

Correspondence

VE-cadherin, a potential marker for endothelial cell activation during hereditary angioedema attacks

To the Editor:

Kajdácsi et al.¹ have recently published an excellent article about endothelial cell (EC) activation during hereditary angioedema (HAE) attacks. The authors pointed out that EC activation in HAE has been barely investigated, and they referred to the data from Cruetz et al.,² which demonstrated an elevated level of E-selectin in HAE attacks. Because bradykinin is a key player involved in EC destabilization and increased permeability during HAE attacks, the authors wanted to assess the *in vivo* functions of ECs. Because the endothelium is not a well-localized organ, the authors suggested that exploring endothelial plasma markers is a classical and frequently used method. Thus, they investigated the level of a combination of 3 markers: von Willebrand factor, soluble E-selectin, and endothelin-1. The aim of the present commentary was to recall that the maintenance and regulation of normal microvascular function is dependent on endothelial adherens junctions located at intercellular contacts and crucial for the vascular integrity. The major cell-cell adhesion molecule at endothelial adherens junctions is vascular endothelial cell cadherin (VE-cadherin), a cadherin family member specifically expressed in endothelial cells.³ In adults, the adhesive properties of VE-cadherin are crucial to maintain endothelial cells adherent to one another. Tyrosine phosphorylation of the cadherin-catenin complex has been proposed as a mechanism that regulates the stability of cell-cell junctions. Importantly, VE-cadherin tyrosine phosphorylation is weak or undetectable in endothelial cells from resting tissues but is increased in angiogenic organs.⁴ Indeed, the major modulator of the tyrosine phosphorylation status of VE-cadherin is the tyrosine kinase Src in response to vascular endothelial growth factor.⁵ We recently reported that the tyrosine phosphorylation of VE-cadherin preceded the cleavage of its extracellular domain.⁶ In our previous study,⁷ we have highlighted the molecular mechanisms of the vascular permeability in the context of HAE. We demonstrated that bradykinin and kallikrein stimulations of a confluent endothelial cell monolayer induced a time-dependent release of soluble VE-cadherin fragments, and an increase in vascular permeability secondary to the

disruption of cell-cell junctions.⁷ We thus explored soluble VE-cadherin during an attack and between attacks in a patient. We showed the presence of a 90-kDa VE-cadherin extracellular domain in the patient's serum during the attack, whereas it was barely detectable before and after the attack; thus, we concluded that the detection of a soluble VE-cadherin in the patient's serum during an HAE attack might have potential clinical interest as a biomarker for the diagnosis. We are pleased to see that Kajdácsi et al. comfort our data about endothelial cell activation, but we regret that our work was not included in the discussion of their article.

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