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Review Article

Platelet-derived microparticles and hematological diseases

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ABSTRACT

Platelet-derived microparticles (PMPs) are extracellular vesicles (EVs) released by platelets when they are activated, undergo apoptosis, or are exposed to stress. These particles cannot be detected through routine platelet counting, and include proteins, lipids, RNAs and other substances. Their role in thrombosis and inflammation is well-established, but emerging evidences highlight their involvement in the pathogenesis and progression of hematological diseases. This review focuses on the current understanding of PMPs in diverse hematological diseases, including immune thrombocytopenia (ITP), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), myeloproliferative neoplasms (MPNs), multiple myeloma (MM), and other hematologic diseases. Additionally, it explores the potential of PMPs as diagnostic and prognostic biomarkers, emphasizing their significance in understanding the pathogenesis and potential treatment of diverse hematological diseases.

Keywords: platelet-derived microparticles, hematological diseases, pathogenesis, biomarkers, treatment

INTRODUCTION

Platelet-derived microparticles (PMPs) have emerged as a crucial element in the complex pathophysiology of hematological diseases. It has been discovered that when activated, blood platelets release two main types of extracellular vesicles (EVs) into the bloodstream, specifically PMPs and exosomes (EXOs)[1]. PMPs are larger plasma membrane-derived vesicles (0.1–1 μm) released during cellular stress (activation/apoptosis) and exhibit platelet/megakaryocyte immunophenotypes. In contrast, smaller PL-EXOs (30–100 nm) originate from endosomal multivesicular bodies/α-granules, whose secretion and composition are dynamically shaped by environmental cues. Currently, research focus across diverse disciplines is predominantly directed toward exosomes, whereas thorough investigations into PMPs remain comparatively scarce. These submicron vesicles are recognized for their procoagulant properties and involvement in hemostasis[2–3]. PMPs play an important role in intercellular communication by carrying various bioactive molecules (procoagulant factors, adhesion molecules, and cytokines), allowing them to influence processes in target cells[4].

PMPs have been implicated in a variety of diseases, including traumatic injury[5], inflammation[6], cardiovascular disorders[7–8], autoimmune diseases[9–10], throm-

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bosis[11], and cancers[4,12]. However, a detailed review of the roles of PMPs in hematological diseases has not been conducted.

Hematological malignancies are frequently characterized by disrupted cellular interactions and an altered immune landscape[13]. Emerging research has elucidated the roles of PMPs in hematological diseases, revealing complex interactions with cells and the surrounding microenvironment[14–19]. This review aims to synthesize current knowledge regarding the biogenesis, molecular composition, and emerging roles of PMPs in hematological diseases, emphasizing their potential as biomarkers and therapeutic targets.

PMPS: FORMATION AND COMPOSITION

Microparticles, a distinct subclass of EVs, are membrane-derived particles released from the cell surface during cellular activation or apoptotic processes. Among circulating microparticles, PMPs represent the predominant population, accounting for 70% to 90% of the total microparticle population[20–22].

PMP generation is a dynamic process mediated by diverse stimuli. Primarily, PMPs formation is triggered by platelet activation in response to soluble agonists, including von Willebrand factor (vWF), adenosine diphosphate (ADP), thrombin, collagen, and platelet-activating factor), activators of second messengers (such as calcium ionophores), and other triggering factors (such as pathogens and high shear stress[1,23–24]. Moreover, calcium-dependent scramblases are activated, facilitating the movement of phospholipids and phosphatidylserine (PS) exposure on the outer membrane surface of PMPs[4,11]. The shedding of PMPs involves cytoskeletal reorganization enabling cell-structure changes, accompanied by membrane blebbing that forms small bulges on the cell surface.

These membrane alterations involve multiple processes, including the emergence of lateral heterogeneity within membrane sub-domains with distinct properties and the establishment of transverse asymmetry in lipid distribution with PS and phosphatidylethanolamine (PE) playing a predominant role[24]. Mechanical stress, such as supraphysiologic shear forces imparted by cardiovascular devices, can also trigger PMP release through mechanodestructive pathways. Studies have demonstrated that such prolonged shear stress leads to increased membrane porosity, subsequent influx of calcium, and membrane fragmentation[23].

Therefore, following platelet activation, the cell contracts and its membrane extends to create pseudopods. Some of these pseudopods fragment, while vesicles bud off from the deformed membrane. These fragments and vesicles are subsequently released into circulation, ultimately generating PMPs (***Fig. 1***)[1].

The composition of PMPs reflects their cellular origin, encompassing a complex array of proteins, lipids, and genetic material. PMPs inherit numerous platelet-derived receptors, including platelet-specific glycoprotein (GPIIb/IIIa, GPIb/IX/V, GPVI), adhesion proteins (P-selectin (CD62P)), coagulation ligands (fibrinogen), coagulation-associated proteins (FVa, FVIII, TF), and ubiquitously expressed molecules (PECAM-1 (CD31), CD47)[1,4,9,20]. The surface expression of these receptors on PMPs is subject to dynamic regulation.

PMPs possess angiogenic potential in both *in vitro* and *in vivo* settings, primarily mediated by their cytokines which include vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and platelet-derived growth factor (PDGF)[22]. Lipids, particularly PS, play a pivotal role in PMPs function, as PS exposure on the PMPs surface confers procoagulant properties. These characteristics contribute to the prothrombotic state commonly linked to pathological conditions characterized by elevated circulating PMP levels[25]. Additionally, PMPs contain diverse genetic material such as mRNA and microRNA (miRNA), which participate in regulating various cellular processes, including apoptosis, angiogenesis, and immune responses[26–28]. Indeed, studies have demonstrated that PMPs can affect the phenotype of their target cells by transferring mRNA and non-coding RNAs, such as miRNAs (miR-142, miR-223, miR-185, miR-126, miR-103, miR-92a, miR-191, miR-150, miR-140, miR-221, miR-222, miR-296, miR-96, miR-22, and miR-320)[26–27]. Specific miRNAs within PMPs were shown to play roles in inflammation[29], thrombosis[30], cancer metastasis[31], and hematologic diseases[32]. In addition to RNA, PMPs also contain and release complete functional mitochondria upon platelet activation[15,33], as well as transcription factors[34].

