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Review Article

Platelet-derived microparticles and their cargos: The past, present and future

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ABSTRACT

All eukaryotic cells can secrete extracellular vesicles, which have a double-membrane structure and are important players in the intercellular communication involved in a variety of important biological processes. Platelets form platelet-derived microparticles (PMPs) in response to activation, injury, or apoptosis. This review introduces the origin, pathway, and biological functions of PMPs and their importance in physiological and pathological processes. In addition, we review the potential applications of PMPs in cancer, vascular homeostasis, thrombosis, inflammation, neural regeneration, biomarkers, and drug carriers to achieve targeted drug delivery. In addition, we comprehensively report on the origin, biological functions, and applications of PMPs. The clinical transformation, high heterogeneity, future development direction, and limitations of the current research on PMPs are also discussed in depth. Evidence has revealed that PMPs play an important role in cell-cell communication, providing clues for the development of PMPs as carriers for relevant cell-targeted drugs. The development history and prospects of PMPs and their cargos are explored in this guidebook.

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1. Introduction

Extracellular vesicles are cystic vesicles with a double-membrane structure, and almost all eukaryotic cells (including leukocytes, erythrocytes, endothelial cells and various cancer cells [1], oligodendrocytes [2], glial cells [3,4], and neural stem cells [5] in the central nervous system [6]) can secrete extracellular vesicles (such as exosomes, microparticles, and apoptotic bodies, which different in size and range) after stimulation or apoptosis [7]. Extracellular vesicles participate in cellular communication and various important biological processes in Alzheimer's disease [8], Parkinson's disease [9], and other neurodegenerative diseases. Platelets are small anucleated cells (3–5 μm in size) that can induce the coagulation cascade. When exposed to chemical compounds (such as epinephrine, thrombin, ADP, collagen, and A23187), platelets respond to activation, injury, or apoptosis and generate and shed PMPs, which have high levels of phosphatidylserine (PS) on their surface [10] and contain lipids, proteins, messenger RNA (mRNA), microRNA (miRNA), and even DNA [11]. Among all plasma-borne microparticles (MPs), PMPs account for more than 45% [12,13]. PMPs are highly heterogeneous and participate in numerous biological processes. For example, they promote hemostasis, thrombosis, endothelial repair, angiogenesis, and inflammation; modulate intercellular communications; and not only reprogram the phenotype and physiological functions of neighboring cells [14,15], such as neutrophils, monocytes, and vascular endothelial cells (ECs) in the peripheral bloodstream, but are also involved in the pathogenesis of some diseases [16]. Flow cytometry is used to characterize the PMPs as $CD41^+$, $CD31^+CD41^+$, $CD31^+CD42^+$, or Annexin $V^+/CD61^+$ particles. Among these, CD31 and CD41 are the most commonly used markers for PMP detection [17–20]. Other characterization and analysis methods for PMPs include nanoparticle tracking analysis (NTA), electron microscopy (EM), cryo-EM, etc. [21–31] (Table 1).

The miRNAs enriched in PMPs are miR-19, miR-21, miR-24, miR-27a, miR-126, miR-133, miR-146, miR-155, miR-195, miR-223 and let-7a/b [32–35]. PMPs promote the expression of adhesion molecules and angiogenic factors and regulate the release and secretion of cytokines such as interleukin (IL)−17 and interferon-γ [36–38]. Various MPs are shed from many cell types; among the plasma cell populations, PMPs account for at least 45% [13]. Research on PMPs has developed rapidly in recent years, but there are no comprehensive reviews of PMPs, we provide a systematic and comprehensive description of PMPs from their origins, generation pathways, and biological functions to their applications as well as a critical discussion of their heterogeneity, clinical translation, and risks and discuss the prospects of PMP-mimicking nanovehicle delivery.

2. Origin of PMPs

2.1. *The traditional way*

PMPs are ultra-micro membranous vesicles shed from the serous membranes of platelets. The diameters of PMPs are 0.1–1.0 μm according to transmission electron microscopy. When platelets are activated by factors (such as adrenaline, thrombin, adenosine diphosphate, collagen, A23187, fibrinolysin, complement C, antiplatelet antibodies, and high shear force), phospholipase C promotes the breakdown of phosphatidylinositol (PI) into inositol triphosphate (IP3). IP3 binds to its IP3 receptor in the dense tubular system of the platelet cytoplasm, causing the dense tubular system to release Ca^{2+}. At the same time, some extracellular Ca^{2+} can enter platelets through intracellular Ca^{2+} channels, causing an increase in the intracellular Ca^{2+} concentration. There are more than 10 layers of microtubules arranged in parallel circles under the platelet membrane on the peripheral edge of platelets, and near the platelet membrane, there are denser microfilaments (actin) and myosin, which are related to the maintenance of platelet morphology and deformation. When the Ca^{2+} concentration increases, myosin light chain phosphokinase is activated and phosphorylates myosin light chains in the cytoskeleton under the regulation of Ca^{2+} and calmodulin. The phosphorylated light chains enhance the activity of Mg^{2+}-ATPase, which causes myosin to assemble into filaments and contract toward the center of the cell, resulting in cell contraction. Simultaneously, the increase in intracellular Ca^{2+} can shorten the actin microfilaments in the membrane skeleton through Ca^{2+}-dependent coagulant proteins, prevent the polymerization of microfilaments in

Table 1 – Characterization and analysis methods for PMPs.

Method/Technique	Characterization	Ref
Flow cytometry	Count; Phenotype determination	[21]
NTA	Count; Size distribution; Concentration and phenotype when combined with fluorescence (F-NTA)	[22]
EM	Size distribution; Structure analysis	[23]
Cryo-EM	Morphology and size; Spatial visualization	[24]
Atomic force microscopy (AFM)	Size distribution; Morphology	[25]
Tunable resistive pulse sensing (tRPS)	Count; Size distribution	[26]
Dynamic light scattering (DLS)	Size distribution	[27]
ELISA	Count; Function	[28]
Proteomic and lipidomic analysis	Origins and functions	[29,30]
NanoBioAnalytical	Count	[31]

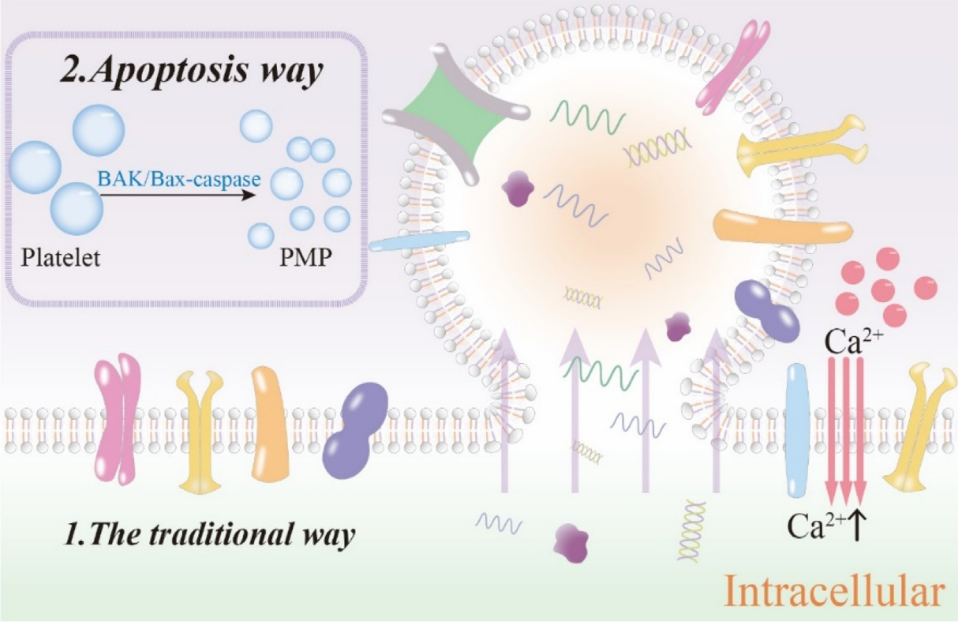

Fig. 1 – The origins of PMPs include the Ca^{2+}-dependent traditional pathway and the Ca^{2+}-independent apoptotic pathway.

the membrane skeleton, and increase membrane motility. Therefore, after platelet activation, the cell contracts, and the cell membrane extends outward and forms pseudopods. At some sites on the deformed cell membrane, the membrane buds into vesicles that eventually fall off. Some of the pseudopods break and the fragments enter the circulating blood, thus producing PMPs (Fig. 1). In addition, some studies have shown that the number of PMPs formed by budding is small, whereas that formed by pseudopod fractures is large [39].

