Microparticles and Fibrinolysis

Loris Vallier, Sylvie Cointe, Romaric Lacroix, Amandine Bonifay, Coralie Judicone, Francoise Dignat-George, Hau C Kwaan

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Loris Vallier, PharmD[1] Sylvie Cointe, PharmD, PhD[1,2] Romaric Lacroix, PharmD, PhD[1,2] Amandine Bonifay, PharmD[1] Coralie Judicone, MS[2] Françoise Dignat-George, PharmD, PhD[1,2] Hau C. Kwaan, MD, FRCP[3]

[1] VRCM, UMR_S1076, UFR de Pharmacie, Aix-Marseille Université, INSERM, Marseille, France
[2] Department of Hematology and Vascular Biology, CHU La Conception, APHM, Marseille, France
[3] Division of Hematology/Oncology, Northwestern University Feinberg School of Medicine, Chicago, Illinois

Address for correspondence Hau C. Kwaan, MD, FRCP, Division of Hematology/Oncology, Northwestern University Feinberg School of Medicine, Chicago, IL (e-mail: h-kwaan@northwestern.edu).

Abstract

Microparticles (MPs) are submicronic vesicles which are formed by budding of the cellular membrane of virtually any cell type in response to cell activation or apoptosis. Both circulating MPs and MPs generated within tissues harbor molecules with a large repertoire of biological activities and transfer material to target cells. Depending on their cellular origin, the stimuli triggering their formation, or their localization, they may participate in the maintenance of organ or vascular homeostasis as well as inducing dysfunction. MPs have mostly been described as having procoagulant properties. However, the fact that some MP subsets are able to efficiently generate plasmin suggests that the role of MPs in hemostasis is more complex than initially thought. In this review, we summarize key findings showing that MPs provide a heterogeneous catalytic surface for plasmin generation, according to their cellular origin. We further address the specific features of the MP-dependent fibrinolytic system. Potential consequences of this MP-associated fibrinolytic activity in pathology are illustrated in cancer.

Keywords
- extracellular vesicles
- cancer
- fibrinolysis
- hemostasis
- microparticles

All normal eukaryotic and prokaryotic cells and cancer cells release extracellular vesicles (EVs) in response to stress, activation, or apoptosis.[1] These EVs are heterogeneous, with three main types: exosomes, microvesicles/microparticles (MPs), and apoptotic bodies. They differ by their sizes, the mechanism of their production mechanism, as well as their composition and functions[2,3]: MPs are submicronic vesicles which are formed by calcium-dependent cellular events such as remodeling of membrane phospholipids, cytoskeleton cleavage, and contraction of the actin cytoskeleton. Their membrane consists of a phospholipid bilayer enriched in negative phospholipids such as phosphatidylserine (PS) on the external leaflet. MPs exhibit surface proteins and glycoproteins representative of their parental cells. These proteins could vary depending on the stimuli which triggered their formation. Despite the lack of nucleus, they can vectorize nucleic acids (mRNA and miRNA). MPs are present in all body fluids: blood, urine, cerebrospinal fluid, saliva, pleural fluid, synovial fluids, and vitreous humor. The majority of MPs detected in peripheral blood are derived from platelets and erythrocytes as well as leukocyte, endothelial cells, or nonhematopoietic cells such as syncytiotrophoblasts and circulating tumor cells. MPs have to be distinguished from exosomes, which are small vesicles measuring between 30 and 100 nm.[4,5] Exosomes are formed in endosomes which become multivesicular bodies, fused with cellular membrane and releasing their content into the extracellular environment. Usually, exosomes do not express anionic phospholipids on their surface and are enriched in molecules of the tetraspanin family, such as CD63 and CD81. Apoptotic bodies, unlike other vesicles, are formed exclusively from programmed cell death

(apoptosis).[6] Generally, these bodies measure between 500 and 4000 nm and are characterized by the presence of nuclear material such as histones and DNA.[7]

