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SPECIAL REVIEW: PLATELET MICROVESICLES

## Platelet microvesicles in health and disease

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### Abstract

Interest in cell-derived extracellular vesicles and their physiological and pathological implications is constantly growing. Microvesicles, also known as microparticles, are small extracellular vesicles released by cells in response to activation or apoptosis. Among the different microvesicles present in the blood of healthy individuals, platelet-derived microvesicles (PMVs) are the most abundant. Their characterization has revealed a heterogeneous cargo that includes a set of adhesion molecules. Similarly to platelets, PMVs are also involved in thrombosis through support of the coagulation cascade. The levels of circulatory PMVs are altered during several disease manifestations such as coagulation disorders, rheumatoid arthritis, systemic lupus erythematosus, cancers, cardiovascular diseases, and infections, pointing to their potential contribution to disease and their development as a biomarker. This review highlights recent findings in the field of PMV research and addresses their contribution to both healthy and diseased states.

### Introduction

In 1967, Peter Wolf described the presence of elements, “originating from platelets, but distinguishable from intact platelets” in the plasma and serum of healthy individuals that were capable of supporting coagulation [1]. The tiny elements, smaller than platelets, proved to be extracellular vesicles produced by platelets in response to activation [1,2]. Further investigations revealed that two types of vesicles are in fact released by activated platelets: exosomes (approximately 40–100 nm in diameter), released by exocytosis from the multivesicular body and alpha-granules, and microparticles (approximately 100–1000 nm in diameter), also called microvesicles (MVs) or ectosomes that are released by budding of the cytoplasmic membrane [3,4]. For historical reasons, the term microparticles is the most commonly used to describe PMVs [5] and, although we use the term *microvesicle* in this review, we also considered the more commonly used term *microparticle* while performing relevant literature searches.

The platelet plasma membrane is composed of a phospholipid bilayer, with an outer leaflet enriched in phosphatidylcholine and sphingomyelin, and an inner leaflet that comprises anionic phospholipids such as phosphatidylserine (PS) [6]. Membrane asymmetry is actively regulated by a mechanism called “flip-flop,” which is mediated by phospholipid transporters. The flippases (aminophospholipid translocases) and floppases ensure the inward (flip) and outward (flop) traffic of phospholipids at the membrane bilayer [6]. In response to activation by agonists like thrombin, collagen or ADP, or by the calcium carrier ionophore,

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an increase in intracellular calcium induces the activation of scramblase, a bidirectional phospholipid transporter, thereby leading to rapid exposure of the negatively charged phospholipid PS at the platelet surface [7]. Of importance is that the disruption of the platelet plasma membrane results in PMV release [8]. Whereas the exact molecular mechanisms implicated in PS exposure are not completely understood, compelling studies have revealed the critical role of the transmembrane proteins 16 (TMEM16) family, in  $\text{Ca}^{2+}$ -dependent scrambling of membrane phospholipids and PS exposure [9,10]. In particular, TMEM16F, the unique TMEM16 protein highly expressed in mouse platelets, is necessary for phospholipid scrambling, and the ablation of its gene in mice abrogates the release of PMVs from platelets [9,10]. The proteasome also appears to be implicated, as bortezomib, a proteasome inhibitor, reduces the shedding of PMVs from platelets activated by thrombin, ADP, or lipopolysaccharide [11]. Furthermore, recent observations made on platelet activation under flow conditions shed light on a novel mechanism implicated in PMV production [12]. It was found that long (250  $\mu\text{m}$ ) membrane tendrils trailed from adherent platelets under physiological flow conditions. Of interest is that the flow-induced protrusions (FLIPR) can be fragmented into PS-exposing PMVs within a few seconds after release [12].

