Role of platelet-derived extracellular vesicles in traumatic brain injury-induced coagulopathy and inflammation

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Abstract
Extracellular vesicles are composed of fragments of exfoliated plasma membrane, organelles or nuclei and are released after cell activation, apoptosis or destruction. Platelet-derived extracellular vesicles are the most abundant type of extracellular vesicle in the blood of patients with traumatic brain injury. Accumulated laboratory and clinical evidence shows that platelet-derived extracellular vesicles play an important role in coagulopathy and inflammation after traumatic brain injury. This review discusses the recent progress of research on platelet-derived extracellular vesicles in coagulopathy and inflammation and the potential of platelet-derived extracellular vesicles as therapeutic targets for traumatic brain injury.

Key Words: angiogenesis; clotting factors; coagulopathy; delivery; inflammation; platelet-derived extracellular vesicles; review; target; traumatic brain injury

Introduction
Traumatic brain injury (TBI) progresses through several phases. The initial injury, caused by mechanical forces, disrupts the functional and structural integrity of the brain. A series of subsequent reactions, including peroxide release, ischemia, coagulopathy and inflammation, leads to secondary injury in patients with TBI (Zhao et al., 2017). Secondary injury, especially coagulopathy, is the main cause of high mortality and disability rates in patients with TBI (Stein et al., 2002; Cap and Spinella, 2011; Zhao et al., 2020).

Injury to the blood-brain barrier releases procoagulant materials that quickly and widely activate the exogenous coagulation pathway (Kurland et al., 2012; Joseph et al., 2014). Thus, TBI-induced coagulopathy manifests as a consumptive hypocoagulable state after rapid transition from a hypercoagulable state (Stein et al., 2002; Cap and Spinella, 2011; Yang et al., 2021), resulting in progressive bleeding and poor clinical outcomes.

Inflammation is another factor responsible for poor clinical outcomes in patients with TBI (Bonsack et al., 2020; Cheng et al., 2020). However, the mechanisms of TBI-induced inflammation remain poorly understood, as TBI-induced inflammation is also associated with central nervous system cells, such as astrocytes, neurons and glial cells.

Recently, the roles of extracellular vesicles (EVs), especially platelet-derived EVs (pEVs), in TBI-induced coagulopathy and inflammation have been of increasing interest. pEVs carry a variety of components, such as lipids, proteins (e.g., IL-1β, IL-6, IL-8 and tumor necrosis factor (Balvers et al., 2014)), nucleic acids (e.g., microRNAs (Nagalla et al., 2011)) and organelles (e.g., mitochondria (Boudreau et al., 2014)), which are involved in various biological processes, including hemostasis, inflammation (Puhm et al., 2021), angiogenesis (Hayon et al., 2012b) and intercellular delivery (Sprague et al., 2008). pEVs are a by-product of platelets (Wolf, 1967) and have similar, identical, and even more comprehensive functions than platelets. However, there is increasing support in the literature for the involvement of pEVs in pathological roles, such as in trauma, inflammatory arthritis, atherosclerosis, sepsis, breast cancer and Huntington’s disease. pEVs are associated with disease severity in conditions such as trauma and systemic lupus erythematous (SLE) (Mliasen et al., 2016; Gomes et al., 2017; Denis et al., 2018; Fröhlich et al., 2020; Slomka et al., 2018; Dyer et al., 2019; French et al., 2020; Kerris et al., 2020; Kong et al., 2020; Tessandier et al., 2020). As patients with TBI often show platelet activation and release of pEVs, we suspect that an abnormally high number of pEVs may be responsible for poor outcomes in these patients. This review focuses on the systemic impact of pEVs released after TBI, with specific emphasis on TBI-associated coagulopathy and inflammation.

