Transfusion and Apheresis Science ■■ (2015) ■■–■■

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Review

The role of microparticles in inflammation and transfusion: A concise review

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ARTICLE INFO

Keywords:
MPs
Inflammation
Transfusion

ABSTRACT

Microparticles are small membrane-bound vesicles found in body fluids including peripheral blood. Microparticles are an intrinsic part of blood labile products delivered to transfused patients and have active roles in inflammation. They are delimited by a lipid bilayer composed mainly of phospholipids, cholesterol, membrane-associated proteins, intracellular components such as metabolic enzymes, proteins-involved in adhesion and fusion, cytoskeletal-associated proteins, surface glycoproteins and/or chemokines. Microparticles can trigger a pro-inflammatory message to neighbouring or target cells. Microparticles originating from platelets, leukocytes, erythrocytes, and endothelial cells are associated with a variety of pathophysiological conditions. This review summarises the role of Microparticles in modulating inflammation.

Contents

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http://dx.doi.org/10.1016/j.transci.2015.10.013
1473-0502/

1. Introduction

Microparticles (MPs) are small (0.05–1.0 μm in diameter) particles, or vesicles, found in the blood circulation and various biologic fluids [1], which are released from cell membranes upon activation and/or apoptosis [2]. MPs originate from several cell types such as leukocytes, erythrocytes, platelets or endothelial cells and may contain various Biological Response Modifiers (BRM) and receptors depending on their origin [3,4]. MPs participate in biological activities associated with inflammation, immune responses and thrombosis [5]. In this review we focus on the current knowledge regarding MP generation, composition, and potential as novel effector elements of inflammation.

2. General aspects of MPs

MPs are vesicles shed from the plasma membrane and are considered biological vehicles that transfer information between cells within their environment or at a distance through the circulation [6–8]. MPs permit intracellular communication through different pathways: (i) directly with ligands present on the surface of target cells, contributing to relocating proteins; (ii) by binding to the membrane of target cells that then acquire a novel surface antigen, thereby exhibiting novel phenotypes and characteristics; (iii) indirectly by interacting with target cells through the modulation of the extracellular environment (such as modification of local oxidative stress); and (iv) internalisation by fusion to influence gene regulation [4,8].

3. Production of MPs

Each side of the plasma membrane has a different lipid composition. Under physiological conditions, two negatively charged amino phospholipids, phosphatidylserine (PS) and phosphatidylethanolamine, are mainly present in the inner layer, whereas neutrally charged phosphatidylcholine (PC) and sphingomyelin are present in the external layer [3,9]. This asymmetrical distribution of phospholipids in the plasma membrane is dynamically maintained by several enzymes: flippases, floppases, and scramblases [10,11].

i. Flippases are a family of transmembrane lipid transporter enzymes positioned in the membrane that help translocate phospholipid molecules between the two sides of cellular membranes. This phenomenon is termed transverse diffusion, often known as flip-flop, and is ATP dependant. However, there are ATP independent/energy-independent flippases that transfer novel synthesised lipids from the outer membrane to the inner membrane [12,13].
ii. A second ATP-dependent activity, catalysed by floppases, transports lipids in the opposite direction. Floppase activity catalyses inner-to-outer monolayer transport selective of PC or cholesterol [14].
iii. Scramblases participate in the translocation of phospholipids between the two monolayers of a lipid bilayer in the cell membrane. Phospholipid redistribution is mediated by augmented cytosolic calcium and appears to be scramblase-dependent, resulting in a symmetric repartition of negatively charged phospholipids between both sides of the lipid bilayer. All scramblases contain an EF hand-like Ca^{2+} binding domain that may be responsible for the calcium mobilisation of the enzyme. The activity of scramblases is ATP independent. In humans, phospholipid scramblases (PLSCRs) constitute a family of five homologous proteins that are named hPLSCR1–hPLSCR5 [15].

During apoptosis or cell activation, the concentration of cytosolic Ca^{2+} increases, stimulating scramblase and floppase activity and inhibiting flippase, resulting in a loss of the asymmetrical distribution of membrane phospholipids [16].

