LETTER

A call for better understanding the role of albumin in mediating VE-cadherin phosphorylation and endothelial barrier dysfunction in septic patients

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Letter to editor regarding “Endothelial damage in septic shock patients as evidenced by circulating syndecan-1, sphingosine-1-phosphate and soluble VE-cadherin: a substudy of ALBIOS” by Piotti et al. [1].

We read with great interest the article by Piotti et al. which showed that soluble VE-cadherin was independently associated with the need for renal replacement therapy during ICU stay and albumin supplementation lowered circulating VE-cadherin consistently over time, which might be partially attributed to an increase in intravascular volume as evidenced by higher NT-proBNP in septic patients receiving albumin supplementation [1]. While the authors briefly proposed the potential mechanisms underlying the endothelial protective effect of albumin (namely their anti-inflammatory and antioxidant properties), here we intend to add more discussion to fuel the understanding of the role of albumin in mediating VE-cadherin phosphorylation and endothelial barrier dysfunction in septic patients.

Cell–cell adherens junctions are regarded as the primary junctions in the peripheral microvasculature. VE-cadherin, the main component of adherens junction, is anchored to the actin cytoskeleton through catenins (α-, β-, γ-, and p120-catenin) and participate in the regulation of endothelial barrier integrity and permeability [2]. In sepsis, inflammatory mediators (namely lipopolysaccharide, cytokines, thrombin, and complement 5a etc.) could not only down-regulate the expression of VE-cadherin on the membrane of endothelial cells, but also impair the cytoskeleton-junction response characterized by myosin light chain phosphorylation and tyrosine phosphorylation of VE-cadherin through the activation of Src family kinases, which significantly contributes to adherens junction dissociation [3]. Meegan and colleagues further identified citrullinated histone 3 as a functional contributor to cell–cell adherens junction opening and cytoskeleton reorganization, causing microvascular endothelial barrier dysfunction [4]. Since a previous publication has suggested the remarkable histone-neutralization effect of albumin characterized by decreased histone-induced endothelial cell damage [5], we speculate that albumin might also alleviate the impaired cell–cell adherens junctions and endothelial barrier function possibly by antagonizing histone-mediated adherens junction loss and cytoskeleton reorganization. Of note, this protective effect of albumin might be independent of the expression of VE-cadherin on the surface of endothelial cells. Future explorations are thus encouraged to clarify the mechanisms underlying the effect of albumin supplementation in mediating tyrosine phosphorylation of VE-cadherin, preventing endothelial barrier dysfunction and improving survival in patients with sepsis.

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To the editor

We read with interest the letter by Yupei Li and colleagues, discussing a potential novel mechanism by which albumin might counteract the altered endothelial permeability characterizing patients with sepsis. In support to the histone-neutralizing effect of albumin, in cultured endothelial cells, we reported that higher PTX3 at day 1 was associated with greater hemodynamic instability, suggesting increase in PTX3 secretion as a compensatory response. Similarly, in patients receiving albumin supplementation, PTX3 appeared significantly lower than in patients receiving crystalloids [6]. In another in-vitro study, Otero K and colleagues reported that advanced-glycation end-product-modified bovine serum albumin (BSA), an abnormal form of albumin, induces endothelial dysfunction and increased permeability through VE-cadherin complex disruption, as observed in diabetes or aging, an effect not observed with normal BSA [7]. Taken together, these findings suggest that albumin, when normally functioning, may preserve endothelial permeability also by maintaining the integrity of VE-cadherin complex.

Despite these interesting speculations, the overall picture of the role of albumin in relation to endothelial permeability is likely more complex. Very often, hypoalbuminemia, during septic shock, is considered per se a proof of increased endothelial permeability, although this statement remains unproven. Indeed, during sepsis, hypoalbuminemia is a common finding often associated with an increased risk of death, but several data have shown that during systemic inflammation albumin transcapillary escape rate may not be different from that of healthy subjects [8]. Moreover, even the association between glycocalyx disruption, as denoted by elevated levels of syndecan-1, and endothelial permeability has been challenged [9]. Finally, volume expansion with 20% albumin as observed in clinical conditions characterized by increased endothelial permeability, such as in patients with burns, appeared similar to that observed in normal conditions [10].

Independent of the mechanisms potentially involved, albumin supplementation targeting the restoration of its normal serum concentration appears a reasonable approach during sepsis. When compared to a fluid strategy including only crystalloids, in the ALBIOS trial, albumin replacement appeared associated with a faster normalization of cardiovascular dysfunction, as well as with a reduced net positive fluid balance during the resuscitation phase. Whether or not these advantages are related to ancillary functions of albumin (in addition to its primary oncotic property) remains unproven. We are currently conducting a novel multicenter randomized controlled trial, the ALBumin Italian Outcome Septic Shock—BALANCED (ALBIOSS-BALANCED) trial (#NCT03654001), comparing, in patients with septic shock, albumin replacement in addition to crystalloids to the use of only crystalloids over the first 90 days of treatment. Already 400 patients have been enrolled and we do hope that the results of such a trial, together with the ARISS trial (Albumin Replacement Therapy in Septic Shock, #NCT03869385) ongoing in Germany, will definitely prove whether albumin supplementation in septic shock improves survival.

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LYP and SBH conceived of the concept and planned the content. LYP and JJJ wrote the first draft. SBH reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Competing interests
The authors declare that they have no competing interests.

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