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Review Article

Platelets and Liver Regeneration

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Abstract

Platelets contain growth factors and cytokines such as hepatocyte growth factor, tumor necrosis factor-α, interleukin-6, serotonin, insulin-growth factor-1, transforming growth factor-α, endothelial growth factor, sphingosine 1-phosphate, etc. Platelets are activated by various types of stimulation and release these physiologically active substances depending on each context. In addition to primary roles as hemostasis and thrombosis, recent studies have reported the roles of platelets on promoting liver regeneration, improving liver fibrosis, and attenuating liver damage. In this article, we reviewed the recent advances in knowledge of the role of platelets in accelerating liver regeneration.

Keywords: Platelet; Hepatectomy; Liver regeneration; Hepatocytes; Growth factor; Cytokine

Introduction

Platelets are anucleated cytoplasmic fragments originating from mega karyocytes in the bone marrow [1]. After leaving the bone marrow, platelets circulate in the blood for about ten days in the body. Platelets contain three specific granule populations, i.e., dense granules, lysosomal granules, and α-granules which store various type of growth factors and cytokines such as Hepatocyte Growth Factor (HFG), insulin-like growth factor-1 (IGF-1), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), transforming growth factor-α (TGF-α), endothelial growth factor (EGF), vascular endothelial growth factor (VEGF), sphingosine 1-phosphate (S1P) [2,3], platelet derived growth factor (PDGF), etc [4-7]. Platelets are activated by physical and physiological stimulation and release these biologically active substances depending on each context [8]. Platelets are involved in various processes including stopping hemorrhage following vascular injury [9-11], fighting against microbial infections [12-14], tissue repairing [15-17], promoting metastasis [18-20] etc. In recent years, platelets are highlighted to have role in promoting liver regeneration [21-25], improving liver fibrosis [26-30], and attenuating liver damage [31-33]. In this review, we described the most-updated experimental and clinical evidences of platelets in accelerating liver regeneration.

Platelet and Liver Regeneration

Partial hepatectomy is a feasible and relatively safe procedure for benign and malignant liver tumors and living liver donor liver transplantation. Despite substantial improvements in surgical techniques and perioperative care, liver failure after hepatectomy is a devastating complication with considerable high morbidity and mortality, and it still remains an important concern after surgery [34-37]. The incidence of liver failure ranges from 0-13% [35] or 0.7-9.1% [36]. The presence of comorbid conditions, pre-existing underlying parenchymal disease, and extent resection are the major risk factors. Preventive methods should be applied, and adequate preoperative risk evaluation and an optimal postoperative treatment are essential. Postoperative management principles resemble those applied to acute liver failure, focusing on support of liver and end-organ function, such as plasma exchange [36,38,39], molecular absorbent re circulating system such as (MARS®, Gambro, Lund Sweden) [40] and Prometheus (Fresenius Medical Care, st, wendel, Germany) [41], bio artificial liver, [42,43] and liver transplantation [44]. On the other hand, one of the recent strategies for liver failure after hepatectomy is to augment the remnant liver regeneration [45-47]. In the past, several attempts have been made in this field, i.e., stem cell injection therapy [48], erythropoietin and granulocyte macrophage colony stimulating factor administration therapy [49], gene therapy [50-54], hepatocyte transplantation [45] etc. However, there are few reports on their clinical application.

Liver regeneration after partial hepatectomy is very complex phenomenon, which is carried out by the all mature liver cell types. Intercellular interaction by growth factors and cytokines, such as HGF, EGF, TNF-α, IL-6, and serotonin, which play important roles during this process [55-57]. Hepatocytes are the first cells to enter into the cell cycle and undergo proliferation. Hepatocytes produce mitogenic signals for other liver cell types, and each mediator leads activations of downstream cascades, which transfer hepatocytes from the quiescent status into cell cycle [55,56,58]. TNF-α/nuclear factor-kappa B (NF-κB) [59,60], IL-6/signal transducer and activator of transcription 3 (STAT3) [61], phosphatidylinositol-3-kinase (PI3K)/Akt pathways [62], HGF/HFG receptor (cMet) pathway [63], and extracellular signal-regulated kinase 1/2 (ERK1/2) [64], are the major cascades during liver regeneration. Serotonin signaling is mediated through a number of specific receptors, most of them coupled with G-proteins [65]. G-proteins link the receptors to a variety of downstream pathways that elicits cellular responses. These pathways include PI3K/Akt pathways, MAPK pathways, and STAT-JAK pathway [65]. Through these proliferative signals, hepatocyte undergoes DNA synthesis, peaking at 24 hours for the rat and at approximately 36 hours for the mouse [66]. More than 95% of hepatocyte go through cell proliferation during the first 48 hours and normal liver weight is reestablished within 5-7 days for the rodents and 8-15 days for the human [56,66].