Phospholipid translocation in cellular membranes during apoptosis is considered an essential marker of the initial phases of apoptosis [17]. In addition, PS exposure on the cell surface and mitochondria-specific phospholipid cardiolipin movement between the mitochondrial membranes are considered major events involved in apoptosis [18,19]. The loss of membrane asymmetry and phospholipid translocation in cellular membranes is followed by membrane budding and MP release.

MPs express protein membranes that are specific to the parent cells and thus can be used to characterise their antigen expression. These diverse protein expression patterns distinguish the subpopulation phenotypes of circulating MPs released after cell activation or apoptosis.

4. Origin of MPs

MP formation in platelets results from activation induced by several stimuli (collagen, thrombin, epinephrine, adenosine diphosphate, or A23187 ionophore) [20] and is stimulated by *ex vivo* preparation and storage of blood components used for transfusion [21,22]. Increased platelet MP (PMP) formation has been reported to contribute to the inflammatory role of platelets in a variety of clinical conditions [23] (Table 1). PMPs express plasma membrane glycoproteins (GP), such as GP IIb/IIIa (CD41) and GP Ib/IX complex, and the alpha-granulate membrane protein (GMP-140) [67]. PMPs are also the major transporters of platelet-activating factor (PAF), a potent phospholipid involved in the pathogenesis of inflammation [68]. Moreover, they can expose characteristic activated platelet markers such as P-selectin (CD62P) [69]. CD61 is a less specific platelet marker as this integrin is also expressed on blood monocytes; therefore antibodies to the CD61 epitope can bind to both platelets and monocyte-derived MPs.

Erythrocyte-derived MPs (EMPs) represent an abundant source of MPs newly generated in certain pathological states. Erythrocyte [70] activation and/or apoptosis stimulate calcium influx and participate in the disruption between membrane and cytoskeleton proteins, specifically spectrin and protein 4.1R. Consequently, the membrane becomes unstable, leading to MP release. During the lifetime of RBCs, a certain amount of haemoglobin content and surface area is lost through this mechanism [71]. When RBCs, which have a limited ability for self-repair, are exposed to constant oxidative stress, vesicle formation allows senescent antigens to be cleared whilst avoiding the activation of molecular

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Table 1
Summary of MP-related pathological conditions.

