Platelets and Platelet-Derived Extracellular Vesicles in Liver Physiology and Disease

Alexandre Balaphas,1,3 Jeremy Meyer,1,3 Karin Sadoul,4 Pierre Fontana,5,6 Philippe Morel,1,3 Carmen Gonelle-Gispert,2,3* and Leo H. Bühler1,3*

Beyond their role in hemostasis, platelets are proposed as key mediators of several physiological and pathophysiological processes of the liver, such as liver regeneration, toxic or viral acute liver injury, liver fibrosis, and carcinogenesis. The effects of platelets on the liver involve interactions with sinusoidal endothelial cells and the release of platelet-contained molecules following platelet activation. Platelets are the major source of circulating extracellular vesicles, which are suggested to play key roles in platelet interactions with endothelial cells in several clinical disorders. In the present review, we discuss the implications of platelet-derived extracellular vesicles in physiological and pathophysiological processes of the liver. (Hepatology Communications 2019;3:855-866).

Although the primary function of platelets is hemostasis, they also transport molecules implicated in numerous physiological processes, such as wound healing, (1-3) cell activation and proliferation, (3-5) angiogenesis, (3,6-8) and immune responses. (2,4,9-11) Platelet interactions with liver cells protect hepatic tissue and stimulate liver regeneration after parenchyma transection or ischemia-reperfusion injury. (12-15) However, platelets also contribute to liver injury, as detailed below. (12)

The human platelet proteome is comprised of >1,500 different proteins. (16) Platelet “releasate” designates the supernatant solution after platelets have released their granules; it contains membrane fragments called extracellular vesicles (EVs). (17,18) The term EV includes microparticles (also called microvesicles), exosomes, and apoptotic bodies. (19) In a healthy condition, platelet-derived EVs account for 70% to 90% of circulating EVs in the blood. (20) EVs carry proteins, lipids, lipoproteins, messenger RNA, micro-RNA (miRNA), and possibly DNA, (21,22) and they interact with target cells by means of endocytosis, surface contact, or membrane fusion. (21) EVs permit intercellular communication and were shown to be involved in various physiological and pathological processes. (17,23-26) The topic of EV has become increasingly popular throughout the years, with research teams using different methods and tools for EV isolation and characterization, thereby producing variable and sometimes contradictory results. (27-29) Despite a call from international societies for increased standardization, researchers nevertheless continue to employ the protocol and standards they see fit. (27,28)
Platelet-derived EVs (PEVs) transport mainly procoagulant material, recapitulating most platelet function processes. They were also demonstrated to be involved in vascular integrity and immune processes. Moreover, PEVs are involved in the pathogenesis of chronic inflammatory processes, such as rheumatoid arthritis and hypercoagulability, and could play a role in endothelial dysfunction in patients with metabolic syndrome. Interestingly, PEVs seem to be implicated in regenerative processes. However, despite the potential importance of the interplay between PEVs and liver tissue, the literature on this topic remains sparse.

### Features of PEVs

Platelets largely produce platelet microparticles (PMPs), which are defined as complete membrane fragments with sizes ranging from 0.1 μm to 1 μm. PMPs are produced by platelet vesiculation following platelet activation by strong or weak agonists in the presence of low shear stress or by strong shear stress alone. Release of PMPs following platelet activation is a means for platelets to accelerate hemostasis locally at sites of activation by increasing the phospholipid surface for anchoring and assembling procoagulant factors.

The formation of microparticles is a process similar to cytokinesis. It involves the disruption of the calcium-dependent actin cytoskeleton and the proteolysis of actin bonds from plasma membrane phospholipids. This induces the membrane to bleb spontaneously because of the pressure difference. However, other mechanisms have been implicated, such as membrane curvature proteins, lipid membrane reorganization, and actin–myosin contraction elicited through guanosine triphosphate-binding protein, adenosine diphosphate-riboseylation factor 6, or rho-associated protein kinase 1 signaling. It has been proposed that microparticle formation is a spontaneous and nonregulated process. However, PMP quantity and content vary according to platelet activators, and the microparticle generation can be blocked by pharmacologic agents, suggesting a regulated mechanism. PMPs are mainly characterized by expression of clusters of differentiation (CD)41, CD42b (glycoprotein Ib), and phosphatidylserine (the binding partner of annexin V), which vary according to the manner in which platelets are activated. Moreover, phosphatidylserine expression appears to correlate with the procoagulant activity of PMPs. Exosomes are smaller than microparticles (0.03 μm up to 0.1-0.2 μm) and are released from cells by a true exocytosis process that is highly regulated. Exosomes originate from multivesicular bodies that arise from late endosomes. Exosome secretion is regulated either by endosomal sorting complexes required for transport (ESCRT) or by an ESCRT-independent pathway. The latter mechanism implicates ceramide and some tetraspanins (CD63 and CD81), and the entire process is regulated by RAB family proteins. Apoptotic bodies are remnant.

---

**ARTICLE INFORMATION:**

From the 1Division of Digestive Surgery; 2Surgical Research Unit, Geneva University Hospitals, Geneva, Switzerland; 3Geneva Medical School, University of Geneva, Geneva, Switzerland; 4Regulation and Pharmacology of the Cytoskeleton, Institute for Advanced Biosciences, Université Grenoble Alpes, Grenoble, France; 5Division of Angiology and Hemostasis, Geneva University Hospitals, Geneva, Switzerland; 6Geneva Platelet Group, University of Geneva, Geneva, Switzerland.

**ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:**

Alexandre Balaphas, M.D.
Division of Digestive Surgery
Geneva University Hospitals
Rue Gabrielle-Perret-Genbtil 4
1211 Geneva, Switzerland
E-mail: alexandre.balaphas@unige.ch
Tel.: +41 22 379 52 52
fragments of cells with sizes ranging from 0.3 μm to 5 μm with fibrogenic properties on the liver. Apoptotic bodies are difficult to characterize as they share similar markers with other EVs and are likely to be isolated along with exosomes or microparticles as few authors report methods to select or exclude them. (49) Due to an overlap between microparticles, exosomes, and apoptotic bodies and a lack of reliable standardized characterization methods, the term PEV will be used in the following sections.

Acute Liver Injury

Acute liver injury encompasses any insult to the liver that provokes an acute inflammatory response. The insults include physical (e.g., trauma or liver surgery) or chemical agents (e.g., acetaminophen toxicity). Acute liver injury can rapidly lead to acute liver failure, a life-threatening condition characterized by a severe loss of homeostatic functions of the liver and a mortality rate of >30%. (50)

In a mouse model of Fas-antibody-induced hepatitis, Hisakura et al. (51) demonstrated that thrombocytosis had a protective effect on hepatocytes apoptosis as well as on liver sinusoidal endothelium injury. In a model of acute cholestatic injury induced by α-naphthylisothiocyanate in mice, Sullivan et al. (52) concluded that platelets are implicated in hepatocyte necrosis as platelet depletion induced the pooling of blood into liver parenchyma (liver peliosis) and blocking of the P2Y12 receptor expressed on platelets reduced the severity of hepatocyte injury. On a clinical level, recent meta-analyses indicate that low perioperative platelet counts after liver surgery were correlated with higher risk of postoperative liver failure. (53) Moreover, thrombocytopenia occurring during the first week of hospital admission for acute liver failure was associated with either death or listing on a liver transplantation waiting list. (54) These data show that low circulating platelet levels correlate with poor liver regeneration.