Relationship between platelets and liver regeneration was first described by Murata et al. [67], in 2004. After this report, there has been piling evidence of platelets contributing in liver regeneration from clinical and experimental data.

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Experimental Evidences

In vivo

Murata et al. [22], induced thrombocytosis by thrombopoietin administration and conducted 70% partial hepatectomy to the mice and liver regeneration was evaluated. Liver/body weight increased significantly in the thrombocytotic condition compared with the normal platelet conditions. Akt was strongly phosphorylated under thrombocytosis. The authors described that platelets affect liver regeneration after hepatectomy and PI3K/Akt was the main signaling pathway involved in platelet-mediated liver regeneration.

Lesurtel et al. [21], focused that platelets are the major carriers of serotonin in the blood. They found that expression of serotonin receptors in the liver increased after hepatectomy and antagonist of serotonin receptors inhibited liver regeneration. Liver regeneration was blunted by inhibiting synthesis of peripheral serotonin, which was rescued by serotonin administration. They conclude that platelet derived serotonin is involved in the initiation of liver regeneration.

Shimabukuro et al. [68], performed 70% partial hepatectomy on rats given thrombopoietin. They compared liver regeneration, DNA synthesis, and HGF mRNA expressions in the liver. They reported that liver regained the pre-hepatectomy weight levels much faster when treated with thrombopoietin. Thrombopoietin significantly enhanced the DNA synthesis and HGF mRNA expressions.

Matsuo et al. [46], transfused platelet-rich plasma to rats after 70% partial hepatectomy. Platelet-rich plasma infusion increased liver/body weight ratio and Ki-67 labeling index after hepatectomy. Platelet-rich plasma infusion accelerated Akt activation and prolonged ERK 1/2 phosphorylation. These results indicated that platelet-rich plasma infusion had a positive impact on accelerating liver regeneration.

Myronovych et al. [69], examined using 90% partial hepatectomy model, which was considered as fatal. They induced thrombocytosis by thrombopoietin administration, and evaluated survival rate and liver regeneration. They found that all mice with the normal platelet level died early after hepatectomy, whereas half with thrombocytosis survived after hepatectomy. Liver/body weight ratio was significantly increased in the mice with thrombocytosis compared to the mice with normal platelet counts. Phosphorylation of Akt and STAT3 were earlier and stronger under thrombocytotic conditions. These results implied that thrombocytosis promoted liver regeneration through early activation of PI3K/Akt and IL-6/STAT3 pathways.

Lopez et al. [70], implanted platelets in the peritoneum of the rats after 90% partial hepatectomy. They found that although there were no difference in hepatocyte mitosis and DNA synthesis, platelets implanted group showed higher survival rate. They concluded that platelets enhanced survival by an early protective effect on hepatocyte.

Murata et al. [71], reported that liver regeneration in the cirrhotic liver after hepatectomy was significantly decreased when compared to the normal liver, and liver regeneration in the cirrhotic liver with thrombocytosis was the same level as those of the normal liver. The authors further reported that fibrosis decreased significantly in the cirrhotic liver under thrombocytotic conditions. The authors proved that these effects were due to increased number of platelets, not by thrombopoietin administration itself, by using antiplatelet serum in the thrombocytotic condition.

In vitro

Matsuo et al. [72], reported that DNA synthesis of the hepatocyte was increased by co-culturing with platelets. DNA synthesis was depended on the platelet concentration. In order to determine which fragment of platelets exert hepatocyte proliferative effect, they separated platelet extract and assessed mitogenic activity. DNA synthesis was strong in the fragment of HGF, IGF-1, and VEGF, implying that these growth factors are the key mediators for liver regeneration.

Hoshi et al. [73] reported that freeze-dried platelets preserved stored adenine nucleotides, PDGF, and IGF-1, which were the same levels as those of fresh platelets. The authors described that freeze-dried platelets induced stimulatory effect on the DNA synthesis of hepatocyte. They proved usefulness of freeze-dried platelets on promoting liver regeneration.