Pathophysiology	Microparticle involvement in disease	References
Atherosclerosis	• Leukocyte-derived MPs, identified by affinity for CD11a, are increased in subjects with ultrasound evidence of subclinical atherosclerosis • Bioactive lipids in PMPs have been shown to have important effects on angiogenesis	[24,25]
Vasculitis	• Endothelial MPs may provide a window to the activated endothelium and could provide important pathophysiologic insights into the vascular injury associated with vasculitis of the young • Expression of TF in neutrophil extracellular traps and neutrophil derived MPs suggests a novel mechanism for the induction of thrombosis and inflammation in active associated vasculitis	[26,27]
Venous thromboembolism	• Release of positive MPs may contribute to venous thromboembolism • Patients with venous thromboembolism have marked elevations of EMP identified by CD31+/CD42b–, EMP E-selectin, and EMP-monocyte conjugates	[28,29]
Acute coronary syndromes	• MPs of endothelial origin are significantly elevated in patients with acute coronary syndromes • EMPs have a prognosis value following ACS (Acute Coronary Syndromes) • Small-size MPs might be implicated in the modulation of the post-acute coronary syndromes' reparative response to injury, with prognostic implications	[30–33]
Diabetes	• The absolute median number of EMPs (EMPs/μL) specific for CD31, CD105, and CD106 is significantly increased in the Diabetes Mellitus population • Levels of platelet-derived MPs and monocyte-derived MPs correlate with diabetic complications or the extent of diabetic retinopathy, which is associated with microvascular damage	[34,35]
Metabolic syndrome	• PMPs, EMPs and leukocyte-platelet aggregates are associated with obesity, independent of metabolic abnormalities • Circulating MPs from metabolic syndrome patients influence endothelial dysfunction	[36–38]
Malignancy	• Patients with malignancy and patients with thrombosis have increased levels of circulating MPs and MP-dependent thrombogenic potential • Tumour-derived-bearing MPs are associated with venous thromboembolic event in cancer patients and may be central to the pathogenesis of cancer-associated thrombosis	[39,40]
Multiple sclerosis	• MPs from relapsing-remitting multiple sclerosis patients induce, at equivalent concentrations, a stronger disruption of endothelial barriers than those from healthy donors or from patients with clinically isolated syndrome • MPs play a role in multiple sclerosis pathogenesis, reflecting disease status with an increment of their shedding during inflammatory periods and turning to baseline during chronic progressive degeneration	[41,42]
Rheumatoid arthritis	• PMPs are associated with rheumatoid arthritis, and their level is correlated with disease activity • Collagen receptor glycoprotein VI is a key trigger for platelet microparticle generation in arthritis pathophysiology	[43,44]
Systemic lupus erythematosus	• SLE patients have increased numbers of MPs that are heavily tagged for removal and fewer MPs with normal protein composition • Circulating cell-derived MPs in SLE patients carry increased loads of IgG, IgM, and C1q and that IgG MPs are associated with autoantibodies and complement activation	[45,46]
Anti-phospholipid antibody syndrome	• EMPs (CD51 and CD105) are significantly increased in patients with PAPS (Primary Antiphospholipid Antibody Syndrome) and aPL compared to healthy controls • Levels of MPs that stained for CD105 and CD144 show a positive correlation with IgG and IgM anti-beta2-glycoprotein I antibodies	[47,48]
Paroxysmal nocturnal haemoglobinuria	• Significant amounts of procoagulant MPs are released from paroxysmal nocturnal haemoglobinuria red blood cells • Elevated CD54+ endothelial MPs may reflect the inflammatory status of endothelial cells in paroxysmal nocturnal haemoglobinuria	[49,50]
Heparin-induced thrombocytopenia	• In positive heparin-induced thrombocytopenia patients, PMPs expressing phosphatidylserine are generated with low UH concentration, whereas the PMP rate decreases significantly in the presence of high UH concentrations • Heparin-induced thrombocytopenia Ab complex induced expression in monocytes and the release of TF-positive MPs	[51,52]
Thrombotic, thrombocytopenic purpura	• Chronic ITP (Immune Thrombocytopenia) was associated with increased levels of RMPs and PMPs • Endothelial MPs that co-express von Willebrand factor and CD62E might play a role in the pathogenesis of thrombotic thrombocytopenic purpura	[53,54]
Sickle cell disease	• PMP and ErMP (erythrocyte-derived MPs) overproduction may be considered a potential biological marker for vascular dysfunction and disease severity in Sickle cell disease and may be implicated in the pathogenesis of coagulation abnormalities encountered in those patients • Procoagulant state in sickle cell disease is partially explained by the factor XI-dependent procoagulant properties of circulating erythrocyte-derived MPs	[55,56]
Cerebral malaria	• MPs localised at neurovascular lesions *in vivo* and MPs transfer elicited cerebral malaria-like histopathology in the brain and lung of healthy recipients, supporting a role for MPs in cerebral malaria pathogenesis • Cerebral malaria patients, platelet MPs, are the most abundant and their levels significantly correlated with coma depth and thrombocytopenia	[57]
Sepsis	• Septic MPs induce deleterious changes in the expression of enzyme systems related to inflammation and oxidative stress • Patients with meningococcal sepsis have elevated numbers of circulating MPs that are procoagulant	[58,59]

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Table 1 (*continued*)

Pathophysiology	Microparticle involvement in disease	References
HIV infections	• Plasma from patients with HIV specifically inhibits DC function by elevated apoptotic MPs derived from dying cells during acute HIV-1 infection. Apoptotic MPs bound to and inhibited DCs through the hyaluronate receptor CD44 • Residual MP-activity amongst treated patients is associated with biomarkers of inflammation and coagulation and is consistent with the hypothesis that residual inflammation may contribute to HIV-related coagulation abnormalities through increased circulating activity	[60,61]
Inflammatory bowel diseases	• TF expressed on the surface of MPs or delivered to the site of thrombosis via circulating blood cells and MPs may initiate an event in the extra intestinal thrombosis elicited during Inflammatory bowel diseases • MPs from Crohn's disease patients significantly alter endothelial and vascular functions and therefore may play a role in Crohn's disease pathophysiology by contributing to uncontrolled vascular-dependent intestinal damage	[62,63]
Renal diseases	• Increased levels of endothelial platelets and erythrocyte-derived MPs in end-stage renal failure • Kidney-derived mesenchymal stem cell-derived MPs may act as a source of proangiogenic signals and confer renoprotective effects in ischaemic kidneys • Thrombophilia of the nephrotic syndrome may be partly ascribed to MP release and phosphatidylserine exposure of red blood cells, platelets and endothelial cells. • Endothelial derived MPs isolated from ESRF (end-stage renal failure) induce endothelial dysfunction by decrease in nitric oxide production	[64–66]

