

COMMENTARY

Microparticles as biological vectors of activated protein C treatment in sepsis

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See related research by Pérez-Casal *et al.*, <http://ccforum.com/content/15/4/R195>

Abstract

Activated protein C (APC), a physiological coagulation inhibitor, has been shown to reduce mortality in patients with severe sepsis. APC exerts pleiotropic cytoprotection by a mechanism that requires its interaction with endothelial cell protein C receptor and protease-activated receptor-1 on target cells. In the previous issue, Pérez-Casal and colleagues elegantly demonstrate that APC, using its recombinant form (rhAPC), can communicate to target cells through release of microparticles (MPs), small membrane vesicles released from activated cells, to induce anti-apoptotic and anti-inflammatory properties that might participate in the improvement of patient outcome. Of interest is the fact that APC itself promotes the release of MPs from target cells including endothelial cells and monocytes. These MPs bear the endothelial cell protein C receptor/APC molecules and can transfer the message to target cells including those of origin to induce cytoprotection. The long-range APC signal can thus be mediated by MPs *in vivo* upon pharmacological treatment using rhAPC in severe septic patients. A novel pharmacological approach targeting MP production and properties could therefore be used to treat severe sepsis in addition to other well-known actions of APC via direct interaction with the cells of interest.

Sepsis has been classically considered the archetypal clinical condition with molecular links between inflammation and coagulation. Both inflammation and thrombosis can be orchestrated by the interactions between circulating cells, such as lymphocytes, platelets, and

vascular cells, which under activation or apoptosis lead to the release of circulating microparticles (MPs).

In the previous issue of *Critical Care*, Pérez-Casal and colleagues hypothesized that circulating MPs may retain their anti-inflammatory and cytoprotective properties in septic patients during recombinant human activated protein C (rhAPC) infusion *in vivo* and probably participate in its clinical benefit [1]. The same group has previously shown that activated protein C (APC) can generate MPs *in vitro* from endothelial cell protein C receptor (EPCR)-expressing cells, which retain anticoagulant and protease-activated receptor-1 (PAR-1)-dependent anti-inflammatory properties [2]. APC binding to EPCR at the endothelial cell surface and APC on MP-EPCR could cleave and activate PAR-1, sphingosine 1-phosphate receptor and kinase insert domain receptor [3].

The main findings reported were as follows. rhAPC treatment for severe sepsis can induce the generation and release of MPs *in vivo*, with a clinical correlative trend towards improved outcome. Circulating MPs from patients during rhAPC treatment express APC, EPCR and CD13. These MPs interact with endothelial cells and induce changes in gene expression to inhibit apoptosis and reduce endothelial permeability. These effects require PAR-1 activation by APC in an EPCR-bound conformation, confirming the evidence for the assembled EPCR-APC complex on *in vivo*-derived MPs.

The present work suggests that MPs could disseminate APC function and activate endothelial PAR-1 at distal vascular sites. The MPs represent an additional circulatory form of APC receptor in human plasma, which is different from soluble EPCR. MP-associated APC is stable in measurable levels, and activities would point to physiological and clinical relevance as bioactive effectors in rhAPC-treated patients and contribute to the effectiveness of rhAPC in severe sepsis.

Some limitations of the present study should be addressed. The authors did not analyze the subpopulation of CD13⁺ MPs upon rhAPC treatment, whether they are from endothelial or leukocyte origins. Indeed, they have shown that APC induces MP-associated EPCR formation from monocytes and human endothelial cells [2].

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Furthermore, whether such MPs contribute to the ability of rhAPC treatment to improve cardiovascular function – including arterial contractility and endothelial dysfunction by decreasing tissue inflammation and oxidative stress as reported in an experimental model of sepsis [4,5] – remains to be determined. A fragile balance between the harmful and helpful effects of MPs especially during severe sepsis should be underlined. Circulating MPs from septic patients might exert a protective role at the vascular level by compensating hyporeactivity [6], but they might also contribute to the cause of multiorgan failure in sepsis and induce deleterious protein changes in target tissues [7]. It would be of interest to test the hypothesis that rhAPC via increased certain subtypes of MPs bearing EPCR/APC would contribute to the correction of multiple organ failure, which would lead to increased survival. The clinical relevance of rhAPC treatment via increased APC/EPCR-MPs requires further exploration, especially in larger numbers of patients with septic shock and higher mortality.

In conclusion, the present study provides further convincing evidence that MPs can have beneficial properties. MPs could potentially be developed as new therapeutic tools to transfer biological vectors of cellular communication and are able to modulate important cellular regulatory functions at a distal site of its production in response to pharmacological agents such as rhAPC.

Abbreviations

APC, activated protein C; EPCR, endothelial protein C receptor; MP, microparticle; PAR-1, protease-activated receptor-1; rhAPC, recombinant human APC.

Competing interests

The author declares that he has no competing interests.

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