Because of the variety of molecules that MPs can transfer to target cells, they display a large repertoire of biological activities, among which is participation in the maintenance of vascular homeostasis as well as inducing vascular dysfunction. Over the past decades, MPs have been shown to play a role in hemostasis, inflammatory response, vascular tone, immune responses, angiogenesis, and tumor growth.[8,9] Among these functions, the role of MPs in hemostasis has been extensively documented.[10] MPs have been described as primarily having procoagulant properties because of two components of the MP's bilayer. First, MPs expose anionic phospholipids such as PS on their outer leaflet, which assemble calcium-dependent coagulation factors on the surface of MPs, thus forming tenase and/or prothrombinase complexes, leading to thrombin formation. The second component is tissue factor (TF), a surface-bound, transmembrane glycoprotein which triggers the coagulation cascade in a factor VII-dependent manner. Not all MPs display PS or TF; thus, their capacity to generate thrombin is heterogeneous depending on their cellular origin and the stimulus which triggered their formation. For instance, erythrocyte-MPs (Ery-MPs) derived from transfused red blood cells generated significantly more thrombin than platelet-derived MPs (PMPs) in β-thalassemic major patients.[11] The thrombin generation capacity of PMPs is also increased when these patients were splenectomized independently of the platelet and PMP numbers, suggesting that splenectomy impacts the PMP quality and their ability to generate thrombin.

Published data showed that anticoagulant proteins are present on the surface of MPs,[10] including thrombomodulin on monocyte-derived MPs, endothelial protein C receptor on endothelial-derived MPs (EMPs), TF pathway inhibitor on MPs derived from cancer cells,[12–14] endothelial cells,[15] platelets,[16,17] smooth muscle cells,[18] syncytiotrophoblasts,[19] and monocytes,[20] while Ery-MPs can bind activated protein C and protein S.[21] Moreover, data showing that some MP subpopulations are able to efficiently generate plasmin suggest that the role of MPs on hemostasis is more complex than initially thought.[22]

In this review, we summarize the key findings showing that MPs heterogeneously behave as an efficient surface for plasmin generation depending on their cellular origin. In addition, we address the specificities of this MP-dependent fibrinolytic system. Potential consequences of this MP-associated fibrinolytic activity in pathology are illustrated in patients with solid tumors and acute promyelocytic leukemia (APL).

Microparticle-Dependent Fibrinolytic System

Diversity of Microparticles and Their Capacity to Generate Plasmin

Initially, the presence of both active metalloproteinases and urokinase plasminogen activator (uPA) on the MP surface suggests a possible activation of the system on MPs derived from tumor cells (tum-MPs).[23] Several studies published since 1994 have confirmed the presence of these proteolytic enzymes, both in vitro and ex vivo, on tum-MPs isolated from culture supernatant of human tumor cell lines or ascites fluid from patients with ovarian cancer.[23–29] Lytic bands on fibrin–agar zymography indicated a fibrinolytic activity of tum-MPs dependent not only on uPA but also on the tissue plasminogen activator (t-PA) as shown on a carcinoma line of prostate cancer by zymography. Inhibitors that regulate the plasmin-generating system such as plasminogen activator inhibitor-1 (PAI-1) also found on the surface of tum-MPs.[28]

In hematopoietic cells, plasmin generation was first described in vitro on MPs derived from human microvascular endothelial cells after stimulation with tumor necrosis factor-α. Plasminogen binds to the MP surface by C-terminal lysine residues on proteins such as α-enolase. Plasminogen activation involves uPA and its receptor uPAR, whose presence on the EMPs has been demonstrated by enzyme-linked immunosorbent assay, zymography, electron microscopy, and flow cytometry.[22] Thus, plasminogen can be activated on the surface of EMPs in a dose-dependent, saturable, and specific manner as evidenced by zymography or chromogenic tests.[22] Plasminogen can also be activated to plasmin by EMPs generated without specific cell stimulation. Plasmin generating capacity has been shown on EMPs generated from mature primary endothelial cells from different organs (kidney: renal artery; heart: heart coronary artery; and skin: human dermal microvascular endothelial cells) and endothelial progenitors isolated from cord blood. MPs generated from human leukocytes (LMPs; neutrophils, monocytes, and lymphocytes) also have this property.[30]

Plasmin-generating capacity was found on MPs isolated from human plasma by ultracentrifugation or immunomagnetic separation. Interestingly, in contrast to their procoagulant activity, not all MPs have a plasmin-generation activity. It is mainly seen in circulating EMPs and LMPs but not in Ery-MPs and PMPs.[30] More accurately, although most MPs can bind plasminogen and provide an efficient surface for plasminogen activation, only EMPs and LMPs contain plasminogen activators. Depending on their cellular origin, different plasminogen activators are present on MPs. LMPs express uPA and its receptor urokinase plasminogen activator receptor (uPAR) while EMPs contain t-PA and the t-PA/PAI-1 complex.[23] The presence of plasminogen receptors has been found on the surface of MPs, such as annexin II on circulating MPs from APL patients.[31] Conversely, some subpopulations such as PMPs may negatively regulate the MP-plasmin generation capacity being enriched in PAI-1.[32]

