-efficiency over other treatments. We propose that in the future, platelet therapy will play a promising role in the treatment of the various liver disorders that currently challenge the surgical field, such as liver failure after a massive hepatectomy, hepatectomy of a cirrhotic liver, and small grafts in liver transplantation.

Key words: Platelet therapy; Liver regeneration; Liver fibrosis; Hepatocyte apoptosis; Growth factor

Core tip: Platelets have conventionally been considered to exacerbate the inflammatory response and liver injury. Recently, some studies have demonstrated a role for platelets in promoting liver regeneration, improving liver fibrosis, and attenuating hepatitis. In this review, the experimental and clinical evidence that platelets accelerate liver regeneration and attenuate fibrosis and apoptosis are described, as are the mechanisms of action. Platelet therapies, such as thrombopoietin, thrombopoietin receptor agonists, and platelet transfusion, will play a promising role in the treatment of the various liver disorders that currently challenge the surgical field.

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INTRODUCTION

Platelets contain bio-physiological substances, such as

growth factors and cytokines[1,2]. Platelets are activated by various types of stimulation, and they release these physiologically active substances in a context-dependent manner[3]. The predominant function of platelets is in hemostasis and thrombosis, where they play a complex role with other cellular participants[2,4]. Recently, platelets have been determined to have various roles in the body in addition to these primary functions[5-7]. Platelet-rich plasma is a source of platelet growth factors and cytokines[8] and has increased in popularity since the late 1990s[9]. Currently, platelet-rich plasma is widely accepted as the best treatment to promote would healing and tissue regeneration in many fields, including orthopedics[10,11], plastic surgery[12,13], and maxillofacial surgery[14].

Thrombocytopenia is frequently observed in patients with chronic liver disease[15]. This condition results from hypersplenism secondary to portal hypertension and decreased thrombopoietin production by hepatocytes[16]. Liver regeneration after hepatectomy in this patient population is severely impaired, and preventing postoperative liver failure has long been considered a critical issue in the surgical fields[17,18]. Recently, several attempts have been made to overcome this problem, including gene therapy[19], bone marrow cell infusion therapy[20], macrophage therapy[21], and platelet therapy. In platelet therapy, thrombopoietin treatment and platelet transfusions have positive effects on the liver and are innovative treatments for various pathological liver conditions[22,23]. Eltrombopag, an oral thrombopoietin agonist, has recently been developed[24] and is beginning to be utilized to treat various health conditions, including liver disease[25,26].

In this review, we present the experimental and clinical evidence that platelets accelerate liver regeneration and inhibit fibrosis and apoptosis; we also present the mechanisms of action for these functions. We propose that platelet therapy, including thrombopoietin and eltrombopag treatment and platelet transfusion, has a promising role in the treatment of the various liver problems, such as liver failure after a massive hepatectomy[27], hepatectomy of a cirrhotic liver[18], and small grafts in liver transplantation[28], that currently challenge the surgical field.

PLATELETS AND LIVER REGENERATION

Liver regeneration after a hepatectomy is accomplished *via* the proliferation of hepatocytes, biliary epithelial cells, liver sinusoidal endothelial cells, Kupffer cells, and hepatic stellate cells[29-31]. Intercellular interactions between numerous growth factors and cytokines, including hepatocyte growth factor (HGF), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), transforming growth factor-α, and endothelial growth factor, play important roles during this process[29,30]. Each mediator activates downstream cascades by releasing hepatocytes from a quiescent state and allowing them to enter the cell cycle[29,30]. The TNF-α/nuclear factor-kappa B (NF-κB)[32,33], IL-6/signal transducer and activator of transcription 3 (STAT3)[34], and phosphatidylinositol-3-kinase (PI3K)/Akt[35] pathways are the three major signaling cascades that are engaged during liver regeneration.

In 2004, Murata *et al*[36] were the first to demonstrate that platelets promoted liver regeneration during the early phases after a partial hepatectomy. Using mouse models, Lesurtel *et al*[37] reported that platelet-derived serotonin mediated liver regeneration. In this section, the clinical and experimental evidence that platelets promote liver regeneration and the three different mechanisms involved in this process are described.