Search Strategy
The articles used in this narrative review were retrieved by replicating the search terms of Boilard et al. (2010) and Zhao et al. (2017). We performed an electronic search of the PubMed database (https://pubmed.ncbi.nlm.nih.gov/) for literature describing animal models of traumatic brain injury from 1967 to 2021 using the following medical subject headings (MeSH) search terms: TBI AND (models, animal) AND inflammation AND coagulants AND animal experimentation. In addition, we performed an electronic search of the PubMed database for methods of inducing plasticity by pEVs in humans. We included publications prior to May 2021, with the following search terms: traumatic brain injury (TBI), platelets, microvesicles, and inducing plasticity.

Platelet-Derived Extracellular Vesicles in Traumatic Brain Injury-Induced Coagulopathy

Tissue factor (TF), a membrane-transfer glycoprotein expressed by healthy fibroblasts, combines clotting factor VII (FVII) and Ca++. Therefore, the procoagulant FVII (FVIIa)-TF complex, which can act as a bridge between the exogenous coagulation pathway and the intrinsic coagulation pathway (Butenas et al., 2009; D’Alessandro et al., 2018; Grover and Mackman, 2018) (Figure 1). However, the amount of TF in circulating blood is not sufficient to cause clotting.

It has been shown that phosphatidylserine (PS) and phosphatidylethanolamine regulate the function of TF (Morrissey et al., 2010). Intriguingly, Rosas et al. (Rosas et al., 2020) demonstrated by mass spectrometry that pEVs express high levels of PS on their external leaflets, suggesting that pEVs exert an influence on coagulation through PS (Tripisciano et al., 2017). Additionally, the exposure of PS on pEVs promotes coagulation via another pathway that involves the transformation of TF from a quiescent form into a biologically active state (Chen and Hogg, 2013; Ansari et al., 2016; Bengtsson and Rönnblom, 2017; Grover and Mackman, 2018). Therefore, the procoagulant activity of pEVs is partly related to increasing activity of TF (Rosas et al., 2020).

In addition, Tripisciano et al. (2017) found that pEVs are unable to facilitate...
the production of thrombin in the presence of corn trypsin inhibitor that specifically inhibits the activity of factor XII; however, in the absence of corn trypsin inhibitor, large amounts of thrombin are produced, suggesting that pEVs also promote clotting directly through the intrinsic coagulation pathway. Overall, pEVs significantly increase the amount of prothrombin complex through both intrinsic and exogenous coagulation pathways.

Boudreau et al. (2014) found that mitochondria can be incorporated into pEVs after platelet destruction. Interestingly, the inner membrane of mitochondria contains cardiolipin, which has a homologous structure to PS. Therefore, mitochondria promote coagulation by regulating the function of TF (Zhao et al., 2016). In addition to the effect of the contents of pEVs on coagulation, pEVs can directly bind to fibrin fibers to promote the generation of thrombin and formation of clotting through CD61 (Zubairova et al., 2015; Figure 2).

The role of pEVs in promoting coagulation has been demonstrated in many diseases. For example, patients with idiopathic thrombocytopenic purpura (ITP) have fewer platelets and therefore have a higher risk of bleeding than healthy people; however, some patients with ITP do not bleed more easily owing to the presence of considerably higher numbers of pEVs than in patients with ITP and increased bleeding (Jy et al., 1992; Álvarez-Román et al., 2016). Therefore, pEVs may have a protective effect on patients with ITP by promoting coagulation. However, high levels of pEVs are associated with an increased risk of thrombotic conditions, such as cancer, atherosclerosis, SLE and arthropathy (Levi et al., 2013; Boilard, 2017; Lacroix et al., 2019; Matsumura et al., 2019; Puhm et al., 2021). Conversely, PS exposure and dysregulation of T-cell release may result in severe hemorrhagic disorders, such as Scott syndrome (Zwaal et al., 2004). Stormorken syndrome, also called inverse Scott syndrome (Ridger et al., 2017), is a representative example of a condition presenting with mild bleeding even with high concentration of pEVs and is associated with either a gain-of-function mutation in the STIM1 gene (Misseco et al., 2014) or a loss-of-function mutation in the ORAI calcium release-activated calcium modulator 1 gene, a calcium channel pore-forming protein (Nesin et al., 2014).