In-depth PMV characterization has highlighted the complexity of their surface markers as well as heterogeneity with regard to size distribution and content [13–16]. Whereas it is generally admitted that membrane scrambling and PS exposure are crucial for PMV release, a large proportion of the PMVs present in blood [17], lymph [18], and synovial fluid of rheumatoid arthritis patients [19] do not expose surface PS (referred to as  $\text{PS}^-$  PMV). The molecular mechanisms underlying formation of  $\text{PS}^-$  PMV is unknown, but it might be implicating specific phospholipases [20] or the presence of enzymes in PMVs involved in the maintenance of membrane asymmetry may be implicated.

Imene Melki and Nicolas Tessandier contributed equally to this work.

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Another explanation is that PS is indeed exposed on all PMVs, but that certain factors (*e.g.* insufficient PS expression, membrane curvature) prohibit their detection by PS-binding probes such as annexin V and lactadherin [21].

PMVs also display platelet-derived glycoproteins (GP) such as GPIIb/IIIa (CD41/CD61) and activation markers such as P-selectin (CD62P) [22,23]. Flaumenhaft and colleagues have proposed that the majority of the CD41<sup>+</sup> PMVs in plasma were in fact shed from megakaryocytes (MK), not from platelets [24]. They suggested that PMVs could be distinguished from MK-derived MVs through detection of CD62P and lysosome-associated glycoprotein-1 (LAMP-1), present on PMVs [24]. These data were recently corroborated by an independent group, who further suggested that MK-derived MVs in the plasma of healthy individuals express C-type lectin domain family 1 member B (CLEC-2) and GPVI, whereas GPVI is absent from PMVs [25]. These observations might imply that MKs also play a role in the physiological effects commonly attributed to PMVs in blood.

Along with the heterogeneity of their surface markers, PMVs are also highly diverse in content [22]. They bear coagulation factors and immune mediators in addition to active enzymes such as cyclooxygenase-1 and 12-lipoxygenase [26,27] (Figure 1). A

proteomic study revealed a correlation between content and size distribution: small PMVs (100–500 nm) are enriched in proteins, especially those originating from  $\alpha$ -granules, whereas larger PMVs are enriched in lipid mediators and mitochondrial proteins [13]. Recently, Boudreau et al. revealed that platelets eject their mitochondria during activation, resulting in the release of PMVs that indeed contain functional and intact mitochondria [28] (Figure 1). In addition to organelles, PMVs also harbor a broad spectrum of platelet-derived cytokines, enzymes, nucleic acids (messenger RNA and microRNA) and even transcription factors [26,27,29,30]. A recent study [31], revealed an extremely high degree of correlation between the identities of miRNAs and mRNAs present in platelets and those reported in PMVs by Ducheze et al. [27], indicating that PMVs can serve as a source of circulating nucleic acids.

There is growing evidence that cell-derived MVs are not restricted to pathological onset and in fact circulate in blood at a steady state [32,33]. Indeed, albeit the fact that erythrocytes are more numerous (approximately 30 times) than platelets in blood, PMVs are amongst the most abundant MVs in the blood of healthy individuals [33,34], and outnumber those from erythrocytes by approximately 2-4 fold, depending on the

