Role of microparticles in sepsis

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Editor’s key points

- Microparticles are intact vesicles derived from the plasma membrane during cellular activation and apoptosis.
- They have both physiological and pathological functions in sepsis.
- Microparticles have a key role in the endothelial and haemostatic responses to sepsis.
- Evidence of their use as diagnostic and prognostic biomarkers in sepsis is required.

Summary. This review discusses the role of microparticles in inflammation, coagulation, vascular function, and most importantly, their physiological and pathological functions in sepsis. Microparticles are proinflammatory, procoagulant membrane vesicles released from various cell types. They are detectable in normal individuals and basal levels correlate with a balance between cell proliferation, stimulation, and destruction. Microparticles release a number of proinflammatory, procoagulant properties in health and disease. They have both physiological and pathological roles in sepsis. Microparticles are considered as a biomarker in sepsis.

Physiological role of microparticles

First recognized in 1949,1 microparticles are intact vesicles measuring 0.2–2 μm derived from the plasma membrane during cellular activation and apoptosis. The formation of microparticles occurs through an exocytic budding process2 in several cell types, including platelets,3 endothelial cells,4 vascular smooth muscle cells,6 erythrocytes,7 polymorphonuclear leucocytes,6,9 lymphocytes,10 and monocytes.11 Microparticles present cell-specific surface antigens that reflect the parent cell from which they originate.12 Thus, microparticle subpopulations are heterogeneous with different antigenic profiles and function12 13 (Table 1). The formation of microparticles is characterized by an increase in intracellular calcium, degradation of the cytoskeleton, and exposure of the membrane phospholipid phosphatidylserine, which normally resides on the cytoplasmic surface of the resting cell membrane.14 An electron microscopy image of microparticles produced by cell blebbing of cultured mouse megakaryocytes is shown in Figure 1.15

Microparticles are present at low levels in the blood of healthy individuals with the majority derived from circulating platelets.15 The level of circulating microparticles is raised in a number of pathological states associated with inflammation, activated coagulation, and fibrinolysis including acute coronary syndrome, metabolic syndrome, cardiopulmonary bypass, antiphospholipid syndrome, rheumatoid arthritis, pre-eclampsia, and sepsis.13 17 18 The cellular origin, lipid, and protein composition of microparticle populations varies with different disease states. Exposure of phosphatidylserine and other anionic phospholipids on the exoplasmic surface of microparticles explain, in part, their prothrombotic potential in health and disease.19 Microparticles are considered as a distributed storage pool of bioactive effectors, exerting proinflammatory,20 21 and prothrombotic properties22 23 in the immediate microenvironment of their formation.24 Microparticles may therefore play a critical role in both the initiation and propagation of sepsis. In this review, the physiological and pathological roles of microparticles will be outlined with particular reference to their role in sepsis.
The deleterious effect of microparticles on vascular function

Proinflammatory microparticles

Microparticles play an important role in vascular haemostasis. A growing body of evidence, however, suggests that they induce deleterious effects on vascular function through increased synthesis of inflammatory cytokines and chemokines, and increased expression of endothelial adhesion molecules. 

Platelet-derived microparticles induce platelet aggregation through changes in transcellular lipid metabolism in endothelial cells. Arachidonic acid borne on platelet-derived microparticles is donated to endothelial cells and subsequently metabolized to thromboxane A2. Platelet-derived microparticles exposed to endothelial cells and monocytes in vitro can also induce de novo expression of cyclooxygenase-2 (COX-2) and prostacyclin (PGI2) production. Through concentrated delivery of bioactive lipids including arachidonic acid, these microparticles induce cell-cell interaction of monocytes to endothelial cells by an intracellular cell adhesion molecule-1 (ICAM-1)-dependent process and increased chemotaxis of monocyteid cells.

