

## REVIEW

# Bench-to-bedside review: Circulating microparticles - a new player in sepsis?

Ferhat Meziani<sup>1,2</sup>, Xavier Delabranche<sup>1,2,3</sup>, Pierre Asfar<sup>4,5</sup> and Florence Toti<sup>3,6,7\*</sup>

### Abstract

In sepsis, inflammation and thrombosis are both the cause and the result of interactions between circulating (for example, leukocytes and platelets), endothelial and smooth muscle cells. Microparticles are proinflammatory and procoagulant fragments originating from plasma membrane generated after cellular activation and released in body fluids. In the vessel, they constitute a pool of bioactive effectors pulled from diverse cellular origins and may act as intercellular messengers. Microparticles expose phosphatidylserine, a procoagulant phospholipid made accessible after membrane remodelling, and tissue factor, the initiator of blood coagulation at the endothelial and leukocyte surface. They constitute a secretion pathway for IL-1 $\beta$  and up-regulate the proinflammatory response of target cells. Microparticles circulate at low levels in healthy individuals, but undergo phenotypic and quantitative changes that could play a pathophysiological role in inflammatory diseases. Microparticles may participate in the pathogenesis of sepsis through multiple ways. They are able to regulate vascular tone and are potent vascular proinflammatory and procoagulant mediators. Microparticles' abilities are of increasing interest in deciphering the mechanisms underlying the multiple organ dysfunction of septic shock.

### Introduction

In the 1960s and 70s Wolf [1] was the first to describe platelet derivatives of less than 0.1  $\mu\text{m}$  as procoagulant vesicles. Later, having been given the name of 'microparticles' (MPs), these vesicles were described as membrane-derived nano-fragments (0.05 to 1  $\mu\text{m}$ ) that

are active in coagulation and inflammation. MPs are released in the extracellular environment through a membrane reorganization and blebbing process following cell activation or apoptosis. They constitute a storage pool of bioactive effectors with varied cellular origins and are able to act as intercellular messengers [2]. They are present in body fluids where they reflect normal tissue homeostasis, but undergo phenotypic and quantitative changes to play a pathophysiological role in several diseases, most of them associated with thrombotic disorders [3,4] (Figure 1).

MPs often convey tissue factor (TF) that may contribute to the dissemination of coagulopathy in sepsis [5,6] and cytokines up-regulating deleterious inflammatory responses [7]. Circulating MPs can also provoke vascular dysfunction, and they reduce available nitric oxide (NO) and increase levels of reactive oxygen species, thereby promoting oxidative stress [8].

This review will focus on the role of MPs during sepsis, with a special emphasis on coagulation and inflammation disturbances.

### Microparticles are potential intercellular messengers during sepsis

Sepsis is a syndrome characterized by excessive cellular activation involving a systemic inflammatory response to severe infection. Its most severe form may lead to septic shock. The ongoing circulatory failure is characterized by vasoplegia-related arterial hypotension and may include vasopressor resistance, and myocardial and local blood flow impairments. Inflammation plays a key role in the acute activation of the vascular wall and is associated with local thrombosis and changes in vasomotricity [9]. Thus, the endothelium-derived TF initiates the coagulation process and a proteolytic cascade [10]. The endothelial damage furthermore leads to the expression of adhesion molecules and other vasoactive factors involved in inflammation and coagulation.