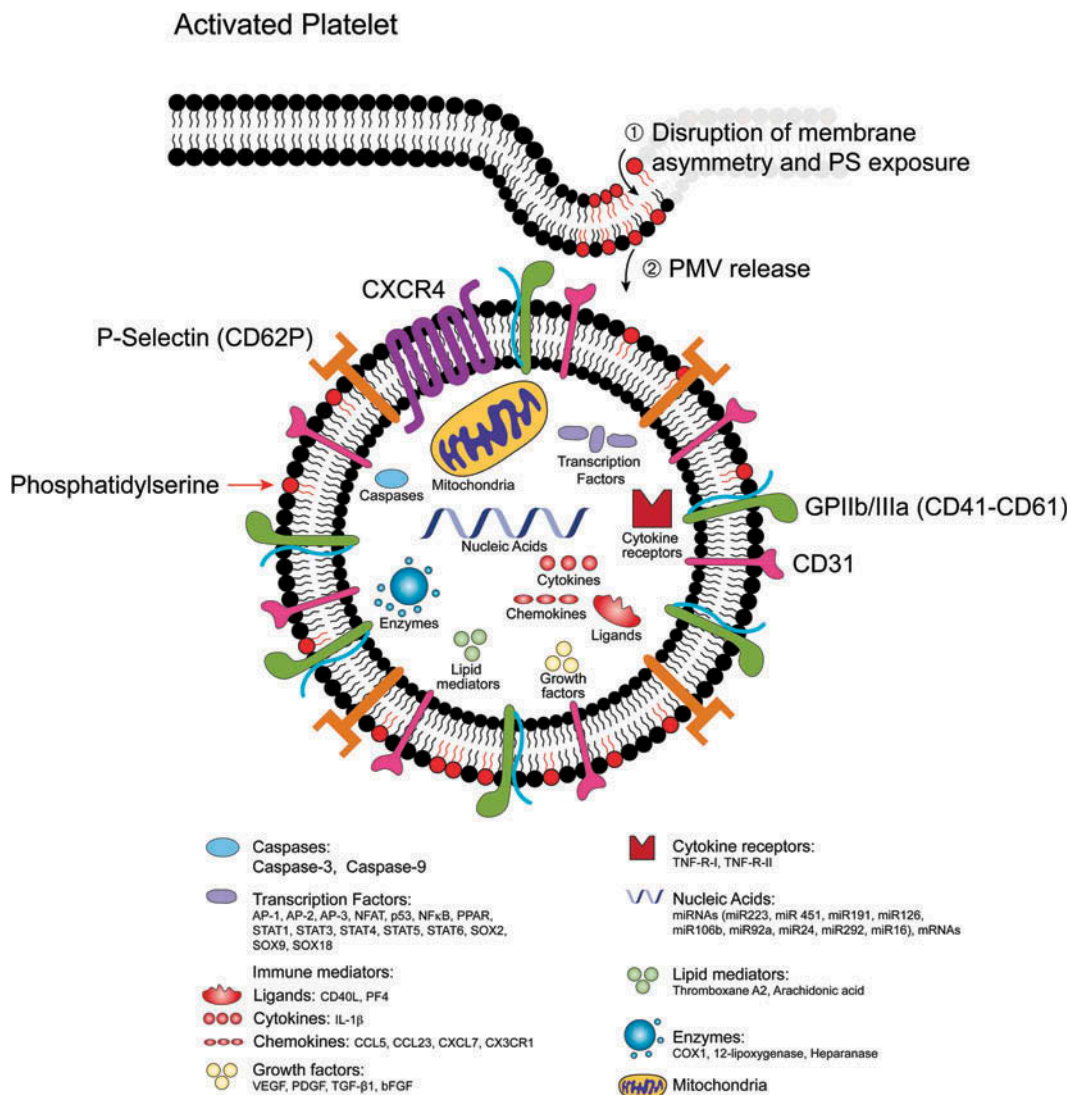


Figure 1. Diverse components are present in PMVs. Despite the fact that PMVs derive from platelets, which are anucleated, various molecules and organelles are present either on or inside PMVs. The PMV cargo includes functional enzymes, transcription factors, receptors, cytokines, nucleic acid, lipid mediators and mitochondria. Note that different platelet activating pathways or experimental parameters might have an impact on PMV content, and that the list of molecules described herein stems from multiple studies and remains non-exhaustive.