Mechanisms of liver regeneration induced by platelets

Murata et al. [22], reported that platelets accumulated in the liver immediately after hepatectomy. Transmission electron microscopy revealed platelet migration from the sinusoidal space into the space of Disse and platelets were in direct contact with hepatocyte in the thrombocytotic condition. Matsuo et al. [72], clarified the necessity of direct contact between hepatocyte and platelets using co-culturing chamber system, which separates upper and lower chambers by a permeable membrane. They indicated that upon direct contact with hepatocytes, platelets release soluble factors that induce hepatocyte proliferation. Through these two studies, it was considered that platelets accumulate in the liver immediately after hepatectomy, translocation from the liver sinusoids to the space of Disse and release growth factors through direct contact with hepatocyte. Growth factors stimulate initiation of hepatocyte mitosis, which eventually promotes liver regeneration.

Kawasaki et al. [74], evaluated the role of platelets in relation to liver sinusoidal endothelial cells. They proved that IL-6 concentration was increased in the supernatant of the liver sinusoidal endothelial cells co-cultured with platelets, which was cancelled by application of S1P receptor antagonist. DNA synthesis and STAT3 phosphorylation of the hepatocyte were enhanced when applying supernatant of liver sinusoidal endothelial cells co-cultured with platelets. The authors concluded that platelets induced IL-6 release from liver sinusoidal endothelial cells, which accelerated hepatocyte DNA synthesis through IL-6/STAT3 pathway. In addition, they proved that S1P induced IL-6 secretion from liver sinusoidal endothelial cells.

Takahashi et al. [75,76], clarified that hepatic expressions of TNF-α and IL-6 were enhanced by platelet transfusion after hepatectomy. Since TNF-α and IL-6 are predominantly produced by Kupffer cells [56,77], these results indicated that platelet transfusion enhanced TNF-α and IL-6 secretion from Kupffer cells. Furthermore, the authors indicated that although only a few transfused platelets were adhering to the Kupffer cells without hepatectomy, the majority of platelets transfused were adhering to the surface of Kupffer cells without being phagocytosed after hepatectomy. Based on the findings, it was assumed that platelets promoted liver regeneration by

interactions with Kupffer cells.

From these studies, three different mechanisms are clarified, i.e., i) the direct effect on hepatocyte, ii) the cooperative effect with liver sinusoidal endothelial cells, and iii) the collaborative effect with Kupffer cells.

Clinical Evidences

Partial hepatectomy

Kaneko et al. [78], described that preoperative platelet counts less than 100 x 10^3/μl was the strongest independent factor for postoperative mortality among patients with hepatocellular carcinoma who underwent hepatectomy. Alkozai et al. [79], reported that immediate post-operative platelet count below 100 x 10^3/μl was an independent risk factor for delayed postoperative liver function recovery and was associated with increased risk of postoperative mortality among patients who underwent partial hepatectomy for colorectal metastasis. They described that there was no association between preoperative platelet counts and delayed postoperative liver function recovery. Sratlinger et al. [80,81], described that patients suffering from postoperative liver dysfunction and morbidity were found to have reduced intra-platelet serotonin levels during the entire perioperative period and reduced preoperative intra-platelet serotonin was associated with and increased incidence of postoperative liver dysfunction and morbidity. They demonstrated that intra-platelet serotonin levels were an independent predictor of poor clinical outcome. On the other hand, Kim et al. [82], described that substantial portion of patients exhibited decrease in platelet counts after hepatectomy. However, such change did not affect postoperative liver function, liver regeneration, or overall complications.

Liver transplantation

Marubashi et al. [83], reported that there was a positive correlation between graft size and post-transplant thrombocytosis after living donor liver transplantation. They mentioned that splenectomy is an option in cases with a small graft. Kim et al. [84], described that total units of platelet concentrate transfused was found to be significantly associated with the graft regeneration after living donor liver transplantation. Lesurtel et al. [85], described that platelet counts < 6.0×10^9 on postoperative day five was associated with a higher risk of severe complication graft loss, and decreased chance of patient survival after liver transplantation.

Perspectives

In this review, we demonstrated the most-updated evidences of platelets promoting liver regeneration and their mechanisms. Thrombopoietin receptor agonist [86-88], artificial platelets [89,90], and freeze-dried platelets [73,91,92], are developing, and some of them are beginning to be utilized in the clinical practices. However, there are still side effects and unsolved problems such as production of anti-platelet antibodies following platelet transfusion [93], and of anti-thrombopoietin antibodies after thrombopoietin administration [94], as well as the several-day delay between thrombopoietin-receptor agonist administration and increases in platelet counts. We hope platelets can add strategies for the surgical challenges, such as post-hepatectomy liver failure after massive hepatectomy and small-graft syndrome after liver transplantation [95,96].