Clinical evidence

In a retrospective analysis of 216 consecutive patients who underwent a partial hepatectomy for colorectal metastasis, Alkozai *et al*[38] reported that an immediate post-operative platelet count below 100000/μL was an independent risk factor for the delayed recovery of postoperative liver function and was associated with an increased risk of postoperative mortality. Kim *et al*[39] analyzed 87 patients who received adult-to-adult living donor liver transplants and determined that the total number of units of transfused platelet concentrate was significantly associated with graft regeneration, which was assessed by CT scan. Furthermore, the stepwise regression analysis revealed that the total amount of the platelets was independently associated with graft regeneration.

Effect of thrombocytosis on liver regeneration

Murata *et al*[22] determined that a 2- to 3-fold elevation in platelet count induced by thrombopoietin increased the liver/body weight ratio, the hepatocyte Ki-67 labeling index, and the mitotic index after a 70% partial hepatectomy. Myronovych *et al*[40] reported that the incremental increase in platelet count after thrombopoietin treatment accelerated liver regeneration within 24 h after a 90% hepatectomy and improved the postoperative survival rate. They determined that under thrombocytotic conditions, there was a significant increase in HGF expression in liver tissue and the early phosphorylation of Akt and STAT3. These results implied that the thrombocytotic state induced by thrombopoietin promoted liver regeneration *via* an early activation of the PI3K/Akt and IL-6/STAT3 pathways, leading to hepatocyte cell cycle entry and mitosis. In both studies, thromboembolic events, organ damage, and other side effects were not observed in response to the increased platelet count.

Effect of platelet transfusion on liver regeneration

Matsuo *et al*[23] examined the effects of platelet transfusion on liver regeneration by transfusing platelet-rich plasma into rats after a 70% partial hepatectomy. After a hepatectomy, platelet transfusion increased the liver/body weight ratio and the hepatocyte Ki-67 labeling index at 24 h without damaging the liver. Furthermore, platelet transfusion accelerated Akt phosphorylation and prolonged the activation of the extracellular signal-reg-