methodological approach used for quantification [35,36]. Surprisingly, little is known regarding the half-time of PMVs in the circulatory system, with reports ranging from 10 minutes to several hours depending on the study [37,38]. Of interest is that Rand et al. showed that calcium ionophore-generated PS<sup>+</sup> PMVs were cleared from the bloodstream in less than 10 minutes after their transfusion in rabbits [37], whereas Rank and colleagues monitored human PMVs in the circulation of transfused patients and found that PMVs had a half-life of more than three hours [38]. However, these studies focused on PS exposing PMVs, whereas the clearance rate of PS<sup>-</sup> PMVs is currently unknown. Among the mechanisms proposed to explain rapid clearance, is lactadherin-promoted phagocytosis mediated by macrophages [39]. The endothelium has also been implicated in the elimination of PS<sup>+</sup> PMVs from the circulation, notably by endocytosis through developmental endothelial locus-1 (Del-1), a protein mainly expressed by the endothelium that serves as an anchor between endothelial cells and PS-exposing MVs [40]. Moreover, mice lacking the expression of Del-1 showed delayed PMV clearance after endotoxemia induced by lipopolysaccharide injection [40]. Another candidate is growth arrest specific 6 (Gas6) and its tyrosine receptor Axl, both of which are involved in endothelial cell survival [41]. In this study, Gas6 and Axl interaction was proven to regulate the uptake of PMVs by the endothelium; however, Gas6<sup>-/-</sup> mice did not present higher counts of PMVs than Gas6<sup>+/+</sup> mice, suggesting that this pathway might be implicated in the local clearance of PMVs at sites of platelet activation, or that compensatory mechanisms might be implicated *in vivo*. Moreover, given the dominance of PS<sup>-</sup> PMVs in the lymphatic circulation [18], it could be hypothesized that lymphatic drainage could compensate for the clearance of these PMVs. Despite their abundance, the physiological roles of PMVs and their function in healthy individuals are still not completely understood and represent an exciting field of research in the future.

### PMVs in hemostasis and thrombosis

Although platelets play a central role in coagulation and clot formation, it is suggested that the coagulation capacity of PMVs is 50 to 100-fold higher than activated platelets [42], pointing to a key role for PMVs in blood coagulation. The coagulation process is initiated by the exposure of tissue factor (TF) and its binding to coagulation factor FVII, leading to the formation of the extrinsic tenase complex (TF and factor VIIa) and the assembly of the intrinsic tenase complex (activated FVIII and FIX) and the prothrombinase complex (activated FV and FX). The formation of prothrombinase and tenase complexes requires a negatively charged surface. Therefore, like platelets, PS<sup>+</sup> PMVs provide a catalytic surface for coagulation [34,43] and bind coagulation factors like FIXa [44] and FVIII [45]. In addition to supplying a coagulation surface, Zubairova et al. demonstrated that CD61<sup>+</sup> (GPIIIa), present on PMVs in healthy donors, supports fibrin clot formation by direct attachment to fibrin fibers and by enhancing rapid thrombin generation [46]. Although the presence of TF in platelets is still the subject of debate [47–49], platelets internalize TF-rich MVs [50] that might serve as a potential source of TF in PMVs. Several studies suggest a role for PMVs in the promotion of coagulation; however, studies also suggest heterogeneous distribution of coagulation capacities between subgroups of PMVs, especially PS<sup>-</sup> PMVs. Trans et al. suggested that platelet activation results in both pro-coagulant and anti-coagulant PMVs [51], which might participate in the maintenance of hemostasis via the generation of low levels of thrombin and the subsequent activation of anticoagulant proteins [33].

Consistent with their contribution to hemostasis and thrombosis [26], PMVs are also involved in a variety of coagulation and bleeding disorders. Patients affected by Castaman's defect, a

disease characterized by a bleeding tendency associated with prolonged bleeding time [52,53], showed an inability to generate PMVs. Surprisingly, no alteration in prothrombinase activity or PMV intrinsic properties were detected in these patients, pointing to a potential contribution of basal levels of PMVs in coagulation. Conversely, patients with Scott syndrome, which is a congenital autosomal recessive bleeding disorder [54,55], display a normal PMV count, but impaired procoagulant prothrombinase activity [56]. PMVs in these patients show an impaired coagulation capacity due to defective translocation of PS into the membrane and therefore insufficient procoagulant surface for coagulation factors. The molecular mechanisms underlying low PS exposure are not yet completely understood, but might be related to an inefficient shedding mechanism due to scramblase and floppase defects [56,57]. A mutation in the scramblase TMEM16F has been identified in patients with Scott syndrome [10,58] and has been linked to defects in PS exposure [9,10]. Of particular interest is that mice deficient in TMEM16F expression have altered PMV levels and a phenotype resembling that of patients with Scott syndrome [9].