PEVs are involved in chronic and acute inflammatory processes, including systemic inflammatory response syndrome and sepsis. (55,56) PEVs promote inflammation at the level of endothelial cells, which are the first static cells they reach. It has been shown in vitro that PEVs increase the adhesion of monocytes to human umbilical vein endothelial cells (HUVECs) (57) and induce the expression of genes coding for inflammatory markers, including adhesion receptors, such as intercellular adhesion molecule 1, CD11a, and CD11b. (58) Moreover, PEVs induce the presentation of Von Willebrand factor at the surface of HUVECs and carry interleukin (IL)-1β, which is known to stimulate the adhesion of leukocytes to the endothelium. (58) Moreover, PEVs enhance the aggregation of neutrophils (60,61) and monocytes (62) in vitro and stimulate the maturation of dendritic cells, which can further activate T lymphocytes. (63,64) PEVs were shown to transport mitochondria, which may trigger leukocyte adhesion to the endothelium if they are released. (65) Finally, PEVs induce platelet adhesion to the endothelium through CD61 (glycoprotein IIb/IIIa) binding. (66)

Liver sinusoidal endothelial cells (LSECs) are key actors in liver regeneration (67) and therefore are important for withstanding liver injury. As platelets, PEVs could be of importance in the regulation of cytokine production and release by LSECs during acute liver injury. Of interest, Stravitz and colleagues (68) showed that patients suffering from acute liver failure had an increased amount of circulating microparticles that were essentially PEVs (Table 1). Furthermore, these microparticles were independent predictors of liver transplantation complications and mortality. (68)

Chronic Liver Diseases

FATTY LIVER DISEASE AND STEATOHEPATITIS

The role of platelets in nonalcoholic steatohepatitis remains contentious (Table 1). Some studies attribute a proinflammatory effect to platelets, whereas others demonstrate an anti-inflammatory role. (69) Studies by Kanellopoulou et al. (70) did not detect differences in PEV counts between healthy volunteers and patients with nonalcoholic fatty liver disease (NAFLD), although Kornek et al. (71) reported a decrease in PEV counts for patients with NAFLD. Alcohol directly affects platelet counts independently of liver implication, (72) but little is known on the effect of platelets on alcoholic steatohepatitis. Ogasawara and colleagues (73) found a statistically significant increase in PEV counts in patients with alcoholic fatty liver disease when
compared to healthy patients. Moreover, PEV counts decreased 10 days after alcohol withdrawal. However, the effect and the clinical significance of these variations in PEV counts remain unknown.

**LIVER FIBROSIS**

Liver fibrosis results from a complex interplay between nonparenchymal cells and dying hepatocytes. Activation of hepatic stellate cells (HSCs), their transformation into myofibroblasts, and their interaction with Kupffer cells represent the key events of the fibrotic process. (74)

Platelets were demonstrated to protect liver tissue against drug-induced fibrosis in rodents by an action on the redox status and an increase in intracellular cyclic adenosine monophosphate in HSCs. (75) Hepatocyte growth factor (HGF) released by platelets contributes to alleviate the fibrotic process, (76, 77) and platelet transfusion improved residual liver function in patients with cirrhosis. (78) On the other hand, platelets contain numerous factors (transforming growth factor β, platelet-derived growth factor b, and platelet factor 4) that are known to promote liver fibrosis. (69) *In vitro*, platelet lysates were shown to induce HSC proliferation and profibrogenic cytokine production. (79) Additionally, *in vivo* experiments in a rodent model of biliary-induced fibrosis established that platelet-derived growth factor b plays a role in HSC activation. (80) A study by Vasina and colleagues (81) also demonstrated that PEVs were implicated in monocyte polarization and thus maturation and may therefore be implicated in the turnover of liver macrophages, particularly in the case of chronic inflammation, such as steatohepatitis, where circulating monocytes are recruited. (82)

The correlation between PEV counts and liver fibrosis is controversial. Some clinical studies demonstrated that PEV blood levels were higher than normal in patients with alcoholic cirrhosis or hepatitis C virus–induced cirrhosis (73) or in patients with Child-Pugh A cirrhosis. (83) Furthermore, Fusegawa and colleagues (84) demonstrated that blood PEV counts were correlated with indirect markers of liver fibrosis in blood (serum hyaluronate and N-terminal propeptide of type III procollagen) in patients with chronic hepatitis B or C. PEVs are induced by platelet activation, and it was proposed that PEV levels reflect the systemic inflammatory state associated with liver cirrhosis. (85) However, Rautou et al. (86) did not report any difference in PEV counts

---

**TABLE 1. PEV COUNTS COULD CONSTITUTE A MARKER OF LIVER INFLAMMATORY PROCESSES AND WERE CHARACTERIZED BY FLOW CYTOMETRY**

| Type of Pathology/Injury | Publication | Platelet-Derived EV Blood Count* | Characterization Markers | Species | Target Cells and Effect* |
|-------------------------|-------------|----------------------------------|--------------------------|---------|-------------------------|
| Acute liver injury      | Stravitz et al. (68) | Increase CD41+, Annexin V+ | Human | NA |
| Ischemia-reperfusion injury | Freeman et al. (116) | Increase CD41+, Annexin V+ | Mouse | NA |
| | Teoh et al. (117) | Increase CD41+, Annexin V+, CD62P+ | Mouse | Enhanced neutrophil migration, hepatocyte injury, platelet activation |
| Hepatectomy              | Banz et al. (130) | Increase CD41+, Annexin V+ | Human | NA |
| Alcoholic fatty liver disease | Ogasawara et al. (73) | Increase CD61+ | Human | NA |
| NAFLD                   | Konellopoulou et al. (70) | Normal CD61+, Annexin V+ | Human | NA |
| Chronic active hepatitis C virus | Konellopoulou et al. (70) | Decrease CD41+ | Human | NA |
| HCC                     | Levi et al. (104) | Increase CD41+ | Human | NA |
| Cirrhosis               | Ogasawara et al. (73) | Increase CD61+ | Human | NA |
|                         | Fusegawa et al. (84) | Increase CD61+ | Human | NA |
|                         | Sayed et al. (83) | Increase CD41+ | Human | NA |
|                         | Rautou et al. (86) | Normal CD41+, Annexin V+ | Human | NA |
|                         | Kornek et al. (71) | Normal CD41+ | Human | NA |

*Fluctuations are relative to healthy individuals. Abbreviation: NA, not applicable.
between patients with cirrhosis and healthy participants. The same observation was made by Kornek et al.\(^{(71)}\) who also reported the absence of correlation between PEV counts and alanine transaminase level or biopsy stage of fibrosis. Moreover, liver cirrhosis is associated with thrombocytopenia, which appears to be multifactorial following a reduced production, a splenic sequestration, or an increased destruction of platelets.\(^{(87)}\) Two early publications reported an inverse correlation between platelets and PEV counts,\(^{(73,84)}\) but recent publications did not.\(^{(71,83,86)}\) This discrepancy can be explained by the methods used to characterize PEVs. Thus, it appears that platelet numbers did not influence the generation of PEVs.