Although originating from platelets, PMPs carry diverse molecules and organelles such as nucleic acids, lipid mediators, mitochondria, and various proteins, with their cargo content potentially modulated by different platelet activation pathways or experimental conditions (***Fig. 2***)[9].

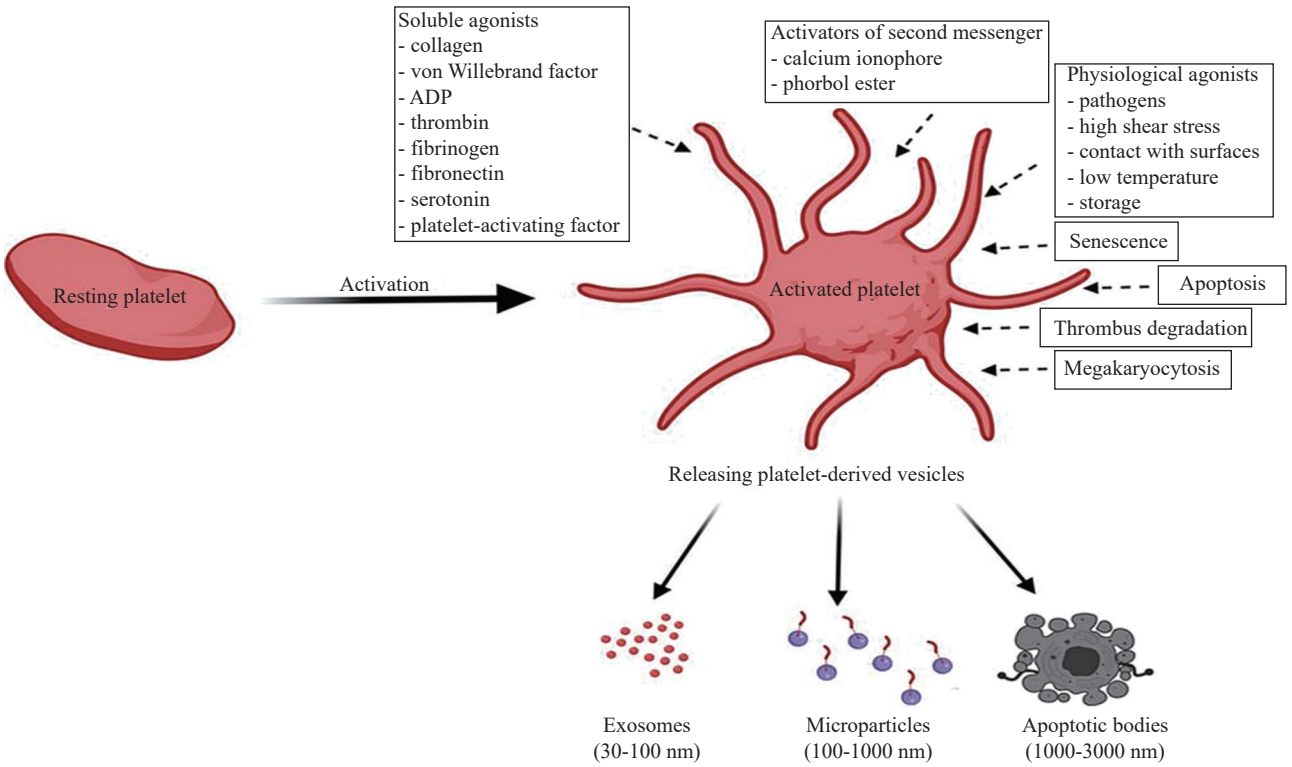

Fig. 1 **Activation process of platelets in blood and release of PMPs as a result of morphological and functional changes.** PMPs: platelet-derived microparticles.