A potential role for PMVs has also been described in other bleeding disorders, including immune thrombocytopenia (ITP). Patients with ITP have circulating anti-platelet surface GP antibodies, leading to platelet destruction [59]. Higher PMV levels were observed in asymptomatic patients when compared to symptomatic patients with ITP, suggesting a protective role for PMVs in this disease [60]. Furthermore, a recent study described that ITP patients, despite having low platelet counts, presented a procoagulant profile, in part due to increased levels PMVs in their blood [61]. In fact, PMVs may help to overcome the coagulation defects associated with ITP by promoting blood clotting and maintaining tissue integrity. However, in some ITP patients, high levels of PMVs were also associated with elevated risk of thrombotic events [59,60]. Therefore, further studies are required to clarify the contribution of PMVs to ITP.

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disorder due to a somatic mutation resulting in the absence of glycosylphosphatidylinositol-anchored proteins on the cell surface [62]. Complement proteins CD55 and CD59 are among the deleted proteins, which results in an elevated complement sensitivity leading to higher platelet activation and elevated risk of thrombotic events [62]. Patients with PNH show elevated numbers of circulating pro-coagulant MVs, the majority being derived from platelets [63]. *In vitro* studies revealed that platelets from PNH patients lacking CD59 are more sensitive to C5b-9 complement subunit binding, and release PMVs with 10-fold higher prothrombinase activity than platelets from matched controls [64]. Despite progress in understanding the roles of PMVs in coagulation, the exact mechanisms by which they contribute to coagulation defects or to pro-thrombotic events remain to be clarified.

### Transfusion adverse reactions

Transfusion of blood products can result in an immune reaction in the recipient. Of interest is that transfusion of platelet concentrates is much more frequently associated with adverse reactions than red blood cell (RBC) transfusions [65]. PMVs are detected in platelet concentrates [66] and show activation marker CD62P, thereby enabling their adhesion to P-selectin glycoprotein ligand-1 (PSGL-1) expressed on the leukocyte surface [67]. PMVs are rich in inflammatory molecules such as platelet CD40L (CD154). High levels of CD40L were detected in platelet concentrates and associated with adverse reactions to transfusion [68] and transfusion-related acute lung injury (TRALI), an acute lung insufficiency [69]. In addition to inflammatory mediators, PMVs also transport mitochondria of platelet origin [28]. Circulating mitochondrial DNA (mtDNA) is a strong pro-

inflammatory trigger and its role as a damage-associated molecular pattern is well recognized [70]. Of relevance, mtDNA is present in blood products [28,71,72], including those associated with adverse reactions to transfusion [28]. Interestingly, Yasui et al. showed that platelet concentrates associated with non-hemolytic transfusion reactions contained higher levels of mtDNA than plasma and RBC products, suggesting that PMV levels in transfused platelet concentrates may be a donor exclusion criterion [73].