Microparticles derived from leucocytes also circulate at low levels in the bloodstream of healthy individuals and are up-regulated in inflammation. Such microparticles activate
endothelial cells in vitro, stimulating gene expression and release of inflammatory cytokines such as interleukin-6 (IL-6) and interleukin-8 (IL-8), and up-regulation of leucocyte-endothelial cell adhesion molecules ICAM-1, vascular adhesion molecule-1 (VCAM-1), and E-selectin. In addition, microparticles produced after platelet activation may enhance leucocyte aggregation and accumulation through expression of P-selectin, a functional adhesion receptor for P-selectin glycoprotein ligand-1 (PSGL-1) expressed on the surface of leucocytes. Platelet-derived microparticle binding to neutrophils can also increase neutrophil aggregation and phagocytic activity. In human airway epithelial cells, monocyte-derived microparticles contribute to the pathogenesis of inflammatory airway disease through the up-regulation of IL-8, monocyte chemotactic protein-1 (MCP-1), and ICAM-1. More recently, monocyte-derived microparticles have been shown to induce superoxide anion production, cytokine release, and nuclear factor kappa B (NF-kB) activation in monocytes. Taken together, these findings suggest that in certain pathological states, elevated levels of microparticles may amplify inflammation and vascular injury.

Prothrombotic microparticles

In healthy individuals, low numbers of circulating microparticles, predominantly platelet and endothelial cell in origin, trigger low levels of thrombin generation in vitro. Platelet-derived microparticles exhibit an important role in primary haemostasis in response to endothelial injury. Through transverse migration and exposure of anionic phospholipids including phosphatidylserine, platelet-derived microparticles provide a catalytic surface for the prothrombinase enzyme complex (factors Va and Xa) with subsequent thrombin formation. In addition to accessible phospholipids, microparticles also carry cell-specific antigens. Microparticles bind to the subendothelial matrix, adhere to immobilized and soluble fibrinogen, and coaggregate with platelets, through a glycoprotein IIb/IIIa (GPIIb/IIIa) complex-dependent process. Platelet-derived microparticles are also carriers of platelet-activating factor (PAF), a potent phospholipid generated in various cells including platelets. The activation of platelets and the subsequent formation of microparticles with procoagulant potential enable both an increase locally in the procoagulant surface by retained microparticles and dissemination of biological activity and thrombin generation.
Endothelium-derived microparticles also induce a prothrombotic state. They express ultra large von Willebrand factor multimers resulting in platelet aggregation, and these aggregates are resistant to dissociation. Furthermore, exposure of complement proteins C5b-9 to endothelial cells promotes microparticle formation with expression of factor Va binding sites and prothrombinase activity. Elevated levels of plasminogen activator inhibitor-1, an early marker of endothelial dysfunction, may also initiate microparticle formation from endothelial cells and procoagulant activity through exposure of anionic phospholipids. Such microparticles may play a pivotal role in the widespread deposition of fibrin and platelets observed in fatal cases of cerebral malaria.

Circulating microparticles have also been shown to express functional tissue factor, and endotoxin stimulation of monocytes stimulates the production of microparticles with surface expression of active tissue factor. Leucocytes carrying tissue factor are concentrated in sites of vascular injury by interaction of platelet P-selectin and PSGL-1 expressed on microparticles derived from leucocytes. These findings suggest that thrombin formation is propagated by recruitment of haematopoietic-derived tissue factor on microparticles to enable platelet aggregation and formation of the fibrin plug. Consistent with these findings, elevated levels of microparticles generated in patients during cardiopulmonary bypass and in Ebola haemorrhagic fever demonstrate procoagulant activity through a tissue factor/factor VIIa-dependent pathway.

**Fig 3** Procoagulant potential of microparticles. Procoagulant phospholipids (including phosphatidylserine) are exposed on the exoplasmic surface of platelet-derived microparticles (PMPs) during microparticle (MP) formation. Phosphatidylserine enhances factor VaXa (FVaXa) and tissue factor (TF) activity. Through processes partly dependent on the GPIb/IIIa complex, PMPs adhere to the subendothelial matrix and coaggregate with platelets. PMPs also express coagulation factor binding sites for factor IXa, Xa, and VIII (FIXa, FVa, and FVIII, respectively). Endothelial-derived MPs (EMPs) potentiate platelet aggregation and thrombus formation by expression of ultra large von Willebrand factor (ULvWF) antigen and coagulation factor binding sites. MPs including PMPs, EMPs, and leucocyte-derived MPs (PMNL-MPs) constitute a circulating storage pool of blood-borne TF, where leucocytes carrying TF are concentrated at sites of vascular injury via interaction of platelet P-selectin and PSGL-1 expressed on LMPs.