Currently, the available data do not allow conclusions to be drawn regarding the implication of PEVs in liver cirrhosis.\(^{(85,86,88)}\) Notably, the clinical data show contradictory results regarding PEV blood levels in patients with cirrhosis. Further experimental research is needed to clarify the implication and the causality of PEV in liver cirrhosis.

**VIRAL INFECTIONS**

Platelets were shown to have a deleterious role in viral hepatitis by promoting cytotoxic T lymphocyte recruitment to the liver in rodents.\(^{(69,89-95)}\) This effect was reported to be mediated by serotonin released from platelets.\(^{(92)}\) Hepatitis B and E virus highjack trafficking machineries (respectively, multivesicular bodies and ESCRT III) that are usually used by EVs,\(^{(96,97)}\) but little is known about the direct involvement of PEVs during infection. There are some studies analyzing PEV levels during viral infections. One such study reported a correlation between PEV count and active chronic hepatitis C infection\(^{(70)}\) (Table 1). In this study, the increased levels of PEVs returned to baseline when sustained virologic responses to interferon-\(\alpha\) and ribavirin were observed. Another study found that the levels of PEVs in blood were higher in patients with chronic hepatitis C than in patients with chronic hepatitis B.\(^{(84)}\)

**LIVER METASTATIC DISEASE AND LIVER PRIMARY CANCER**

Platelets play a role in carcinogenesis. After contact with epithelial cancer cells or by secretion of cytokines, platelets facilitate the epithelial-mesenchymal transition, a cardinal step in the metastatic process.\(^{(77,98)}\) Moreover, platelets are able to protect free cancer cells from shear stress and natural killer cells during their circulation in the blood.\(^{(77,99-101)}\) They allow their extravascular migration (mainly through their releasate)\(^{(77,102)}\) and facilitate metastases implantation and proliferation.\(^{(77)}\) Platelets were also suggested to be implicated in hepatocellular carcinoma (HCC) growth and migration.\(^{(103)}\)

A study by Bihari and colleagues\(^{(103)}\) analyzed blood platelet smears and clustering around tumor cells after fine needle aspiration of HCC nodules. They found positive correlations between distant metastasis and platelet/lymphocyte ratio, platelet clustering, and HCC group (according to the extent of disease) invasiveness assay and platelet concentration. They suggested that platelets are implicated in HCC growth and migration (Table 1). Furthermore, Levi and colleagues\(^{(104)}\) reported that EVs, identified as PEVs, were significantly elevated in the blood of patients with HCC.

**Ischemia-Reperfusion Injury**

Liver ischemia–reperfusion injury occurs following the arrest of blood circulation to liver tissue, as occurs during clamping of the portal pedicle. Clamping may be necessary during major liver resection to prevent blood oozing or control bleeding or during organ donor liver transplantation. Indeed, liver tissue ischemia activates resident Kupffer cells, which produce free reactive oxygen species following reperfusion of the liver. These oxygen species combined with the secretion of proinflammatory cytokines induce an overwhelming inflammatory reaction involving the recruitment of neutrophils and CD4+ T lymphocytes.\(^{(105)}\) Free reactive oxygen species are responsible for tissue injury but also for the amplification of this phenomenon. Further, liver ischemia–reperfusion injury is characterized by alteration of the microcirculation.\(^{(106,107)}\) Platelets were shown to play a key role in this process. First, platelets aggregate within sinusoids during the ischemic phase, contributing to the propagation of no-reflow zones during reperfusion.\(^{(108)}\) Second, platelets induce apoptosis of LSECs following a synergistic interaction with Kupffer cells and leukocytes.\(^{(109,110)}\) This effect was proposed to be
induced by a platelet nitric oxide combination with free oxygen radicals and the release of pro-apoptotic factors.\(^{(108,111,112)}\) Finally, platelets contain numerous factors that, when released, could worsen liver tissue damage following extravasation into the space of Disse.\(^{(113)}\)

Gambim and colleagues\(^{(115)}\) reported that PEVs collected from patients with septic shock, a condition known to impair microcirculation,\(^{(114)}\) directly induce apoptosis of rabbit endothelial cells.\(^{(115)}\) Using a mouse model of ischemia-reperfusion injury, Freeman and colleagues\(^{(116)}\) reported an acute elevation of platelet- and neutrophil-derived EVs in blood followed by a delayed elevation of endothelial cell-derived EVs. The highest concentration of PEVs in the blood lasted for 1 hour. Interestingly, PEV concentration in the blood dropped after 8 hours to a level that was significantly lower than in the control group (sham procedure). Moreover, Teoh and colleagues\(^{(117)}\) reported that liver ischemia-reperfusion injury in mice generated a mixed population of microparticles, some of which were positive for platelet markers (CD41 and CD62P). These microparticles promoted migration of liver-isolated neutrophils in ThinCert chambers. Additionally, the authors demonstrated that co-incubation of these mixed microparticles with hepatocytes induced cell injury by activation of c-jun N-terminal kinase and nuclear factor-kappa B (Fig. 1). This effect was mediated by oxidative stress and mitochondrial membrane permeability transition as it could be blocked by N-acetylcyesteine and cyclosporine A, respectively. In summary, PEV release is increased after liver ischemia-reperfusion injury and has a cytotoxic effect on hepatocytes and possibly on LSECs.

Liver Regeneration

Liver has the unique ability to regenerate and recover a functional volume sufficient to ensure the physiological needs of the organism. This regenerative property has been recognized since Greek antiquity and gave life to the myth of the scourge of Prometheus. Recent advances indicate that liver regeneration involves cytokine interplay between nonparenchymal and parenchymal cells to induce hepatocyte hyperplasia,\(^{(118)}\) whereas most reparative processes in humans imply cellular hypertrophy. Importantly, liver regeneration does not occur when its functional volume is below 25%. This has major consequences for patients with extended oncological diseases that cannot benefit from liver resection.\(^{(119,120)}\)

Platelets have been shown to contribute to liver regeneration in many ways\(^{(13-15)}\) (Fig. 1). Platelet counts were demonstrated to directly correlate to hepatocyte proliferation\(^{(121-126)}\) and improved survival after critical liver resection in a rodent model.\(^{(124)}\) Furthermore, low platelet counts were shown to correlate with the occurrence of liver failure after hepatectomy in humans.\(^{(53,127)}\) It has been proposed that platelets might directly stimulate hepatocytes to proliferate by releasing promitogenic factors and also by inducing LSECs to secrete IL-6, which stimulates hepatocyte proliferation.\(^{(13)}\)

The release of granule contents during platelet activation has been suggested to trigger liver regeneration. Notably, it was suggested that platelet serotonin, vascular endothelial growth factor, HGF, and insulin like-growth factor are involved.\(^{(13-15)}\)

PEVs play a role in angiogenesis and endothelial regeneration.\(^{(37-41)}\) PEV injection in a rat model of myocardial ischemia promoted myocardial angiogenesis.\(^{(38)}\) Moreover, PEVs are implicated in bone regeneration and neuronal proliferation, suggesting therapeutic potential in stroke victims.\(^{(128,129)}\) As previously described, PEVs are generated in the blood following liver injury (e.g., partial hepatectomy)\(^{(116,130)}\) (Fig. 1). Of interest, Nomura and colleagues\(^{(131)}\) showed that shear stress generated PEV-induced IL-6 secretion from endothelial cells.