As platelets are activated and pEVs are released after TBI, we speculate that pEVs are one of the important components present in the complex of procoagulant materials that are released after TBI. An early hypercoagulation response is followed by considerable depletion of coagulation-related factors, causing consumptive coagulation disorders and, eventually, delayed intracerebral hemorrhage.

Thus, pEVs are involved in both procoagulation and anticoagulation (Tans et al., 1991; Dahlbäck et al., 1992). However, the conditions and mechanisms behind the involvement of pEVs in procoagulation and anticoagulation remain to be studied further.

Platelet-Derived Extracellular Vesicles in Traumatic Brain Injury-Induced Proinflammatory Response

TBI is accompanied by inflammation. Damage to brain cells results in the release of brain-derived microparticles (BDMPs), including microparticles derived from astrocytes, neurons, glial cells and mitochondria (Zhao et al., 2016). In particular, adenosine triphosphate release from damaged brain cells stimulates the release of microvesicles from microglial cells (immune cells of the central nervous system) (Bianco et al., 2005), and subsequently, IL-1β, a proinflammatory cytokine and a component of the microglial microvesicles, is released after cleavage by its processing enzyme caspase 1 (Bianco et al., 2005). Similarly, astrocytes release microvesicles that contain IL-1β after stimulation by adenosine triphosphate (Figure 2) (Bianco et al., 2009). In addition, Hayakawa et al. (2016) showed that astrocytes release mitochondrial microvesicles in a calcium-dependent manner that involves signals from CD38 and cyclic adenosine diphosphate ribose. This process increases the release of reactive oxide species and activation of caspases, inducing neural cell apoptosis and subsequent release of neuronal microvesicles containing IL-1β and miRNA-21, which ultimately leads to neuronal inflammation and nervous injury after TBI (Cheng et al., 2012; Harrison et al., 2016). In contrast, we observed that mice treated with lactadherin, an apoptotic cell-scavenging factor that promotes the clearance of BDMPs (Zhou et al., 2018), had improved TBI prognosis compared with BDMP-treated mice. Lactadherin increased the expression of the anti-inflammatory factor IL-10 and decreased the expression of the proinflammatory factor IL-1.
Many publications report that pEVs promote inflammation via inflammatory-mediated molecules and receptors (Semple and Freedman, 2010; Morrell et al., 2014; Kapur et al., 2015), including platelet surface glycoprotein receptor Ib α chain, cytokines, lipid mediators, chemokines (e.g., regulated on activation normal T expressed and secreted), and lipids, and transcription factors and damage-associated molecular patterns (DAMPs) (Lindemann et al., 2001; Ray et al., 2008; Boilard et al., 2010; Sahler et al., 2011; Laffont et al., 2013; Duchez et al., 2015; Boilard, 2018; Maugeri et al., 2019). DAMPs are intracellular molecules released after tissue injury and cell death to initiate and propagate sterile inflammation (Seong and Matzinger, 2004; Rubartelli and Lotze, 2007). DAMPs include the heterodimeric protein S100A8/A9, the DNA-binding protein high mobility group box protein-1, and mitochondrial DNA (mtDNA) (Zhang et al., 2010; Boudreau et al., 2014; Wang et al., 2014; Vogel et al., 2015). DAMPs facilitate activation of endothelial cells and innate immune cells, adhesion and transfer of white cells, monocyte maturation, and generation of cytokines and reactive oxygen species (Boilard et al., 2010), causing an innate immune response and directly or indirectly initiating the adaptive immune response. Therefore, there is growing interest in DAMPs, and many studies have revealed that mitochondrial DAMPs, such as mtDNA, are closely associated with inflammation (Hajizadeh et al., 2003; Nakahira et al., 2013; Boudreau et al., 2014; Caelli et al., 2016; Garcia-Martinez et al., 2016; Lood et al., 2016; Zhao et al., 2016; Marcouil and Boilard, 2017; Simmons et al., 2017). For example, in a study of adverse reactions to platelet concentrate transfusion, including hemolysis, anaphylaxis and non-hemolytic febrile transfusion reactions, the levels of mtDNA, soluble CD40L, CD41 and soluble P-selectin in platelet concentrates were higher in patients with non-hemolytic febrile transfusion reactions than in those with hemolytic reactions (Boilard et al., 2014; Lee et al., 2014; Cognasse et al., 2016; Yasiu et al.; Simmons et al., 2017). In addition, reports have revealed that mitochondria, CD40L, CD41 and CD62P are components of pEVs (Dean et al., 2009), suggesting that pEVs may serve as a new type of extracellular vesicle (Boilard et al., 2019). Furthermore, CD41 and CD45 have been used experimentally to label pEVs and leukocytes, respectively, and pEVs can combine with leukocytes to induce inflammation through platelet-type lipoyxgenase 12 and group IIA phospholipase A2 carried by pEVs (Boilard et al., 2010; Duchez et al., 2015).