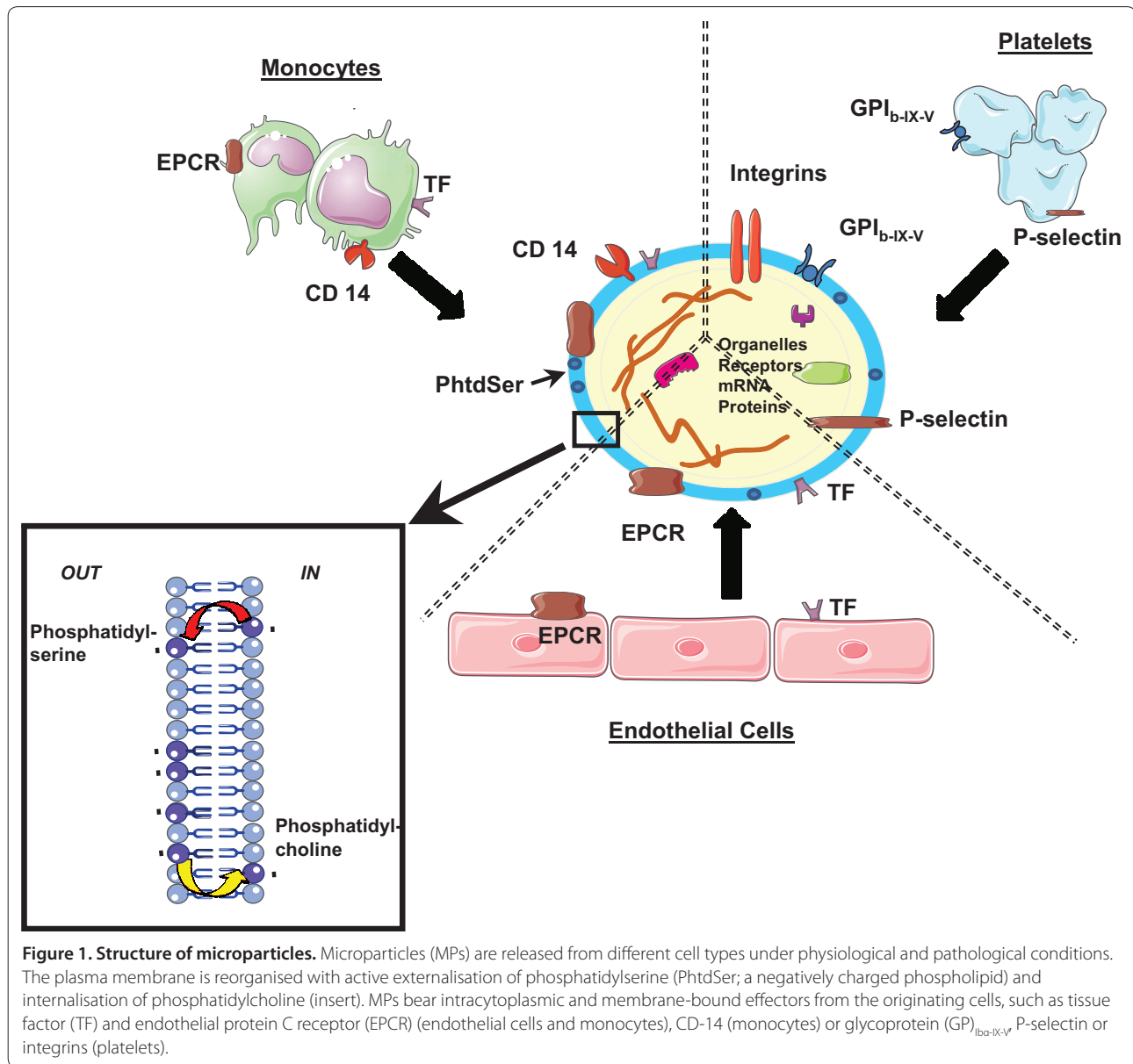
### Biogenesis and general features of microparticles

MPs are produced following cellular activation or apoptosis. The increase in intracellular calcium activates various cytosolic enzymes, including calpains, that cleave

\*Correspondence: florence.toti@unistra.fr

<sup>3</sup>Institut d'Hématologie et d'Immunologie, Faculté de Médecine, Université de Strasbourg, 4 rue Kirschleger, F-67085 Strasbourg, France

Full list of author information is available at the end of the article



the cytoskeleton and facilitate the role of procaspase-3 in apoptosis [11]. As a response to stimulus, the cytoskeleton is reorganized and the asymmetric distribution of the phospholipid membrane modified with exposure of phosphatidylserine at the cell surface. Cellular blebbing then occurs, ultimately leading to the release of MPs. In addition to phosphatidylserine exposure, protein-lipid raft domains are formed and furnish the MP with its specificities and biological roles [12] (Figure 1).