Furthermore, PEVs obtained after platelet activation are able to deliver Ag0 2-miRNA complexes to cultured endothelial cells and thereby modulate endothelial gene expression.\(^{(132)}\) Later, it was demonstrated that platelets stimulate liver regeneration by the delivery of miRNA to hepatocytes.\(^{(133)}\) Therefore, platelets and/or platelet-derived EVs may stimulate liver regeneration by delivering proproliferative molecules and/or miRNAs.

Conclusion and Perspectives

Platelets are involved in physiological and pathophysiological liver processes. However, delineating the mechanisms by which platelets mediate these effects warrants further investigation. Notably, platelets may be likened to a double-edged sword.
Fig. 1. Roles of platelets and PEVs in ischemia-reperfusion injury and acute liver injury. (A) After liver ischemia-reperfusion injury and acute liver injury, such as hepatectomy, activated platelets in the sinusoid release several growth factors that can directly stimulate hepatocytes to proliferate or activate LSECs to further produce growth factors or factors, such as IL-6, that regulate liver regeneration. (B) PEVs have opposite effects on the liver after injury. (B1) In ischemia/reperfusion, PEVs activate c-jun N-terminal kinase and nuclear factor-kappa B in hepatocytes and contribute to cell injury. (B2) After acute liver injury and ischemia/reperfusion, PEVs can induce endothelium activation, which further promotes the recruitment, adhesion, and migration of monocytes and neutrophils and the secretion of cytokines, such as IL-6. (B3) We propose that growth factor production by LSECs could modulate liver regeneration. Moreover, PEVs might have a direct effect on hepatocytes.
depending on the specific pathology. Platelets may have either deleterious effects on liver tissue, as during ischemia-reperfusion injury, or beneficial effects, as in liver regeneration. To explain these contrasting effects, some researchers proposed that platelet α-granules contain multiple subsets of antagonist factors (notably pro-angiogenic and anti-angiogenic factors) that may be differentially released depending on platelet activators. PEVs constitute alternative candidates to explain the discrepant effects of platelets.

PEVs are generated following liver injury and could serve as transporters of molecules necessary for signaling a regenerative process, even at remote sites. Platelet exosomes and PMPs could be part of a common transport system; identical proteins are transported by both of them, and recent evidence suggested that PMP production is also regulated. Regulation of PEVs at the level of their production and release as well as their content could explain the dual role of platelets in liver physiology and pathophysiology.

Some reports show contradictory results regarding the association between PEVs and particular diseases in patients. This discrepancy likely reflects the lack of consensus in the way PEVs are quantified. In order to understand the role of platelets in liver diseases and regeneration, it will be necessary to focus future research on the generation of PEVs, their content, and their uptake by hepatocytes and nonparenchymal cells. This field of research still requires improved standardization for PEV isolation and characterization.

Acknowledgment: We thank Mrs. Lucille Solomon for the Fig. 1 design and the American Manuscript Editors for the language editing service.

REFERENCES

1) Pietrzak WS, Eppley BL. Platelet rich plasma: biology and new technology. J Craniofac Surg 2005;16:1043-1054.
2) Nurden AT. Platelets, inflammation and tissue regeneration. Thromb Haemost 2011;105(Suppl 1):S13-S33.
3) Xu X, Zhu F, Zhang M, Zeng D, Luo D, Liu G, et al. Stromal cell-derived factor-1 enhances wound healing through recruiting bone marrow-derived mesenchymal stem cells to the wound area and promoting neovascularization. Cells Tissues Organs 2013;197:103-113.
4) Anitua E, Andia I, Ardanza B, Nurden P, Nurden AT. Autologous platelets as a source of proteins for healing and tissue regeneration. Thromb Haemost 2004;91:4-15.
5) Mazzucco L, Borzini P, Gope R. Platelet-derived factors involved in tissue repair-from signal to function. Transfus Med Rev 2010;24:218-234.
6) Pintucci G, Froum S, Pinnell J, Mignatti P, Rafii S, Green D. Trophic effects of platelets on cultured endothelial cells are mediated by platelet-associated fibroblast growth factor-2 (FGF-2) and vascular endothelial growth factor (VEGF). Thromb Haemost 2002;88:834-842.
7) Bikfalvi A. Recent developments in the inhibition of angiogenic examples from studies on platelet factor-4 and the VEGF/VEGFR system. Biochem Pharmacol 2004;68:1017-1021.
8) Bikfalvi A. Platelet factor 4: an inhibitor of angiogenesis. Semin Thromb Hemost 2004;30:379-385.
9) von Hundlehausen P, Weber C. Platelets as immune cells: bridging inflammation and cardiovascular disease. Circ Res 2007;100:27-40.
10) Semple JW, Italiano JE, Freedman J. Platelets and the immune continuum. Nat Rev Immunol 2011;11:264-274.
11) Yeaman MR. Platelets: at the nexus of antimicrobial defence. Nat Rev Microbiol 2014;12:426-437.
12) Ripoche J. Blood platelets and inflammation: their relationship with liver and digestive diseases. Clin Res Hepatol Gastroenterol 2011;35:353-357.
13) Meyer J, Léjmi E, Fontana P, Morrel P, Gonnelle-Gispert C, Bühler L. A focus on the role of platelets in liver regeneration: do platelet-endothelial cell interactions initiate the regenerative process? J Hepatol 2015;63:1263-1271.
14) Meyer J, Fontana P, Gonnelle-Gispert C, Bühler L. Reply to: «The role of platelets in liver regeneration - what don't we know?» J Hepatol 2015;63:1538-1539.
15) Meyer J, Balaphas A, Fontana P, Sadoul K, Morrel P, Gonnelle-Gispert C, et al. Platelets in liver regeneration. ISBT Sci Ser 2017;12:455-462.
16) Zufferey A, Fontana P, Reny JL, Nelli S, Sanchez JC. Platelet proteomics. Mass Spectrom Rev 2012;31:331-351.
17) Italiano JE, Mairuatu AT, Flamenhaft R. Clinical relevance of microparticles from platelets and megakaryocytes. Curr Opin Hematol 2010;17:578-584.
18) Giacomazzi A, Degan M, Calabra S, Meneguzzi A, Minuz P. Antiplatelet agents inhibit the generation of platelet-derived microparticles. Front Pharmacol 2016;7:314.
19) Hirsiova P, Ibrahim SH, Verma VK, Morton LA, Shah VH, LaRusso NF, et al. Extracellular vesicles in liver pathobiology: small particles with big impact. Hepatology 2016;64:2219-2233.
20) Teixeira JH, Silva AM, Almeida MI, Barbosa MA, Santos SG. Circulating extracellular vesicles: their role in tissue repair and regeneration. Transfus Apher Sci 2016;55:55-61.
21) van der Pol E, Böing AN, Gool EL, Nieuwland R. Recent developments in the nomenclature, presence, isolation, detection and clinical impact of extracellular vesicles. J Thromb Haemost 2016;14:48-56.
22) Cai S, Cheng X, Pan X, Li J. Emerging role of exosomes in liver physiology and pathology. Hepatol Res 2017;47:194-203.
23) Mulcahy LA, Pink RC, Carter DR. Routes and mechanisms of extracellular vesicle uptake. J Extracell Vesicles 2014;3. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4122821/
24) Muralidharan-Chari V, Clancy JW, Sedgwick A, D’Souza-Schorey C. Microvesicles: mediators of extracellular communication during cancer progression. J Cell Sci 2010;123:1603-1611.
25) Prakash PS, Caldwell CC, Lentsch AB, Pritts TA, Robinson BR. Human microparticles generated during sepsis in patients with critical illness are neutrophil-derived and modulate the immune response. J Trauma Acute Care Surg 2012;73:401-406.
26) Tetta C, Bruno S, Fonsato V, Deregibus MC, Camussi G. The role of microvesicles in tissue repair. Organogenesis 2011;7:105-115.

