

Letter

To be or not to be protease activated receptor-1 in activated protein C-initiated endothelial barrier protection?

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Published: 19 February 2007

This article is online at <http://ccforum.com/content/11/1/407>

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Critical Care 2007, **11**:407 (doi:10.1186/cc5149)

See related review by Looney and Matthay, <http://ccforum.com/content/10/6/239>

The review by Looney and Matthay summarized recent progress in basic and preclinical research of activated protein C (APC), a novel therapeutic agent for the treatment of severe sepsis [1]. APC is traditionally an anticoagulant and profibrinolytic agent, and has been appreciated to possess anti-inflammatory and anti-apoptotic properties, yet the exact mechanisms by which APC executes its clinical effects in sepsis are not defined [2]. Emerging evidence has suggested that APC might exert its clinical benefit, at least in part, by maintaining endothelial barrier function [3,4]. The authors reviewed conflicting results of endothelial barrier protection of APC in the literature and pointed out that caution must be taken to interpret cell culture experiments and their relationship to *in vivo* conditions. Indeed, one should exercise caution while reviewing controversial data.

Looney and Matthay stated that 'in two different *in vitro* investigations [3,4], APC promoted endothelial barrier protection in a PAR-1- and S1P₁-dependent mechanism', which represents a misinterpretation. These two papers did conclude that APC enhanced endothelial barrier function in different cell lines by a sphingosine 1-phosphate receptor-1 (S1P₁)-dependent signaling pathway, but it is still arguable whether this is protease activated receptor-1 (PAR-1) dependent. Finigan and colleagues showed that anti-PAR-1 blocking antibody did not interfere with either APC-mediated myosin light-chain phosphorylation or S1P₁ receptor phosphorylation/activation, and concluded that it was endothelial protein C receptor (EPCR) ligation with APC and the resulting S1P₁ transactivation that led to endothelial cell cytoskeletal rearrangement and barrier protection [4]. There is therefore no evidence so far to support the notion that the 'APC ... effect on endothelial cytoskeletal rearrangement ... appears to operate in a PAR-1- ... dependent manner' [1].

Authors' response

Mark R Looney and Michael A Matthay

We agree with Dr Li that reconciling the *in vitro* and *in vivo* effects of APC is a complicated endeavor. It is still not clear how APC and thrombin, operating through the same receptor (PAR-1), can induce sometimes opposite effects. The role of EPCR and PAR-1 is clear regarding APC's anti-apoptotic effects – both receptors are essential [5]. The role of EPCR in APC's endothelial barrier protection is also clear – it is also essential, as reported in two different investigations [3,4]. We disagree on the role of PAR-1 in endothelial barrier protection. Feistritzer and Riewald showed convincingly that APC's barrier-enhancing

properties were abolished by PAR-1 blocking antibodies [3]. The only more conclusive experimental results would be obtained by challenging endothelium from PAR-1 knockout animals with thrombin and APC. The investigation by Finigan and colleagues admittedly focused more on the role of EPCR, and only tested the role of PAR-1 mechanistically and not in the transendothelial electrical resistance experiments [4]. Much more clearly remains to be discovered about APC and its many potential beneficial properties, including its activation of PAR-1 and endothelial barrier protection.

APC = activated protein C; EPCR = endothelial protein C receptor; PAR-1 = protease activated receptor-1; S1P₁ = sphingosine 1-phosphate receptor-1.

Competing interests

The authors declare that they have no competing interests.

References

1. Looney MR, Matthay MA: **Bench-to-bedside review: The role of activated protein C in maintaining endothelial tight junction function and its relationship to organ injury.** *Crit Care* 2006, **10**:239.
2. Mosnier LO, Zlokovic BV, Griffin JH: **The cytoprotective protein C pathway.** *Blood* 2006 [Epub ahead of print].
3. Feistritzer C, Riewald M: **Endothelial barrier protection by activated protein C through PAR1-dependent sphingosine 1-phosphate receptor-1 crossactivation.** *Blood* 2005, **105**:3178-3184.
4. Finigan JH, Dudek SM, Singleton PA, Chiang ET, Jacobson JR, Camp SM, Ye SQ, Garcia JG: **Activated protein C mediates novel lung endothelial barrier enhancement: role of sphingosine 1-phosphate receptor transactivation.** *J Biol Chem* 2005, **280**:17286-17293.
5. Cheng T, Liu D, Griffin JH, Fernandez JA, Castellino F, Rosen ED, Fukudome K, Zlokovic BV: **Activated protein C blocks p53-mediated apoptosis in ischemic human brain endothelium and is neuroprotective.** *Nat Med* 2003, **9**:338-342.