References

1. Cimmino G, Golino P. Platelet biology and receptor pathways. See comment in PubMed Commons below J Cardiovasc Transl Res. 2013; 6: 299-309.
2. Yatomi Y. Plasma sphingosine 1-phosphate metabolism and analysis. See comment in PubMed Commons below Biochim Biophys Acta. 2008; 1780: 606-611.
3. Morozov VI, Sakuta GA, Kalinski MI. Sphingosine-1-phosphate: distribution, metabolism and role in the regulation of cellular functions. See comment in PubMed Commons below Ukr Biokhim Zh. 2013; 85: 5-21.
4. Polasek J. Platelet secretory granules or secretory lysosomes? See comment in PubMed Commons below Platelets. 2005; 16: 500-501.
5. Holmsen H. Physiological functions of platelets. See comment in PubMed Commons below Ann Med. 1989; 21: 23-30.
6. Koseoglu S, Flaumenhaft R. Advances in platelet granule biology. See comment in PubMed Commons below Curr Opin Hematol. 2013; 20: 464-471.
7. Dhillon MS, Behera P, Patel S, Shetty V2. Orthobiologics and platelet rich plasma. See comment in PubMed Commons below Indian J Orthop. 2014; 48: 1-9.
8. Blair P, Flaumenhaft R. Platelet alpha-granules: basic biology and clinical correlates. See comment in PubMed Commons below Blood Rev. 2009; 23: 177-189.
9. Broos K, De Meyer SF, Feys HB, Vanhoorelbeke K, Deckmyn H. Blood platelet biochemistry. See comment in PubMed Commons below Thromb Res. 2012; 129: 245-249.
10. Broos K, Feys HB, De Meyer SF, Vanhoorelbeke K, Deckmyn H. Platelets at work in primary hemostasis. See comment in PubMed Commons below Blood Rev. 2011; 25: 155-167.
11. Pereboom IT, Lisman T, Porte RJ. Platelets in liver transplantation: friend or foe? See comment in PubMed Commons below Liver Transpl. 2008; 14: 923-931.
12. Xiang B, Zhang G, Guo L, Li XA, Morris AJ, Daugherty A, et al. Platelets protect from septic shock by inhibiting macrophage-dependent inflammation via the cyclooxygenase 1 signalling pathway. See comment in PubMed Commons below Nat Commun. 2013; 4: 2657.
13. Jeong YI, Jung ID, Lee CM, Chang JH, Chun SH, Noh KT, et al. The novel role of platelet-activating factor in protecting mice against lipopolysaccharide-induced endotoxic shock. See comment in PubMed Commons below PLoS One. 2009; 4: e6503.
14. McMorran BJ, Burgio G, Foote SJ. New insights into the protective power of platelets in malaria infection. See comment in PubMed Commons below Commun Integr Biol. 2013; 6: e23653.
15. Menter DG, Tucker SC, Kopetz S, Sood AK, Crissman JD, Honn KV. Platelets and cancer: a casual or causal relationship: revisited. See comment in PubMed Commons below Cancer Metastasis Rev. 2014.
16. Borsig L. The role of platelet activation in tumor metastasis. See comment in PubMed Commons below Expert Rev Anticancer Ther. 2008; 8: 1247-1255.
17. Honn KV, Tang DG, Crissman JD. Platelets and cancer metastasis: a causal relationship? See comment in PubMed Commons below Cancer Metastasis Rev. 1992; 11: 325-351.
18. Ramos-Torrecillas J, García-Martínez O, Luna-Bertos ED, Ocaña-Peinado FM, Ruiz C. Effectiveness of Platelet-Rich Plasma and Hyaluronic Acid for the Treatment and Care of Pressure Ulcers. See comment in PubMed Commons below Biol Res Nurs. 2014.
19. Gilli SC, do Valle Oliveira SA, Saad ST. Autologous Platelet Gel: Five Cases Illustrating Use on Sickle Cell Disease Ulcers. See comment in PubMed Commons below Int J Low Extrem Wounds. 2014; 13: 120-126.
20. Crovetti G, Martinelli G, Issi M, Barone M, Guizzardi M, Campanati B, et al. Platelet gel for healing cutaneous chronic wounds. See comment in PubMed Commons below Transfus Apher Sci. 2004; 30: 145-151.

21. Lesurtel M, Graf R, Aleil B, Walther DJ, Tian Y, Jochum W, et al. Platelet-derived serotonin mediates liver regeneration. See comment in PubMed Commons below Science. 2006; 312: 104-107.

22. Murata S, Ohkohchi N, Matsuo R, Ikeda O, Myronovych A, Hoshi R. Platelets promote liver regeneration in early period after hepatectomy in mice. See comment in PubMed Commons below World J Surg. 2007; 31: 808-816.