The cellular origin of MPs can be determined by assessment of the antigens that they expose at their surface. However, the complete protein content of MPs remains difficult to establish. More than 300 proteins

have been reported by proteomics, some of which are cytosolic and some membranous [13]. The MP phenotype is, however, known to vary according to cellular origin and parental cell response to stimulus [7,14].

#### Microparticle survival and clearance

Although bearing phosphatidylserine, which is a signal for phagocytosis, MPs seem to survive longer than their parental apoptotic cell, probably because of their size, which does not allow optimal exposure of a cluster of senescence signals. Dasgupta and colleagues [15] recently described the major role of lactadherin in the removal of phosphatidylserine-expressing platelet MPs from human

plasma. Lactadherin is a macrophage opsonin that mediates the clearance of apoptotic lymphocytes and knockout lactadherin (-/-) mice have increased levels of circulating platelet MPs and a hypercoagulable state; lactadherin supplementation restores the normal clearance of MPs. To date, there are no data on the effect of MP clearance on the haemostatic balance under physiological or pathological settings.

#### **Microparticles as messengers in blood flow**

As mediators of cellular communication, MPs are actors and possible mediators in the interplay between thrombosis and inflammation, a process previously described for vascular injury in inflammatory diseases [5]. They can transfer receptors, organelles, mRNA and other proteins to target cells [16] and also comprise a secretion pathway for several cytokines, such as mature IL-1 $\beta$  [17]. The multiple properties of MPs and the variety of their possible cellular targets support them having a key role in cell reprogramming and tissue remodeling with physiological or pathological consequences [4]. Thus, MPs could play a major role in propagating proinflammatory and procoagulant states in sepsis. In the vascular compartment, including the arterial wall, the particular settings of sepsis and the tuning abilities of MPs point to the endothelium as a pivotal target [18,19].

#### **How to detect and measure microparticles?**

The International Society for Thrombosis and Haemostasis (ISTH) provides information on technical procedures and recommendations for the detection and measurement of MPs. Although no standardized procedures for MP measurement are available yet, a consensus is forming on blood sampling and MP isolation by centrifugation steps that avoid exosome contamination of MP samples [20]. Several assays and phenotyping methods coexist, but these are not necessarily comparable, thus making the interpretation of results across studies difficult. MPs can be analyzed through capture techniques (using immobilized annexin V - a high affinity probe for phosphatidylserine - quantitative assessment, or insolubilized antibodies for phenotyping) combined with a functional prothrombinase assay. Flow cytometry is another method for the study of MPs. This method allows quantification and determination of cellular origin via the use of specific fluorescent antibodies and calibration beads. The protein content of MPs can also be assayed and expressed in molecular mass units [21]. Caution should be taken in the interpretation of MP analyses, taking into account the pitfalls of each method and the purpose of the experiment or clinical investigation. Furthermore, control cohorts are of prime importance in clinical investigations of MP pattern variations.

#### **Microparticles as a player in coagulation disorders of sepsis**

In the defence against pathogens, haemostasis is as fundamentally important as innate immunity and complement-mediated cell lysis. Haemostasis is activated during sepsis and septic shock, leading to thrombin and fibrin generation with dual effects: limitation of pathogen diffusion and invasion; and fibrin deposition in vessels, resulting in thrombotic microangiopathy or disseminated intravascular coagulopathy. As detailed above, MPs are efficient effectors in the haemostatic response and pathogenic markers of thrombotic disorders (Figure 2).