2.2. *Apoptosis pathway*

In addition, Cauwenbergh et al. [40] found that platelets stored for 24 h under standard storage conditions in blood banks released PMPs with procoagulant activity. The mechanism involves αIIBβ3-mediated actin rearrangement and cytoskeletal remodeling by internal and external signaling. This is different from the traditional MP release pathway in that it does not depend on Ca^{2+} influx or Ca^{2+}-dependent proteases. Therefore, Cauwenbergh hypothesized that the mechanism of PMP production under storage conditions involves platelet apoptosis. Schoenwaelder et al. [41] further confirmed that in addition to the traditional activator pathway, apoptosis-related pathways also promote platelet clotting functions. Researchers have found that treatment with ABT-737 induces PS exposure in platelets and significantly increases thrombase production *in vitro* to enhance clotting. This mechanism involves the Bax/caspase pathway (Fig. 1). The increase in procoagulant effects was dependent on BAK/Bax and caspase but was not affected by platelet activation inhibitors or extracellular calcium chelators. In contrast, agonist-induced procoagulant functions in platelets did not significantly change in response to Bax or caspase inhibitors but could be completely eliminated by extracellular calcium chelators or platelet activation inhibitors. Zhu et al. [42] found that αIIbβ3 antagonists inhibited platelet apoptosis, suggesting that there are two procoagulant regulatory pathways and that platelets are able to produce PMPs under different modes of induction, both traditional and apoptotic, but do not affect each other. Zhang et al. [43] found that the apoptotic pathway released a large number of PMPs, and the yield was much higher than that obtained using the traditional method, with differences in total protein extracts, such as CD81 enrichment. Notably, PMP production by the apoptotic pathway was accompanied by cytochrome c release, caspase-3 activation, and an increase in reactive oxygen species (ROS) production. Whether the procoagulant effect of PMPs can be achieved in two ways remains unknown.

3. Biological functions

3.1. *Promoting hemostasis and thrombosis*

Physiological hemostasis and procoagulation are the main biological functions of PMPs. PMPs can be used as substrates to enhance platelet adhesion to ECs by binding glycoprotein Ib (GPIb) to the vascular subcutaneous matrix to stop bleeding [44] and promote blood coagulation. Sinauridze et al. [45] showed that the procoagulant activity of PMPs is 50–100 times higher than that of activated platelets. This procoagulant effect is mainly mediated by PS, an anionic phospholipid, on the surface of the PMP membrane. Therefore, PS^{+} PMPs can bind to procoagulant proteins via the cationic γ-carboxylic glutamate (GLA) domain to form the procoagulant protein complex and promote thrombus formation. All vitamin K-dependent coagulation factors, such as factors II, VII, IX and X, contain GLA domains that bind to

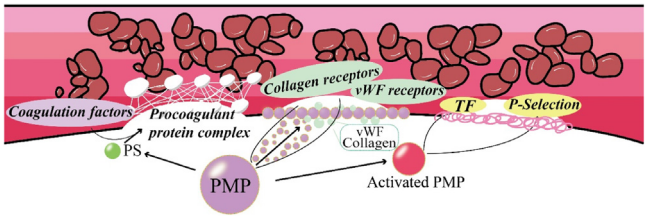

Fig. 2 – The main biological functions of PMPs are physiological hemostasis and procoagulant; the procoagulant activity of PMPs is higher than that of activated platelets mainly through the enhancement of platelet adhesion to other cells and mediation of the coagulation cascade by PS, TF, P-selectin in PMPs.

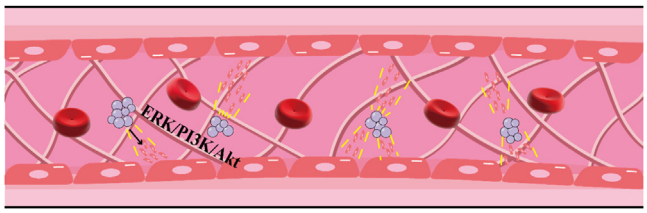

Fig. 3 – The mechanism by which PMPs promote angiogenesis is related to the involvement of angiogenic factors and activation of the ERK/PI3K/Akt pathway.

the PS surface in a Ca^{2+}-dependent manner [46]. In addition, collagen receptors and von Willebrand factor (vWF) receptors are expressed on the surface of PS^{+} PMPs, which can bind to exposed collagen and vWF in the blood after vascular wall damage, and PMPs can aggregate and adhere to the vascular wall [47] to achieve primary hemostasis. However, not all PMP surfaces are PS^{+}. In addition, activated PMPs can enhance the procoagulant activity of tissue factor (TF). When PMPs express PS or TF, they activate platelets and upregulate Xase and prothrombinase to facilitate blood coagulation and thrombogenesis [48]. Another marker, P-selectin [49], mediates the adhesion of activated platelets and other cells to the platelet membrane, leading to a hypercoagulant state in the blood [50] with or without vWF and thrombospondin-1 [51] (Fig. 2).

A decrease in PMPs in the blood can directly lead to increased bleeding susceptibility in patients. Castaman deficiency is characterized by a lack of PMP production capacity, and patients are prone to bleeding [52]. Platelets in patients with Scott syndrome (a rare inherited bleeding disorder) have also been shown to have defective PMP production [53].

In venous thromboembolism, PMPs play a key role in pathophysiological conditions, and there are potential correlations between platelet degranulation and oxidative stress biomarkers (malondialdehyde [MDA], 4-hydroxynonenal, superoxide dismutase, and galectin-3) [54]. Further studies are needed to identify differences in the roles of PMPs under physiological and pathophysiological conditions.

The surface of PMPs is rich in clotting proteins and PS [10], and γ-carboxyglutamic acid in clotting proteins can upregulate procoagulant factors (factors VIII/IX and V/X) [55]. Furthermore, PMPs promote thrombin generation and transfer and release of TF, which initiates coagulation and thrombin generation. Activated platelets release calcium ions, which bind to phospholipids on PMPs and activated platelets, facilitating the coagulation cascade and the formation of prothrombin complexes [56].

3.2. *Promoting endothelial repair and angiogenesis*

In healthy individuals, PMPs can promote the proliferation and survival of ECs as well as capillary formation [38]. Kim et al. found that PMPs promoted the proliferation, survival, migration, and angiogenesis of human umbilical vein endothelial cells (HUVECs). To determine which components of PMPs play a major role in angiogenesis, heat treatment (which removes protein growth factors) and activated carbon treatment (which assorted lipid growth factors) were used, and the results showed that the effects of PMPs on EC proliferation, migration, and angiogenesis were significantly inhibited after activated carbon treatment. These results suggest that lipids may be the main components by which PMPs promote angiogenesis. Vascular endothelial growth factor (VEGF) and S1P (a lipid growth factor) promote angiogenesis by activating the extracellular signal-regulated kinase (ERK)/phosphoinositide 3-kinase (PI3K)/Akt pathway via the VEGF receptor 2 and Gi proteins, respectively. Therefore, cells were treated with wortmannin (a PI3K inhibitor), PD98059 (an ERK1/2 inhibitor), and pertussis toxin (PTx) (a Gi protein inhibitor), and the results showed that PMP-mediated promotion of EC proliferation, migration, and angiogenesis was significantly inhibited. These findings suggest that the mechanism by which PMPs promote angiogenesis is related to the involvement of angiogenic factors and activation of the ERK/PI3K/Akt pathway (Fig. 3).