Several inflammatory diseases are associated with pEVs. In rheumatoid arthritis, platelets penetrate BM and are stimulated to release pEVs by platelet glycoprotein VI, a collagen receptor expressed on the surface of platelets (Boilard et al., 2010). Furthermore, IL-1 carried by pEVs induces fibroblasts to release heparin-like anticoagulant to directly promote megakaryocyte regeneration in BM and to signal the occurrence of inflammation in BM. Changes also occur to pEVs in response to the plasma environment, so pEVs may transfer non-normal components to BM that interact with BM cells to influence their function. This process explains how BM cells can respond quickly to inflammation (French et al., 2020).

pEVs may exert an inhibitory effect on inflammation by reducing the production of tumor necrosis factor-α released by macrophages and IL-8 released by plasma dendritic cells (Ceroi et al., 2016). Thus, similar to coagulopathy, pEVs may exert bidirectional effects on inflammation depending on the conditions (Johnson et al., 2021).

### Role of Platelet-Derived Extracellular Vesicles in Angiogenesis in Traumatic Brain Injury

pEVs play a unique role in the treatment of intractable injuries, such as burns, tympanic membrane regeneration and chronic wounds caused by diabetes, by promoting angiogenesis and re-epithelialization (Guo et al., 2017; Huang et al., 2021; Schulz et al., 2021). Kim et al. (2014) identified that the lipids present in pEVs regulate proliferation, migration and tube formation in human umbilical vein endothelial cells, and Brill et al. (2005) demonstrated that the proteins present in pEVs contribute to revascularization, including vascular endothelial growth factor, basic fibroblast growth factor and nerve growth factor. The benefits of angiogenesis and re-epithelialization promoted by pEVs have been demonstrated under a variety of conditions. For example, outcomes for an animal model of stroke can be improved by enhancing the differentiation potential of neural stem cells to form glial cells and nerve cells after addition of pEVs (Hayon et al., 2012a,b). Several studies have confirmed that pEVs positively modulate growth, migration and the differentiation potential of BM mesenchymal stem cells by upregulating the gene expression of human telomerase reverse transcriptase (Torreggiani et al., 2014; Rivera et al., 2015) to prolong the lifespan of mesenchymal stem cells (Johnson et al., 2021). Qu et al. (2020) recently reported in mice with acute liver injury, the density of neutrophil granulocytes increased with an increase in circulating pEVs, but the amount of thrombopoietin was not upregulated. Co-culture of pEVs and hematopoietic stem/progenitor cells promotes the differentiation of hematopoietic stem/progenitor cells into megakaryocytes and the subsequent generation of platelets by transferring mir-191-3p to target cells to inhibit the expression of Rho-related GTP-binding protein RhoB, which is the only gene that downregulates the differentiation of megakaryocytes (Qu et al., 2020). A report suggests that proteins, lipids and nucleotides present in pEVs act as new effectors of tissue regeneration (Johnson et al., 2021).