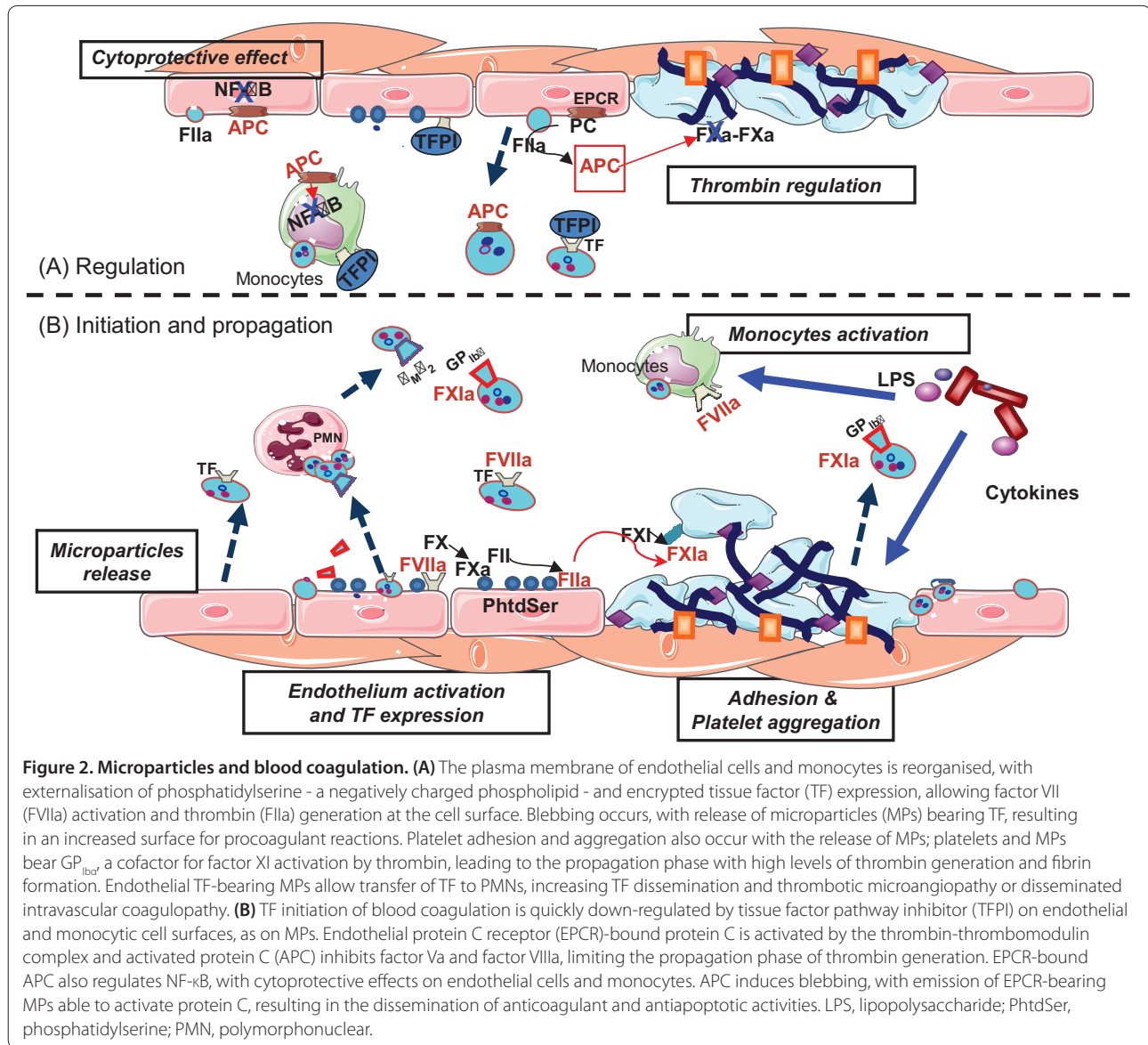
#### **Microparticles and thrombin generation**

Thrombin generation requires activation of coagulation factors, which is made possible after their assembly on a catalytic surface constituted of anionic phospholipids. Cell activation constitutes the first step by furnishing exposed phosphatidylserine with a negative charge. The required remodelling of plasma membrane, resulting in phosphatidylserine translocation to the outer leaflet of the plasma membrane, occurs in platelets, endothelial cells and monocytes at sites of vascular damage or injury. Calcium ion-mediated interactions between gamma-carboxyl groups of vitamin-K-dependent factors and phosphatidylserine comprise the key step in this assembly, explaining the efficacy of anti-vitamin K treatments in hypercoagulable states [22].