3.3. *Inflammation*

PMPs can directly activate monocytes and ECs and promote the interaction between chemokines that are transferred among cells as well as cytokines that are expressed and secreted by T cells. Activated monocytes secrete a variety of inflammatory factors (such as tumor necrosis factor, IL, adhesion molecules, and proteolytic enzymes), damage ECs, recruit inflammatory cells, and participate in immune inflammatory responses. Furthermore, PMP released by activated platelets stimulates the expression of various adhesion molecules in vascular ECs and neutrophil receptors. Monocytes and neutrophils are recruited near ECs and attach to their surface through ligands, whereas neutrophils undergo transendothelial migration to the site of inflammation. Tamagawa-Mineoka et al. [57] found that the PMP and soluble P-selectin levels in patients with atopic dermatitis were higher than those in the control group and patients with nonspecific urticaria. After skin lesions improved with treatment, the PMP and soluble P-selectin levels significantly decreased. These findings suggest that PMPs and soluble P-selectin play important roles in the pathogenesis of atopic dermatitis. By delivering arachidonic acid to ECs,

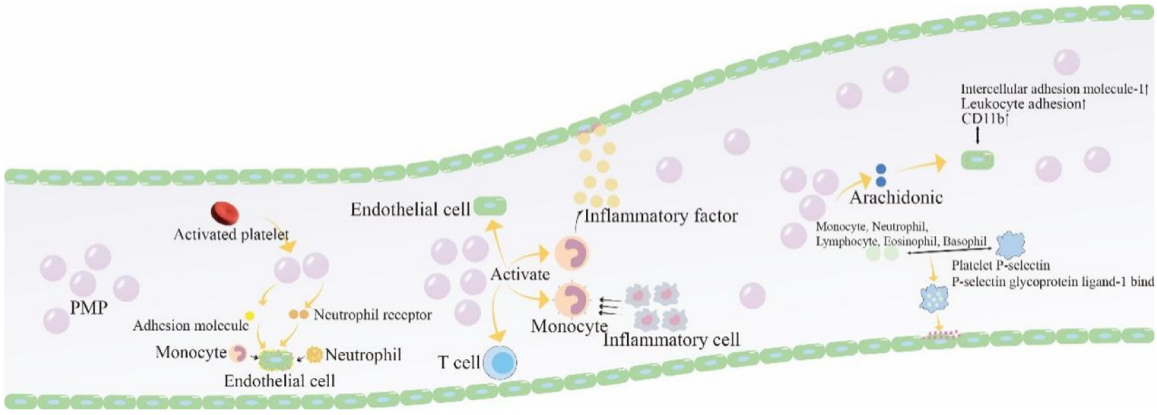

Fig. 4 – PMPs can directly activate monocytes, ECs, etc. to participate in the immune response.

PMPs upregulate intercellular adhesion molecule-1 and subsequent leukocyte adhesion. They can also upregulate CD11b expression on the surface of leukocytes and enhance their phagocytic activity, thus playing a role in immune and inflammatory responses (Fig. 4). Platelet P-selectin and its main ligand, P-selectin glycoprotein ligand-1, bind to leukocytes, including monocytes, neutrophils, lymphocytes, eosinophils, and basophils, leading to the formation of a platelet-leukocyte complex and the induction of leukocyte migration. This phenomenon allows white blood cells to migrate to the inner subcutaneous tissues and participate in the inflammatory response.

3.4. *Intercellular interactions*

The PMP surface expresses a variety of proteins and receptors and carries a series of cytokines, chemokines, signaling proteins, growth factors, mRNAs, and miRNAs. After interacting with specific cells, PMPs can deliver their components or activate cell surface receptors. In this way, cell activity can be regulated, cell phenotypes can be altered, and cell functions can be reprogrammed [58]. Jy et al. [59] demonstrated that PMP binding to neutrophils increases their phagocytic activity and CD11b expression in a dose-dependent manner. The activation of integrin GPIIB/IIIa on the surface of apoptotic PMP membranes and PS exposure enable interactions with monocytes and change their phenotypic status. For example, increased expression of CD11b, CD14, CD31, CD47 and other chemokine receptors, as well as the expression of low-density lipoprotein receptors, eventually promotes the differentiation of monocytes into macrophages [60] and mediates immune evasion by inhibiting phagocytosis via binding to signal regulatory proteins on macrophages [61,62]. PMPs also carry a large number of cytoplasmic components, including miRNAs, and these small vesicle structures may transfer miRNAs to target cells and affect their protein expression. Laffont et al. [35] found that activated platelets release miRNAs (miR-223 being the most abundant type) and form a complex with Argonaute 2 (Ago2). The Ago2-miR223 complex is taken up by HUVECs. The expression of F-box/WD-40 domain protein 7 (FBXW7) and Ephrin A1 (EFNA1) in HUVECs was downregulated at both mRNA and protein levels to achieve biological effects (Fig. 5). Qu et al. [63] found that PMPs transfer miR-1915–3p to hematopoietic stem/progenitor cells (HSPCs) to downregulate the expression of Rho GTPase family member B (RHOB) and drive cells towards megakaryocytes to produce platelets.

4. Applications

4.1. *Cancer progression*

Angiogenesis often occurs to supply blood and nutrients in solid cancers. Solid tumor vasculature is highly permeable, which could facilitate interactions and transfers between PMPs and tumor cells. Interestingly, PMPs can accelerate the production of proangiogenic factors and formation of vascular structures [64]. Many studies have indicated that platelets and PMPs are involved in the exchange of nucleotides and proteins with cancer cells in the tumor microenvironment via receptor-ligand interactions. During the exchange process, platelets and PMPs participate in tumor progression, including cell proliferation, programmed cell death, survival, migration, metastasis, invasion, angiogenesis, immune escape/tolerance, malignant progression, poor prognosis, and distant metastasis [65–68]. When platelets contact tumor cells, but not monocytes, dendritic cells, NK cells, or lymphocytes in colon carcinoma models, they release the chemokines CXCL5 and CXCL7, which facilitate granulocyte recruitment via the CXCR2 receptor. Metastatic niche formation relies on granulocyte recruitment [69]. In addition, CXCL1 and CXCL2 secretion by breast cancer cells during chemotherapy has been shown to recruit granulocytes to primary tumors [70]. These chemokines and receptors may form the CXCL1/2/5/7–CXCR2 signaling axis. Collectively, these findings indicate that platelets and PMPs are involved in granulocyte recruitment via the CXCR2-ligand signaling axis during tumor progression and the metastatic cascade at different stages.

Platelets and PMPs play important roles in the pathophysiology of the cancer microenvironment. Evidence suggests that RNA expression is altered in platelets of patients with breast cancer and other tumors. For example,