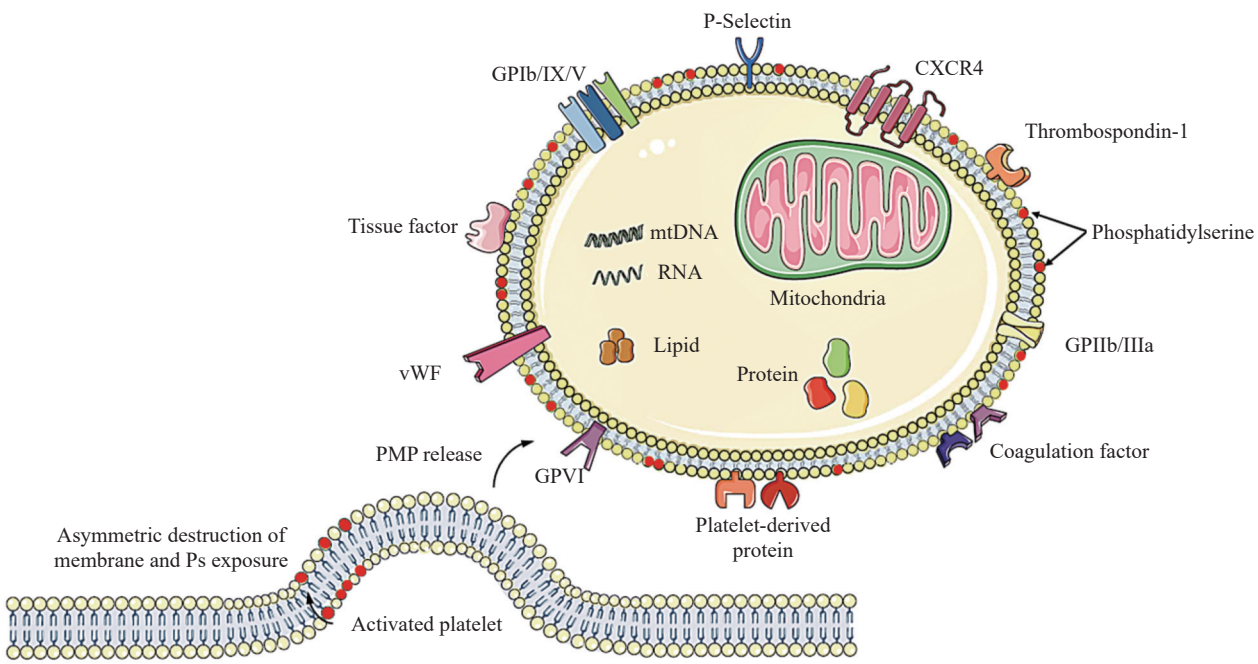

Fig. 2 **Diverse components are present in PMPs.** PMP: platelet-derived microparticle; vWF: von Willebrand factor; GP: glycoprotein; CXCR4: C-X-C chemokine receptor type 4; RNA: ribonucleic acid; mtDNA: mitochondrial deoxyribonucleic acid.

PMPS AND HEMATOLOGICAL DISEASES

Immune thrombocytopenia

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by decreased platelet counts, leading to an increased risk of bleeding[35]. The core aspect of ITP pathogenesis lies in the breakdown of self-tolerance, which triggers autoantibody production and dysregulated $CD8^+$ T cell reactions[36]. Despite the

presence of a low platelet count, severe bleeding episodes occur with relatively low frequency in a subset of ITP patients. The clinical observation implied the potential existence of a protective factor that mitigated the risk of bleeding in these individuals[37]. Compared to healthy individuals, ITP patients demonstrated a predominance of younger, hyperactive platelets, which raised the risk of thrombosis[38].

While historically viewed as a result of autoantibody-mediated platelet destruction and impaired megakaryopoiesis, accumulating evidence suggests a more complex pathophysiology involving PMPs. Studies have shown elevated PMP levels in ITP patients[39–40], with earlier research predominantly centered on their role in hemostasis and proposing that their increase might compensate for bleeding tendencies. Recent research shed light on their potential roles, not only serving as compensatory mechanisms for hemostasis but also exhibiting immune-modulating function[41–42]. Notable elevation in the levels of PMPs was observed in lactadherin-deficient mice. Concurrently, splenic macrophages isolated from these mice exhibited a reduced capacity for phagocytosis[43]. Traditionally, increased PMPs levels in ITP were attributed to autoantibody-induced platelet activation and fragmentation[44]. However, studies are now exploring whether PMPs actively sustain autoimmune responses by functioning as vehicles for pro-inflammatory mediators. In ITP, platelets may secrete pro-inflammatory mediators like chemokines and cytokines into circulation and potentially modulate the immune response by interacting with various immune cells, including B cells, T cells, neutrophils, and dendritic cells (DCs)[45]. Researchers suggest that platelets in ITP might release more PMPs, some with aberrant cargo. Two probable pathways underlying the initial release of PMPs in ITP are the recognition of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) by platelet Toll-like receptors (TLRs) and the binding of immune complexes to FcγRIIa. Additionally, autoantibodies or other immunological changes may induce platelet activation and more PMP shedding[41].

Dysregulation of miRNAs within PMPs is emerging as a critical area of investigation. Sun *et al*. recently identified upregulated miRNAs (miR-142-5p and miR-96-5p) in ITP patients compared to healthy controls[46]. PMP components such as miR-1915-3p were reported to enhance megakaryocyte differentiation and platelet generation in thrombocytopenic mice[30]. Mechanistically, miR-1915-3p, a miRNA highly enriched in PMPs, was transferred to target cells where it downregulated Rho GTPase family member B expression, thereby inducing megakaryopoiesis. They also demonstrated the therapeutic potential of PMPs in treating thrombocytopenia by significantly increasing megakaryocytic cell and platelet counts in semilethally irradiated mice, indicating a definitive therapeutic effect[30].

These findings indicate that unraveling the mechanisms through which PMPs regulate immune responses and interact with megakaryocytes may open doors to new diagnostic biomarkers and targeted therapies for ITP, moving beyond traditional methods that solely focus on elevating platelet counts. Therefore, future research endeavors should concentrate on platelet-receptors, PMPs, and their interactions with inflammatory mediators and immune cells within the context of ITP.

Acute myeloid leukemia

Acute myeloids leukemia (AML), a malignant disorder of the bone marrow that originates from hematopoietic stem cells (HSCs) and progenitor cells, is frequently linked with infection, anemia, and bleeding[47]. The curative treatment involved intensive chemotherapy administering daunorubicin (DNR) and cytarabine (Ara-C)[48], with high-risk patients requiring additional consolidative allogeneic stem cell transplantation —a potentially life-threatening therapeutic approach[49].

Platelets, while traditionally associated with hemostasis, are now being recognized as key regulators of chemoresistance and apoptosis in cancer biology, including AML, with this influence being partially mediated by PMPs[19]. Antigen-specific T cells ($CD4^+$ and $CD3^+$) are vital for immune defense against cancer and form the cellular cornerstone of specific immunotherapy, while platelets regulate hemostasis and interact with leukocytes to prevent substantial blood loss from the circulation. PMPs have been shown to promote effector T cell apoptosis while inducing regulatory responses in T lymphocytes[50]. Research revealed that patients with AML showed significantly elevated cytoplasmic granules content (CD61 PMP), indicating intravascular platelet activation, along with higher levels of $CD4^+$ and $CD3^+$ T cells compared to controls. Moreover, CD61 PMP, crucial for immune regulation *via* T regulatory cell activation, was negatively correlated with $CD4^+$ T cells in AML patients aged ≤ 65 years[50]. However, patients with acute promyelocytic leukemia have low levels of PMPs, likely attributable to decreased platelet counts, as reported by Ma *et al*.[51].