### PMVs in rheumatoid diseases and systemic lupus erythematosus

Several studies determined that PMV levels are increased in rheumatoid arthritis (RA) [25,74]. Using CLEC-2 and GPVI markers to discriminate MK-derived MVs from PMVs, a recent study confirmed that platelets are the main source of MVs in RA, pointing to platelet activation in this disease [25]. In recent years PMVs have also emerged as important players in the exacerbation of inflammation in the synovial joint during RA. It was shown that PMVs were not only abundant in synovial fluid from RA patients [19,75,76], but also in other inflammatory arthritis conditions such as psoriatic arthritis, juvenile idiopathic arthritis and gout [76]. PMVs contain both IL-1 $\alpha$  and IL-1 $\beta$  and induce IL-6 and IL-8 production by synoviocytes, underlying their pro-inflammatory potential [76]. Moreover, PMVs are suggested to participate in overwhelming inflammation in RA by targeting immune cells implicated in the disease pathogenesis. Indeed, PMVs are actively internalized by neutrophils through the coordinated action of 12-LO, present in PMV, and secretory phospholipase A<sub>2</sub>-IIA (sPLA<sub>2</sub>-IIA), induced during inflammation [27]. Consistent with the potential relevance of this mechanism, blockade of PMV internalization by ablation of genes coding for 12-LO or sPLA<sub>2</sub>-IIA reduced arthritis severity in a murine model of rheumatoid arthritis [27]. Furthermore, studies showed that PMVs display surface autoantigens and interact with autoantibodies present in the joint of RA patients [19]. These autoantigens were identified as citrullinated fibrinogen and vimentin, and the formation of PMV-autoantibody complexes was shown to be highly potent at triggering the production of pro-inflammatory leukotrienes from neutrophils [19].

The assessment of PMV levels in rheumatic diseases is the topic of several studies. Whereas some have reported an increase in PMV levels in patients with systemic lupus erythematosus (SLE) [77,78], others reported a decrease in PMVs and an increase in total PS<sup>-</sup> MVs in SLE patients when compared with healthy donors [79]. The explanation for this discrepancy is unclear, but it might be due to the inclusion of SLE patients with different degrees of disease severity or organ damage, or the utilization of distinct technical approaches used for PMV measurements. A recent study revealed that PMVs in SLE were decorated with immunoglobulin G (IgG) in the blood of SLE patients [80]. Further examinations showed that levels of IgG-decorated CD41<sup>+</sup> PMVs, with or without exposed PS, in the plasma of SLE patients correlated with disease activity. Conversely, concentrations of MVs that were not of platelet origin (CD41<sup>-</sup>) correlated with carotid intima-media thickness, which is indicative of the risk of cardiovascular events, a frequent complication associated with SLE [80]. Taken together, these studies suggest that PMV levels are modulated in rheumatic disease, and that an appreciation of their heterogeneity might reveal biomarkers for these diseases.

### Cardiovascular diseases

Levels of PMVs are disturbed in a large set of cardiovascular diseases. For instance, patients with carotid plaques have higher

levels of large PMVs than subjects without carotid atherosclerosis, even after statistical adjustments for cardiovascular risk factors [81]. Similarly, increased PMV levels were found during acute-phase atherosclerotic cerebral infarction [82]. More recently, increased concentrations of PMVs have been associated with extended damage following myocardial infarction (MI) [83]. Monocyte recruitment from the arterial lumen to the subendothelial space occurs in the initial stages of atherosclerosis and is a key event in inflammatory-related atherosclerosis [84]. Of note is that PMVs have been shown to modulate monocyte adhesion to the vascular endothelium [85]. Indeed, Mause et al. demonstrated that PMVs could deliver RANTES (CCL5) to monocytes to promote their arrest at the endothelial wall [86]. Consistent with a potential role for PMV-derived RANTES, pre-treatment of monocytes with the RANTES-receptor antagonist Met-RANTES limited monocytic arrest on atherosclerotic lesions [86]. Furthermore, PMVs are thought to be able to transfer miRNAs [27,29,87]. In fact, PMVs released by activated platelets in myocardial infarction (MI) induce intercellular adhesion molecule 1 (ICAM-1) expression by endothelial cells by delivering miR-320b, a miRNA increased in the plasma of patients with MI [88], which could further contribute to recruitment of inflammatory leukocytes at the arterial wall to initiate the inflammatory response.