Thus, leukocyte, endothelial, and tumoral MP subsets contain both procoagulant and profibrinolytic enzymatic complexes (►**Fig. 1**). The net result of these activities depends on the balance between the procoagulant and profibrinolytic molecules (coagulation/fibrinolytic balance). This balance may be altered according to the MP subset and factors that trigger their formation (►**Fig. 2**).

Specific Features of the Microparticle-Dependent Fibrinolytic System

MPs represent a newly identified pool of circulating plasminogen activators. The majority of uPAR on the EMP surface do not have any ligand bound in the circulation. Exogenous uPA can

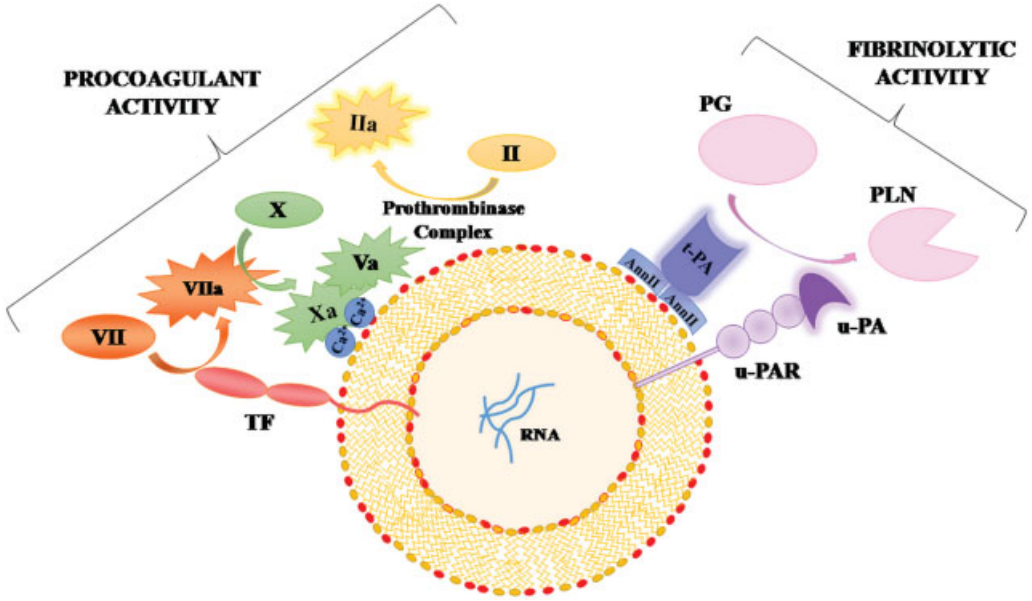

Fig. 1 MPs carry both procoagulant and fibrinolytic activities. MPs carry a procoagulant activity dependent on both tissue factor and phosphatidylserine and a fibrinolytic activity dependent on u-PA/u-PAR and t-PA. Ann II, annexin A2; PG, plasminogen; PLN, plasmin; RNA, ribonucleic acid; TF, tissue factor; t-PA, tissue plasminogen activator; u-PA, urokinase-type plasminogen activator; u-PAR, uPA receptor.

specifically bind to these receptors, which amplifies plasmin generation.[22] These data suggest that uPA released into the local environment can be transferred to the MPs. This mechanism may have implications in tumorigenesis, in which uPA is believed to play an important role. Furthermore, these MPs are able to activate plasminogen bound to fibrin, platelets, and extracellular matrix.[32] Indeed, the uPA–uPAR system does not require plasminogen to be present on the same surface as its activator. Conversely this process is not observed with MPs bearing t-PA.[32]