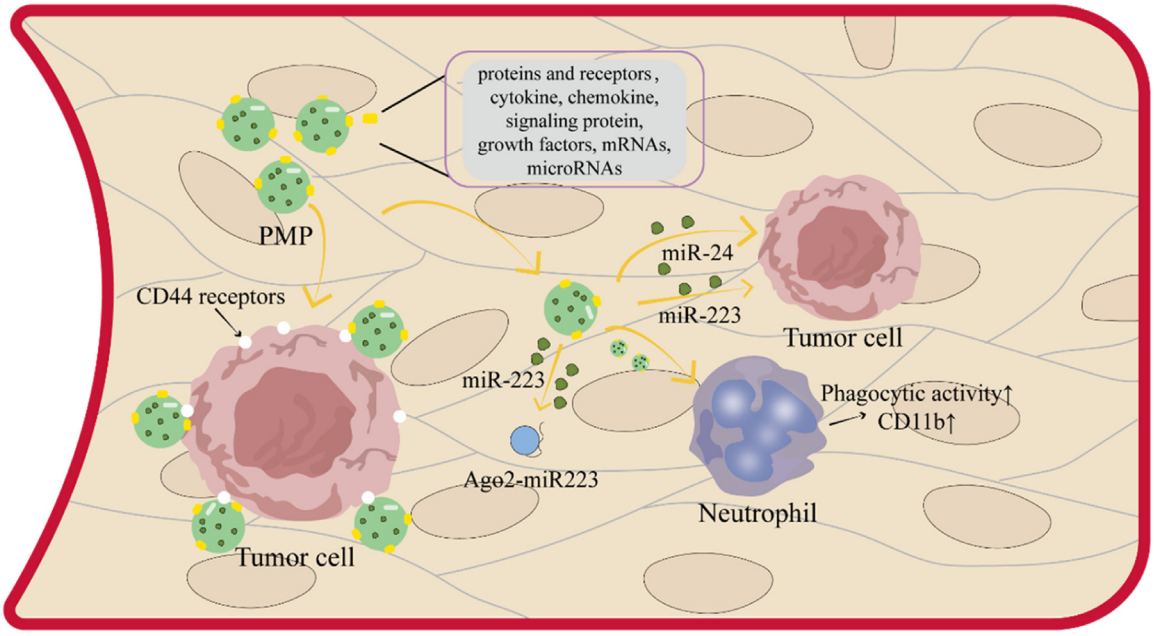

Fig. 5 – A variety of proteins and receptors on the surface of the PMP and a range of PMP contents are involved in cell-cell interactions in vivo.

TPM3 mRNA was elevated in platelets from 549 patients with breast cancer [71], which correlated with metastasis in those patients, and this factor was delivered to tumor cells via PMPs to enhance their migration. James et al. [20] also confirmed that PMPs could infiltrate solid tumors (including lung and colon carcinoma ectopic tumors), possibly through PMP-tumor cell interactions, and that the cargo miR-24 resulted in tumor cell apoptosis. In tumor cells, miR-24 targets and downregulates the expression of mt-Nd2 and Snora75, which are associated with mitochondrial function and growth in the earlier stages. The cargo miR-223 targeted EPB41L3 and suppressed its expression, thus promoting non-small cell lung cancer cell invasion [34]. Gharib et al. [72] found a novel PMP-mediated mechanism of cancer pathogenesis, namely, that PMP induces tumor growth and invasion in chronic lymphocytic leukemia (CLL) through mitochondrial internalization and oxidative phosphorylation stimulation, which is not only similar to CLL disease progression but also leads to increased resistance to related therapeutic drugs in patients with CLL. This study also demonstrated for the first time that PMP plays an important role as a mitochondrial delivery vector in the pathogenesis and progression of leukemia and provides a new strategy for the treatment of leukemia in the future. In the context of enhanced vascular permeability, the transfer, modulation, and cell-cell interactions of PMPs could facilitate the development of PMPs for tumor-targeted delivery. Owing to the characteristics of cancer cells, platelets aggregate around circulating tumor cells (CTCs) and help them survive in the blood and spread to new tissues. P-selectin is also overexpressed on the surface of platelets and can specifically bind to CD44 receptors, allowing PMPs to aggregate on tumor cells. PMPs could be designated as an outer shell to decorate the inner core (such as nanoparticles and nanogels) and target cancer cells with upregulated CD44 expression to achieve antitumor effects [73,74].

Vismara et al. [75] demonstrated that different cell lines in the same cancer model exhibited dramatically different responses when exposed to the same PMP population. Further study of the complex relationship between platelets and cancer is essential before proposing the use of PMPs for tumor promotion or inhibition.

Furthermore, the different roles of platelets, PMPs, and their cargoes in pathological tumor conditions may be attributed to five factors, with the first being differences in cancer cell lines. The second may be the autoimmune response during different stages of cancer. The balance of various biomolecules (such as chemokine C-X-C motif ligand 4 (CXCL4), platelet factor 4, regulatory T cells, infiltrating lymphocytes, and myeloid-derived suppressor cells) in the tumor microenvironment could be a third factor. Fourth, cargo miRNAs target both tumor suppressor genes and oncogenes. Finally, individual differences cannot be ignored. Biomolecules in platelets and PMPs need to be studied further to develop early and reliable diagnostic biomarkers for cancer that could extend the life expectancy of patients with tumors.

4.2. *Vascular homeostasis*

In vascular homeostasis [76], platelets form aggregates with monocytes and neutrophils via P-selectin- and (P-selectin glycoprotein ligand-1) PSGL-1-dependent methods. The mediators of communication between platelets and vascular walls are mainly vWF, chemokine ligand 5 (CCL5), VEGF, basic fibroblast growth factor (bFGF), stromal cell-derived factor-1 (SDF-1 or CXCL12) and platelet-derived growth factor (PDGF). First, the platelets are exposed to subendothelial collagen and become activated. vWF plays

a central role in bridging the activation process. Following activation, platelets release CCL5, which attracts leukocytes, promotes their adhesion, and is subsequently deposited on ECs. Platelets release VEGF or bFGF to repair the vasculature in damaged tissues and release SDF-1 (CXCL12) to recruit endothelial progenitor cells. Additionally, PDGF is released by platelets, which can regulate the proliferation, growth, and differentiation of vascular smooth muscle cells [74] and oligodendrocyte precursor cells [77]. Activated platelets also release PMPs that transfer their cargo, including proteins and miRNAs, to the ECs, thereby influencing their fate and function.

ECs are part of the blood-brain barrier (BBB), and recent research has shown that activated platelets release miR-223 into circulation via PMPs, which are then internalized by ECs. In recipient ECs, the accumulated miR-223 can form miR-223-Ago2 complexes, which repress the expression of FBXW7 and EFNA1 [35] and heterotypically regulate gene expression in ECs. When PMPs deliver miR-142–3p into ECs and induce abnormal EC proliferation, vascular dysfunction occurs via Bcl-2-associated transcription factors under hypertensive conditions [78].

PMPs interact with neutrophils, and their bioactivation component (high mobility group box-1 protein) HMGB1 drives EC damage, contributing to sustained vasculopathy [79]. HMGB1 promotes neutrophil autophagy and survival, endothelial damage, and the generation of (neutrophil extracellular traps) NETs byproducts. The effect of HMGB1 is abrogated by BoxA, a competitive inhibitor of HMGB1. These findings indicate that activated platelets could contribute to systemic sclerosis-associated sustained vasculopathy via PMPs and HMGB1.

These results support a scenario in which functional miRNAs and proteins contribute to the regulation of gene expression in PMP recipient cells in the circulatory system through PMP-dependent intracellular communication. Therefore, further studies on the effects and mechanisms of PMPs, especially their cargo miRNAs and proteins, in various physiological and pathological processes are needed.

4.3. *Thrombosis*

Procoagulant microparticles in the circulation include apoptotic, endothelial-derived, and TF-positive PMPs [80]. The surfaces of PMPs have 5–100-fold higher procoagulant activity than normal platelet surfaces [81]. PMPs mediate coagulation by exposing cells to PS and initiating thrombin generation [80]. Thrombosis is associated with the pathogenesis of many types of pulmonary arterial hypertension (PAH) involving a hypercoagulable phenotype, upregulation of TF, increase in circulating vWF levels, and abnormal platelet aggregation [82,83]. More recently, Ogawa and Matsubara demonstrated that PMP levels were increased in patients with PAH. Furthermore, PMP levels were significantly higher in patients with different subtypes of PAH, including chronic thromboembolic pulmonary hypertension and idiopathic pulmonary arterial hypertension, than in control participants. Among the therapeutic drugs for treating PAH, epoprostenol, a prostaglandin analog, decreases PMP levels in a dose-dependent manner by inhibiting platelet aggregation induced by collagen-ADP [84,85]. Even after excluding patients with connective tissue disease, PMP levels in patients were still significantly higher than those in the control group, especially the levels of procoagulant PS^+ PMPs [86] and $CD40^+$ PMPs [87].