At the monocyte surface a possible encrypted preformed TF would be de-encrypted by plasma membrane remodelling, thereby allowing the (auto-)activation of factor VII. Indeed, TF expression at the surface of monocyte-derived MPs has been demonstrated during *in vitro* endotoxin stimulation [23]. Although TF is the primary initiator of blood coagulation, whether there is a blood-borne TF (activity) is still debated, but there is growing evidence that this activity is directly tied to MPs [5,24]. TF-bearing MPs can interact with neutrophil granulocytes by 'paracrine transfer', as demonstrated *in vitro* [25-27]. Circulating MPs bearing active TF have been associated with a thrombotic status in human meningococcal sepsis [28] and a primate Ebola fever model [29], pointing to their possible role in the dissemination of a procoagulant potential.

#### **Microparticles and amplification loops in thrombin generation**

TF-driven coagulation is under the control of Tissue factor pathway inhibitor (TFPI), an inhibitory complex, with factor Xa and protein S as cofactors. Although this inhibits TF-induced thrombin generation, thrombin is still generated during the propagation phase via the Jossen loop: platelet-exposed factor XI (of megakaryocytic origin) is activated by the GP<sub>Ib/IIIa</sub>-thrombin complex present on the surface of activated platelets. Activated



platelets, and released GP<sub>Iba2</sub>-FXIa bearing MPs, may, in turn, be responsible for increased thrombin generation [30-32]. In addition to blood-borne TF conveyed by MPs, polymorphonuclear (PMN)-derived MPs likely contribute to an additional amplification loop in the generation of thrombin mediated by MPs (Figure 2).

MPs could contribute to such amplification loops in sepsis. Indeed, *ex vivo* activation of human neutrophils by endotoxin, platelet activating factor or phorbol myristate acetate can generate MPs bearing active integrin  $\alpha_M\beta_2$  (CD11b/CD18), which is able to activate GP<sub>Iba2</sub> [33,34].

#### Microparticles in the control of thrombin generation, cytoprotection and tissue remodelling

Interestingly, several cellular models showed that  $\alpha_M\beta_2$  exposed at the MP surface can interact with other ligands,

such as urokinase plasminogen activator, plasminogen and metalloproteases MMP-2 and -5, suggesting a role in fibrinolysis and in local tissue remodelling [30,34,35]. MPs may also display antithrombotic activities, which would be overwhelmed by procoagulant activities when MPs are released under highly thrombotic conditions, as observed during sepsis or myocardial infarction. Indeed, in purified monocyte suspensions, thrombomodulin anticoagulant activity and TF coexist at the MP surface, but when released by lipopolysaccharide treatment, the TF activity is predominant on MPs [31]. The presence of the anticoagulant endothelial protein C receptor (EPCR) at the surface of endothelial-derived MPs (mpEPCR) is another example of a cytoprotective element attached to MPs [32]; EPCR is involved in the activation of anticoagulant protein C by the thrombin-thrombomodulin complex. mpEPCR,