27) Lacroix R, Robert S, Poncelet P, Kasthuri RS, Key NS, Dignat-George F; ISTH SSC Workshop. Standardization of platelet-derived microparticle enumeration by flow cytometry with calibrated beads: results of the International Society on Thrombosis and Haemostasis SSC Collaborative workshop. J Thromb Haemost 2010;8:2571-2574.

28) Lacroix R, Judicone C, Mooberry M, Boucekeine M, Key NS, Dignat-George F; The ISTH SSC Workshop. Standardization of pre-analytical variables in plasma microparticle determination: results of the International Society on Thrombosis and Haemostasis SSC Collaborative workshop. J Thromb Haemost 2013; https://doi.org/10.1111/jth.12207.

29) van der Pol E, Sturck A, van Leeuwen T, Nieuwland R, Coumans F; ISTH-SSC-VB Working Group. Standardization of extracellular vesicle measurements by flow cytometry through vesicle diameter approximation. J Thromb Haemost 2018;16:1236-1245.

30) Boilard E, Nigrovic PA, Larabee K, Watts GF, Coblyn JS, Weinblatt ME, et al. Platelets amplify inflammation in arthritis via collagen-dependent microparticle production. Science 2010;327:580-583.

31) Vinuela-Berni V, Doniz-Padilla L, Figueroa-Vega N, Portillo-Salazar H, Abud-Mendoza C, Baranda L, et al. Proportions of several types of plasma and urine microparticles are increased in patients with rheumatoid arthritis with active disease. Clin Exp Immunol 2015;180:442-451.

32) Wang W, Liu J, Yang B, Ma Z, Liu G, Shen W, et al. Modulation of platelet-derived microparticles to adhesion and motility of human rheumatoid arthritis fibroblast-like synoviocytes. PLoS ONE 2017;12:e0181003. 33)

33) Midura EF, Jernigan PL, Kuethe JW, Friend LA, Veile R, Makley AT, et al. Microparticles impact coagulation after traumatic brain injury. J Surg Res 2015;197:25-31.

34) Midura EF, Kuethe JW, Rice TC, Veile R, England LG, Friend LA, et al. Impact of platelets and platelet-derived microparticles on hypercoagulability following burn injury. Shock 2016;45:82-87.

35) Rousseau A, Van Dreden P, Khatrachi A, Larsen AK, Elalamy M, Gerotziafas GT. Procoagulant microparticles derived from cancer cells have determinant role in the hypercoagulable state associated with cancer. Int J Oncol 2017;51:1793-1800.

36) Agouni A, Lagrue-Lak-Hal AH, Duchateau P, Mostefa HA, Draunet-Busson C, Leftheriotis G, et al. Endothelial dysfunction caused by microparticles from patients with metabolic syndrome. Am J Pathol 2008;173:1210-1219.

37) Kim HK, Song KS, Chung JH, Lee KR, Lee SN. Platelet microparticles induce angiogenesis in vitro. Br J Haematol 2004;124:376-384.

38) Brill A, Dashovsky O, Rivo J, Gozal Y, Varon D. Platelet-derived microparticles induce angiogenesis and stimulate post-ischemic revascularization. Cardiovasc Res 2005;67:30-38.

39) Varon D, Shai E. Role of platelet-derived microparticles in angiogenesis and tumor progression. Discov Med 2009;8:237-241.

40) Mause SF, Ritzel E, Liehn EA, Hristov M, Bidzhekov K, Müller-Newen G, et al. Platelet microparticles enhance the vasoregenerative potential of angiogenic early outgrowth cells after vascular injury. Circulation 2010;122:495-506.

41) Ohruska M, Sasaki K, Ueno T, Seki R, Nakayoshi T, Koiwaya H, et al. Platelet-derived microparticles augment the adhesion and neovascularization capacities of circulating angiogenic cells obtained from atherosclerotic patients. Atherosclerosis 2013;227:275-282.

42) Horstman LL, Ahn YS. Platelet microparticles: a wide-angle perspective. Crit Rev Oncol Hematol 1999;30:111-142.

43) Zimigródzka M, Guzera M, Miśkiewicz A, Jagielski D, Winnicka A. The biology of extracellular vesicles with focus on platelet microparticles and their role in cancer development and progression. Tumour Biol 2016;37:14391-14401.

44) Milioli M, Ibáñez-Vea M, Sidoli S, Palmisano G, Careri M, Larsen MR. Quantitative proteomics analysis of platelet-derived microparticles reveals distinct protein signatures when stimulated by different physiological agonists. J Proteomics 2015;121:56-66.

45) Connor DE, Exner T, Ma DD, Joseph JE. The majority of circulating platelet-derived microparticles fail to bind annexin V, lack phospholipid-dependent procoagulant activity and demonstrate greater expression of glycoprotein Ib. Thromb Haemost 2010;103:1044-1052.

46) Sadoul R, Laporte MH, Chassefroye R, Chi Ki, Goldberg Y, Chatellard C, et al. The role of ESCRT during development and functioning of the nervous system. Semin Cell Dev Biol 2018;74:40-49.

47) Trajkovic K, Hsu C, Chiantia S, Rajendran L, Wenzel D, Wieland F, et al. Ceramide triggers budding of exosome vesicles into multivesicular endosomes. Science 2008;319:1244-1247.

48) Zhan SS, Jiang JX, Wu J, Halsted C, Friedman SL, Zern MA, et al. Phagocytosis of apoptotic bodies by hepatic stellate cells induces NAPDH oxidase and is associated with liver fibrosis in vivo. Hepatology 2006;43:435-443.

49) Hauser P, Wang S, Didenko VV. Apoptotic bodies: selective detectors in extracellular vesicles. Methods Mol Biol 2017;1554:193-200.