Thromboembolic events occur in approximately 90% of cases during induction therapy for acute lymphoblastic leukemia (ALL) [88,89]. PMPs in children with B-cell ALL are significantly higher at diagnosis and during the induction of prednisone and L-asparaginase therapy [90]. Moreover, Periard et al. [18] demonstrated that cisplatin administration was immediately followed by a decrease in the circulating levels of prothrombotic endothelial-derived MPs and PMPs. However, the MP levels increased in the second and third cycles, suggesting that cisplatin-induced stroke was associated with MP release.

The term thrombophilia is increasingly used to describe deep vein thrombosis (DVT) in individuals with genetic or acquired disorders [91]. Compared with controls, PMPs and phospholipid generation were higher and the prothrombinase-induced clotting time assay velocity was lower in patients with DVT [92]. Women with polycystic ovary syndrome (PCOS) are often obese and thought to have increased cardiovascular risk. Several studies have indicated that circulating PMPs are not only elevated in obese patients [93] but are also increased in normal-weight women with PCOS [94]. It is necessary to assess plasma PMPs in overweight/obese women with PCOS, which is thought to be associated with the activation of the coagulation cascade in the prothrombotic state. PMP levels are higher in women with PCOS than in healthy, body mass index-matched women. More studies are required to identify the cause of the increase in PMPs in patients with PCOS and assess the correlation between PMPs and cardiovascular risk [95].

PMPs are released from activated platelets and contain various bioactive macromolecules (chemokines, enzymes, and miRNAs) that contribute to the risk of venous thrombosis. For example, miR-1915–3p [63] is highly enriched in PMPs, inducing HSPCs toward the megakaryocytic lineage and platelet production by suppressing the expression of RHOB. Hu et al. [96] used lipidomics to compare the lipid composition of PMPs in patients with ovarian cancer and healthy controls and identified 12 classes and 177 species. This study focused on seven classes: PS, PI, phosphatidic acid (PA), phosphatidylglycerol (PG), phosphatidylcholine (PC), acylcarnitine (CAR), and sphingomyelin (SM). PS, PI, PA, and PG were in the procoagulant group, whereas the anticoagulant group consisted of PC, CAR, and SM. Among them, 28 species of lipids changed, and the levels in the procoagulant lipid group significantly increased, whereas those in the anticoagulant group did not. These results further proved that the procoagulant lipids in platelets and PMPs increase the risk of venous thrombosis in patients with ovarian cancer.

Furthermore, recent studies [84,86,90,97-99] suggested that PMPs could play pivotal roles in enhancing vessel remodeling, the prothrombotic environment, and cell proliferation by carrying TF, PS, and thromboxane, which makes it possible to develop PMPs as specific biomolecules for the diagnosis of thrombosis-associated disease.

4.4. *Cell-cell communication*

The crosstalk between platelets and other cells (circulating blood cells and those in the vascular wall) involves both direct and indirect pathways. The direct mechanism involves cell-cell interactions through membrane receptors, GPIbα [100], P-selectin [101], and PS [102]. Activated platelets can participate in gene expression in recipient cells through intercellular communication mediated by PMP delivery of bioactivated components that act in an indirect manner. A previous study indicated that platelet- and PMP-derived miRNA-4306 was decreased and acted as a poor prognostic factor for coronary artery disease (CAD) [103]. MiRNA-4306 noticeably inhibited the migration of human monocyte-derived macrophages (HMDMs) and reduced the number of macrophages in the cardiac tissue in a mouse myocardial infarction model through the VEGFA/ERK1/2/NF-κB signaling pathway. Interestingly, PMPs co-fractionated with plasma miRNA-4306 facilitated transfer of miRNAs into HMDMs and inhibited their migration [104].

4.5. *Inflammation*

PMPs may promote an inflammatory response by transferring arachidonic acid to ECs, increasing CD54 (intercellular adhesion molecule-1, ICAM-1) expression, which attracts leukocytes to adhere to the vascular endothelium and migrate into the intima, after which cytokines and growth factors that promote plaque formation and vascular recovery are released [13]. Additionally, Ren et al. [105] demonstrated that an increase in circulating PMPs showed a positive correlation with fibrinogen, IL-6, and tumor necrosis factor α (TNF-α) in patients with oral squamous cell carcinoma (OSCC) compared with healthy controls and patients with keratocystic odontogenic tumors. Zhou et al. [106] found that the PMP levels were not significantly different between the healthy control (HC) and recurrent miscarriage (RM)/antiphospholipid antibody syndrome (APS) groups, demonstrating abnormal activation, and the change in the amount was not the key point during the progression of RM/APS. In the RM/APS group, PMPs were taken up by HUVECs and HTR-8/SVneocells, in which increased inflammatory cytokines (TNF-α), adhesion molecules (ICAM-1), and vascular cell adhesion molecule-1, promoted HUVEC apoptosis and decreased trophoblast invasion and migration.

Inflammation, endothelial injury, dysregulation of the angiogenic balance, uteroplacental circulation deficiency [107,108], and placental apoptosis [109] are the key processes that result in poor obstetric outcomes. Accumulating evidence has shown that PMPs play important roles in inflammation, the prothrombotic state, autoimmune diseases, and preeclampsia [110,111].

4.6. *Neural regeneration*

PMPs contain various cytokines and growth factors that have been shown to affect angiogenesis and postischemic tissue regeneration. In addition, these factors have similar effects on neural stem cell (NSC) proliferation, survival, and differentiation following central nervous system (CNS) injury. Following brain injury, oligodendrocytes release myelin surrounding neuronal axons to aid recovery in a damaged environment [77]. PDGF-AA initiates mitosis in oligodendrocyte precursor cells and stimulates their survival, proliferation, maturation, and differentiation. PMPs also promote NSC proliferation, survival, and differentiation (including neurons and astrocytes); formation of new dendritic spines; and intensified neuronal activity through fibroblast growth factor (FGF), VEGF, and PDGF associated with changes in the phosphorylation of ERK, Akt, and other unknown growth factors [112,113]. Platelets [113] also contribute to neuroinflammation after traumatic brain injury; brain-enriched glycolipids induce platelet degranulation and the production and secretion of platelet-activating factor and serotonin(5-HT) via PMPs, which then modulate neuroinflammation. However, the effects of platelet-derived serotonin on the regulation of inflammation and hemorrhage are contentious, and further studies are necessary.

Interestingly, activated platelets release brain-derived neurotrophic factor (BDNF) after treatment with cigarette smoke, which upregulated TF expression. Additionally, smokers and never-smokers were compared, and in smokers, the TF and BDNF levels were significantly increased in plasma but were decreased in serum; however, whether BDNF is encapsulated in PMPs has not yet been elucidated [114]. These results provide new insights into the relationship between PMPs and neurogenesis, which may be used to treat brain injury and other neurodegenerative diseases by targeting PMPs and their cargos.

4.7. *Biomarkers*

PMPs have recently received considerable attention owing to their important roles in thromboembolism and the release of active components [114], especially PS-positive components, which can promote procoagulant activity [115,116]. The accuracy of PMPs was similar to that of D-dimer in the diagnosis of pulmonary thromboembolism (PTE). The combination of PMPs and D-dimers increased the sensitivity and specificity. The combination of PMPs, platelet distribution width, P-selectin and D-dimer is a noninvasive, affordable, and highly efficient strategy that may be used for diagnosing PTE with increased sensitivity, specificity, and accuracy. These findings indicate that an elevated PMP level is an effective predictor of PTE [117].

Some studies have used circulating levels as diagnostic biomarkers. Whether the levels of circulating MPs could be valuable for predicting the severity and prognostic outcome of lung cancer is currently being researched. Flow cytometric analysis indicated that the circulating levels of platelet-derived activated MPs (PDAc-MPs) and platelet-derived apoptotic MPs (PDAp-MPs) were higher than those in the control group. Although circulating PDAc-MP levels were higher in patients with lung cancer, they were not associated with lung cancer disease status, metastasis, or cell type. Therefore, a better understanding of the mechanisms underlying lung cancer occurrence and progression is needed [118].

