Letter

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

Shi-Sheng Li

Department of Molecular & Experimental Medicine, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA

Corresponding author: Shi-Sheng Li, sshli@scripps.edu

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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 $S1P_1$-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 ($S1P_1$)-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 $S1P_1$ receptor phosphorylation/activation, and concluded that it was endothelial protein C receptor (EPCR) ligation with APC and the resulting $S1P_1$ 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; $S1P_1$ = sphingosine 1-phosphate receptor-1.

Competing interests

The authors declare that they have no competing interests.

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