50) Lee WM, Squires RH, Nyberg SL, Doo E, Hoofnagle JH. Acute liver failure: summary of a workshop. Hepatology 2008;47:1401-1415.

51) Hisakura K, Murata S, Takahashi K, Matsuo R, Pak S, Ikeda N, et al. Platelets prevent acute hepatitis induced by anti-fas antibody. J Gastroenterol Hepatol 2011;26:348-355.

52) Sullivan BP, Wang R, Tawfik O, Luyendyk JP. Protective and damaging effects of platelets in acute cholestatic liver injury revealed by depletion and inhibition strategies. Toxicol Sci 2010;115:286-294.

53) Mehrabi A, Golriz M, Khajeh E, Ghamarnejad P, Probst P, Fonouni H, et al. Meta-analysis of the prognostic role of perioperative platelet count in posthepatectomy liver failure and mortality. Br J Surg 2018;105:1254-1261.

54) Stravitz RT, Ellerbe C, Durkaliski V, Reuben A, Lisman T, Lee WM; Acute Liver Failure Study Group. Thrombocytopenia is associated with multi-organ system failure in patients with acute liver failure. Clin Gastroenterol Hepatol 2016;14:613-620.e4.

55) Ogura H, Kawasaki T, Tanaka H, Koh T, Tanaka R, Ozeki Y, et al. Activated platelets enhance microparticle formation and platelet-leukocyte interaction in severe trauma and sepsis. J Trauma 2001;50:801-809.

56) Lehner GF, Harler U, Haller VM, Feistritzer C, Hasslacher J, Dunzendorfer S, et al. Characterization of microvesicles in septic shock using high-sensitivity flow cytometry. Shock 2016;46:373-381.

57) Barry OP, Praticò D, Savani RC, FitzGerald GA. Modulation of monocyte–endothelial cell interactions by platelet microparticles. J Clin Invest 1998;102:136-144.

58) Beltzer F, Oberle V, Bliss M, Müller E, Ruswurm S, Deigner H-P, et al. Platelet-derived microvesicles induce differential gene expression in mononuclear cells: a DNA microarray study. Platelets 2006;17:571-576.

59) Terrisse AD, Puech N, Allart S, Gourdy P, Xuereb JM, Payrastre B, et al. Internalization of microparticles by endothelial cells.
promotes platelet/endothelial cell interaction under flow. J Thromb Haemost 2010;8:2810-2819.

60) Jy W, Mao WW, Horstman L, Tao J, Ahn YS. Platelet micro-particles bind, activate and aggregate neutrophils in vitro. Blood Cells Mol Dis 1995;21:217-231.

61) Forlow SB, McEver RP, Nollert MU. Leukocyte-leukocyte interactions mediated by platelet microparticles under flow. Blood 2000;95:1317-1323.

62) Lin HC, Chang HW, Hsiao SH, Chou M-L, Seghatchian J, Burnouf T. Platelet-derived microparticles trigger TPH-1 monocytic cell aggregation and release of pro-coagulant tissue factor-expressing microparticles in vitro. Transfus Apher Sci 2015;53:246-252.

63) Kaneider NC, Kaser A, Tilg H, Ricevuti G, Wiedermann JP. Microparticles from apoptotic platelets promote resident macrophage differentiation. Cell Death Dis 2011;2:e211.

64) Badimon L, Suades R, Fuentes E, Palomo I, Padró T. Role of platelet-derived microvesicles as crosstalk mediators in atherothrombosis and future pharmacology targets: a link between inflammation, atherosclerosis, and thrombosis. Front Pharmacol 2016;7:293. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5005978/

65) Boudreau LH, Duchez AC, Cloutier N, Soulet D, Martin N, Bollinger J, et al. Platelets release mitochondria serving as substrate for bactericidal group IIa-secreted phospholipase A2 to promote inflammation. Blood 2014;124:2173-2183.

66) Merten M, Pakala R, Thiggarajan P, Benedict CR. Platelet microparticles promote platelet interaction with subendothelial matrix in a glycoprotein Ib/IIa-dependent mechanism. Circulation 1999;99:2577-2582.

67) Hu J, Srivastava K, Wieland M, Runge A, Mogler C, Besenfelder E, et al. Endothelial cell-derived angioptioetin-2 controls liver regeneration as a spatiotemporal rheostat. Science 2014;343:416-419.

68) Stravitz RT, Bowling R, Bradford RL, Key NS, Glover S, Thacker LR, et al. Role of procoagulant microparticles in mediating complications and outcome of acute liver injury/acute liver failure. Hepatology 2013;58:304-313.

69) Chauhan A, Adams DH, Watson SP, Lalor PF. Platelets: no longer bystanders in liver disease. Hepatology 2016;64:1774-1784.

70) Kanellopoulou T, Alexopoulou A, Kontopidou FN, Konstantinides P, Papanicolaou GS, Papatheodoridis GV. The significance of platelet microparticles in patients with chronic hepatitis C and their association with antiviral treatment and smoking. Ann Gastroenterol 2016;29:201-207.

71) Kornek M, Lynch M, Mehta SH, Lai M, Exley M, Adfhul NH, et al. Circulating microparticles as disease-specific biomarkers of severity of inflammation in patients with hepatitis C or nonalcoholic steatohepatitis. Gastroenterology 2012;143:448-458.

72) Mikhailidis DP, Barradas MA, Jeremy JY. The effect of ethanol on platelet function and vascular prostanooids. Alcohol 1990;7:171-180.

73) Ogasawara F, Fusegawa H, Haruki Y, Shiraishi K, Watanabe N, Matsuzaki S. Platelet activation in patients with alcoholic liver disease. Tokai J Exp Clin Med 2005;30:41-48.

74) Pellicoro A, Ramachandran P, Iredale JP, Fallowfield JA. Liver fibrosis and repair: immune regulation of wound healing in a solid organ. Nat Rev Immunol 2014;14:181-194.

75) Shobin HM, Keshk WA, Poda AM, Abu El Noeaman SE AE. A study on the regenerative effect of platelet-rich plasma on experimentally induced hepatic damage in albino rats. Can J Physiol Pharmacol 2018;96:630-636.

76) Kodama T, Takehara T, Hikita H, Shimizu S, Li W, Miyagi T, et al. Thrombocytopenia exacerbates cholestasis-induced liver fibrosis in mice. Gastroenterology 2010;138:2487-2498, 2498 e1-e7.

77) Kurokawa T, Ohkohchi N. Platelets in liver disease, cancer and regeneration. World J Gastroenterol 2017;23:3228-3239.

78) Maruyama T, Murata S, Takahashi K, Tamura T, Nozaki R, Ikeda N, et al. Platelet transfusion improves liver function in patients with chronic liver disease and cirrhosis. Tohoku J Exp Med 2013;229:213-220.

79) Bachem MG, Melchior R, Gressner AM. The role of thromboocytes in liver fibrogenesis: effects of platelet lysate and thromboocyte-derived growth factors on the mitogenic activity and glycosaminoglycan synthesis of cultured rat liver fat storing cells. J Clin Chem Clin Biochem 1989;27:555-565.