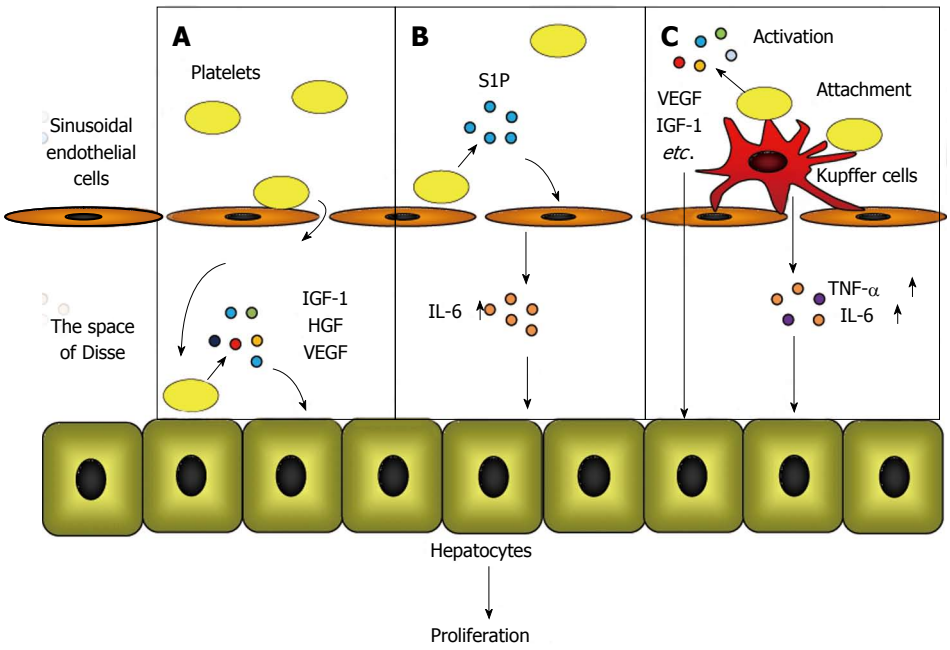

Figure 1 Platelet-mediated liver regeneration. Platelets accumulate in the liver immediately after a hepatectomy. A: Platelets translocate into the space of Disse and release insulin-like growth factor (IGF)-1, hepatocyte growth factor (HGF), and vascular endothelial growth factor (VEGF) by directly contacting hepatocytes; B: Direct contact of platelets with liver sinusoidal endothelial cells induces the release of S1P from platelets and the secretion of interleukin-6 (IL-6) from liver sinusoidal endothelial cells; C: Kupffer cells activated in response to a hepatectomy induce the accumulation and activation of platelets. Growth factors released from platelets and the enhanced release of tumor necrosis factor-α (TNF-α) and IL-6 from Kupffer cells promote liver regeneration.

ulated kinase 1/2 pathway. These results indicated that platelet transfusion had a positive impact by accelerating liver regeneration after a hepatectomy without damaging the liver.

Mechanisms: The direct effect of platelets

Murata *et al*[22] observed that platelets accumulated in the liver immediately after a hepatectomy and translocated into the space of Disse to directly contact the hepatocytes. These data implied that platelets in the liver provide signals for hepatocyte proliferation through direct contact with hepatocytes. To prove this hypothesis, Matsuo *et al*[41] utilized a co-culture chamber system that separates the platelets and hepatocytes with a permeable membrane and clarified that direct contact between platelets and hepatocytes triggered the release of HGF, insulin-like growth factor (IGF)-1, and vascular endothelial growth factor (VEGF) from platelets, resulting in hepatocyte proliferation.

The direct effect of the platelet mechanism occurs when platelets translocate to the space of Disse and directly contact the hepatocytes, which triggers the secretion of HGF, IGF-1, and VEGF from the platelets. These growth factors initiate mitosis in hepatocytes and promote liver regeneration (Figure 1A).

Mechanism: The effect involving liver sinusoidal endothelial cells

Kawasaki *et al*[42] studied the role of platelets in liver regeneration in relation to liver sinusoidal endothelial cells using co-culture chamber systems. They demonstrated that the direct contact of platelets with liver sinusoidal endothelial cells increased the release of IL-6 from liver sinusoidal endothelial cells, which accelerated DNA synthesis through the IL-6/STAT3 pathway in hepatocytes. They also proved that platelet-derived sphingosine-1-phosphate (S1P) induced IL-6 secretion from liver sinusoidal endothelial cells.

In the platelet mechanism of action that involves liver sinusoidal endothelial cells, the direct contact between the platelets and the liver sinusoidal endothelial cells induces S1P release from the platelets, which promotes IL-6 secretion from the liver sinusoidal endothelial cells. IL-6 subsequently accelerates hepatocyte mitosis *via* the IL-6/STAT3 pathway (Figure 1B).

Mechanism: The effect of Kupffer cells

Takahashi *et al*[43] studied the positive impact of platelets on liver regeneration and focused on the role of Kupffer cells by transfusing platelets into mice. These authors discovered that after a 70% hepatectomy, transfused platelets accumulated and acted locally in the residual liver in the presence of activated Kupffer cells. The hepatic expression of TNF-α and IL-6, which are predominantly produced by Kupffer cells[30,44], increased in response to a platelet transfusion, indicating that the function of the Kupffer cells was enhanced by a platelet transfusion. Furthermore, it was determined by electron microscopy that the transfused platelets were attached to the surface of the Kupffer cells, providing a reason why the platelets accumulated and were activated in the liver after a hepatectomy.

The mechanism involving platelets and Kupffer cells occurs when platelets accumulate and are locally activated in the liver by attaching to the surface of activated Kupffer cells. Liver regeneration is promoted by growth factors that are released from accumulated platelets and by the enhanced release of TNF-α and IL-6 from Kupffer cells (Figure 1C).

