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# Epithelium Specific ETS-1: A Counter-regulatory Factor Against Vascular Dysfunction and Inflammation

**Chun Cheng Andy Chen** and **Nicholas R. Ferreri**
Department of Pharmacology, New York Medical College, Valhalla, NY

Increasing evidence suggests that vascular inflammation contributes importantly to the pathogenesis of vascular dysfunction associated with several diseases including hypertension and atherosclerosis. Initial interpretations hinged upon the ability of inflammatory cytokines such as tumor necrosis factor α and interleukin-6 to induce a panoply of molecules that facilitate the interaction between leukocytes and endothelial cells [1], increase the generation of reactive oxygen species, and modulate vascular and renal mechanisms that control blood pressure. Of recent interest is the contribution of cytokine-releasing T-lymphocytes to the generation of angiotensin II (Ang II)-induced vascular dysfunction and hypertension[2]. E26 Transformation-specific Sequence (ETS) factors are a family of transcription factors consisting of 25 to 30 family members that share highly conserved DNA-binding domains[3]. Some members of the ETS family regulate genes involved in both innate and adaptive immunity as targeted disruptions of ETS factors have been shown to reduce the number and function of neutrophils, natural killer cells, and T-lymphocytes[3].

In this issue of the *American Journal of Hypertension,* Yumei Zhan and colleagues[4] studied the effects of epithelium specific ETS factor (ESE-1) gene deletion on blood pressure, vascular inflammation, and remodeling in an Ang II-dependent model of vascular inflammation in mice. In response to Ang II, ESE-1 deficient mice exhibited increased inflammatory cell infiltration, vascular thickening and fibrosis, as well as higher systolic blood pressure compared with wild-type mice. The authors conclude that ESE-1 is part of a counter-regulatory mechanism that offsets Ang II-induced vascular inflammation and remodeling. As nitric oxide synthase 2 (NOS2) was reduced in ESE-1 knockout mice infused with Ang II, maintenance of NOS2 expression may be a mechanism by which ESE-1 offers vascular protection. This is consistent with previous observations that NOS2 is upregulated in a mouse model of acute inflammation[5], although the precise role of NOS2 in various settings of vascular inflammation is still an area of debate and continuing investigation. Interestingly, in their previous work with Ets-1, another ETS transcription factor, Ets-1 deficient mice infused with Ang II exhibited blunted vascular thickening and fibrosis and less inflammatory cell infiltration in the vasculature[6], suggesting that different members of the ETS transcriptional factor family may act in opposition to each other in the same tissue.

The present study provides important insights regarding the involvement of ESE-1 in vascular dysfunction in the context of acute or chronic inflammation. As vascular dysfunction can contribute to hypertension, ESE-1 deficiency may also trigger mechanisms, currently undefined, that contribute to the elevation of blood pressure. While the authors

Address correspondence to: Chun Cheng Andy Chen, PhD, Department of Pharmacology, New York Medical College, Valhalla, NY 10595, Phone: 914-594-4133, Fax: 914-594-4273, andy_chen@nymc.edu.

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pointed out an association of NOS2 in alleviating vascular dysfunction, inflammation, and blood pressure elevation in response to Ang II, currently there is no evidence for the direct involvement of NO. Further studies are needed to confirm vascular protective effects of ESE-1 mediated NO release in the Ang II-dependent model of vascular inflammation. Important questions remain; namely, under what conditions do the actions of one ETS transcription factor dominate over the other to influence the overall vascular phenotype? What are the mechanisms that govern the interactions between ESE-1 and the recruitment of inflammatory cells? Will drugs targeting ESE-1 be able to provide protection in the vasculature against inflammation-induced dysfunction? The results of the present study provide an attractive model for studying mechanisms that underlie vascular inflammation, and may provide a therapeutic target for treatment of vascular diseases.

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