In addition to contributing to adverse reactions of proinflammation and coagulation during the acute phase of TBI, pEVs also play a significant role in improving the outcomes of patients with TBI through vascular regeneration and re-epithelialization in the later stages. However, further understanding of the molecular mechanisms that connect pEVs with vascular regeneration are necessary.

### Therapeutic Potential of Platelet-Derived Extracellular Vesicles

EV-based therapies have attracted a lot of attention, but attaining clinical application remains difficult (Lukomska et al., 2019). Most EV experiments to date have used mesenchymal stromal cell-derived EVs, and the use of platelets as a source of EVs has received relatively little attention (Johnson et al., 2021).

pEVs have several advantages compared with free platelets. pEVs improve hemodynamic stability (Lopez et al., 2019) and possess biological activity even after a freeze-thaw cycle of storage; the addition of pEVs to platelet suspensions also overcomes the challenges of dilutional loss of pEVs and platelets, allowing platelets to be used within their half-life (Lopez et al., 2019). A variety of biological structures are expressed on the surface of EV membranes and allow the targeting of EVs to pathological sites to change the behavior of target cells (Agrahari et al., 2019b; Kao and Papoutsakis, 2019; Mathieu et al., 2019). As pEVs play significant roles in coagulopathy, inflammation and angiogenesis, the findings above further signify the therapeutic potential of pEVs.

Accumulating evidence supports the potential of pEVs for delivery of therapeutics and activation of downstream pathways. According to a study by Agrahari et al. (2020) in the field of environmental science, pEVs can deliver nanoparticles smaller than 2.5 μm to human umbilical vein endothelial cells, leading to vascular endothelial injury. According to another study, pEVs can deliver MSCs to inflammation sites and inhibit the development of atherosclerosis, thereby solving the problem of coronary artery stenosis in the treatment of coronary heart disease (Ma et al., 2021). MCCS05 is a nucleotide-binding domain, leucine-rich-containing family, and pyrin domain-containing-3 activator (Coll et al., 2019). Moreover, in the treatment of acute lung injury, pEVs selectively alleviate pulmonary progression by delivering [3-(3-aminopropyl)triethoxysilyl-2-ureido]phosphine-3-carboxamide, which inhibits the production of inflammatory factors (Ma et al., 2020).

These findings collectively suggest that platelets absorb materials from the bloodstream, including proteins, lipids, nucleic acids and even harmful molecules, and activation of platelets stimulates the packaging of these molecules into EVs; the mechanisms by which EVs then exert therapeutic effects is described by pEVs (Burnouf et al., 2014; Dovizio et al., 2018, 2020). Moreover, the biocompatibility and immune transparency of pEVs enable them to escape

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(Chen et al., 2019), providing further evidence that BDMPs are key players in inflammation.

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removal via biological interactions with the mononuclear phagocytic system or complement system. In addition, platelets are enucleated, which reduces the risk of mutation teratogenesis (Burnouf et al., 2014; Agrahari et al., 2019b). Therefore, pEVs have significant advantages for use in molecule delivery.

pEVs also have limitations. First, pEVs exert different qualitative and quantitative effects, depending on the method of their creation (Aatonen et al., 2014; Bei et al., 2016; Ponomareva et al., 2017; Ambrose et al., 2018). Aatonen et al. (2014) found that use of Ca²⁺ ionophores lead to production of a larger number of pEVs than by using thrombin, collagen or adenine diphosphate. However, proteomic analysis showed that Ca²⁺-generated vesicles are indiscriminately packaged and can carry significantly less protein cargo. Therefore, it is important to establish a more suitable and reproducible method to produce pEVs with optimal characteristics (Johnson et al., 2021). Second, there are currently no therapeutic application guidelines for the use of pEVs or mesenchymal stem cell-derived microvesicles, and there are no standard procedures for the purification and characterization of pEVs. Finally, the concentration of pEVs cannot be accurately defined owing to the lack of a standardized test method, so it is more difficult to choose an appropriate blood concentration of pEVs to use as the treatment standard (Lopez et al., 2018). In conclusion, pEVs have great treatment potential, and this potential will be able to be realized further once standardized procedures have been defined by the research community (Lener et al., 2015, Table 1).