23. Clavien PA, Graf R. Liver regeneration and platelets. See comment in PubMed Commons below Br J Surg. 2009; 96: 965-966.

24. Murata S, Maruyama T, Nowatari T, Takahashi K, Ohkohchi N. Signal transduction of platelet-induced liver regeneration and decrease of liver fibrosis. See comment in PubMed Commons below Int J Mol Sci. 2014; 15: 5412-5425.

25. Takahashi K, Murata S, Ohkohchi N. Novel therapy for liver regeneration by increasing the number of platelets. See comment in PubMed Commons below Surg Today. 2013; 43: 1081-1087.

26. Watanabe M, Murata S, Hashimoto I, Nakano Y, Ikeda O, Aoyagi Y, et al. Platelets contribute to the reduction of liver fibrosis in mice. See comment in PubMed Commons below J Gastroenterol Hepatol. 2009; 24: 78-89.

27. Ikeda N, Murata S, Maruyama T, Tamura T, Nozaki R, Kawasaki T, et al. Platelet-derived adenosine 5'-triphosphate suppresses activation of human hepatic stellate cell: In vitro study. See comment in PubMed Commons below Hepatol Res. 2012; 42: 91-102.

28. Takahashi K, Murata S, Fukunaga K, Ohkohchi N. Human platelets inhibit liver fibrosis in severe combined immunodeficiency mice. See comment in PubMed Commons below World J Gastroenterol. 2013; 19: 5250-5260.

29. Nowatari T, Murata S, Fukunaga K, Ohkohchi N. Role of platelets in chronic liver disease and acute liver injury. See comment in PubMed Commons below Hepatol Res. 2014; 44: 165-172.

30. Hesami Z, Jamshidzadeh A, Ayatollahi M, Geramizadeh B, Farshad O, Vahdati A. Effect of Platelet-Rich Plasma on CCl4-Induced Chronic Liver Injury in Male Rats. See comment in PubMed Commons below Int J Hepatol. 2014; 2014: 932930.

31. Hisakura K, Murata S, Takahashi K, Matsuo R, Pak S, Ikeda N, et al. Platelets prevent acute hepatitis induced by anti-fas antibody. See comment in PubMed Commons below J Gastroenterol Hepatol. 2011; 26: 348-355.

32. Hisakura K, Murata S, Fukunaga K, Myronovych A, Tadano S, Kawasaki T, et al. Platelets prevent acute liver damage after extended hepatectomy in pigs. See comment in PubMed Commons below J Hepatobiliary Pancreat Sci. 2010; 17: 855-864.

33. Nocito A, Georgiev P, Dahm F, Jochum W, Bader M, Graf R, et al. Platelets and platelet-derived serotonin promote tissue repair after normothermic hepatic ischemia in mice. See comment in PubMed Commons below Hepatology. 2007; 45: 369-376.

34. Wang DW, Yin YM, Yao YM. Advances in the management of acute liver failure. See comment in PubMed Commons below World J Gastroenterol. 2013; 19: 7069-7077.

35. Hammond JS, Guha IN, Beckingham IJ, Lobo DN. Prediction, prevention and management of postresection liver failure. See comment in PubMed Commons below Br J Surg. 2011; 98: 1188-1200.

36. van den Broek MA, Olde Damink SW, Dejong CH, Lang H, Malagó M, Jalan R, et al. Liver failure after partial hepatic resection: definition, pathophysiology, risk factors and treatment. See comment in PubMed Commons below Liver Int. 2008; 28: 767-780.

37. Serenari M, Cescon M, Cucchetti A, Pinna AD. Liver function impairment in liver transplantation and after extended hepatectomy. See comment in PubMed Commons below World J Gastroenterol. 2013; 19: 7922-7929.

38. Onodera K, Sakata H, Yonekawa M, Kawamura A. Artificial liver support at present and in the future. See comment in PubMed Commons below J Artif Organs. 2006; 9: 17-28.

39. Liu J, Kjaergard LL, Als-Nielsen B, Gluud C. Artificial and bioartificial support systems for liver failure: a Cochrane Hepato-Biliary Group Protocol. See comment in PubMed Commons below Liver. 2002; 22: 433-438.

40. Sen S, Williams R, Jalan R. Emerging indications for albumin dialysis. See comment in PubMed Commons below Am J Gastroenterol. 2005; 100: 468-475.

41. Krisper P, Haditsch B, Stauber R, Jung A, Stadlbauer V, Trauner M, et al. In vivo quantification of liver dialysis: comparison of albumin dialysis and fractionated plasma separation. See comment in PubMed Commons below J Hepatol. 2005; 43: 451-457.