Programmed death-1 (PD-1) is an immune inhibitory co-receptor expressed on a variety of immune cells such as T cells, B cells, and natural killer cells[52]. Hu *et al*. designed PMPs carrying antibodies against PD1 to prevent the recurrence of AML[53].

Platelet interactions with cancer are becoming increasingly apparent, with evidence showing that cancer can fundamentally alter the platelet transcriptome[54]. Multiple research investigations have provided additional evidence of the involvement of miRNAs in AML by demonstrating a correlation between their expression patterns and adverse clinical outcomes such as heightened mortality and chemotherapy resistance in AML patients, with specific miRNAs notably present at elevated levels in these patients' platelets and PMPs[19,55]. PMPs can be internalized by AML cells, potentially altering their function and contributing to chemoresistance. A study found that the serum levels of PMPs, vWF, and fibronectin (FN) were significantly higher in acute leukemia patients with thrombocytopenia compared to the control group. The bleeding severity showed a negative correlation with PMP levels but positive correlations with both NF and vWF levels[56].

Current research aims to elucidate how PMPs modulate apoptosis and chemotherapy efficacy in AML, with a focus on their involvement in developing resistance to DNR. Cacic *et al*. demonstrated that PMPs were internalized by THP-1 cells, leading to elevated expression of miR-125a-5p, miR-125b-5p, and miR-199-5p[26]. Retroviral transduction studies have implicated the contribution of miR-125a-5p and miR-125b-5p to chemotherapy resistance[57–58]. These miRNAs were empirically shown to suppress protein synthesis at the translational level, thereby promoting chemoresistance. Their overexpression downregulated the apoptotic proteins Grk2 and Puma —a pro-apoptotic BH3-only protein critical for the intrinsic apoptosis pathway —further supporting their role in resistance. Notably, co-incubation with PMPs reduced Puma activation, further reinforcing the resistance mechanism[19]. Additionally, PMPs protect THP-1 and primary AML cells from daunorubicin-induced cytotoxicity, impair cell growth, partially arrest the cell cycle, decrease mitochondrial membrane potential, and induce macrophage-like differentiation in THP-1 cells. They discovered that PMPs significantly reduced the level of DNA damage induced by DNR in THP-1 AML cells by decreasing both caspase-8 and caspase-9 activation in the cell cycle phase independently, and directly modulated intrinsic apoptosis by downregulating the pro-apoptotic protein Puma[16]. Moreover, in addition to the aforementioned miRNAs, PMPs harbor other miRNAs such as miR-221 and miR-222[28], which were documented to be able to decrease the expression of Puma[59]. Nevertheless, their functional significance in THP-1 cells or other AML-relevant cell lines remains to be fully elucidated.

Drug targeting has revolutionized therapeutic approaches through advanced delivery vectors like liposomes and polymeric nanoparticles. Researchers generated biocompatible PMPs that are naturally targeted towards leukemia cells through specific surface ligands such as P-selectin and integrins and have the capability to carry multiple drug payloads, with these PMPs exhibiting significantly improved drug delivery efficiency to leukemia cancer cells compared to free drug delivery[32].

The capacity of PMPs to promote chemoresistance and AML cell survival makes them a potential therapeutic target. Potential treatment strategies to inhibit PMPs formation or block their interaction with AML cells may enhance the efficacy of chemotherapy. Future research should systematically explore the therapeutic potential of targeting PMPs in AML.

Acute lymphoblastic leukemia

Acute lymphoblastic leukemia (ALL) represents an aggressive blood cancer caused by chromosomal and genetic anomalies that perturb the mechanisms underlying the expansion and rapid division of immature T or B lymphocytes[60]. ALL is classified into B cell precursor ALL (BCP-ALL) and T cell ALL (T-ALL) based on the cell of origin, with BCP-ALL constituting 80%–85% of cases[61]. Cytarabine (Ara-C) stands as a highly efficacious chemotherapeutic agent in the management of ALL, with well-documented mechanisms of action and proven therapeutic benefits in clinical settings[62]. Despite therapeutic advances, drug resistance remains a major clinical challenge that significantly compromises treatment outcomes[63].

The research have demonstrated that cancer cells activate platelets, leading to the release of substances from platelet granules and the formation of PMPs. PMPs exert profound influences on the growth, proliferation, apoptosis, and gene expression profiles of target cells through the transfer of genetic and biochemical components. This process underpins their pivotal roles in cellular signaling and disease pathogenesis[64].

Nikravesh *et al*. demonstrated that PMPs synergistically augmented Ara-C's cytotoxicity in ALL by enhancing its ability to suppress Nalm-6 cell viability and increasing Ara-C-induced apoptosis in these cells,

despite PMPs' lacking independent activity[65]. Mechanistically, the combined treatment significantly upregulated pro-apoptotic (Bax) and cell-cycle inhibitory (P21) genes while downregulating anti-apoptotic (Bcl-2) and telomerase-associated (h-TERT) genes, indicating a pathway-specific sensitization to Ara-C. Additional research highlighted that PMPs and sCD40L induced cellular apoptosis in peripheral blood mononuclear cells (PBMCs) derived from patients with pre-B-ALL[66]. Newly discovered evidence revealed lower levels of PMPs ($CD41a^+$) in the peripheral blood (PB) of B-ALL patients compared to controls at baseline diagnosis (D0), reflecting severe thrombocytopenia. However, these levels increased by the end of induction therapy (D35), indicating restored thrombopoiesis and platelet production[67]. From a therapeutic perspective, platelet count is considered a valuable parameter for prognostic assessment in ALL patients, both during and following induction therapy[68]. These observations underscore the importance of further investigating the interactions between PMPs and leukemic blasts, as well as their potential role as biomarkers for thrombopoietic recovery or the restoration of normal hematopoiesis. MiR-125b was proven to be a leukemogenic oncomiR in mouse models by causing ALL phenotypes, and has been linked to chemotherapy resistance in ALL[69].