Because plasminogen can bind MPs, on which plasminogen activators are also in abundance, MPs represent a new surface to efficiently generate plasmin.[31] Once formed, plasmin remains partially attached to the MP surface[22] and can be transferred by circulation to other locations. Interestingly, in contrast to the soluble plasmin, the bound plasmin may be partially protected at the MP surface from inhibitors of the soluble phase such as α2-antiplasmin which can no longer interact with the K1 (Kringle 1) and K4 domains of plasmin.[33] Moreover, because of their negative charge and their expression of adhesive molecules such as integrins or P-selectin glycoprotein ligand-1, MPs can bind to activated endothelial cells and platelets[13,34,35] and

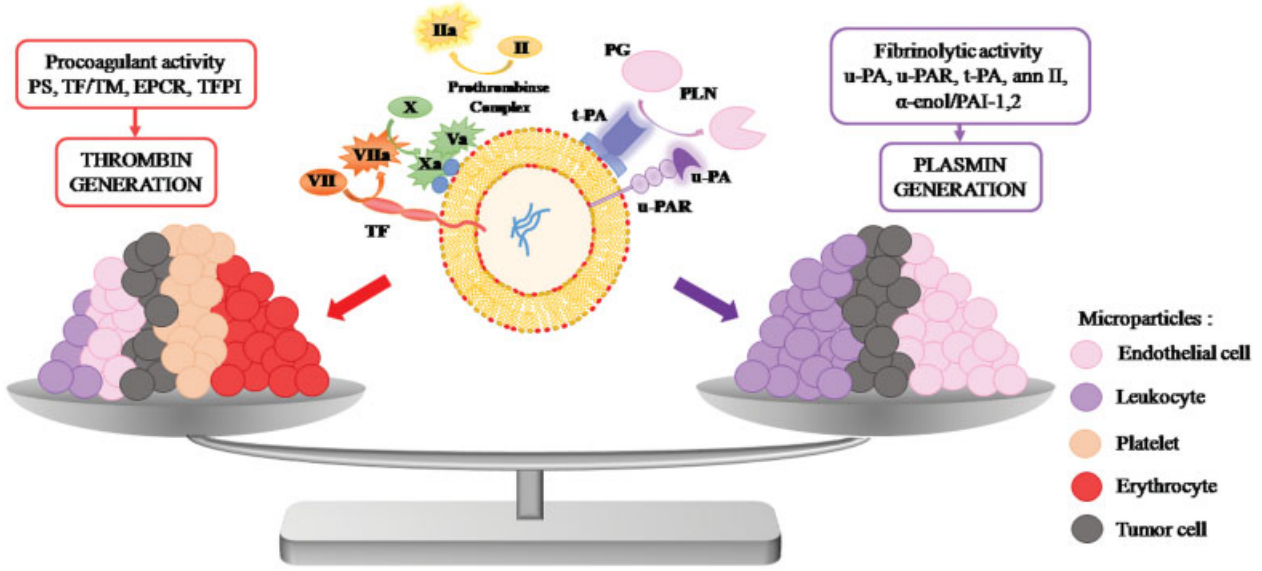

Fig. 2 MP-dependent coagulation/fibrinolytic balance. The MP-dependent coagulation/fibrinolytic balance varies according to the MP subsets. α-enol, α-enolase; EPCR, endothelial protein-C receptor; MP, microparticles; PAI-1, -2, plasminogen activators inhibitor-1, -2; PS, phosphatidylserine; TF, tissue factor; TFPI, tissue factor pathway inhibitor; TM, thrombomodulin; t-PA, tissue plasminogen activator; u-PA, urokinase-type plasminogen activator; u-PAR, u-PA receptor.

therefore may incorporate plasminogen activator within the thrombus.

Thus, these data demonstrated that MPs participate in fibrinolysis; however, the degree of contribution of the MP-dependent plasmin generation capacity compared with that of the soluble phase needs to be further investigated.

Microparticles, Fibrinolysis, and Implications in Cancer

An MP-dependent plasmin generation capacity is measurable in plasma from healthy donors. This activity is modulated in pathological conditions in which increased levels of LMPs and EMPs have been reported, such as atherosclerosis, thrombotic thrombocytopenic purpura, and antiphospholipid syndrome.[30] This fibrinolytic activity may reflect a leuko-endothelial activation associated with inflammatory processes. This activity is also found in biological liquid from cancer patients in which the MP-dependent plasmin generation capacity may represent a new potential biomarker as discussed below in solid tumor and APL.