MP, microparticles; PMP, plasma MP; TF, tissue factor; EMP, endothelial MP; SLE, systemic lupus erythematosus; aPL, anti-phospholipid antibody syndrome; UH, unfractionated heparin; RMP, red blood cell MP; DC, dendritic cell.

sensors of danger. MP formation is considered as an essential step of RBC aging and is significantly correlated with spectrin oxidation. Once vesiculation capacity is exceeded, old erythrocytes are removed by the reticuloendothelial system [49].

White blood cells have an important role in inflammatory and immunological reactions. Monocytes exposed to various stimuli release MPs [72,73]. Monocytes express CD14 (CD14 and MD-2 form a complex with Toll-like receptor [TLR]4, a lipopolysaccharide (LPS) receptor, during LPS-mediated signalling to detect bacterial LPS); thus, monocyte-derived MPs can be detected by their surface expression of CD14. MPs derived from neutrophils have been found in the blood of normal healthy subjects and in patients with various pathologies (Table 1), in particular meningococcal sepsis [74]. Lymphocyte-derived MPs are identified using the lymphocyte-specific markers CD4 and CD8. Finally, polymorphonuclear neutrophilic leukocyte-derived MPs are identified using leukocyte-specific markers, such as lactoferrin or CD66b [75].

High endothelial MP levels are associated with numerous pathological conditions, including atherosclerosis, sepsis, and diabetes mellitus (Table 1). Endothelial cells release different types of endothelial MPs (EnMPs) through the activation and/or apoptosis pathways. Several endothelial specific antibodies are used to detect MPs, including CD31, CD51, CD105, CD144, and CD146 [76]. EnMPs released after inflammatory activation are characterised by the high expression of CD62 (E-selectin) [77,78].

5. MPs and inflammation

The contributions of MPs to the inflammatory process are well documented. MPs up-regulate the synthesis of numerous pro-inflammatory enzymes and active proinflammatory soluble mediators in non-immune and immune cells [43,79,80]. The release of platelet, endothelial and leukocyte MPs is increased during inflammatory conditions [81] (Table 1).

As described previously, MPs contain high levels of amino phospholipids, which are a substrate for phospholipase A2 and thus are associated with the production of lysophosphatidic acid that influences the inflammatory process of platelets [82]. The MP-induced modulation of cyclooxygenase (COX)-2 expression in human monocytoid cell lines prompts the translocation of protein kinase C from the intracellular compartment to the membrane and activates different kinases [83–85]. PMPs support the transcellular transport of arachidonic acid (AA) to increase the expression of COX-2 and intracellular adhesion molecule (ICAM)-1 in endothelial cells, which regulate the interface of vascular cells and platelets [85–88]. Moreover, AA present in PMPs is involved in platelet aggregation and interactions of platelets with immune (e.g. monocyte) and non-immune cells (e.g. endothelial cells) [88]. Previous data have suggested that MPs modulate cell physiology and function by the transcellular distribution of bioactive molecules/receptors.

MPs from platelet and leukocyte origins participate in the production of several endothelial BRMs (interleukin [IL]-1, IL-6, IL-8, monocyte chemoattractant protein [MCP]-1, and tumour necrosis factor [TNF]-α) that assist in interactions between leukocytes and endothelium [73]. Inversely, BRMs are involved in the production of MPs. Arteriosclerosis patients have an augmented concentration of IL-6 associated with an increased expression of P-selectin and a generation of PMPs under shear stress [89].

MPs generated by platelet activation can contribute to *in vitro* leukocyte–leukocyte interactions involving the binding of P-selectin/P-selectin glycoprotein ligand-1 (PSLG-1) and increased accumulation at sites of vascular injury of leukocytes and on activated endothelium [90]. In addition, PMPs might increase the recruitment of immune cells such as monocytes, T and B lymphocytes and natural killer cells that have key roles in inflammation [91].