In addition, EC- and monocyte-derived MPs showed no marked differences among OSCC stages. However, elevated levels of circulating PMPs in stage III–IV OSCC, compared to other stages, may contribute to the use of plasma PMPs as biomarkers in the malignant progression of OSCC [105].

Interestingly, PMPs were significantly higher in the immune-related disease progression group than in the immune-related objective response group after immunotherapy (administration of pembrolizumab [200 mg once every 3 weeks] or nivolumab [240 mg once every 2 weeks] with or without chemotherapy for at least 18 weeks). In multivariate logistic regression analysis, >80 PMP events/μl after immunotherapy were associated with disease progression in advanced non-small cell lung cancer and could independently predict the therapeutic effect of immunotherapy [119].

Overall, circulating PMP levels may be related to the occurrence and progression of cancer and PTE. Measuring PMP levels as a biomarker is a highly efficient, noninvasive, and affordable strategy.

4.8. *Targeted delivery*

Owing to their advantages of long shelf life, high targeting ability, excellent biological adaptability, and biocompatibility [120], Jyotsnan et al. [121] used PMPs as effective delivery vectors. They delivered markedly increased drug levels to cancer cells with less extravasation, resulting in excellent antitumor therapy and minimal off-target side effects.

Soleymani et al. [122] found that, compared to other synthetic nanoparticles, PMP is considered a safe, cheap, and natural carrier of anti-HIV drugs. As a result, the team loaded PMPs with therapeutic-targeted lamivudine and tenofovir, which showed high encapsulation rates and enhanced efficacy compared with monotherapy. Pawlowski et al. [123] reported that PMPs can be used to deliver thrombolytic drugs to achieve targeted fibrinolysis without affecting systemic hemostasis (Fig. 6).

Moreover, Ma et al. [124] and Li et al. [125] developed platelet membrane-mimetic nanocarriers by coalescing liposomes and polydopamine to achieve photothermal sensitivity and near-infrared light absorption/conversion abilities (Fig. 7).

The engineered nanosystem inherited the biological characteristics of adhesion to cancer cells and damaged vasculature, and chemodynamic therapy penetrated deep into the tumors through photothermal or near-infrared irradiation, subsequently targeting two cascades, inducing remarkable tumor ablation, and prolonging the lifespan. Inspired by the clinical success of immune checkpoint inhibitors, anti-PDL1 (engineered monoclonal antibodies against programmed death ligand 1) was conjugated to the surface of platelets to facilitate delivery to the surgical site and target CTCs in the bloodstream during platelet activation, thereby reducing the risk of cancer regrowth and metastatic spread [126]. Immune thrombocytopenic purpura (ITP)/idiopathic thrombocytopenic purpura is characterized by easy or excessive bleeding due to the presence of antiplatelet autoantibodies that decrease platelet levels. Wei et al. [127] demonstrated the use of a platelet-derived membrane-coated nanoparticle platform with native platelet surface proteins that could effectively bind and clear pathological antiplatelet autoantibodies as an antibody decoy to treat ITP, which helped neutralize these autoantibodies in the circulation and enable the survival of healthy platelets.

An important biological characteristic of platelets is their ability to target thrombi, adhere to damaged blood vessels, and bind to platelet-adhering pathogens. Furthermore, their lack of particle-induced complement activation, aggregation around CTCs, and reduced cellular uptake by macrophage-like cells [74] means designing platelet-mimetic nanocarriers is an effective strategy for coronary restenosis, ischemic stroke, and myocardial infarction. Platelet-mimetic nanoparticles have been used to deliver docetaxel and vancomycin and reported to show enhanced therapeutic efficacy against coronary restenosis and systemic bacterial infection [74].

Biomimetic nanocarriers promote the in situ generation of NO to disrupt local platelet aggregation, rapidly target stroke lesions, restore blood flow, and induce reperfusion of the stroke microvasculature [128]. Stem cell transplantation results in low retention and engraftment of transplanted cells, which limits their clinical application. Tang et al. designed modified cardiac stem cells with platelets decorating their surface, which exploited the ability of platelets to home to the injury site and enhance their targeting in myocardial infarction. Engineered cardiac stem cells show increased retention in the heart, reduced infarct size, and improved therapeutic outcomes [129]. This stem cell manipulation approach and its potential applications to multiple cell types are promising. This method is rapid, straightforward, and safe. Thus, these results provide promising strategies for developing PMP-biomimetic delivery for the targeted treatment of tumors, ischemic stroke, and myocardial infarction, which benefits from their nano-to-micron size, large quantities in blood, long life in the circulation, excellent biological adaptability and biocompatibility, and their ability to evade an immune response, adhere to cancer cells, respond to vascular damage, and target tumors [130,131]. There is still a long way to go in the development of PMP delivery systems, from research to clinical practice.

The first barrier of the BBB is the brain ECs. PMPs can be taken up by human brain ECs via phagocytosis and micropinocytosis [132]. Advanced delivery can reduce side effects, improve pharmacokinetics, enhance biocompatibility, prolong circulation time, improve efficiency, and promote therapeutic efficacy. This strategy may be a significant advantage of PMPs as BBB-targeting carriers. Gaining insights into the characteristics and functions of PMP could facilitate the development of PMP-mimicking nanovehicle delivery systems to promote neural and vascular regeneration strategies that target the injured CNS.

5. Discussion

The amount and cargo of PMPs differ depending on the stimulus to which the platelets are exposed [133]. Based on the present results, the contents differ functionally. In future studies, other physiological roles of PMPs in specific diseases should be considered. The heterogeneity of PMPs,