**Summary and Perspectives**

pEVs contain a variety of components that allow them to have diverse functions, such as procoagulation and anticoagulation, proinflammation and anti-inflammation, angiogenesis and specificity in targeting and transport (Table 2). This review article focuses on the role of pEVs in promoting inflammation and coagulation, but owing to the diversity of components carried by pEVs, the many other effects of pEVs have not been described. TBI is accompanied by an increase in the number of pEVs, and pEVs may be a critical player in TBI-induced secondary injury by the promotion of inflammatory and clotting responses. pEVs may also have a similar effect on microglial proliferation, which further promotes inflammation. Additionally, inflammation and coagulopathy reinforce each other, resulting in a vicious spiral. Although pEVs promote pathological conditions after injury, they show potential as a therapeutic target for the prevention and treatment of those pathological conditions. Thus, we eagerly await the development of a targeted method to reproducibly modify pEVs for clinical application to prevent TBI-induced secondary injury. Although pEVs have emerged as a new treatment for some diseases, such as intractable injuries and stroke, their role in TBI is still not well understood, and additional studies are needed to achieve the goal of therapeutic success in TBI.

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### Table 1 | Advantages and disadvantages of using platelet-derived extracellular vesicles for therapy

| Advantage/accessory | Reference |
|---------------------|-----------|
| Improving hemodynamic stability | Lopez et al., 2019 |
| Possessing biological activity even after a freeze-thaw cycle of storage | Lopez et al., 2019 |
| The biocompatibility and immune transparency and the lower risk of migration teratogenesis | Burnouf et al., 2014; Agrahari et al., 2019 |
| Delivery function | Kong et al., 2020 |
| The ability to target pathological sites | Aphonon et al., 2014; Kao and Papatoutsakis, 2019; Mathieu et al., 2019 |
| Disadvantage | Aphonon et al., 2014; Bei et al., 2016; Ponomareva et al., 2017; Ambrose et al., 2018 |
| Exert different qualitative and quantitative effects depending on their formation mechanisms/instability of action | Ponomareva et al., 2017 |
| The lack of therapeutic application guidelines | Lopez et al., 2018 |

### Table 2 | Constituents of platelet-derived extracellular vesicles and their effects on target cells

| Constituent | Tissue/systemic response | Reference |
|------------|--------------------------|-----------|
| Lipid      | Phosphatidylserine | Regulate tissue factor to facilitate coagulation | Morrissey et al., 2010; Tripisciano et al., 2017; Rosas et al., 2020 |
| Glycoprotein | CD61 | Bind to fibrin fibers to promote coagulation | Zabainova et al., 2015 |
| Nucleic acid | Mitochondrial DNA | Recognized by Toll-like receptors and enhance inflammatory and autoimmune response in systemic lupus erythematosus | Cheng et al., 2012; Harrison et al., 2016 |
| miRNA-21 | miRNA-24 | Induce B cell response and IgG production to promote inflammation | Sprague et al., 2008 |
| mRNAs | microRNA-21-4A | Contribute to distinct effects through miRNA translation | Linge et al., 2018 |
| Cytokine | Interleukin-1 | Several potent cytokines have effects on innate and adaptive immune cells | Bestor and Pauini, 2016 |
| Organells | Mitochondria | | Zhao et al., 2016; Linge et al., 2018 |
| Growth factor | Vascular endothelial growth factor | Regulate revascularization | Brill et al., 2005; Guo et al., 2017 |
| | Basic fibroblast growth factor | | |
| | Platelet-derived growth factor | | |

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