ANTI-FIBROSIS EFFECT OF PLATELETS

Liver fibrosis is a major cause of morbidity and mortality in the world[45]. It results in liver failure, portal hy-

pertension, and an increased risk of carcinogenesis[45,46]; liver transplantation is currently the only cure[47]. Fibrosis is characterized by an excessive deposition of extracellular matrix proteins, which disrupt the liver structure and cause pathophysiological damage to this organ[45,46]. Matrix metallopeptidases (MMPs) are enzymes that are responsible for the degradation of extracellular matrix proteins[48,49], and the production of MMPs is regulated by HGF[50,51]. Activated hepatic stellate cells are the primary cells that are responsible for the excessive synthesis of extracellular matrix proteins[47]. Transforming growth factor-β (TGF-β), which is predominately released from hepatic stellate cells and Kupffer cells[52], is the most potent cytokine that activates hepatic stellate cells. The effects of TGF-β are mediated by intracellular signaling *via* Smad proteins[53], and TGF-β is suppressed by HGF[19].

Despite improvements in the preoperative assessment of liver function and advances in surgical techniques, liver resection still carries the risk for postoperative hepatic failure, especially in patients with cirrhosis[54]. This risk occurs because a cirrhotic liver has an impaired regenerative ability, and the risk of post-operative hepatic failure correlates with the degree of fibrosis[55]. Accelerating liver regeneration and improving liver fibrosis would avoid liver failure after a hepatectomy. Although previous studies have viewed platelets as promoters of liver fibrosis[56], recent studies have uncovered anti-fibrotic effects of platelets in the liver. This section describes the experimental and clinical evidence that platelets are anti-fibrotic as well as the mechanisms of action.

Clinical evidence

Maruyama *et al*[57] conducted a prospective clinical trial of the effect of platelet transfusion on liver fibrosis. Patients with chronic liver disease (Child-Pugh classes A and B) and a platelet count below 100000/μL were registered. Ten patients received ten units of platelet concentrate once 1 wk for 12 wk. Four patients discontinued this treatment because of the appearance of mild hives, anti-human platelet antigen, and anti-human leukocyte antigen. Six patients completed the platelet transfusions and were followed for 9 mo after the last treatment; these patients exhibited increased concentrations of serum albumin and cholinesterase. Furthermore, there was a decrease in the serum hyaluronic acid, one of the serum fibrotic markers. It was determined that platelet transfusion improved liver function and decreased liver fibrosis.

Effect of thrombocytosis on liver fibrosis

Watanabe *et al*[58] reported that thrombocytosis induced by thrombopoietin treatment or splenectomy reduced liver fibrosis and the hydroxyproline content of liver tissue. Thrombocytosis suppressed TGF-β mRNA expression and increased MMP-9 expression in the liver. Furthermore, the liver volume, the hepatocyte proliferating cell nuclear antigen (PCNA) labeling index, and the mitotic index in fibrotic liver increased under thrombocytotic conditions. These findings indicated that thrombocytosis reduced liver fibrosis and promoted liver regeneration.

Murata *et al*[59] examined the effect of a single thrombopoietin treatment on fibrosis and liver regeneration in a cirrhotic liver after a 70% partial hepatectomy. Thrombocytosis improved fibrosis and increased the hepatocyte PCNA labeling index and the mitotic index in the cirrhotic liver. The authors also injected anti-platelet serum after administering thrombopoietin to determine whether the effects were due to the thrombopoietin or to the increased platelet number. The anti-platelet serum injection significantly increased liver fibrosis and decreased liver regeneration. According to these studies, increasing the number of platelets attenuated liver fibrosis and accelerated liver regeneration even in a cirrhotic liver.

