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EDITORIAL

Lara Zafrani
Can Ince
Peter S. T. Yuen

Microparticles during sepsis: target, canary or cure?

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L. Zafrani (✉)
Medical Intensive Care Unit, Saint-Louis University Hospital, 1 Avenue Claude Vellefaux, 75010 Paris, France
e-mail: lara.zafrani@sls.aphp.fr
Tel.: +33-142-499419
Fax: +33-142-499426

C. Ince
Department of Translational Physiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

P. S. T. Yuen
Renal Diagnostics and Therapeutics Unit, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, USA

In the present study, Delabranche et al. [1] investigated the time course and cellular origin of circulating microparticles (MPs) in patients suffering from sepsis. They enrolled 92 patients with septic shock and performed an extensive investigation on their hemostatic status. They found endothelium-derived MPs to be relevant biomarkers in this context.

What are microparticles? MPs are small vesicles shed from the surface membranes of apoptotic or stress-activated cells. These MPs are defined by their small size (0.1–1 μm) and the presence of surface antigens from the parental cells. MPs are generated from a variety of different vascular cell types, including endothelial cells, red blood cells, monocytes, and platelets. Due to their protein, lipid, and cytoplasmic contents, MPs can potentially convey a large number of messages between cells and contribute to a variety of physiological and pathological processes (Fig. 1a, b) [2, 3].

The role of MPs during sepsis is complex. It has been shown that circulating levels of MPs are elevated during sepsis and promote tissue injury. However, previous studies describe both protective and deleterious effects [4, 5]. Converging animal and clinical data have emphasized the role of procoagulant MPs in the initiation of disseminated intravascular coagulation (DIC) during sepsis [6–8]. Patients with meningococcal sepsis display elevated numbers of MPs originating from platelets and granulocytes that are prothrombotic [6]. Since the earliest demonstration of MP generation by platelets, it has been known that MPs contribute to thrombin generation by facilitating the assembly of the prothrombinase complex [9]. Although platelet-derived MPs appear to be a significant part of the number of circulating shed membrane vesicles, particles from other cell types such as red blood cells, leukocytes or endothelial cells also contribute to the plasmatic pool. Their procoagulant properties are based on the combined presence of phosphatidylserine, a procoagulant aminophospholipid exposed after stimulation that supports the assembly of blood-clotting enzyme complexes, and tissue factor, a major initiator of the coagulation cascade. As such, mouse models of endotoxemia confirmed activated coagulation due to increased MP tissue factor activity [8].

In the study of Delabranche et al. [1], endothelial- and leukocyte-derived MPs reached higher plasma levels in DIC, while increased soluble glycoprotein V/platelet ratio was delayed. Indeed, they provide new insights on the time course and parent cell origin in septic shock. Leukocytes and endothelial cells were involved in the early stages of sepsis, whereas platelet activation was delayed. These new findings underscore the crucial role of early endothelial injury during sepsis. The role of endothelium-derived MPs as prothrombotic MPs has previously been described: in a mouse model of deep venous thrombosis,

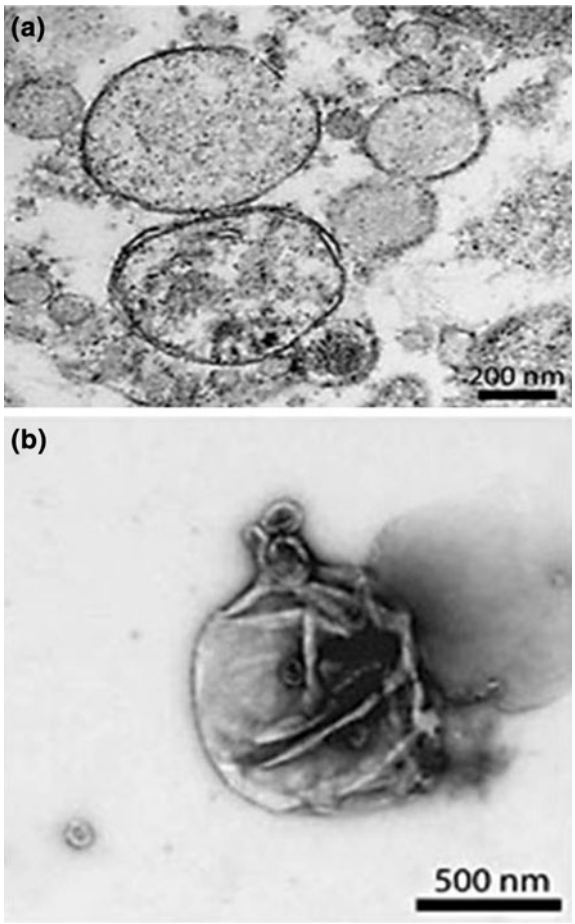

Fig. 1 **a**, **b** Electron microscopy of cell-derived MPs; reproduced with permission from Nephron Exp Nephrol [3]. **a** HUVEC (Human umbilival vein endothelial cells) MPs. **b** negatively stained vesicular HUVEC MPs

E-selectin, expressed by endothelium-derived MPs, reinforces the thrombotic response [10]. In thrombotic thrombocytopenic purpura, endothelium-derived MPs can express very large von Willebrand factor multimers resulting in platelet aggregation [11]. Furthermore, exposure of complement proteins C5b-9 to endothelial cells promotes MP formation with expression of factor Va binding sites and prothrombinase activity [12]. Collectively, these data implicate a specific and early role of endothelium-derived MPs in sepsis-induced DIC.