Further research is necessary to elucidate the precise mechanisms through which PMPs impact the behavior of ALL cells and influence their response to chemotherapy. Exploring the specific molecules carried by PMPs and their downstream effects on recipient cells holds promise for refining ALL treatment strategies.

Myeloproliferative neoplasms

Myeloproliferative neoplasms (MPNs), a group of clonal hematologic malignancies morphologically characterized by the expansion of terminally differentiated myeloid cells (including white blood cells, erythrocytes, and platelets) and encompassing polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), constitute a distinct subset of myeloid malignancies that are unified by the presence of recurrent gain-of-function somatic mutations in three key driver genes: *JAK2*, *CALR*, and *MPL*[70–71]. These mutations dysregulate hematopoietic signaling pathways. Thrombosis is a major complication that affects the life expectancy of patients with MPNs. Both PV and ET involve prolonged, relatively indolent courses with the majority of morbidity and mortality attributed to thrombosis[72]. A recent meta-analysis of > 13 000 individuals revealed a pooled thrombosis prevalence of 20% at diagnosis, with a higher prevalence in PV compared to ET or PMF[73].

PMPs contribute to the enhancement of coagulation *via* the dual actions of exposing the procoagulant anionic PS on their surface and expressing functional tissue factor (TF)[11]. Currently, the roles of PMPs in the pathogenesis and clinical manifestations of MPNs remains underexplored, with limited studies addressing their mechanistic contributions to disease progression, thrombotic risk, or biomarker potential. Previous research demonstrated that patients with ET exhibited significantly elevated circulating levels of PMPs than healthy controls, suggesting a role for the extracellular vesicles in ET-associated thrombo-inflammation and hypercoagulability[74]. However, no studies to date have considered the variation in PMPs levels between patients with PV and PMF.

Subsequently, studies found that among patients with ET, those carrying *JAK2* mutations tend to exhibit higher levels of circulating PMPs. This increased count of PMPs may contribute to a increased risk of thrombosis compared to ET patients without the *JAK2* mutation[75]. Despite the observation that *CALR*-mutated patients exhibited higher platelet counts compared to *JAK2*-mutated patients with significantly lower PMPs counts, a previous study on a $JAK2^{V617F}$ ET mouse model demonstrated that $JAK2^{V617F}$-positive megakaryocytes produced more proplatelets than control megakaryocytes[76]. This observation led to the hypothesis that $JAK2^{V617F}$ may modify megakaryocyte biology beyond merely promoting myeloid proliferation, consequently resulting in increased bone marrow vesiculation and the release of a substantial number of PMPs into the bloodstream[75]. Also, researchers observed that P-$selectin^+$ PMPs, expressed either as counts or percentages, were higher in *JAK2*-mutated patients than in *CALR*-mutated patients. Consequently, the higher count of circulating PMPs might contribute to a higher incidence of thrombosis in *JAK2*-mutated patients than that in other ET patients. The relatively low thrombotic risk observed in *CALR*-mutated patients is primarily attributed to the lack of the $JAK2^{V617F}$ mutation rather than a supposed "protective" effect of *CALR* mutations. Additionally, studies confirmed that BCR/ABL1-negative MPN patients exhibited higher levels of PMPs compared to healthy controls, with elevated PMP values observed in the presence of thrombotic risk factors such as age over 60 years, a history of thrombosis, $JAK2^{V617F}$ mutation, tobacco use, and male sex[77]. These results

can explain the contribution of the *JAK2*^{V617F} mutation to the hypercoagulable state in MPN by supporting its mechanism of inducing persistent platelet activation leading to a proportional increase of PMPs[78].

Emerging evidence have demonstrated that patients with Philadelphia chromosome-negative myeloproliferative neoplasm (Ph$^-$MPN) exhibited significantly elevated circulating levels of PMPs compared to healthy controls. Notably, PMPs concentrations were further increased in patients with PMF relative to those with PV, in Ph$^-$MPN patients with thrombosis *versus* those without thrombosis, and in individuals with splenomegaly compared to those without splenic enlargement. Moreover, PMPs levels were significantly higher in Ph$^-$MPN patients harboring the *JAK2*^{V617F} mutation compared to mutation-negative counterparts, suggesting a link between genetic drivers, platelet activation, and extracellular vesicle shedding in MPN pathophysiology[79]. Previous studies have demonstrated that miRNAs regulate hematopoiesis in HSCs and lineage-committed progenitors, with evolutionarily conserved miRNAs like miR-125a and miR-125b accumulating in HSCs to sustain homeostasis *via* anti-apoptotic mechanisms that expand the stem cell pool[80].

Given the association between thrombosis in MPNs and elevated PMP levels, PMPs have emerged as both a surrogate biomarker for thrombosis and a novel predictive tool for thrombotic complications in MPN patients[79,81], underscoring the need for further well-designed prospective studies to fully elucidate the diagnostic and prognostic utility of PMPs in clinical practice.