42. Selden C, Spearman CW, Kahn D, Miller M, Figaji A, Erro E, et al. Evaluation of encapsulated liver cell spheroids in a fluidised-bed bioartificial liver for treatment of ischaemic acute liver failure in pigs in a translational setting. See comment in PubMed Commons below PLoS One. 2013; 8: e82312.

43. Zheng Z, Li X, Li Z, Ma X. Artificial and bioartificial liver support systems for acute and acute-on-chronic hepatic failure: A meta-analysis and meta-regression. See comment in PubMed Commons below Exp Ther Med. 2013; 6: 929-936.

44. Otsuka Y, Duffy JP, Saab S, Farmer DG, Ghobrial RM, Hiatt JR, et al. Postresection hepatic failure: successful treatment with liver transplantation. See comment in PubMed Commons below Liver Transpl. 2007; 13: 672-679.

45. Wang N, Wang Z, Sun H, Shi X, Zhang Y, Liu Q. Augmenter of liver regeneration improves therapeutic effect of hepatocyte homotransplantation in acute liver failure rats. See comment in PubMed Commons below Int Immunopharmacol. 2013; 15: 325-332.

46. Matsuo R, Nakano Y, Ohkohchi N. Platelet administration via the portal vein promotes liver regeneration in rats after 70% hepatectomy. See comment in PubMed Commons below Ann Surg. 2011; 253: 759-763.

47. Golse N, Bucur PO, Adam R, Castaing D, Sa Cunha A, Vibert E. New paradigms in post-hepatectomy liver failure. See comment in PubMed Commons below J Gastrointest Surg. 2013; 17: 593-605.

48. Li DL, He XH, Zhang SA, Fang J, Chen FS, Fan JJ. Bone marrow-derived mesenchymal stem cells promote hepatic regeneration after partial hepatectomy in rats. See comment in PubMed Commons below Pathobiology. 2013; 80: 228-234.

49. Vassiliou I, Lolis E, Nastos C, Tympa A, Theodosopoulos T, Dafnios N, et al. The combined effect of erythropoietin and granulocyte macrophage colony stimulating factor on liver regeneration after major hepatectomy in rats. See comment in PubMed Commons below World J Surg Oncol. 2010; 8: 57.

50. Atta HM. Gene therapy for liver regeneration: experimental studies and prospects for clinical trials. See comment in PubMed Commons below World J Gastroenterol. 2010; 16: 4019-4030.

51. Takahashi T, Togo S, Kumamoto T, Watanabe K, Kubota T, Ichikawa Y, et al. Transfection of NF-kappaB decoy oligodeoxynucleotides into macrophages reduces murine fatal liver failure after excessive hepatectomy. See comment in PubMed Commons below J Surg Res. 2009; 154: 179-186.

52. Nishino M, Iimuro Y, Ueki T, Hirano T, Fujimoto J. Hepatocyte growth factor improves survival after partial hepatectomy in cirrhotic rats suppressing apoptosis of hepatocytes. See comment in PubMed Commons below Surgery. 2008; 144: 374-384.

53. Ueno M, Uchiyama K, Nakamori M, Ueda K, Iwahashi M, Ozawa S, et al. Adenoviral vector expressing hepatocyte growth factor promotes liver regeneration by preoperative injection: the advantages of performing selective injection to the remnant lobe. See comment in PubMed Commons below Surgery. 2007; 141: 511-519.

54. Shiota G, Kunisada T, Oyama K, Udagawa A, Nomi T, Tanaka K, et al. In vivo transfer of hepatocyte growth factor gene accelerates proliferation of hepatic oval cells in a 2-acetylaminofluorene/partial hepatectomy model in rats. See comment in PubMed Commons below FEBS Lett. 2000; 470: 325-330.

55. Fausto N. Liver regeneration. See comment in PubMed Commons below J Hepatol. 2000; 32: 19-31.

56. Michalopoulos GK, DeFrances MC. Liver regeneration. See comment in PubMed Commons below Science. 1997; 276: 60-66.

57. Gilgenkrantz H, Collin de l'Hortet A. New insights into liver regeneration. See comment in PubMed Commons below Clin Res Hepatol Gastroenterol. 2011; 35: 623-629.

58. Ozaki M. [Role of jak/STAT3 and PI3-K/Akt pathways in liver injury and regeneration]. See comment in PubMed Commons below Seikagaku. 2008; 80: 399-408.