Mechanism: The direct effect of platelets

Ikeda *et al*[60] reported that platelet extracts suppressed hepatic stellate cell activation *in vitro*. They determined that adenine nucleotides, such adenosine triphosphate and adenosine diphosphate, were enriched in platelets and that ecto-nucleotide triphosphate diphosphodiesterase, ecto-nucleotide pyrophosphatase/phosphodiesterase, and ecto-5'-nucleotidase located on the plasma membrane of hepatic stellate cells degraded these adenine nucleotides to adenosine[61]. The authors demonstrated that adenosine increased the intracellular concentration of cyclic adenosine 5'-monophosphate (cAMP) in hepatic stellate cells, which suppressed hepatic stellate cell activation by phosphorylating cAMP-response element binding protein. These findings indicated that hepatic stellate cell activation is directly suppressed by platelets *via* the adenosine-cAMP signaling pathway (Figure 2).

INHIBITION OF LIVER DAMAGE AND APOPTOSIS BY PLATELETS

Liver failure after a hepatectomy is caused by various events, including a massive hepatectomy, ischemic-reperfusion injury, and a postoperative infection[62]. Hepatocyte apoptosis and diminished liver regeneration are the most important molecular events that occur during liver failure[63]. Apoptosis is an active form of cell death, and two signaling pathways lead to apoptosis: the intrinsic and extrinsic pathways[64]. The intrinsic pathway is characterized by mitochondrial dysfunction. Various stimuli damage the mitochondrial inner membrane, resulting in a permeability transition and the mitochondrial release of cytochrome C[64]. In the cytosol, cytochrome C complexes with Apaf-1 to activate procaspase-9, which in turn activates its downstream effectors, caspases 3, 6, and 7, which are responsible for degrading several cellular substrates that are associated with the morphological changes representative of apoptosis[65]. The Fas/Fas

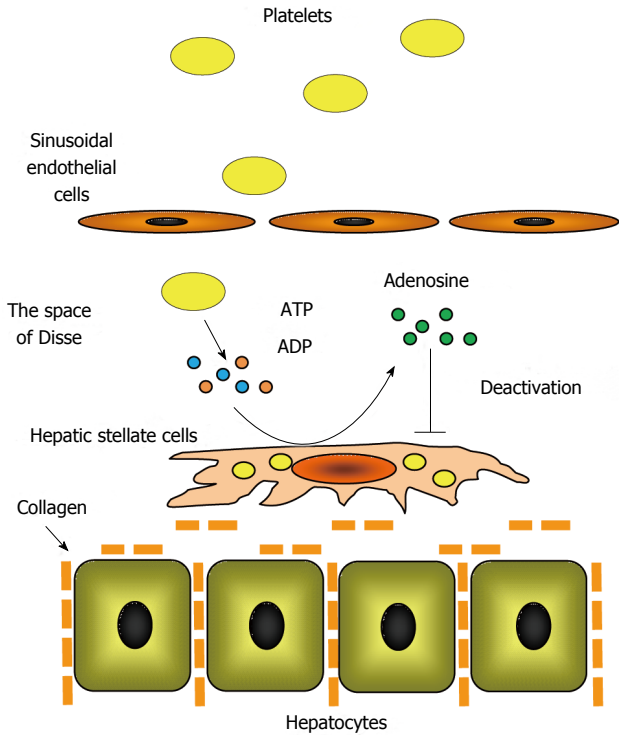

Figure 2 Platelet-mediated inhibition of fibrosis. Platelets release adenosine nucleotides, which are degraded to adenosine by enzymes located on the plasma membrane of hepatic stellate cells. The activation of hepatic stellate cells is directly suppressed by the adenosine-cAMP signaling pathway.