Multiple myeloma

Multiple myeloma (MM) is a plasma cell disorder marked by clonal expansion of bone marrow plasma cells, leading to an overproduction of monoclonal immunoglobulin[82]. Hemorrhage and thromboembolism in MM patients are not only detrimental to their quality of life but also force treatment delays or discontinuations, ultimately reducing overall survival rates and demanding heightened clinical vigilance[83–84]. Platelets, as the primary cellular component in the blood, interact with circulating MM cells to support their proliferation, differentiation, and migration. In turn, these MM cells modulate coagulation function by releasing procoagulant cytokines, as evidenced in clinical studies[85–86]. The research indicated that newly diagnosed MM patients exhibited elevated expression of the platelet activation marker P-selectin and were highly susceptible to treatment-induced thrombosis, particularly venous thromboembolism (VTE)[87].

A study revealed that platelet-derived exosomes promoted MM cell proliferation by enriching leucine-rich-alpha-2-glycoprotein 1 (LRG1), which bound to olfactomedin 4 (OLFM4) through its leucine-rich repeat (LRR) domain to regulate epithelial-mesenchymal transition (EMT) and angiogenesis. Additionally, LRG1 enhanced angiogenesis *via* TGF-β signaling, and the patients with high LRG1 expression exhibited lower overall and disease-free survival than those with low expression[88]. The significance of PMPs in relation to thromboembolic risk has drawn immense attention, driving the launch of dedicated studies focused on plasma cell dyscrasias, particularly MM[89]. PMPs exhibit a procoagulant activity approximately 100-fold higher than that of platelets, primarily owing to their significantly heightened prothrombotic propensity[9,22]. Previous studies confirmed that PMPs and CD138$^+$ MPs were elevated in patients with MM compared to healthy controls[90]. Subsequently, another study demonstrated significant positive correlations between PMPs and PD1$^+$CD4$^+$ T cells. Furthermore, elevated levels of PMPs, CD138$^+$ MPs, PD1$^+$CD8$^+$ T cells, and PD1$^+$CD4$^+$ T cells were positively associated with an increased incidence of bony lesions in the study population[91]. Among MM patients achieving complete remission, levels of PMP and CD138$^+$ MPs decreased significantly compared to those who did not reach remission following bortezomib combination therapy. These proteins were associated with a higher production of PD1$^+$CD4$^+$ T cells and CD8$^+$ T cells, suggesting that microparticles and PD1 contribute to bortezomib resistance. Hu *et al*. previously engineered bortezomib-loaded nanocarriers encapsulating nano-platelets to target the bone marrow microenvironment and myeloma cells. This strategy aimed to suppress multiple myeloma growth while mitigating thrombotic complications *via* precision drug delivery[92].

MiRNAs are bioactive molecules found in PMPs. The researchers confirmed, through independent validation by reverse transcription-quantitative polymerase chain reaction (RT-qPCR), that the levels of miR-140-3p and miR-191-5p were elevated in MM patients compared to patients with extramedullary disease and plasma cell leukemia. These results indicate that dysregulation of miRNAs may contribute to MM progression[93]. Further research have demonstrated that adhesion of wild-type p53 MM cells to bone marrow stromal cells (BMSCs) upregulated miR-125a-5p while downregulating p53. Moreover, inhibition of miR-125a-5p expression in wild-type p53 MM cells dampened cell growth,

increased apoptosis, and reduced cell migration, thereby supporting its oncogenic role in MM pathogenesis[94].

Previous studies have underscored the potential prognostic value of PMPs in MM, as their elevated levels were strongly associated with poor clinical outcomes through mechanisms including promotion of MM cell proliferation, induction of drug resistance, and remodeling of the tumor microenvironment. Future research should focus on developing targeted therapeutic strategies against PMPs and validating their clinical utility as biomarkers to inform novel treatment paradigms in MM.

Thalassemia

Thalassemia is a genetic disorder characterized by a deficiency or complete absence of either α- or β-globin chains within red blood cells (RBCs)[95]. This imbalance in globin chain composition results in shortened red cell lifespan. The surplus globin chains tend to aggregate into hemichromes, which induce oxidative stress and prompt the exposure of PS on the outer leaflet of cell membranes[96]. Patients with β-thalassemia exhibited an elevated risk of hypercoagulability and thrombosis, which significantly contributed to morbidity and mortality[97]. In thalassemia, the aggregability of abnormal RBCs and the elevated levels of membrane-derived MPs from blood cells were thought to contribute to thrombotic risk. Furthermore, the cellular origin of PS-bearing MPs predominantly showed an activated platelet origin, as evidenced by adhesion markers (CD41a/CD62P/CD36)[98].

In thalassemia, activated platelets release PMPs, which play a pivotal role in intercellular communication by delivering biological cargoes like miRNAs to recipient cells. This miRNA delivery induces alterations in functional characteristics of target cells, ultimately triggering a hypercoagulable state in thalassemia patients[96]. The mean expression of platelet P-selectin was significantly elevated in patients with thalassemia major and thalassemia intermedia compared to controls and those with thalassemia minor. Furthermore, Annexin V expression showed a positive correlation with P-selectin, and both markers were positively associated with the frequency of blood transfusions[99].

Multiple studies have revealed that splenectomised β-thalassaemia/HbE patients exhibited significantly higher levels of PMPs compared to non-splenectomised β-thalassaemia/HbE patients and healthy controls. Furthermore, splenectomised patients demonstrated higher platelet procoagulant activity that correlates with PMP levels, suggesting that excessive PMPs derived from activated platelets may exacerbate thrombotic risks — a phenomenon commonly observed in this patient population[98,100]. Other research groups showed that platelets, rather than RBC-derived microparticles, were the primary contributors to procoagulant activity in splenectomized patients undergoing blood transfusions[101]. Clinical studies have demonstrated that dysregulation of miR-125b expression correlated with the severity of anemia and hemolytic activity in β-thalassemia patients[102], while another investigation revealed that miR-92a-3p was significantly downregulated in hematopoietic progenitor cells of HbE/β-thalassemia patients compared to healthy controls[103] — collectively suggesting the potential of these miRNAs as biomarkers for disease progression.