59. Cressman DE, Greenbaum LE, Haber BA, Taub R. Rapid activation of post-hepatectomy factor/nuclear factor kappa B in hepatocytes, a primary response in the regenerating liver. See comment in PubMed Commons below J Biol Chem. 1994; 269: 30429-30435.

60. FitzGerald MJ, Webber EM, Donovan JR, Fausto N. Rapid DNA binding by nuclear factor kappa B in hepatocytes at the start of liver regeneration. See comment in PubMed Commons below Cell Growth Differ. 1995; 6: 417-427.

61. Cressman DE, Diamond RH, Taub R. Rapid activation of the Stat3 transcription complex in liver regeneration. See comment in PubMed Commons below Hepatology. 1995; 21: 1443-1449.

62. Jackson LN, Larson SD, Silva SR, Rychahou PG, Chen LA, Qiu S, et al. PI3K/Akt activation is critical for early hepatic regeneration after partial hepatectomy. See comment in PubMed Commons below Am J Physiol Gastrointest Liver Physiol. 2008; 294: G1401-1410.

63. Michalopoulos GK. Principles of liver regeneration and growth homeostasis. See comment in PubMed Commons below Compr Physiol. 2013; 3: 485-513.

64. Chen XG, Xu CS, Liu YM. Involvement of ERK1/2 signaling in proliferation of eight liver cell types during hepatic regeneration in rats. See comment in PubMed Commons below Genet Mol Res. 2013; 12: 665-677.

65. Fidalgo S, Ivanov DK, Wood SH. Serotonin: from top to bottom. See comment in PubMed Commons below Biogerontology. 2013; 14: 21-45.

66. Michalopoulos GK. Liver regeneration after partial hepatectomy: critical analysis of mechanistic dilemmas. See comment in PubMed Commons below Am J Pathol. 2010; 176: 2-13.

67. Murata S, Ohkohchi N, Abe T, et al. Platelets promote G1-S progression of liver regeneratio after hepatectmoy. XXXXIX ESSR 2004; E512C0241:107-112.

68. Shimabukuro R, Kawanaka H, Tomikawa M, Akahoshi T, Konishi K, Yoshida D, et al. Effect of thrombopoietin on platelet counts and liver regeneration after partial hepatectomy in a rat model. See comment in PubMed Commons below Surg Today. 2009; 39: 1054-1059.

69. Myronovych A, Murata S, Chiba M, Matsuo R, Ikeda O, Watanabe M, et al. Role of platelets on liver regeneration after 90% hepatectomy in mice. See comment in PubMed Commons below J Hepatol. 2008; 49: 363-372.

70. López ML, Kieling CO, Uribe Cruz C, Osvaldt A, Ochs de Muñoz G, Meurer L, et al. Platelet increases survival in a model of 90% hepatectomy in rats. See comment in PubMed Commons below Liver Int. 2014; 34: 1049-1056.

71. Murata S, Hashimoto I, Nakano Y, Myronovych A, Watanabe M, Ohkohchi N. Single administration of thrombopoietin prevents progression of liver fibrosis and promotes liver regeneration after partial hepatectomy in cirrhotic rats. Ann Surg 2008; 248: 821-828.

72. Matsuo R, Ohkohchi N, Murata S, Ikeda O, Nakano Y, Watanabe M, et al. Platelets Strongly Induce Hepatocyte Proliferation with IGF-1 and HGF In Vitro. See comment in PubMed Commons below J Surg Res. 2008; 145: 279-286.

73. Hoshi R, Murata S, Matsuo R, Myronovych A, Hashimoto I, Ikeda H, et al. Freeze-dried platelets promote hepatocyte proliferation in mice. See comment in PubMed Commons below Cryobiology. 2007; 55: 255-260.

74. Kawasaki T, Murata S, Takahashi K, Nozaki R, Ohshiro Y, Ikeda N, et al. Activation of human liver sinusoidal endothelial cell by human platelets induces hepatocyte proliferation. See comment in PubMed Commons below J Hepatol. 2010; 53: 648-654.

75. Takahashi K, Kozuma Y, Suzuki H, Tamura T, Maruyama T, Fukunaga K, et al. Human platelets promote liver regeneration with Kupffer cells in SCID mice. See comment in PubMed Commons below J Surg Res. 2013; 180: 62-72.

76. Miller SG, Pritts TA. Platelets and Kupffer cells: partners in liver regeneration: commentary on "Human platelets promote liver regeneration with Kupffer cells in SCID mice". See comment in PubMed Commons below J Surg Res. 2014; 186: 83-84.

77. Decker K. The response of liver macrophages to inflammatory stimulation. See comment in PubMed Commons below Keio J Med. 1998; 47: 1-9.