### PMVs in cancer and angiogenesis

Kim and colleagues demonstrated that angiogenic factors and lipids contained in PMVs promote proliferation and survival of human umbilical vein endothelial cells (HUVECs) *in vitro*, pointing toward a role for PMVs in tumor growth and angiogenesis [89]. These results were supported by the work of Brill et al., who demonstrated a vascular endothelial growth factor (VEGF)-dependent role for PMVs in the induction of angiogenesis *in vitro*, and in a rat model of myocardial ischemia [90]. Although a direct contribution of PMVs to cancer pathogenesis has not yet been demonstrated, some studies suggest a link between PMVs and cancer [91–93]. For instance, the total number of PS<sup>+</sup> MVs is higher in breast cancer metastasis compared with less severe cases [91]. Characterization of these MVs further revealed that 82% are of platelet origin [91]. An elevated MV level was also reported in patients with oral [92] and colorectal cancers [93]. The exact contribution of PMVs to cancer as well as their potential use as biomarkers for diagnosis, prognosis, and treatment follow-up remain to be determined.

### PMVs in infections and immunity

Despite limited documentation, PMVs are also described as key players in infection. In a similar manner to platelets [94], PMVs actively participate in the host immune response. They promote leukocyte recruitment to the infection site and leukocyte–leukocyte interactions via a CD62P-dependent mechanism [95]. CD62P<sup>+</sup> PMVs attenuate and stabilize inflammation by attenuating the differentiation of T-cells into IL-17 and IFN $\gamma$ -producing pro-inflammatory T cells [96]. Sprague and co-workers demonstrated that PMVs deliver platelet CD40L to B cells, thereby inducing the B cell response and IgG production [97]. PMVs also play a role in viral infection. Corrales-Medina et al. reported that PMV levels were higher in a cohort of HIV-infected patients compared with healthy donors [98]. Interestingly, PMVs have been shown by Rozmyslowicz et al. to be capable of transferring CXCR4, (a chemokine receptor mediating HIV entry into target cells, mainly T lymphocytes) to CXCR4-negative cells, thereby rendering them susceptible to infection by the X4 HIV strain [99].