Pulmonary arterial hypertension (PAH) is a critical complication in β-thalassemia, driven by chronic platelet activation and RBC membrane abnormalities that promote hypercoagulability and thrombosis, ultimately leading to pulmonary vascular dysfunction. Flow cytometric analysis revealed significantly elevated levels of PS-bearing platelets and PMPs in PAH patients compared to healthy controls. Antiplatelet therapy can reduce platelet activity and the number of PMPs in this patient population[104].

Based on these studies, PMPs emerge as a highly promising avenue for developing diagnostic and predictive biomarkers aimed at enhancing the management of thalassemia.

Chronic myeloid leukemia/chronic lymphocytic leukemia

Chronic myeloid leukemia (CML), a malignant hematopoietic stem cell proliferative disorder driven by the t(9;22)(q34;q11) chromosomal translocation-induced BCR-ABL1 fusion gene and characterized by abnormal myeloid cell proliferation, accounts for approximately 15% of all newly diagnosed leukemia cases in adults[105]. The development of BCR-ABL1 tyrosine kinase inhibitors (TKIs) revolutionizes the treatment of CML and marks the start of a new era in oncology, with the majority of CML patients now achieving long-term remissions and near-normal life expectancies[106]. While TKIs have led to significant advances in the treatment of CML, increased resistance to treatment and disease prevalence highlight the need for more detailed studies on the pathophysiological mechanisms affecting the biology of this leukemia[107].

CML patients exhibit abnormal megakaryocytes that release unusual blast fragments into the peripheral

blood and frequently present with large, heterogeneous platelets, which are significantly affected during disease progression and treatment[108]. Previous research demonstrated a conspicuous increase in the concentration of PMPs and transforming growth factor β1 (TGFβ1) in CML patients. These elevated levels were reduced following TKI treatment, particularly with dasatinib[107]. TGFβ1, an important inhibitor of B-cell proliferation and autoantibody production, additionally induces the conversion of Foxp3-negative T cells to Foxp3-positive Tregs and is essential for Treg maintenance. Meanwhile, PMPs promote Treg proliferation in a TGFβ1-dependent manner[109], collectively suggesting that dasatinib-associated Treg dysfunction may be modulated through PMPs and TGFβ1 signaling pathways.

A recent study has highlighted the intricate roles of PMPs in the CML microenvironment, demonstrating their abilities to reduce metabolic activity and proliferation of K562 cells, modulate gene expression, upregulate tumor suppressor genes (P53/P21), and suggest a potential anti-leukemic effect through these mechanisms[17,110]. Michael JV's work demonstrated that PMPs induced tumor cell growth inhibition *via* miR-24[111], which suppressed cell proliferation through p53-dependent pathways[112], thereby supporting the therapeutic potential of P53-activating agents for achieving operational cures in CML[113].

Chronic lymphocytic leukemia (CLL) represents one of the most prevalent forms of leukemia[114], primarily affecting elderly individuals and demonstrating considerable heterogeneity in clinical progression[115].

PMPs serve as physiological vehicles of bioactive molecules for intercellular communication. Previous studies have implicated the role of PMPs in modulating human stromal cells within B-CLL, particularly concerning VEGF production[116]. A recent research by Gharib E *et al*. revealed that PMP-derived mitochondrial transfer to CLL cells enhanced cancer metabolism *via* metabolic reprogramming, elevating oxygen consumption rates (OCR), ATP levels, and ROS production[15]. This process promoted CLL cell proliferation, migration, invasiveness, and resistance to chemotherapeutics (e.g., cytarabine, venetoclax, plumbagin). Fundamentally, given the effectiveness of PMPs to increase CLL mitochondrial mass and functions, which concomitantly leads to metabolic-gene expression and malignant CLL processes, PMPs may govern CLL disease progression.

Recent therapeutic advances in CLL have focused on targeting the B cell receptor pathway and, more innovatively, inhibiting the Bcl-2 protein[117]. Bcl-2, an anti-apoptotic protein located in mitochondrial membrane, is a major contributor to the pathogenesis of lymphoid malignancies and is overexpressed in CLL cells, promoting clonal cell survival. Venetoclax, a physiologic antagonist of Bcl-2, demonstrates rapid, profound, and durable responses in relapsed/refractory CLL patients, including those with high-risk features[118]. Additionally, PMPs can further promote tumor progression by stimulating oxidative phosphorylation (OXPHOS)[119], mirroring metabolic adaptations in advanced CLL. Comparative analyses revealed significantly higher miR-223 expression in healthy controls compared to CLL patients, and its downregulation was associated with poor prognosis, suggesting its potential as a predictive marker[120]. The study also highlighted that miR-142-3p down-regulation promoted cell proliferation in B-cell acute lymphoblastic leukemia (B-ALL) with MLL-AF4 fusion, whereas its expression was upregulated in pre-B-ALL.

These findings demonstrate the fact that PMPs serve as a rich and invaluable resource for exploring cancer biology in both CML and CLL. Furthermore, current evidence suggests their promising potential in the formulation of novel treatment strategies for these leukemia types.

SUMMARY AND PROSPECT

PMPs are emerging as significant contributors to the pathogenesis and progression of various hematological diseases. Previous studies have indicated that PMPs exhibit an overall elevation across various hematologic diseases, with varying roles and distinct mechanisms in disease pathogenesis, as summarized in ***Table 1***. This review briefly summarizes the potential pathogenesis of PMPs in different hematological diseases according to current research. It highlights their complex interactions with immune cells, stromal cells, and tumor micro-environment, underscoring their dual potential as both diagnostic biomarkers and therapeutic targets. Nevertheless, basic research on PMPs remains in its early stages, with insufficient mechanistic exploration hindering both clinical application and a comprehensive understanding of their functional roles - particularly in hematologic diseases where their precise mechanisms and interactions remain poorly defined.