80) Yoshida S, Ikenaga N, Liu SB, Peng ZW, Chung J, Swardov DY, et al. Extrahepatic platelet-derived growth factor-β, delivered by platelets, promotes activation of hepatic stellate cells and biliary fibrosis in mice. Gastroenterology 2014;147:1378-1392.

81) Vasina EM, Cauwenberghs S, Feige MA, Heemskerk JW, Weber C, Koener RN. Microparticles from apoptotic platelets promote resident macrophage differentiation. Cell Death Dis 2011;2:e211.

82) Devischer L, Scott CL, Lefere S, Raevens S, Bogaerts E, Paridaens A, et al. Non-alcoholic steatohepatitis induces transient changes within the liver macrophage pool. Cell Immunol 2017;322:74-83.

83) Sayed D, Amin NF, Galal GM. Monocyte-platelet aggregates and platelet micro-particles in patients with post-hepatic liver cirrhosis. Thromb Res 2010;125:e228-e233.

84) Fusegawa H, Shiraishi K, Ogasawara F, Shimizu M, Haruki Y, Miyachi H, et al. Platelet activation in patients with chronic hepatitis C. Tokai J Exp Clin Med 2002;27:101-106.

85) Tapper EB, Robson SC, Malik R. Coagulopathy in cirrhosis – the role of the platelet in hemostasis. J Hepatol 2013;59:889-890.

86) Rautou P-E, Vion AC, Valla D, Boulanger CM. Circulating platelet derived microparticles are not increased in patients with cirrhosis. J Hepatol 2013;59:912.

87) Mitchell O, Feldman DM, Diakow M, Sigal SH. The pathophysiology of thrombocytopenia in chronic liver disease. Hepatic Med 2016;8:39-50.

88) Tapper EB, Robson S, Malik R. Reply to: <<Cirulating platelet derived microparticles are not increased in patients with cirrhosis>. J Hepatol 2013;59:913.

89) Iannacone M, Sita G, Isogawa M, Marchese P, Castro MG, Lowenstein PR, et al. Platelets mediate cytotoxic T lymphocyte-induced liver damage. Nat Med 2005;11:1167-1169.

90) Iannaccone M, Sita G, Ruggeri ZM, Guidotti LG. HBV pathogenesis in animal models: recent advances on the role of platelets. J Hepatol 2007;46:719-726.

91) Iannaccone M, Sita G, Narvaiza I, Ruggeri ZM, Guidotti LG. Antiplatelet drug therapy moderates immune-mediated liver disease and inhibits viral clearance in mice infected with a replication-deficient adenovirus. Clin Vaccine Immunol 2007;14:1532-1535.

92) Lang PA, Contaldo C, Georgiev P, El-Badry AM, Recher M, Kurrer M, et al. Aggravation of viral hepatitis by platelet-derived microparticles in vivo. Hepatology 2007;45:1532-1535.

93) Kurokawa T, Ohkohchi N. Platelets in liver disease, cancer and regeneration. World J Gastroenterol 2017;23:3228-3239.

94) Guidotti LG, Iannacone M. Thrombocytopenia exacerbates liver disease. Hepatology 2010;51:599-600.

95) Guidotti LG, Iannacone M. Platelet microparticles promote platelet/endothelial cell interaction under flow. J Hepatol 2013;59:912.

96) Iannaccone M, Battegay E, Sverdlov E, Delivoria-Papadopoulos M, Miyachi H, et al. Platelet activation in patients with chronic hepatitis C. Tokai J Exp Clin Med 2002;27:101-106.

97) Bollinger J, et al. Antiplatelet drug therapy moderates immune-mediated liver damage and platelet micro-particles in patients with post-hepatic liver cirrhosis. J Hepatol 2005;43:667-673.

98) Lowenstein PR, et al. Platelets mediate cytotoxic T lymphocyte-induced liver damage. Nat Med 2005;11:1167-1169.

99) Lowenstein PR, et al. Platelets mediate cytotoxic T lymphocyte-induced liver damage. Nat Med 2005;11:1167-1169.

100) Lowenstein PR, et al. Platelets mediate cytotoxic T lymphocyte-induced liver damage. Nat Med 2005;11:1167-1169.