78. Kaneko K, Shirai Y, Wakai T, Yokoyama N, Akazawa K, Hatakeyama K. Low preoperative platelet counts predict a high mortality after partial hepatectomy in patients with hepatocellular carcinoma. See comment in PubMed Commons below World J Gastroenterol. 2005; 11: 5888-5892.

79. Alkozai EM, Nijsten MW, de Jong KP, de Boer MT, Peeters PM, Slooff MJ, et al. Immediate postoperative low platelet count is associated with delayed liver function recovery after partial liver resection. See comment in PubMed Commons below Ann Surg. 2010; 251: 300-306.

80. Starlinger P, Assinger A, Haegele S, Wanek D, Zikeli S, Schauer D, et al. Evidence for serotonin as a relevant inducer of liver regeneration after liver resection in humans. See comment in PubMed Commons below Hepatology. 2014; 60: 257-266.

81. Lesurtel M, Clavien PA. Platelet-derived serotonin: Translational implications for liver regeneration. See comment in PubMed Commons below Hepatology. 2014; 60: 30-33.

82. 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. See comment in PubMed Commons below J Gastrointest Surg. 2013; 17: 1576-1583.

83. Marubashi S, Dono K, Miyamoto A, Takeda Y, Nagano H, Umeshita K, et al. Impact of graft size on postoperative thrombocytopenia in living donor liver transplant. See comment in PubMed Commons below Arch Surg. 2007; 142: 1054-1058.

84. Kim J, Yi NJ, Shin WY, Kim T, Lee KU, Suh KS. Platelet transfusion can be related to liver regeneration after living donor liver transplantation. See comment in PubMed Commons below World J Surg. 2010; 34: 1052-1058.

85. Lesurtel M, Raptis DA, Melloul E, Schlegel A, Oberkofler C, El-Badry AM, et al. Low platelet counts after liver transplantation predict early posttransplant survival: the 60-5 criterion. See comment in PubMed Commons below Liver Transpl. 2014; 20: 147-155.

86. Schipperus M, Fijnheer R. New therapeutic options for immune thrombocytopenia. See comment in PubMed Commons below Neth J Med. 2011; 69: 480-485.

87. Zhang Y, Kolesar JM. Eltrombopag: an oral thrombopoietin receptor agonist for the treatment of idiopathic thrombocytopenic purpura. See comment in PubMed Commons below Clin Ther. 2011; 33: 1560-1576.

88. Svensson T, Chowdhury O, Garelius H, Lorenz F, Saft L, Jacobsen SE, et al. A pilot phase I dose finding safety study of the thrombopoietin-receptor agonist, eltrombopag, in patients with myelodysplastic syndrome treated with azacitidine. See comment in PubMed Commons below Eur J Haematol. 2014.

89. Bode AP, Fischer TH. Lyophilized platelets: fifty years in the making. See comment in PubMed Commons below Artif Cells Blood Substit Immobil Biotechnol. 2007; 35: 125-133.

90. Okamura Y, Takeoka S, Eto K, Maekawa I, Fujie T, Maruyama H, et al. Development of fibrinogen gamma-chain peptide-coated, adenosine diphosphate-encapsulated liposomes as a synthetic platelet substitute. J Thromb Haemost. 2009; 7: 470-477.

91. Horimizu M, Kawase T, Nakajima Y, Okuda K, Nagata M, Wolff LF, et al. An improved freeze-dried PRP-coated biodegradable material suitable for connective tissue regenerative therapy. See comment in PubMed Commons below Cryobiology. 2013; 66: 223-232.

92. Nakajima Y, Kawase T, Kobayashi M, Okuda K, Wolff LF, Yoshie H. Bioactivity of freeze-dried platelet-rich plasma in an adsorbed form on a biodegradable polymer material. See comment in PubMed Commons below Platelets. 2012; 23: 594-603.

93. Howard JE, Perkins HA. The natural history of alloimmunization to platelets. See comment in PubMed Commons below Transfusion. 1978; 18: 496-503.

94. Wörmann B. Clinical indications for thrombopoietin and thrombopoietin-receptor agonists. See comment in PubMed Commons below Transfus Med Hemother. 2013; 40: 319-325.

95. Dahm F, Georgiev P, Clavien PA. Small-for-size syndrome after partial liver transplantation: definition, mechanisms of disease and clinical implications. See comment in PubMed Commons below Am J Transplant. 2005; 5: 2605-2610.

96. Tucker ON, Heaton N. The 'small for size' liver syndrome. See comment in PubMed Commons below Curr Opin Crit Care. 2005; 11: 150-155.

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