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Several studies suggest that MPs may contribute to the amplified risk of thrombosis in systemic inflammatory diseases [69,79,92]. However, other reports proposed a possible anti-inflammatory role of MPs [93,94]. This pleiotropic characteristic is supported by differences in the composition of MPs, which is a function of the parent cell they originated from and the stimulus that induced their release. It was reported that MPs released by neutrophils do not have proinflammatory functions on human macrophages, but rather they enhance the release of transforming growth factor (TGF)β1 and decrease macrophage activation [93].

6. MPs in stored erythrocyte and platelet products

Blood storage lesions include morphological and biochemical modifications of RBCs [95]. This occurs in parallel to the conversion of disc morphology from biconcave to spherical, a decrease in mean corpuscular haemoglobin concentration, a variation in mean corpuscular volume, a reduction of erythrocyte membrane integrity leading to MP release and increased cell-free haemoglobin [96]. The concentration of MPs in RBC-derived vesicles increases over time in packed red-blood cell units. Therefore, RBC-MPs are suspected to be involved in the pathogenesis of different adverse clinical events related to multiple transfusions through the activation of the haemostatic system and their effects on nitric oxide (NO) bioavailability. Different studies from the Gladwin group investigated the effects of stored blood cell-free haemoglobin and MPs on NO metabolism. Data showed that RBC-derived MPs generated during storage could scavenge NO within encapsulated haemoglobin molecules and thus decrease its bioavailability. This interaction between MPs and NO could lead to endothelial dysfunction and increase vasoconstrictive tone *in vivo*, which might explain several clinical side effects observed following blood transfusion.

In 1967, Wolf described the first MPs as “platelet-dust” in platelet free plasma, validated their procoagulant activity and showed that MPs could be isolated by ultracentrifugation [97]. Whilst “platelet-dust” was known for more than four decades, the purification method and quantification of MPs are still difficult although new technologies are now becoming available, thanks to the development in nanosciences [8,98]. PMPs are the most abundant MPs in the bloodstream, constituting approximately 70%–90% of circulating MPs [99,100]. Because MPs are present in high amounts in the bloodstream, “naturally-occurring” MPs can be found in all blood labile cellular products, such as plasma and cryoprecipitate preparations, and are distributed to transfused patients. They can be generated by blood processing [22], and can accumulate in cellular concentrates as well as in platelet concentrates, fresh frozen plasma (FFP), and RBCs during storage [101]. Because PMPs are highly abundant in the human circulation, they are considered markers of platelet activation if present in elevated amounts. In addition, platelet concentrate processing and storage under blood bank conditions for transfusions appear to be associated with the generation of new classes of MPs with other characteristics such as coagulation or inflammatory activity [102]. Furthermore, during platelet concentrate storage, an increase in PMPs was observed as a consequence of the process [103]. Similar to other blood products, increased MPs are observed after prolonged storage. The release of storage-dependent MPs is the consequence of platelet activation [21]. In addition, PMPs can be collected from platelet concentrate supernatants after prolonged storage (5–7 days of storage induces functional active caspase 3 and apoptosis in human macrophages) [104].

The clinical relevance of PMPs on coagulation is evident in leukaemic and thrombocytopenic patients, as those with high levels of circulating PMPs do not bleed despite their low platelet counts [105].

PMPs have 100-fold higher procoagulant activity than platelets [106]. The mutual activities and interactions of clotting factors, inhibitors, MPs, and other plasma components contribute to the overall haemostatic characteristics of plasma. However, an excess of transfused MPs might have deleterious prothrombotic and proinflammatory effects and modify vascular functions. Cryoprecipitation concentrates include abundant contact-promoting proteins that cooperate with the platelet surface, namely fibrinogen, fibronectin, von Willebrand factor, factor VIII and other proteins. It has been proposed that the high concentration of PMPs in cryoprecipitates might contribute to its haemostatic effects in bleeding patients due to their capacity to bind to fibrinogen, fibronectin, or von Willebrand factor similar to how platelets cooperate with fibrinogen and von Willebrand factor when bound onto a solid support [107,108].

