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

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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]

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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.[20] Moreover, PEVs are involved in the pathogenesis of chronic inflammatory processes, such as rheumatoid arthritis[20,30-32] and hypercoagulability,[33-35] and could play a role in endothelial dysfunction in patients with metabolic syndrome.[36] Interestingly, PEVs seem to be implicated in regenerative processes.[37-41] 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.[17] 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.[17,18] 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.[42]

The formation of microparticles is a process similar to cytokinesis.[24] It involves the disruption of the calcium-dependent actin cytoskeleton and the proteolysis of actin bonds from plasma membrane phospholipids.[43] This induces the membrane to bleb spontaneously because of the pressure difference.[24,43] 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-ribosylation factor 6, or rho-associated protein kinase 1 signaling.[19,24] 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.[18,44] 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.[45] Moreover, phosphatidylserine expression appears to correlate with the procoagulant activity of PMPs.[45]

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.[19] Exosomes originate from multivesicular bodies that arise from late endosomes.[46] Exosome secretion is regulated either by endosomal sorting complexes required for transport (ESCRT) or by an ESCRT-independent pathway.[19] The latter mechanism implicates ceramide and some tetraspanins (CD63 and CD81),[19,47] and the entire process is regulated by RAB family proteins. Apoptotic bodies are remnant

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fragments of cells with sizes ranging from 0.3 μm to 5 μm with fibrogenic properties on the liver.[48] Apoptotic bodies are difficult to characterize as they share similar markers with other EVs[49] 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 alpha-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 $P2Y_{12}$ 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[59] 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

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	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
Chronic	Alcoholic fatty liver disease	Ogasawara et al.[73]	Increase	CD61+	Human	NA
	NAFLD	Kanellopoulou et al.[70]	Normal	CD61+, Annexin V+	Human	NA
		Kornek et al.[71]	Decrease	CD41+	Human	NA
	Chronic active hepatitis C virus	Kanellopoulou et al.[70]	Increase	CD61+	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.

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

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 hepatits C infection[70] (Table 1). In this study, the increased levels of PEVs returned to baseline when sustained virologic responses to interferon-α 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-acetylcystein 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
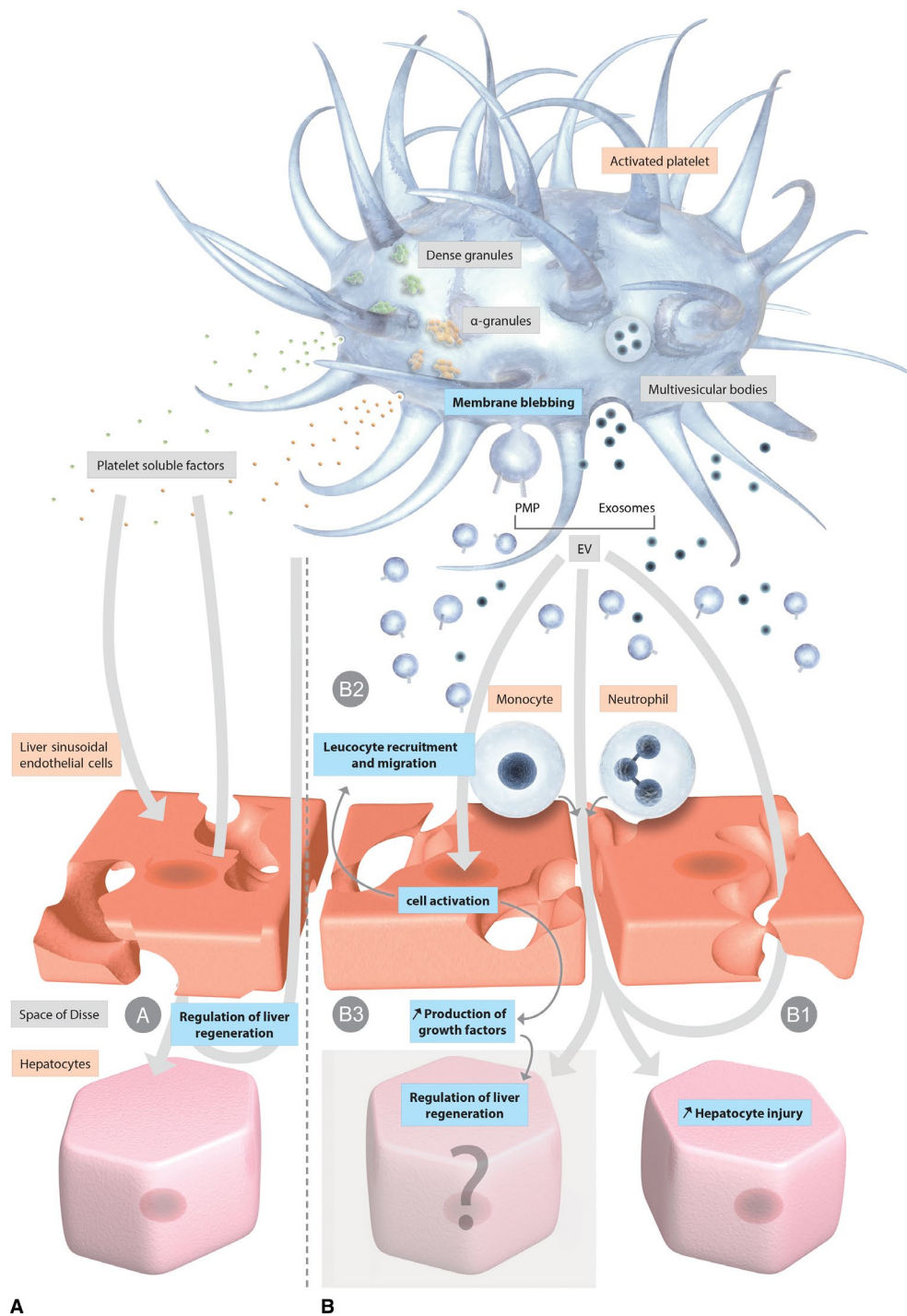
FIG. 1. Roles of platelets and PEVs in ischemia-reperfusion injury and acute liver injury. (A) After liver ischemia-reperfusion injury and acute liver injury, such as hepatectomy, activated platelets in the sinusoid release several growth factors that can directly stimulate hepatocytes to proliferate 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.[134-140] PEVs constitute alternative candidates to explain the discrepant effects of platelets.[141]

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.[18,141] 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.

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