released in response to activated protein C (APC), may switch the procoagulant properties of endothelial MPs to anticoagulant and anti-apoptotic properties. On the surface of MPs bearing mpEPCR, APC inactivates procoagulant cofactors factor Va and factor VIIIa, thereby down-regulating thrombin generation. Because a circulating soluble form of EPCR (sEPCR) has been described in sepsis, and its concentration possibly correlates with the severity of the illness, the respective contributions of mpEPCR and sEPCR is a matter of clinical relevance. sEPCR binds protein C and APC, thereby blunting their actions. The efficacy of therapeutic activated protein C (rhAPC; drotrecogin alfa (activated)) may depend on the balance between circulating sEPCR and mpEPCR [32]. Recent investigations in human endothelial cells reported that free rhAPC and rhAPC bound to mpEPCR have similar effects. rhAPC cleaves protease activated receptor-1 and induces significant changes in the activation/inhibition of genes with direct anti-apoptotic effects or indirect cell barrier protective effects, the latter requiring transactivation of KDR (vascular endothelial growth factor receptor 2/kinase insert domain receptor) via the phosphoinositide 3-kinase-Akt pathway and S1P<sub>1</sub> (sphingosine 1-phosphate receptor) [36].

In sepsis, procoagulant MPs of endothelial, platelet, erythroid, and leukocyte origins have been reported [28,37].

### **Microparticles as potential effectors in the inflammatory response of sepsis**

Circulating MPs have been reported to be present in various inflammatory diseases, including sepsis [7]. MPs are a source of phospholipids, a substrate for phospholipase A2, which facilitates platelet aggregation [38,39]; they may also provoke vascular inflammation during sepsis via lysophosphatidic acid and facilitate chemotactic migration of platelets and/or leukocytes to the endothelium, thus playing the role of trigger in the production of monocyte cytokines (IL-1 $\beta$ , IL-8 and tumour necrosis factor- $\alpha$ ) [8,40,41] (Figure 3).

### **Microparticles targeting the endothelial function**

During sepsis, the endothelial function is altered and the endothelial surface becomes proadhesive, procoagulant and antifibrinolytic [42]. The endothelium is one of the primary targets of circulating MPs, as demonstrated by Barry and colleagues [43] *in vitro*. Indeed, they showed that arachidonic acid exposed by platelet MPs promotes the up-regulation of cyclooxygenase-2 (COX-2) and intercellular adhesion molecules in endothelial cells. Platelet-derived MPs have been shown to modulate interactions between monocytes and endothelial cells. Released proinflammatory endothelial cytokines may themselves also contribute to the production of MPs [44],

thereby amplifying the inflammatory response and the consecutive alteration of the vascular function [45]. Platelet activating factor present in endothelial cells and leukocytes is also involved in the proinflammatory effect of MPs [46].

### **Endothelial microparticles and inflammatory status**

Circulating MPs of endothelial origin may thus vary with respect to quantity and phenotype according to the endothelial response and have been reported in inflammatory diseases and disorders [47]; the endothelial response to inflammation stimuli may be immediate, delayed or reflect a chronic endothelial activation. They were reported to participate in the regulation of arterial tone in several diseases in which oxidative stress is involved, such as human acute coronary syndromes [48] or preeclampsia [49] associated with altered NO bioavailability [50].