**Microparticles and endothelial dysfunction**

Microparticles may play a paracrine role in promoting endothelial dysfunction. Elevated levels of circulating endothelium-derived microparticles are seen in a number of cardiovascular diseases characterized by endothelial dysfunction and high levels of thrombogenic microparticles, mainly monocyctic and lymphocytic in origin, are present in human atherosclerotic plaques. In vitro, microparticles isolated from the blood of patients with highly thrombogenic conditions such as acute myocardial infarction, pre-eclampsia, and end-stage renal disease induced vascular hyporeactivity. Vascular hyporeactivity was observed in arteries taken from mice treated in vivo with microparticles from patients with pre-eclampsia. In agreement with these findings, pre-eclampsia-derived microparticles have been shown to induce NF-κB activation, increase nitric oxide release, and enhance oxidative stress.

Endothelium-derived microparticles appear also to directly alter endothelial function in vitro with increased superoxide anion generation in rat aortic rings and endothelial cells (Fig. 4). Microparticles derived from T-lymphocytes also induce endothelial dysfunction in arteries in vitro with reduced endothelial nitric oxide synthase (NOS3) expression. These findings are supported by in vivo studies using circulating microparticles derived from patients with diabetes mellitus and human immunodeficiency virus. Microparticles derived from T-lymphocytes also act directly on vascular smooth muscle cells where they induce vascular hyporeactivity in response to a number of vasoconstrictor
agents. The activation of transcription factor NF-κB drives an up-regulation of inducible nitric oxide synthase (NOS2) and COX-2 leading to increased production of nitric oxide and vasodilator prostanoids.

In coronary artery disease, increased endothelium-derived microparticle levels positively correlate with the degree of endothelial dysfunction and high levels of circulating endothelium-derived microparticles in patients with coronary artery disease are associated with a worse clinical outcome. Measurement of plasma endothelium-derived microparticles predicts future cardiovascular events and mortality in high-risk patients, including end-stage renal disease. Taken together, plasma levels of endothelium-derived microparticles may present a novel biomarker for risk stratification and identification of patients at high risk of cardiovascular complications.

Microparticles may have some beneficial effects on vascular function. As previously discussed, platelet-derived microparticle-borne arachidonic acid induces COX-2 expression and vasodilatation through PGJ2 production in the endothelium. Both platelet- and endothelium-derived microparticles stimulate endothelial proliferation and induce angiogenesis both in vitro and in vivo. Microparticles isolated from human atherosclerotic plaques promote endothelial proliferation, in vivo neovascularization after CD40 ligation, and plaque instability. Of note, endothelium-derived microparticles at pathological but not physiological levels impair angiogenesis. The precise mechanism of angiogenesis is unknown; however, endothelium-derived microparticles are known to express several proteases, including matrix metalloproteinases (MMPs), MMP-2 and MMP-9, to enable vascular invasion of the basement membrane.

**Protective effects of microparticles in health and disease**

**Anti-inflammatory and anticoagulant microparticles**

As previously noted, the biological activity of microparticles reflects their cellular origin, and cytoplasmic and membrane composition. Microparticles derived from leucocytes may in fact induce protective, immunosuppressive effects at the early stages of inflammation to down-regulate parallel proinflammatory mechanisms. Recent findings suggest that leucocyte-derived microparticles drive an anti-inflammatory macrophage response with release of transforming growth factor β1 (TGF-β1), and inhibition of IL-8, interleukin-10 (IL-10), and tumour necrosis factor α (TNF-α) to inhibit macrophage activation. These microparticles contain the anti-inflammatory protein Annexin 1. More recently, it was demonstrated that monocyte-derived microparticles enhance peroxisome proliferator-activated receptor γ (PPAR-γ) protein expression in monocytes and macrophages, which has anti-inflammatory properties. Endothelium-derived microparticles may also be important in maintaining vascular integrity by stimulating vascular repair in vitro. Thus, at least a subpopulation of microparticles may play a novel role in promoting inflammatory resolution.

Novel findings suggest that activated protein C can induce the formation and release of endothelial protein C receptor (EPCR) containing microparticles.
microparticles contain functionally and actively bound protein C, a coagulation pathway inhibitor of factors Va and VIIIa. Thus, raised levels of microparticles do not necessarily lead to thrombosis. Endothelium-derived microparticles bearing anticoagulant activity may be beneficial in correcting haemostatic imbalance to counterweigh thrombosis driven by procoagulant microparticles. Thus, it is possible that in sepsis, these mechanisms are overwhelmed by the proinflammatory and thrombogenic effects of microparticles leading to a systemic inflammatory response to infection.