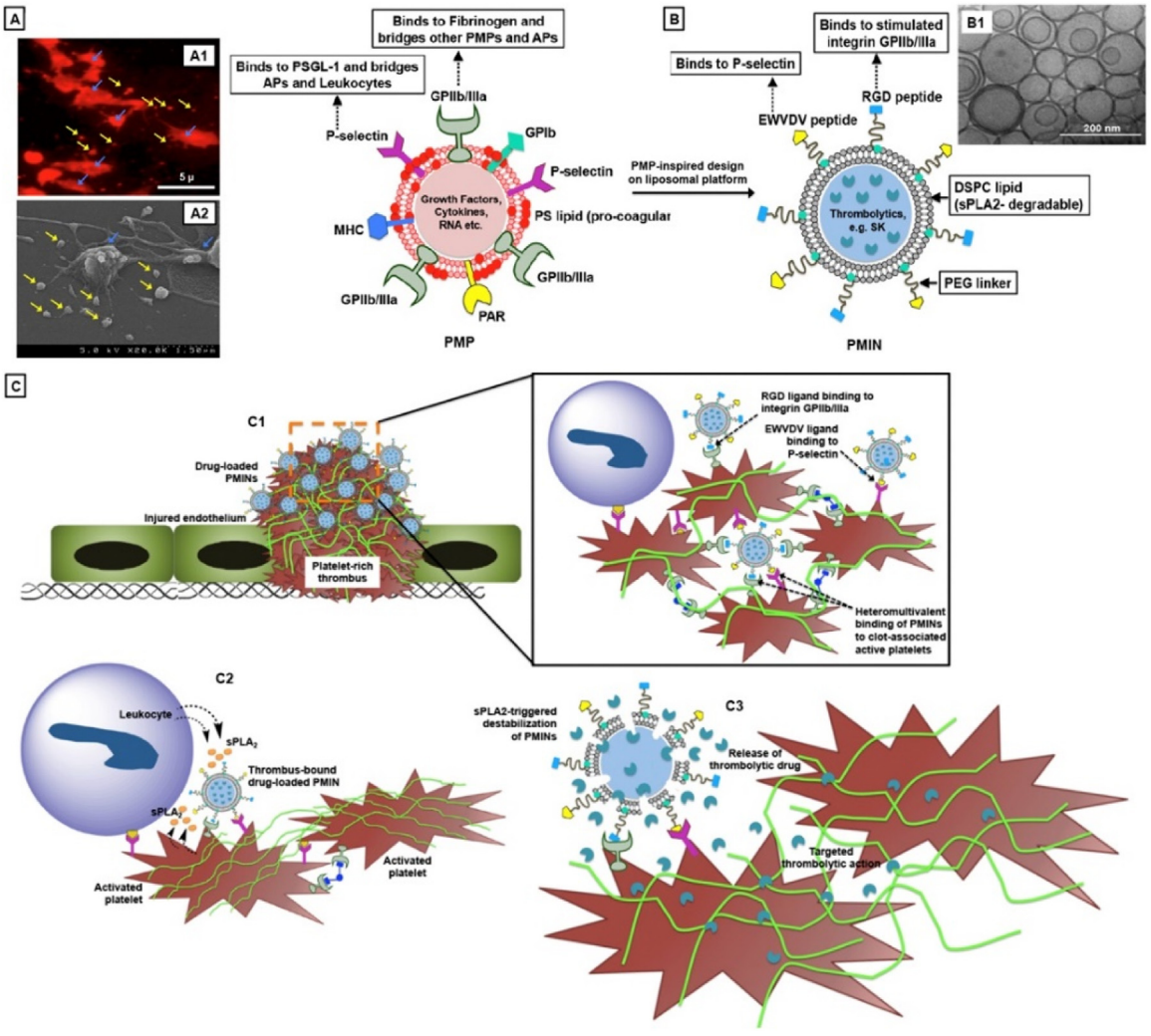

Fig. 6 – Schematic representation of PMP-inspired nanovesicles (PMINs), including characterization and mechanism of action of PMINs. PMINs protect circulating encapsulated thrombolytic drugs against off-target uptake and action by actively anchoring to platelet-rich thrombi through heteropolyvalent binding to integrins GPIIb-IIIa and P-selectin on activated platelets, and allowing the drug to trigger release via thrombus-associated enzymes. (A) Schematic representation of platelet-derived microparticles (PMPs) showing characteristic surface entities. (B) Schematic representation of PMP-inspired nanovesicle (PMIN). (C) Envisioned mechanism of targeted thrombolytic action using PMINs. (Reproduced with permission from [123]. Copyright 2018 Elsevier.).

including their activation modes, membrane surface proteins, phospholipids, contents, and biological functions, provides a rich source of disease-screening biomarkers (Table 2).

The highly heterogeneous nature of PMPs may be caused by the different pathological and physiological environments in which platelets respond to achieve precise regulation of target cells. More studies are needed to clarify the differences between different PMPs and to probe deeply into the feasibility of their application in various diseases and development of targeted drug-carrying systems. This suggests that when using PMPs to study a certain field, such as tumor research, other biological functions of PMPs (such as procoagulant and inflammation) need to be considered simultaneously. This further indicates that the occurrence and progression of disease is a complex process with many influencing factors and complex molecular regulatory mechanisms, which should be taken into account in both basic and clinical research. We hope that this paper will provide ideas for the development of cross-disciplinary and multiple therapeutic means and joint applications.

According to current studies, PMP generation includes traditional and apoptotic pathways, both of which regulate cytoskeletal remodeling through αIIbβ3, but the specific mechanism of the apoptotic pathway remains to be investigated. We found that apoptosis may be related to platelet storage lesions because they have similar manifestations. Cytoskeletal remodeling affects the motility and stability of platelets to produce PMPs, suggesting that the production of PMPs can be affected by inhibition or activation of αIIbβ3, a well-recognized antithrombotic target, and its

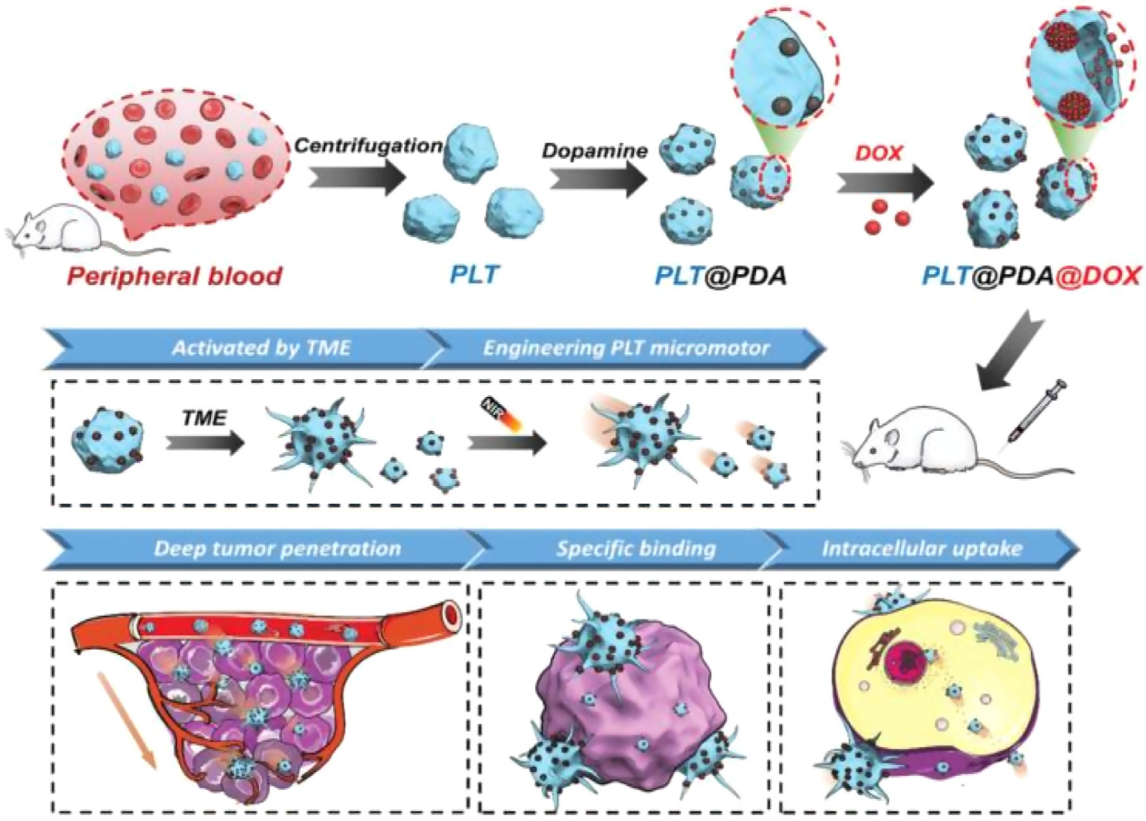

Fig. 7 – Schematic illustration of the preparation and application of engineered platelet-based micro/nanomotors in enhanced cancer therapy. (Reproduced with permission from [125]. Copyright 2021 John Wiley and Sons.).

antagonists can be used in antithrombotic therapy research [134]. Meanwhile, further evaluation of αIIbβ3 as a marker of PMP generation is needed.