101) Lowenstein PR, et al. Platelets mediate cytotoxic T lymphocyte-induced liver damage. Nat Med 2005;11:1167-1169.
97) Nagashima S, Jirintai S, Takahashi M, Kobayashi T, Tanggis Nishizawa T, et al. Hepatitis E virus egress depends on the exosomal pathway, with secretory exosomes derived from multivesicular bodies. J Gen Virol 2014;95:2166-2175.
98) Labelle M, Begum S, Hynes RO. Direct signaling between platelets and cancer cells induces an epithelial-mesenchymal-like transition and promotes metastasis. Cancer Cell 2011; 20:576-590.
99) Niewandt B, Hafner M, Echtenacher B, Mannel DN. Lysis of tumor cells by natural killer cells in mice is impeded by platelets. Cancer Res 1999;59:1295-1300.
100) Placke T, Örgel M, Schaller M, Jung G, Rammensee H-G, Kopp H-G, et al. Platelet-derived MHC class I confers a pseudonormal phenotype to cancer cells that subverts the antitumor reactivity of natural killer immune cells. Cancer Res 2012;72:440-448.
101) Egan K, Cooke N, Kenny D. Living in shear: platelets protect cancer cells from shear induced damage. Clin Exp Metastasis 2014;31:697-704.
102) Guerrero JA, Bennett C, van der Weyden L, McKinney H, Chin M, Nurden P, et al. Gray platelet syndrome: proinflammatory megakaryocytes and α-granule loss cause myelofibrosis and confer metastasis resistance in mice. Blood 2014;124:3624-3635.
103) Bihari C, Rastogi A, Shashtry SM, Bajpai M, Bhandari AS, Rajesh S, et al. Platelets contribute to growth and metastasis in hepatocellular carcinoma. APMIS 2016;124:776-786.
104) Levi C, Payance A, Bissone J, Tanguy M, Roux O, Porte RJ, et al. Factors in the pathophysiology of the liver transplantation: relationship to hemodynamics, serum mediators, and outcome. Liver Transplant 2017;23:8221.
105) Jaeschke H. Molecular mechanisms of hepatic ischemia-reperfusion injury and preconditioning. Am J Physiol Gastrointest Liver Physiol 2003;284:G15-G26.
106) Hide D, Ortega-Ribera M, García-Pagan JC, Peralta C, Bosch J, Gracia-Sancho J. Effects of warm ischemia and reperfusion on the liver microcirculatory phenotype of rats: underlying mechanisms and pharmacological therapy. Sci Rep 2016;6:22107.
107) Pulitano C, Joseph D, Sandroussi C, Verran D, Prin H, Debiasio M, et al. Postreperfusion microcirculatory derangements after liver transplantation: relationship to hemodynamics, serum mediators, and outcome. Liver Transplant 2017;23:527-536.
108) Montalvo-Jave EE, Escalante-Tattersfield T, Ortega-Salgado JA, Piña E, Geller DA. Factors in the pathophysiology of the liver ischemia-reperfusion injury. J Surg Res 2008;147:153-159.
109) Sindram D, Porte RJ, Hoffman MR, Bentley RC, Clavien PA. Platelets induce sinusoidal endothelial cell apoptosis upon reperfusion of the cold ischemic rat liver. Gut. Gastroenterology 2000;118:183-191.
110) Sindram D, Porte RJ, Hoffman MR, Bentley RC, Clavien PA. Synergism between platelets and leukocytes in inducing endothelial cell apoptosis in the cold ischemic rat liver: a Kupffer cell-mediated injury. FASEB J 2001;15:1230-1232.
111) Jaw AJ, Thoms SR, Ischiropoulos H. Nitric oxide and peroxynitrite-mediated pulmonary cell death. Am J Physiol 1998;274:L112-L118.
112) Selzner N, Rudiger H, Graf R, Clavien P-A. Protective strategies against ischemic injury of the liver. Gastroenterology 2003;125:917-936.
113) Miyashita T, Nakamura S, Ahmed AK, Makino I, Hayashi Y, Oyama K, et al. Ischemia reperfusion-facilitated sinusoidal endothelial cell injury in liver transplantation and the resulting impact of extravasated platelet aggregation. J Surg Research 2016;168:92-98.
114) Kanoore Edul VS, Ince C, Dubin A. What is microcirculatory shock? Curr Opin Crit Care 2015;21:245-252.
115) Gambim MH, do Carmo Ade O, Marti L, Verissimo-Filho S, Lopes LR, Janiszewski M. Platelet-derived exosomes induce endothelial cell apoptosis through peroxynitrite generation: experimental evidence for a novel mechanism of septic vascular dysfunction. Crit Care 2007;11:R107.
116) Freeman CM, Quillin RC, Wilson GC, Nojima H, Johnson BL, Sutton JM, et al. Characterization of microparticles after hepatic ischemia-reperfusion injury. PLoS ONE 2014;9:e97945.
117) Teoh NC, Ajamieh H, Wong HJ, Croft K, Mori T, Allison AC, et al. Microparticles mediate hepatic ischemia-reperfusion injury and are the targets of Diannexin (AP8597). PLoS ONE 2014;9:e104376.
118) Fausto N, Campbell JS, Riehle KJ. Liver regeneration. Hepatology 2006;43(Suppl. 1):S45-S53.
119) Kawasaki T, Murata S, Takahashi K, Nozaki R, Ohoshi Y, Ikeda N, et al. Activation of human liver sinusoidal endothelial cell by human platelets induces hepatocyte proliferation. J Hepatol 2010;53:648-654.
120) 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. Liver Int 2008;28:767-780.
121) Tomikawa M, Hashizume M, Highashi H, Ohta M, Sugimachi K. The role of the spleen, platelets, and plasma hepatocyte growth factor activity on hepatic regeneration in rats. J Am Coll Surg 1996;182:12-16.
122) Murata S, Ohkohchi N, Matsuo R, Ikeda O, Myronovych A, Hoshi R. Platelets promote liver regeneration in early period after heptectomy in mice. World J Surg 2007;31:808-816.
123) 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 heptectomy in cirrhotic rats. Ann Surg 2008;248:821-828.
124) Myronovych A, Murata S, Chiba M, Matsuo I, Ikeda O, Watanabe M, et al. Role of platelets on liver regeneration after 90% hepatectomy in mice. J Hepatol 2008;49:363-372.
125) 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. Surg Today 2009;39:1054-1059.
126) Matsuo R, Nakano Y, Ohkohchi N. Platelet administration via the portal vein promotes liver regeneration in rats after 70% hepatectomy. Ann Surg 2011;253:759-763.
127) Taketomi A, Kitagawa D, Inoh S, Kazimoto N, Yamashita Y, Gion T, et al. Trends in morbidity and mortality after hepatic resection for hepatocellular carcinoma: an institute's experience with 625 patients. J Am Coll Surg 2007;204:580-587.
128) Burnouf T, Goubaren HA, Chou ML, Deves D, Radosевич M. Platelet microparticles: detection and assessment of their paradoxical functional roles in disease and regenerative medicine. Blood Rev 2014;28:155-166.
129) Torreggiani E, Perut F, Roncuzzi L, Zini N, Baglioni SR, Baldini N. Exosomes: novel effectors of human platelet lysate activity. Blood Rev 2014;28:155-166.
130) Banz Y, Irem GM, Vogt A, Rieben R, Candinas D, Beldi G. Endothelial- and platelet-derived microparticles are generated during liver resection in humans. J Invest Surg 2016;29:20-31.
131) Nomura S, Tandon NN, Nakamura T, Cone J, Fukuhara S, Kambayashi J. High-shear-stress-induced activation of platelets and microparticles enhances expression of cell adhesion molecules in THP-1 and endothelial cells. Atherosclerosis 2001;158:277-287.
132) Laffont B, Corduan A, Plé H, Duchez AC, Cloutier N, Boilard E, et al. Activated platelets can deliver mRNA regulatory Ago2•microRNA complexes to endothelial cells via microparticles. Blood 2013;122:253-261.

133) Kirschbaum M, Karimian G, Adelmeijer J, Giepmans BN, Porte RJ, Lisman T. Horizontal RNA transfer mediates platelet-induced hepatocyte proliferation. Blood 2015;126:798-806.

134) Ma L, Hollenberg MD, Wallace JL. Thrombin-induced platelet endostatin release is blocked by a proteinase activated receptor-4 (PAR4) antagonist. Br J Pharmacol 2001;134:701-704.

135) Ma L, Perini R, McKnight W, Dicay M, Klein A, Hollenberg MD, et al. Proteinase-activated receptors 1 and 4 counter-regulate endostatin and VEGF release from human platelets. Proc Natl Acad Sci U S A 2005;102:216-220.

136) Sehgal S, Storrie B. Evidence that differential packaging of the major platelet granule proteins von Willebrand factor and fibrinogen can support their differential release. J Thromb Haemost 2007;5:2009-2016.

137) Italiano JE, Richardson JL, Patel-Hett S, Battinelli E, Zaslavsky A, Short S, et al. Angiogenesis is regulated by a novel mechanism: pro- and antiangiogenic proteins are organized into separate platelet alpha granules and differentially released. Blood 2008;111:1227-1233.

138) Italiano JE, Battinelli EM. Selective sorting of alpha-granule proteins. J Thromb Haemost 2009;7(Suppl. 1): 173-176.

139) Bambace NM, Levis JE, Holmes CE. The effect of P2Y-mediated platelet activation on the release of VEGF and endostatin from platelets. Platelets 2010;21:85-93.

140) Chatterjee M, Huang Z, Zhang W, Jiang L, Hultenby K, Zhu L, et al. Distinct platelet packaging, release, and surface expression of proangiogenic and antiangiogenic factors on different platelet stimuli. Blood 2011;117:3907-3911.

141) Aatonen M, Grönholm M, Sijjander PR. Platelet-derived microvesicles: multitalented participants in intercellular communication. Semin Thromb Hemost 2012;38:102-113.

Author names in bold designate shared co-first authorship.