PMPs and exosomes both emerge from activated platelets, carrying diverse cargos like proteins, lipids,

Table 1 **The association of PMPs with hematological diseases**

Hematological diseases	PMP level change	Disease-related molecules	Pathogenic roles of PMP	References
ITP	Increased	PS, sCD40L, PAMPs/DAMPs-related molecules, pro-inflammatory cytokines, necrosis factors, miR-191-3p, miR-142-5p, miR-96-5p	1. PMPs may interact with myeloid and lymphoid cells, affecting immune balance; 2. Impairing bone marrow megakaryocytes, leading to platelet production defects; 3. Increased pro-inflammatory cytokines promote platelet clearance; 4. Promoting coagulation.	[30,39–46]
AML	Increased (decreased in APL, possibly due to reduced platelet count)	miR-125a-5p, miR-125b-5p, miR-109-5p, vWF, fibronectin	1. PMPs can be internalized by AML cells, altering their behavior and promoting chemoresistance; 2. Reducing DNA damage, decreasing caspase activation, and downregulating Puma protein.	[16,19,26,50–58]
ALL	Decreased at initial diagnosis; increased after induction therapy	sCD40L, miR-125b	1. PMPs synergistically augmented Arc-C's cytotoxicity in ALL by enhancing the suppressive effects on Nalm-6 cell viability and increasing Ara-C-induced apoptosis; 2. Upregulating pro-apoptotic genes (Bax) and cell cycle inhibitory genes (P21), while downregulating anti-apoptotic genes (Bcl-2) and telomerase-related genes (h-TERT).	[64–69]
MPNs	Increased, more significantly inJAK2-mutated ET patients	P-selectin, JAK2V617F, miR-125a, miR-125b	1. Promoting coagulation, associated with thrombotic risk; 2. Higher PMP levels in JAK2-mutated ET patients may contribute to increased thrombotic risk.	[74–81]
MM	Increased	Leucine-Rich α-2-Glycoprotein 1 (LRG1), miR-140-3p, miR-191-5p	1. Promoting MM cell proliferation, associated with bortezomib treatment resistance.	[87–94]
Thalassemia	Increased, more significantly in splenectomized patients	P-selectin, miR-125b, miR-92a-3p	1. Promoting coagulation, associated with thrombotic risk; 2. Activating target cells, leading to a pro-thrombotic state in thalassemia patients.	[98–104]
CML	Increased, decreased after treatment	TGFβ1, miR-24, Bcl-2, miR-223	1. PMPs modulate human stromal cells within B-CLL; 2. Dasatinib-associated Treg dysfunction may be modulated through PMPs and TGF-β1; 3. Signaling pathways promote upregulation of tumor suppressor genes (P53?P21), induce tumor cell growth inhibition *via* miR-24.	[107–113]
CLL	Complex mechanism	PMP-derived mitochondrial, Bcl-2, miR-223, miR-142-3p	1. Enhancing tumor metabolism through metabolic reprogramming, increasing oxygen consumption, ATP levels, and ROS generation; 2. Increasing CLL cell proliferation, migration, invasion, and chemoresistance.	[116–120]

ITP: immune thrombocytopenia; PS: phosphatidylserine; PAMPs/DAMPs: pathogen-associated molecular patterns/damage-associated molecular patterns; PMPs: platelet-derived microparticles; AML: acute myeloid leukemia; APL: acute promyelocytic leukemia; vWF: von Willebrand factor; ALL: acute lymphoblastic leukemia; Ara-C: arabinofuranosyl cytosine; MPNs: myeloproliferative neoplasms; JAK2: Janus kinase 2; MM: multiple myeloma; CML: chronic myeloid leukemia; TGF-β1: transforming growth factor beta 1; Bcl-2: B-cell lymphoma 2; CLL: chronic lymphocytic leukemia; ATP: adenosine triphosphate; ROS: reactive oxygen species.

and nucleic acids, suggesting potential synergistic interactions in modulating cellular behavior. Studies have unveiled synergistic effects between PMPs and exosomes, as evidenced by their complementary roles in thrombocytopenic mouse models where PMPs enhance megakaryopoiesis and platelet production. This review further reveals that PMPs exhibit a dual functional paradigm in cancer: on one hand, they induce chemoresistance through internalization by AML cells; on the other hand, they synergistically interact with Ara-C in ALL, enhancing the drug's antitumor efficacy by suppressing Nalm-6 cell viability and augmenting apoptosis. This paradoxical capability of PMPs to either promote malignancy or suppress tumor growth underscores the complex nature of PMP-tumor cell interactions, influenced by dynamic factors including PMP biogenesis conditions, recipient cell phenotypes, and tumor micro-environmental contexts. Therefore, before PMPs can be safely and effectively translated into clinical diagnosis, monitoring, and treatment of hematological diseases, it is necessary to conduct more research on

PMPs, including: (1) in-depth exploration of synergistic or antagonistic roles of PMPs and exosomes in various hematological diseases; (2) research of PMPs in diagnosis of various hematologic diseases and in tissue engineering (such as induction of differentiation and tissue repair); (3) development of PMPs-specific inhibitors or engineered PMPs for targeted therapy and evaluation of drug safety. A deeper mechanistic understanding will enable more precise utilization of PMPs in managing these diseases.

Author contributions

Conceptualization, Yanyan Xie and Yang Chen; Writing – Original Draft Preparation, Yanyan Xie, Xiaojun Kong, Hongmei Zhang, Chen Yan, Zhenhua Yin, and Hong Li; Writing – Review & Editing, Yanyan Xie and Yang Chen; Supervision, Yang Chen; Funding Acquisition, Yanyan Xie.

Ethics statement

Not applicable.

Informed consent statement

Not applicable.

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Declaration of competing interest

The authors declared no conflict of interests.

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