Leytin et al. [135] demonstrated that platelet activation (Day 2) triggers and produces PMPs earlier than platelet apoptosis (Day 13) during the storage of platelet concentrates under blood bank conditions. As platelet concentrates stored at 22 ± 2 °C for 24 h (normal and storage bags) or 5 d (specialised storage bags) are currently used in clinical therapy, the effects of platelet activation on patients after PMP secretion should be noted. Regarding clinical and laboratory protocols, apoptotic PMPs are arrested after storage for 13 d at room temperature, potentially resulting in PMPs with minimal clinical blood products. The procoagulant effect of PMPs is beneficial in cases of hemorrhage or coagulation disorders but is not feasible in patients at high risk of cardiovascular or thrombotic disorders, and in patients with cancer, consideration should be given to whether PMPs may contribute to tumor progression. To reduce the waste of platelet concentrates, it is important to study their coagulation effect after long-term storage; however, the safety of platelet concentrates after apoptosis should be fully considered. We considered whether the shelf life of platelet concentrates could be prolonged by improving platelet storage methods, such as inhibiting platelet apoptosis using an αIIbβ3 antagonist and apoptosis inhibitor. Reddoch-Cardenas et al. [136] kept platelets refrigerated (1–6 °C) with platelet additive solution (unknown active ingredient) for 15 d and found that refrigerated platelets could maintain hemostatic function for at least 15 d

The procoagulant activity of PMPs is higher than that of platelets, and it is feasible to administer PMPs alone to patients with coagulation disorders. PMPs are also rich in biological functions, and it is important to evaluate whether they can be used as indicators of platelets in clinical therapy to ensure that the platelets the patient receives for transfusion are harmless.

The risk of thrombosis is associated with the prognosis of many diseases, including tumors that put patients in a hypercoagulable state by releasing large amounts of inflammatory factors, and PMP-mediated thrombosis further increases this risk. Further studies on the feasibility of PMPs as markers of thrombotic risk are warranted, and the preparation of drug-carrying systems using PMPs loaded with, for example, αIIbβ3 antagonists targeting platelets to inhibit thrombosis, is of clinical interest.

Although the proof-of-concept that PMPs can be used as an anticancer drug carrier has been demonstrated in some studies [121–123], the contents and various glycoproteins and integrins on the membrane can promote the development of cancer by helping tumor cells achieve immune escape, promoting tumor angiogenesis, and providing material and energy to support tumor metastasis; therefore, studying the security of PMPs in the future is essential [15,137].

Table 2 – Biological functions and applications of the active molecules carried by PMPs.

Cargo	Biological functions
• Lipid	
PS	• Bind to procoagulant proteins. • Calcium ions bind to PMP and phospholipids on activated platelets to promote the coagulant cascade reaction and thrombospondin complex formation[56]. • Initiator of coagulation and thrombin generation
TF	• PS and TF activate platelets and upregulate Xase and prothrombinase to facilitate blood coagulation and thrombogenesis[46].
Arachidonic acid	• Upregulate intercellular adhesion molecule-1 and subsequent leukocyte adhesion to promote plaque formation and vascular recovery. • Upregulate the expression of CD11b on the surface of leukocytes and enhance their phagocytic activity. • Regulate immune response. • Promote angiogenesis. • Application: Procoagulant lipids in platelets and PMPs increase the risk of venous thrombosis in ovarian cancer patients[96].
• Protein	
CD41+CD31+	• CD31 and CD41 are the most commonly used markers for PMP detection [17-20].
P-selectin	• Mediate the adhesion of activated platelets and other cells[49]. • Target cancer cells with upregulated CD44 expression. • Application: PMPs could be designated as an outer shell to decorate the inner core to achieve antitumour effects[73,74].
• Nucleic acid	
miR-24	• miR-24 targets and downregulates the expression of mt-Nd2 and Snora75 leading to apoptosis in tumour cells[20].
miR-223	• miR-223 forms a complex with Argonaute 2 (Ago2), Ago2-miR223, which downregulated the expression of FBXW7 and EFNA1 at the mRNA and protein levels to achieve biological effects[35]. • miR-223 targets EPB41L3 and suppresses its expression, thus promoting non-small cell lung cancer (NSCLC) cell invasion [34].
miR-142-3p	• miR-142-3p induces abnormal ECs proliferation. • Application: Vascular dysfunction occurs via Bcl-2-associated transcription factor (BCLAF) in hypertensive conditions [78].
miR-1915-3p	• miR-1915-3p induces driving haematopoietic stem/progenitor cells (HSPCs) towards the megakaryocytic lineage and platelet production by suppressing the expression of RHOB.
miRNA-4306	• miRNA-4306 noticeably inhibited the migration of human monocyte-derived macrophages (HMDMs) and reduced the number of macrophages in the cardiac tissue of myocardial infarction model mice through the VEGFA/ERK1/2/NF-κB signalling pathway. • Application: Decreased miRNA-4306 is a poor prognostic factor in CAD.

Furthermore, different tumor cell lines differ in their responsiveness to PMPs, and, for example, because PMPs may have a weaker pro-tumorigenic effect on SKBR3 and MDA-MB-231 cells, due consideration should be given to the increased tumor-promoting risk of PMPs [75]. Further consideration should also be given to investigating the possible regulatory mechanisms of different cell lines for differences in PMP responsiveness to reduce the pro-tumor risk of PMPs in model cells and animals or to exploit the pro-tumor effects of PMPs to improve the success rate of creating tumor-bearing experimental animals for tumor research. The distinction between PMPs and their cargo cannot be ignored.

In the process of the clinical transformation of PMPs, in addition to the need for further study of their safety, the large-scale preparation of PMPs also has problems. The preparation of PMPs is complex, and the process lacks standard separation, determination, quantification, and storage methods, leading to poor reproducibility [138]. For example, differential ultracentrifugation used to prepare PMPs destroys the structure of the PMPs and increases the preparation time. The size of the PMPs may lead to inaccurate results in flow cytometry. Transmission electron microscopy can improve the accuracy of PMP detection, but there are problems, such as complicated experimental preparation and small detection amounts. These factors are not conducive to large-scale production of PMPs [139]. There are also differences between laboratory and clinical anticoagulants. To minimize platelet activation in vitro and the subsequent release of PMPs, the most commonly used anticoagulant in the laboratory is sodium citrate, whereas heparin, which is commonly used in clinics, can affect the quantification of PMPs [140]. Therefore, there is still a long way to go before PMPs can be used in the clinical setting.

In recent studies, several different terms, such as platelet-derived microvesicles and platelet extracellular vesicles, are used for what we have been calling PMPs in this paper. To facilitate the description and to find relevant studies, we propose to designate platelets that shed ultra-microfilm vesicles with diameters ranging from 0.1 to 1.0 μm as PMPs.

At present, there are still some limitations to research on PMPs [71,75]. First, researchers have mostly used differential ultracentrifugation to separate PMPs, but each team has

chosen a different centrifugal force. Excessive centrifugal force destroys the structure of the PMPs, and an inappropriate design may affect the experimental results. Second, current methods for detecting PMPs include flow cytometry, western blotting, and transmission electron microscopy. However, these methods require different sample sizes and have different detection sensitivities and specificities. More accurate, uniform, and repeatable MP detection methods are required. Standardized protocols are required to ensure the stability and safety of the PMPs. Finally, most experimental studies involve only one or several human cell lines, and because there is insufficient validation of animal models, more comprehensive results cannot be obtained. Furthermore, there is a relationship between other types of programmed cell death (such as pyroptosis, ferroptosis, and necrosis) and PMP generation. Therefore, specific biomarkers for different PMPs are required. In future research, standardized protocols for preparation and detection of different types and sources of PMPs should be strengthened, and relationships between different types of PMPs and diseases should be explored. In addition, animal model validation and large-scale clinical studies should be conducted to fully reveal the pathophysiology of PMPs and their mechanisms.

6. Conclusion

This study focuses on the origin, biological functions, and applications of PMPs. Current evidence indicates that PMPs play important roles in cancer progression, vascular homeostasis, thrombosis, cell-cell communication, inflammation, neural regeneration, biomarkers, and targeted delivery. These findings shed light on the potential development of PMPs as cell-targeting drug carriers. However, the safety of PMPs and the stability of their large-scale production should be considered before their application. For example, PMPs play a role in the procoagulant cascade and mediate thrombogenic risk, while the PMP-derived or -mimetic delivery system circulates in the blood system. To explain the differences in correlation between PMPs and thromboembolic events, further research and clinical studies are required to evaluate the long-term performance of these applications before PMPs can be safely recommended as alternative biomarkers and carriers. Further research is needed to study these paradoxical roles under physiological and pathological conditions.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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