### Microparticles in sepsis

Sepsis is a clinical syndrome characterized by a systemic inflammatory response to infection. It is characterized by the activation of the coagulation system, inhibition of anticoagulant mechanisms, and fibrinolysis leading to disseminated intravascular coagulation (DIC) with microvascular thrombosis. The up-regulation of inflammatory responses and neuroendocrine systems leads to vascular hyporeactivity, and enhanced apoptosis which may contribute to multiple organ dysfunction and septic shock. A hallmark of sepsis is endothelial dysfunction with increased endothelial permeability, increased levels of nitric oxide, reduced nitric oxide availability, and enhanced reactive oxygen species (ROS)-induced oxidative stress. Sepsis may be complicated by acute lung injury (ALI) or acute respiratory distress syndrome (ARDS), where extrapulmonary infection can cause tissue factor-mediated coagulation and accumulation of neutrophils in the alveolar compartment. Models of sepsis involving bacterial products such as lipopolysaccharide (LPS) are well known to directly induce microparticle shedding, and it has been suggested that these may then go on to cause the endothelial activation leading to the inflammatory response.

**Microparticles have a proinflammatory effect in sepsis**

Raised levels of platelet, granulocyte, and endothelium-derived microparticles were first reported in patients with meningococcal sepsis. Platelet-derive MPs (PMPs) and PMNL-MPs are procoagulant with thrombin generation occurring via a tissue factor (TF)/factor VIIa (FVIIa)-dependent pathway. PMNL-MPs demonstrate increased expression of adhesion molecules and EC-derived MPs adhere to leucocytes and increase phagocytic activity. MPs isolated from septic rats induce vascular hyporeactivity via NF-κB activation, enhanced expression of NOS2, and increased oxidative stress. Increased production of thromboxane A2 (TXA2) may compensate for vascular hyporeactivity associated with hypotension in septic shock. Through differential effect on target tissues, microparticles induce expression of enzyme systems related to inflammation and nitrative and oxidative stress.
oxidative activity. Paradoxically, circulating levels of monocyte-derived microparticles are reduced in sepsis compared with controls and may reflect monocyte deactivation and dysfunction as previously described in severe sepsis.

In patients with sepsis, activated leucocytes enhance the production of leucocyte-derived microparticles with increased expression of adhesion molecules. Further, interaction between activated leucocytes and endothelium-derived microparticles through adhesion molecules is enhanced in patients with systemic inflammatory response syndrome and these microaggregates increase oxidative activity (Fig. 5). Microparticles may therefore serve as important bioeffectors of inflammation and thrombosis in sepsis and contribute to tissue injury and organ dysfunction.

**Role of circulating microparticles in endothelial dysfunction in sepsis**

Microparticles from septic patients induce ROS production and apoptosis of endothelial cells and smooth muscle cells in vitro through a nicotinamide adenine dinucleotide phosphate oxidase-dependent pathway. Healthy rats inoculated with microparticles isolated from septic rats exhibited an increase in superoxide anion production, NF-κB activation, enhanced expression of NOS2, and over-production of nitric oxide in the vascular wall. Microparticles produced during sepsis may therefore play an important role in vascular redox signalling and endothelial dysfunction, leading to circulatory failure in septic shock.

Surprisingly, microparticles isolated from patients with septic shock enhanced the sensitivity of contraction of mouse aorta in response to serotonin and LPS and associated with increased production of the vasoconstrictor TXA2. Microparticles may therefore exert a protective effect against vascular hyporeactivity in septic shock. Such protective effects may be important during the early phase of septic shock by compensating for vascular hyporeactivity associated with hypotension.