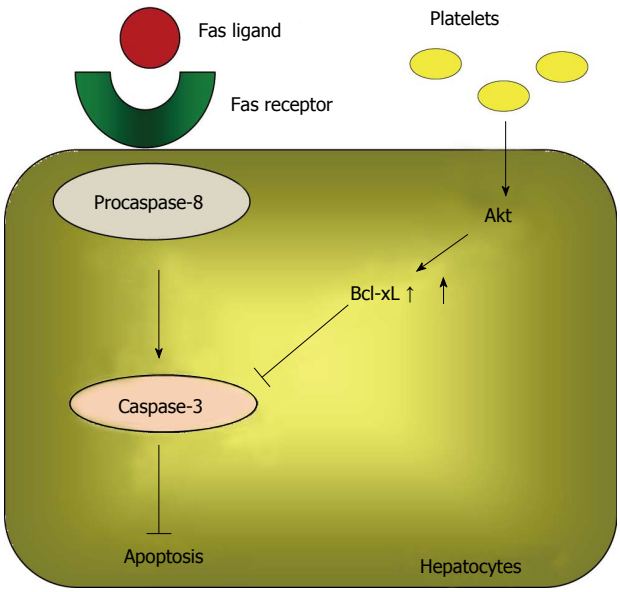

Figure 3 Platelet-mediated inhibition of apoptosis. Platelets activate the Akt pathway and up-regulate Bcl-xL, which suppresses caspase-3 activation to prevent hepatocyte apoptosis.

ligand system plays an important role in the extrinsic pathway. Upon activation by the Fas ligand, Fas complexes with procaspase-8. The aggregation of this complex initiates the cleavage of procaspase-8 into its active form, which subsequently activates caspase-3, its downstream effector[66]. Therefore, the Fas/Fas ligand system affects both the intrinsic and extrinsic pathways. Bcl-xL, a member of the Bcl-2 family, prevents mitochondria permeability transition and Fas-mediated apoptosis by inhibiting the signaling cascades[67].

This section describes the effect of thrombocytosis on liver damage and apoptosis. Because the Fas/Fas ligand system and apoptosis are hypothesized to be responsible for hepatitis[68,69], we examined the anti-apoptotic effects using a hepatitis model.

Effect of platelets on liver damage and apoptosis after a massive hepatectomy

Hisakura *et al*[70] examined the ability of thrombopoietin-mediated thrombocytosis to protect the liver from damage after an extended hepatectomy using a pig model. The authors discovered that in thrombocytotic conditions, liver cholestasis, ballooning, and necrosis were attenuated and that serum aspartate amino transferase and alkaline phosphatase (ALT) levels were low after an extended hepatectomy. Furthermore, electron transmission microscopy revealed that the structure of the endothelial lining was well preserved in thrombocytotic conditions. These data indicated that thrombocytosis protects the sinusoidal lining and prevents acute liver damage after an extended hepatectomy.

Hisakura *et al*[71] also investigated the effects of thrombocytosis in acute hepatitis induced by an anti-Fas antibody. The authors demonstrated that serum ALT levels were significantly decreased in thrombocytotic conditions at 6, 24 and 72 h after administering an anti-Fas antibody. They also determined that the percent of TdT-mediated dUTP-biotin nick end labeling-positive hepatocytes and the expression of cleaved caspase-3 in the liver were significantly decreased by thrombocytosis. Furthermore, *in vitro* Akt phosphorylation, increased Bcl-xL, and decreased cleaved caspase-3 were observed sequentially in hepatocytes co-cultured with platelets. Because Akt is a critical suppressor of apoptosis[72,73], the above data suggested that an increase in the platelet count prevents hepatocyte apoptosis by activating the Akt pathway and up-regulating Bcl-xL, which suppresses caspase-3 activation (Figure 3).

CONCLUSION

This review describes the published evidence that platelets promote liver regeneration, attenuate liver fibrosis, and prevent liver damage and hepatocyte apoptosis; it also details the mechanisms of action. In the blood, platelets are constituents that contain numerous biologically active growth factors and cytokines, and it was recently determined that platelets have various functions in addition to hemostasis and thrombosis[5-7]. Currently, thrombopoietin[22,40,58,59,70], thrombopoietin receptor agonists[24], artificial platelets[74,75], and freeze-dried platelets[76] are in development and are beginning to be utilized in various clinical settings, and the importance of platelets is becoming more obvious. Despite some side

effects[57], platelet therapy has advantages in its convenience and cost-efficiency, and it provides another therapeutic strategy to address the current surgical issues and challenges, such as liver failure after a massive hepatectomy, hepatectomy of a cirrhotic liver, and small grafts in liver transplantation, in the near future.

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