Solid Tumors

Cancer is associated with a hypercoagulable state, and an elevated risk of thrombosis has an adverse effect on the morbidity and mortality.[36,37] Cancer patients have high levels of circulating procoagulant MPs.[38] A challenging question is whether these MPs can be used as an independent predictor of thrombosis in cancer patients. Results from a few longitudinal clinical studies are promising,[39–41] but large-scale prospective studies are needed to determine the true value of MPs as a biomarker of thrombotic risk for a particular individual. It is as yet unclear whether the lack of definitive data on the predictive value of MPs on thrombosis risk in patients with solid tumors is the result of current technical concerns and limited standardization, or whether the predictive value of MPs depends on the origin and characteristics of the MPs. As EMPs, LMPs, and tum-MPs can either promote or inhibit coagulation and fibrinolysis, the thrombotic risk associated with cancer will be determined by the coagulation/fibrinolytic balance (►**Fig. 3**).

Besides being a potential regulator of the increased risk of thrombosis in patients with cancer, the fibrinolytic potential of tum-MPs is associated with increased cellular invasiveness and metastasis. It has been shown that vesicle-associated uPA promotes invasion of prostate cancer cell lines through modification of adhesive and proteolytic properties of tumor cells.[28] Moreover, as demonstrated by Graves et al, MPs extracted from ascites in ovarian cancer stimulate cellular invasion and may account for the extremely aggressive metastatic behavior exhibited by these tumors.[29] Interestingly, another study demonstrated that EVs from a pancreatic adenoma cell line bearing u-PAR, metalloproteinase-2 and -9 cooperate with CD44v6 which plays an important role in cell motility through hyaluronic acid binding or association with integrins, cytoskeletal proteins, and metalloproteinases contributing to metastasis.[42] Thus, the fibrinolytic system vectorized by MPs contributes to the dissemination of tumor by promoting matrix remodeling.

Acute Promyelocytic Leukemia

Coagulopathy and hemorrhagic complications are major presenting features in acute APL. This type of leukemia is characterized by a chromosomal translocation t(15;17) encoding the formation of a PML–RAR fusion protein, and