Human and murine platelets express CD40 ligand (CD40L; also called CD154 and gp39), a transmembrane member of the TNF family, and its receptor, CD40 [109,110]. CD40L is translocated to the surface membrane during platelet storage, then cleaved, and shed by activated platelets. In addition, activated platelets are the principal source of plasma CD40L [111–117]. Inflammatory and immune activities of platelet CD40L have been extensively published. Soluble (s)CD40L exists both as an independent cleaved form or as a form bound to PMPs. These two populations of sCD40L are not easily distinguished. Furthermore, the purification methods and characterisation of MPs are still being developed. Platelets contain abundant CD40L in alpha-granules, and after platelet activation, express it on their membrane. The cleavage and MP release of sCD40L occur in activated platelets.

Additionally, various technologies are accessible for the production of platelet concentrates. Krailadsiri et al. compared the characteristics of PCs prepared by three commonly used techniques and showed that the degree of phosphatidylserine exposure on platelet was different depending on leucodepleted platelet concentrate methods. Furthermore, a significant correlation was found (i) between the expression of CD62P on platelet surface and soluble CD62P in the plasma and (ii) between phosphatidylserine exposure and microvesiculation [118].

The pathophysiological functions of circulating MPs generated from various blood and vascular cells are generally unidentified and can be favourable or damaging depending on the pathology and diseases state. Several laboratories have recently begun to apply proteomic approaches to the study of platelet storage to confirm the clinical relevance of PMPs in various pathologies [119,120].

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Krailadsiri et al. have measured MV derived from red cells (RBC-MV), platelets (PLT-MV), and white blood cells (WBC-MV) in blood components produced by various procedures. RBC-MV and PLT-MV were either unchanged or reduced by all processes, with PLT-MV reduced 10-fold by RBC leucodepletion (LD) and greater than 300-fold by plasma LD. There were differences between various filters and techniques, which were generally minor compared to the overall effect. Interestingly, microvesicles derived from both RBC-MV and PLT-MV were present in whole blood before LD, and RBC-MV but not PLT-MV was detected in processed RBCs before LD suggesting that microvesiculation occurs during storage in the plastic bag before LD [121]. Most studies so far have relied on the use of standard flow-cytometry instrumentation, a technique that fails to detect MPs smaller than approximately 500 nm, therefore justifying to revisit the impact of blood processing methods on MP generation using improved flow cytometry and other assessment methods as reviewed in this Theme issue [122,123].

7. Microparticle contribution to pathophysiology

MPs are present in the blood circulation of healthy subjects and patients, but also participate in the maintenance of homeostasis as well as pathological situations. Various levels and concentrations of MPs have been reported to be elevated in several different pathophysiologies (Table 1), but which all presented with inflammation and haemostasis characteristics. Inflammation and haemostasis are interconnected pathophysiologic processes that significantly affect each other. Amongst the investigated diseases are stable and unstable atherosclerosis [24,25,30,31], diabetes [34,35], metabolic syndrome [36,37], malignancy [39,40], multiple sclerosis [41,42], sepsis [58,59], rheumatoid arthritis [43,44], vasculitis [26,27], systemic lupus erythematosus [45,46], anti-phospholipid antibody syndrome [47,48], venous thromboembolism [28,29], paroxysmal nocturnal haemoglobinuria [49,50], heparin-induced thrombocytopenia [51,52], thrombotic thrombocytopenic purpura [53,54], sickle cell disease [55,56], HIV infections [60,61], inflammatory bowel diseases [62,63], cerebral malaria [57], and renal diseases [64,65]. We noted that MP levels diverged from the normal concentration found in healthy individuals. Table 1 summarises some pathological conditions, their manifestations and the MP levels detected in plasma.

8. Conclusion

There has been an increasing interest in cell-derived blood-borne MPs, and studies have indicated their critical role in haemostatic and inflammatory responses as well as their potential as disease markers. They originate from different cell types including platelets, the main source of MPs, RBCs, leukocytes and endothelial cells. Currently, the analysis of MPs remains challenging, in particular the assessment of their pleiotropic characteristics [122,123].

Nevertheless, MP generation processes are now better understood and it is increasingly recognised that MPs may represent exceptional markers of disease activity. Moreover, progress is being made in understanding the blood product manufacturing steps that might trigger the release of MPs and their potential effects on the inflammatory status of patients. Future research will help define the roles of MP subpopulations in inflammatory diseases and their cellular origin. This knowledge is likely to stimulate the development of new therapeutic strategies that target either MP release or action.

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