The authors suggest that very high initial levels of cytokines and chemokines may have prompted endothelial and leukocyte activation prior to septic-shock-induced DIC. Septic shock is a prime example of the link between inflammation and thrombosis, and MPs are crucial effectors in this context. Previous studies have shown that a variety of proinflammatory agents, such as tumor necrosis factor alpha or interleukin-6, can activate endothelial cells and induce the release of MPs. Proinflammatory mediators directly induce tissue factor expression in endothelial cells, and the coagulation protease thrombin can directly induce the expression of proinflammatory mediators in endothelial cells, thus creating a positive feedback loop.

Another level of complexity in the understanding of the role of MPs in patients affected by sepsis stems from the pleiotropic and differential effects depending on target tissues. Hence, a straightforward pharmacological approach on MPs seems unlikely. Mastronardi et al. injected MPs obtained from septic patients into mice, being able to alter recipient inflammatory enzyme systems, nitrosative and oxidative stress; heart and lung tissues were affected to a greater degree by MPs from septic patients, compared with liver and kidney tissues. The same authors had previously reported that circulating MPs from septic patients can exert a protective role against vascular hyporeactivity induced by lipopolysaccharide in mice [4].

Although the results of Delabranche et al. [1] shed new light on the complex role of MPs in DIC during sepsis, the clinical implication of such findings remains somewhat uncertain. In their cohort, the authors found a subset of patients with increased endothelium-derived MPs (CD105-MPs) before fulfilling DIC criteria later during the course of sepsis. Thus, they suggest using these MPs as predictors of DIC occurrence. Nonetheless, the clinical relevance of such prognosis biomarkers remains to be ascertained (Table 1). A clinically relevant biomarker must be relatively easy to measure and have the potential to change how patients are managed. Although efforts

Table 1 Role of endothelium-derived MPs in sepsis

Role of endothelium-derived MPs in sepsis	Clinical perspectives
Biomarkers in sepsis-induced DIC [1]	Stratification and allocation to better anticoagulant therapeutic strategies
Deleterious effects of endothelium-derived MPs Bioeffectors of inflammation and thrombosis → contribute to tissue injury – Promote platelet aggregation and thrombin generation [11, 12] – Adhere leukocytes → increase phagocytic activity [5] – Increase pulmonary endothelial permeability and promote acute lung injury [13]	Pharmacological control of circulating endothelium-derived MPs in stratified patients = inhibition of the shedding of MPs
Protective effects of endothelium-derived MPs – Protection against vascular hyporeactivity [4]	Therapeutic use of endothelium-derived MPs in stratified patients

have been made recently to standardize MP analysis, standardized measurement of MP populations remains a key limitation for their use as biomarkers in routine laboratory clinical medicine. The most common approaches to investigate MPs are flow cytometry, coagulation assays (prothrombinase assay, chosen by Delabranche et al. [1]), proteomics, and enzyme-linked immunosorbent assay (ELISA)-based solid-phase capture assays. Technical discrepancies between studies represent additional shortcomings that may obscure the interpretation of the existing literature, and there is a great need for standardized methods to allow clinicians to perform accurate and reproducible measurements in a routine laboratory setting or maybe even at the bedside in a point-of-care setting. In addition, if, as the authors suggest, the appearance of MPs precedes the occurrence of DIC, a more precise identity of the origin and pathogenicity of MPs will need to be developed. The frequency of measurement is also a key factor yet to be established, because it will allow the identification of a therapeutic window.

Another main question raised by the present study is whether MPs should be primarily regarded as a fuel to organ failure in need of treatment and scavenging or rather as an early indicator of coagulatory disturbances. Are MPs a therapeutic target or biomarkers? In this context it could be speculated, for example, that, if MPs are a major contributor to evolving organ failure, then prevention of the release of MPs should be regarded as a major avenue to be explored, whereas if one is to view MPs rather as a biomarker of tissue injury, then other issues are more important and these would be related to diagnostic kits and timing. Finally, there may need to be a combinatorial approach that is biomarker based to heal the cell making MPs and reduce the impact of the MPs once released.

The study by Delabranche et al. [1] adds a new milestone in MP research during sepsis and underscores the role of endothelial-derived MPs during sepsis-induced DIC. However, further methodological standardization and translational studies are needed to confirm these findings and link these findings to clinical interventions.

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Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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