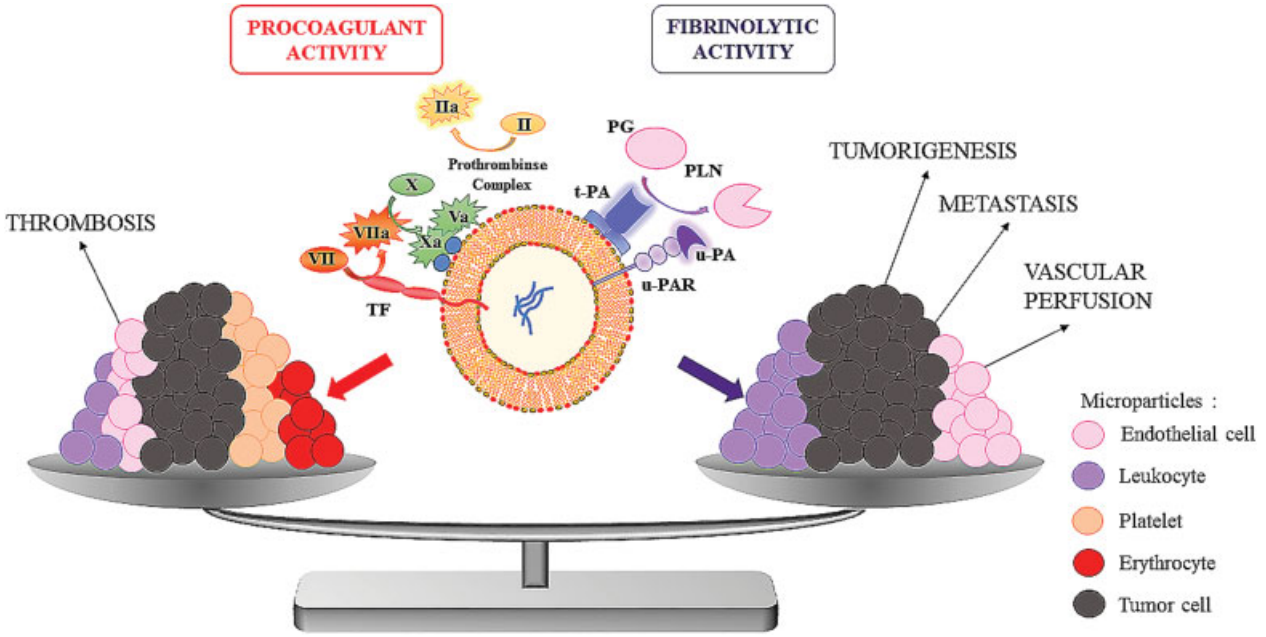

Fig. 3 MP-dependent coagulation/fibrinolytic balance in cancer. The thrombotic risk associated with cancer or the maintenance of the vascular perfusion may be determined by the MP-dependent coagulation/fibrinolytic balance. The fibrinolytic activity of MPs also contributes to tumorigenesis and metastasis. PG, plasminogen; PLN, plasmin; TF, tissue factor; t-PA, tissue plasminogen activator; u-PA, urokinase-type plasminogen activator; uPAR, u-PA receptor.

resulting in the arrest of the differentiation of the promyelocytes. Differentiation therapy with all-trans retinoic acid (ATRA) or arsenic trioxide can achieve >90% remission after induction therapy.[43–45] However, the unique coagulopathy stands in the way of achieving a complete cure for this condition, with an early mortality rate up to 10% within the first 30 days of diagnosis, mainly due to bleeding complications.[46,47] The laboratory picture at presentation is one of activated coagulation with increased levels of fibrinopeptide A, prothrombin fragment 1 + 2 and thrombin-antithrombin complexes, with an increase in fibrin degradation products such as D-dimer and decreased fibrinogen level indicative of a consumptive coagulopathy.[48–50]

In essence, the pathogenesis of the coagulopathy of APL is, in part, a disseminated intravascular coagulation (DIC) caused by increased expression of TF by the leukemia promyelocytes.[51] In addition, the fibrinolytic system is abnormal with increased t-PA, uPA, and plasmin, and decreased PAI-1 and α2-antiplasmin.[50–54] The excessive fibrinolysis in APL is distinct from that seen as secondary response to DIC, because of these additional features: (1) both t-PA and uPA are increased[52,55]; (2) increased expression of annexin A2-S100A10 complex, a receptor for plasminogen and t-PA, was found on APL promyelocytes[56,57] and (3) the activity of thrombin activable fibrinolytic inhibitor, an inhibitor of fibrinolysis, is reduced by as much as 60%.[58] These findings were observed respectively on cell surface of the human APL cell line NB4 and of the APL promyelocytes in peripheral blood and bone marrow, as well as in conditioned medium of NB4 cultures and patient plasma.

The changes in fibrinolytic factors have also been found in MPs. Fibrinolytic factors are present in those MPs derived from both NB4 cells, and the leukemic myeloid (CD33) cells in patients.[59,60] Using flow cytometry,[60] antigens of TF, t-PA, annexin A2, uPA, uPAR, and PAI-1 were found to be present in MPs derived from CD33 positive cells prepared from APL patients.[60] The levels of TF, t-PA, annexin A2 and PAI-1 were much higher than those in healthy controls, while levels of uPA and uPAR were not. Remarkably, longitudinal observations revealed that these increased levels returned to normal at the time of remission following differentiation therapy with ATRA.[60]

When t-PA and PAI-1 in the MPs were tested for their functional activities by chromogenic methods, their levels were same as healthy controls. The absence of functional activity of the t-PA could be due to its binding to annexin A2/S100 protein or to complex formation with PAI-1. In the case of uPA, both the free form and uPA–PAI-1 complex were present. MPs were also able to generate plasmin. Ongoing studies indicate that there is a correlation of the amount of plasmin generated with clinical events of bleeding.[61] Thus in APL, MPs participate in the pathogenesis of the coagulopathy and the altered fibrinolysis.

Conclusion

Beyond their well-described procoagulant property, accumulated data have shown that MPs selectively shed by endothelial cells, leukocytes, and tumor cells bind plasminogen and vectorize plasminogen activators. These novel properties identify MPs as efficient catalytic surfaces for plasmin generation. The existence of MP-dependent fibrinolytic potential in the circulation or in body fluids raises the question about the physiological relevance of this activity. However, further studies will be necessary to determine the extent in which, in vivo, MPs contribute to these pathophysiological mechanisms and how this recently reported blood-borne proteolytic properties identify MPs as a new biomarker in specific clinical situations such as cancer.

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