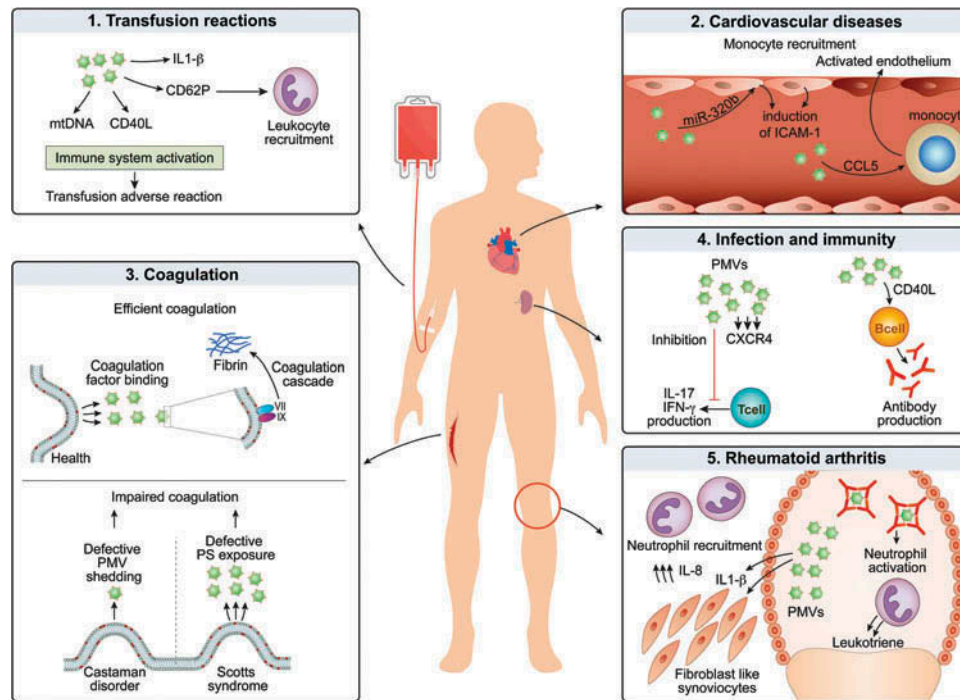


Figure 2. PMV contributions in health and pathological conditions. 1. PMVs play a role in transfusion-induced adverse reactions through mitochondrial DNA (mtDNA) release. PMVs also interact with leukocytes through CD62P and activate the immune system via CD40L. 2. PMVs promote monocyte arrest on activated endothelium, as well as atherosclerotic lesions, by a CCL-5 dependent mechanism. Furthermore, PMVs are able to deliver miR-320b, and thereby contribute to the recruitment of leukocytes at the arterial wall. 3. PMV surface form a potent interface for the initiation of the coagulation cascade, and contributes to efficient coagulation. When PMV levels are reduced (defective PMV shedding, i.e. Castaman disorder) or when PMVs display limited PS levels (i.e. Scott syndrome), patients suffer from impaired coagulation. 4. PMVs transfer CXCR4 to CXCR4<sup>-/-</sup> cells, thus enabling their infection by HIV. Moreover, PMVs are able to modulate IL-17 and IFN $\gamma$  production through a CXCR3 dependent mechanism. PMVs can also deliver functional CD40L to B cells, thereby inducing efficient IgG production. 5. PMVs are involved in amplification of inflammation in rheumatoid arthritis by forming immune complexes when recognized by autoantibodies, which stimulate leukotriene production by neutrophils. PMVs also activate fibroblast-like synoviocytes through their IL-1 $\beta$  content and stimulate them to produce IL-8, which recruits neutrophils to the synovial tissue.

Viruses can also activate platelets, thereby directly affecting PMV levels in blood [100]. It was shown that the influenza virus H1N1 could activate PMV release from platelets. Studies revealed that platelet activation by H1N1 implicated IgG from the immunized host, and Fc $\gamma$ RIIA on platelets [100]. As humans have antibodies directed against a variety of viruses, it is suggested that this mechanism might occur during different types of infections if the host is immunized against the invading microbial agent.

During Dengue virus (DENV) infection, PMVs in infected patients expose viral antigens derived both from DENV structural and non-structural proteins [101], suggesting a potential role for PMVs in virus propagation. The same study demonstrated a decrease in plasma levels of PMVs in patients with severe bleeding tendency [101], pointing to the use of PMVs as a biomarker to predict dengue-associated bleeding.

PMVs are also emerging as players in *Plasmodium* parasite infections, a parasite that invades the host RBCs and in particular cases sequesters them from the circulating blood [102]. In fact, increased levels of PMVs were reported in the blood of patients infected with *Plasmodium Vivax*, the most widespread *Plasmodium* species. Of relevance, high PMV concentrations were associated with the duration of acute malaria symptoms [103]. Faillie et al. demonstrated that during *Plasmodium falciparum* infection, PMVs adhere to RBCs in the brain of malaria patients and increase the binding of sequestered RBCs to endothelial cells in this organ [104]. The same study showed that PMVs adhere to endothelial cells inducing their activation and the expression of adhesion molecules, and thus participate in the mechanisms of *Plasmodium* infection [104].

## Conclusion

A role for PMVs as an essential contributor to the coagulation capacities of human blood has long been suggested [1]. PMVs have also been associated with multiple physiological processes and diseases, with implications based on statistical and clinical associations, and on experimental evidence. A non-exhaustive summary of the known mechanisms by which PMVs contribute to particular diseases is presented in Figure 2. However, more investigations are required to completely ascertain the role of PMVs in health and disease. As standardization of protocols and new experimental approaches arise, PMVs could realize their potential as predictors of disease before the appearance of overt clinical symptoms. In the near future, new panels of PMVs might be identified based on their content and their role in physiological processes. A better understanding of PMV biology will permit the deciphering of PMV networks and might highlight their role as potential biomarkers or their development as the target of choice in different pathologies.

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## Declaration of interest

The authors report no conflicts of interest.

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