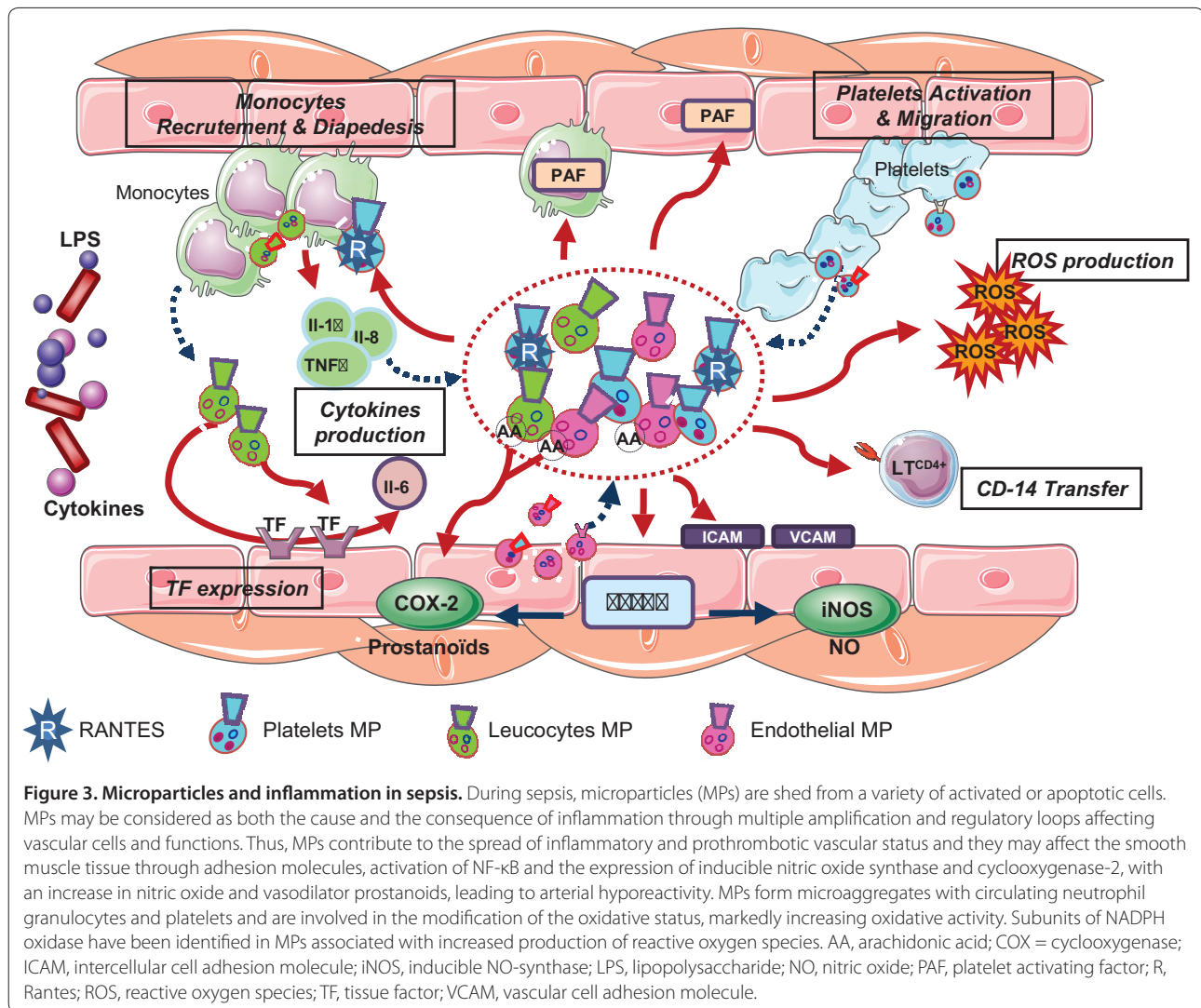
Sepsis induces a phenotypic change of the endothelium and the endothelial surface becomes proinflammatory, expresses cell adhesion molecules (intercellular cell adhesion molecule 1, vascular cell adhesion molecule 1) [51] and becomes prothrombotic through the increased expression of membrane TF and the inhibition of thrombomodulin and EPCR synthesis. In parallel, endothelial cells become capable of recruiting and activating platelets [52].

### **Microparticles contribute to the spreading of inflammatory and prothrombotic vascular status**

MPs may be considered as both the cause and the consequence of inflammatory diseases through multiple amplification and regulatory loops affecting vascular cell functions. *In vitro* incubation of leukocyte-derived MPs with endothelial cells allowed Mesri and Altieri [53] to demonstrate their role in the secretion of inflammatory IL-6 and in the production of TF [54]. Furthermore, platelet MPs are able to deliver RANTES at the inflamed endothelium, thus promoting leukocyte recruitment and diapedesis [55]. MPs may affect the smooth muscle tissue through the activation of the transcription factor NF- $\kappa$ B and favour the expression of inducible NO-synthase and COX-2, resulting in an increase in NO and vasodilator prostanoids, leading to arterial hyporeactivity [45].