**Microparticles are implicated in the pathogenesis of ALI and ARDS in sepsis**

Novel data demonstrate that in mechanically ventilated patients with ARDS, microparticles are released into the alveolar space, and contain high levels of functional tissue factor. These microparticles, which originate from alveolar epithelial cells, are highly procoagulant and have the potential to contribute to fibrin deposition in the alveolar compartment in ARDS. Alveolar microparticles can originate from a number of cell types, including alveolar epithelial cells, macrophages, platelets, leucocytes, and endothelial cells. Endothelial dysfunction is also important in the pathogenesis of acute lung dysfunction. Indeed, endothelium-derived microparticles injected into mouse and rat lung demonstrated features of ALI including pulmonary oedema, neutrophil recruitment, and compromise of the endothelial–alveolar epithelial barrier. Given that ARDS is associated with a high mortality in critically ill patients, the presence of microparticles in the alveolar space may be of prognostic significance. Indeed, higher levels of leucocyte-derived microparticles in the blood and bronchoalveolar lavage were associated with a better prognosis in patients with early-stage ARDS. This is in keeping with the notion that an initial, exaggerated, pulmonary inflammatory response is associated with a worse outcome in ARDS. Thus, a subpopulation of microparticles may play a protective role in the pathogenesis of ARDS and may serve as a novel biomarker of prognostic significance.

**Microparticles have differential effects on target tissues in septic shock**

Raised levels of circulating microparticles from platelets, granulocytes, and endothelial cells have been identified in patients with meningococcal septicaemia, septic shock, severe trauma, and traumatic brain injury. Sustained high levels of endothelium-derived microparticles are associated with vascular dysfunction and may contribute to tissue hypoperfusion and ultimately organ dysfunction.

Microparticles from septic shock patients exert pleiotropic and differential effects on target tissues. Microparticles obtained from patients with early-stage septic shock were injected into mice and the expression of enzyme proteins-related inflammation and oxidative and nitrative stress were analysed. In the heart and lungs, increased expression of proinflammatory proteins NOS2, COX-2, and NF-κB was found along with increased oxidative and nitrative stress. However, tissue nitric oxide production was unaffected. Decreased nitric oxide bioavailability in the lungs may result from scavenging of nitric oxide by superoxide anions to produce peroxynitrate. In the liver, there was increased oxidative stress, and the kidneys were least affected. This is consistent with clinical findings of cardiac depression, acute lung dysfunction, and hepatic dysfunction seen in early septic shock. Microparticles therefore have deleterious effects on a number of tissues and may contribute to organ dysfunction in septic shock. Further research is required to assess the effect of septic microparticles on human tissues.

Conversely, it has been reported that elevated levels of platelet, endothelium-, and leucocyte-derived microparticles predict a more favourable outcome in severe sepsis in terms of mortality and organ dysfunction. Indeed, endothelium-derived microparticles carry functional EPCR and inhibit coagulation via activated protein C. The beneficial effects of microparticles in sepsis remain unclear and further study of this issue is required.

**Detection of circulating microparticles**

Despite an unprecedented interest in microparticles in the last decade, no standardized laboratory method is available for the evaluation of plasma microparticles, and few procedures are directly comparable. The Scientific Standardization Committee of the International Society on Thrombosis and Haemostasis are currently addressing this issue. The most common method used is flow cytometry, which
enables simultaneous detection, quantification, and phenotyping of microparticle subpopulations in one blood sample by detection of size and the binding of fluorescently labelled antibodies to cellular markers. The appropriate sampling conditions have been recently reported in a forum article.

In conclusion, although once felt to be inert remnants of cell destruction, microparticles are now considered to be a disseminated storage pool of bioactive effectors of inflammation and immunity, thrombosis, and vascular homeostasis. Microparticles are present in the blood at low levels in healthy individuals, and pathological states including sepsis and DIC are associated with both an increase in number and phenotypic change of circulating microparticles. Microparticles play an important role in endothelial dysfunction. Microparticles may exhibit differential mechanisms on tissues depending on their cell of origin.

Protective effects on the vascular endothelium to compensate for vascular hyperreactivity seen in septic shock are exerted by at least a subset of microparticles. Microparticles seem to play a key role in multi-organ dysfunction and septic shock through differential tissue expression of enzymes related to inflammation and oxidative stress. This developing subject provides new insight into the pathogenesis of sepsis. Plasma levels of microparticles are an emerging surrogate marker of thrombosis, inflammation, and endothelial dysfunction. They may be of prognostic value in sepsis and cardiovascular disease and act as novel therapeutic targets. Investigations of the role of circulating microparticles as potential diagnostic and prognostic biomarkers in sepsis are awaited.

Declaration of interest

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