The interactions between platelets, leukocytes and endothelium clearly contribute to the vascular dysfunction observed in sepsis and various MPs were reported to alter the arterial wall directly or indirectly [56,57].

Endothelial MPs may play a role in the spread of sepsis inflammatory responses leading to multiple organ dysfunction [18,58]. They may participate in the potentialisation of the procoagulant state associated with sepsis by providing renewed lipid surfaces of human endothelial



cells for the generation of thrombin and by up-regulating monocyte TF expression, as demonstrated *in vitro* [59]. In sepsis, blockade of the human TF pathway by TFPI is very quickly overridden, clearing the way for a detrimental procoagulant state [28]. Indeed, in humans, a single endotoxin administration provokes a significant increase in endothelial-cell- or monocyte-derived MPs displaying potentiated TF [60]. This state is worsened by the exhaustion and/or faulty activation of the two other regulatory molecules, antithrombin and APC.

Several reports illustrate well the cascade of interwoven events that link cellular activation, TF up-regulation, the release of MPs presenting active TF and the triggering of disseminated intravascular coagulopathy and shock [28,29]. With regard to vascular tone, MPs could promote the significant vasoplegia observed in septic shock [8]. Arachidonic acid transfer may up-regulate COX-2 expression and the production of prostacyclin, which is

implicated in vasodilation and the inhibition of platelet activation [32].

#### Microparticles and oxidative stress

During sepsis, generated MPs are involved in the modification of the oxidative status; they form microaggregates with circulating neutrophil granulocytes and markedly increase oxidative activity [8]. Subunits of NADPH oxidase have been identified in endothelial- and platelet-derived MPs associated with increased production of reactive oxygen species [18,61] (Figure 3).

#### Conclusion

The systemic inflammatory response that is a characteristic feature of sepsis is a major cause of cellular dysfunction that may lead to the exaggerated generation of MPs. These plasma membrane fragments are circulating markers of vascular inflammatory diseases. They also

behave as pathogenic shuttles able to disseminate their deleterious proinflammatory and procoagulant potential in the systemic circulation and may be implicated in the multiple organ dysfunction characterizing sepsis and septic shock. To date, however, we have insufficient evidence to determine whether MPs are major players or bystanders in the development of the sepsis syndrome.

#### Abbreviations

APC, activated protein C; COX, cyclooxygenase; EPCR, endothelial protein C receptor; IL, interleukin; MP, microparticle; mpEPCR, microparticle endothelial protein C receptor; NF, nuclear factor; NO, nitric oxide; rhAPC, therapeutic activated protein C; sEPCR, soluble endothelial protein C receptor; TF, tissue factor; TFPI, Tissue factor pathway inhibitor.

#### Competing interests

The authors declare that they have no competing interests.

#### Author details

<sup>1</sup>Service de réanimation médicale, Nouvel Hôpital Civil, Hôpitaux universitaires de Strasbourg, F-67091 Strasbourg, France. <sup>2</sup>Laboratoire de Biophotonique et Pharmacologie, UMR 7213 CNRS, Université de Strasbourg, Faculté de Pharmacie, F-67401 Illkirch, France. <sup>3</sup>Institut d'Hématologie et d'Immunologie, Faculté de Médecine, Université de Strasbourg, 4 rue Kirschleger, F-67085 Strasbourg, France. <sup>4</sup>Laboratoire HIFIH, UPRES EA 3859, IFR 132, Université d'Angers, F-49045 Angers, France. <sup>5</sup>Département de réanimation médicale et médecine hyperbare, CHU Angers, F-49933 Angers, France. <sup>6</sup>Inserm U770, Hôpital de Bicêtre, F94275 Le Kremlin Bicêtre, France. <sup>7</sup>Université Paris-Sud 11, Faculté de Médecine, F94275 Le Kremlin-Bicêtre, France.

#### Authors' contributions

All authors participated in the design of this review and in drafting the manuscript. FM and FT supervised the manuscript. All authors read and approved the manuscript.

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