



## Commentary on “Failer et al. (2022) Developmental endothelial locus-1 protects from hypertension-induced cardiovascular remodeling via immunomodulation” J Clin Invest 2022 (<https://doi.org/10.1172/JCI126155>)

Markus Sperandio<sup>1</sup>

Received: 15 June 2022 / Accepted: 24 June 2022 / Published online: 28 June 2022  
© The Author(s) 2022

Hypertension is a very frequent chronic disease associated with significant cardiovascular morbidity and mortality. Pathological findings in patients with chronic hypertension include aortic fibrosis and loss of elastic fibers leading to arterial stiffening which further increases systolic blood pressure. Chronically elevated blood pressure eventually also affects the heart with the development of left ventricular hypertrophy and fibrosis [1]. An essential component in the pathophysiology of hypertension is inflammation which can be triggered by various mechanisms including chronically elevated angiotensin II levels through activation of the renin–angiotensin–aldosterone system [1]. Accordingly, recruitment of neutrophils and monocytes as well as T-cells into the arterial wall has been well-documented in patients with hypertension as well as in various animal models, including angiotensin II–induced hypertension [2]. In this context, IL-17 turned out to be a critical pro-inflammatory mediator in hypertension-induced inflammation [3, 4]. Recently, developmental endothelial locus-1 (DEL-1) encoded by *EDIL3* has been described to be a negative regulator of IL-17-dependent pathologies [5]. In addition, DEL-1 significantly impacts on neutrophil homeostasis, recruitment, and clearance and promotes FOXP3<sup>+</sup> regulatory CD4<sup>+</sup> T-cell differentiation during inflammation [6]. These anti-inflammatory effects are mostly exerted via the inhibition of  $\beta_2$  integrins and modulation of  $\alpha_v\beta_3$  integrin function [5].

Hypothesizing that therapeutic use of DEL-1 might be an interesting and effective way to attenuate hypertension-induced cardiovascular remodeling, Failer and colleagues performed an excellent study to address a potential beneficial effect of therapeutic DEL-1 in hypertension-induced cardiovascular disease [7]. The authors used two models of hypertension (angiotensin-II–induced and deoxycorticosterone acetate (DOCA)-salt–induced hypertension) and applied various ways of DEL-1 treatment including the use of endothelial cell–specific DEL-1 overexpressing mice as well as injection of recombinant DEL-1. While in both hypertension models the increase in blood pressure during the early phase of induced hypertension was independent of DEL-1 treatment, the later increase in systolic blood pressure was significantly reduced in the presence of DEL-1. This was accompanied by reduced vascular and cardiac remodeling exemplified by less pronounced aortic stiffening and attenuated LV hypertrophy. These findings strongly suggest that the inflammatory response that takes place during hypertension contributes to disease progression (with  $\alpha_v\beta_3$  integrin and activated MMP2 playing major roles), opening new avenues in treating patients with chronic hypertension. This might be true for both the early and later phases of the disease when vascular and cardiac remodeling has already progressed to substantial changes in vascular and left ventricular tissue architecture. Although the microcirculation was not the focus of the study by Failer et al. [7], arterial vessels in the microcirculation exposed to hypertension might also benefit from DEL-1 treatment in terms of arterial wall hypertrophy, vascular tone regulation, and inflammation-induced alterations of the vascular wall. Anti-adhesive properties by DEL-1 had already been reported some time ago in a microcirculatory model (dorsal skinfold chamber), where the loss of DEL-1 facilitates LFA-1 binding to ICAM-1 leading to an increase in leukocyte adhesion

✉ Markus Sperandio  
markus.sperandio@lmu.de

<sup>1</sup> Institute of Cardiovascular Physiology and Pathophysiology, Walter Brendel Center for Experimental Medicine, Biomedical Center (BMC), LMU München, Großhaderner Str. 9, 82152 Planegg-Martinsried, Germany

to the inflamed endothelium [8]. Additional experimental studies clarifying the role of DEL-1 in the microvasculature exposed to hypertension may further support a protective role of DEL-1 in the microcirculation of patients with chronic hypertension and promote the use of DEL-1 treatment in those patients.

Taken together, Failer and colleagues present convincing evidence that DEL-1-dependent modulation of the inflammatory response during chronic hypertension might offer an interesting new treatment strategy to complement conventional antihypertensive therapy [7]. Applied as antihypertensive and anti-inflammatory combination therapy, it might provide an attractive approach to further increase efficiency in preventing disease progression in hypertension-induced cardiovascular damage.

**Author contribution** M.S. wrote the manuscript.

**Funding** Open Access funding enabled and organized by Projekt DEAL. Deutsche Forschungsgemeinschaft SFB914, B01.

**Data availability** Not applicable.

## Declarations

**Ethics approval and consent to participate** Not applicable.

**Consent for publication** Yes.

**Competing interests** The author declares no competing interests.

**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are

included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

## References

1. Choi EY et al (2008) Del-1, an endogenous leukocyte-endothelial adhesion inhibitor, limits inflammatory cell recruitment. *Science* 322:1101–1104
2. Failer T et al (2022) Developmental endothelial locus-1 protects from hypertension-induced cardiovascular remodeling via immunomodulation. *J Clin Investig* 132. <https://doi.org/10.1172/JCI126155>
3. Hajishengallis G, Chavakis T (2019) DEL-1-regulated immune plasticity and inflammatory disorders. *Trends Mol Med* 25:444–459. <https://doi.org/10.1016/j.molmed.2019.02.010>
4. Li X et al (2020) The DEL-1/beta3 integrin axis promotes regulatory T cell responses during inflammation resolution. *J Clin Invest* 130:6261–6277. <https://doi.org/10.1172/JCI137530>
5. Madhur MS et al (2010) Interleukin 17 promotes angiotensin II-induced hypertension and vascular dysfunction. *Hypertension* 55:500–507. <https://doi.org/10.1161/HYPERTENSIONAHA.109.145094>
6. Madhur MS et al (2021) Hypertension: do inflammation and immunity hold the key to solving this epidemic? *Circ Res* 128:908–933. <https://doi.org/10.1161/CIRCRESAHA.121.318052>
7. Saleh MA et al (2016) Inhibition of interleukin 17-A but not interleukin-17F signaling lowers blood pressure and reduces end-organ inflammation in angiotensin II-induced hypertension. *JACC Basic Transl Sci* 1:606–616. <https://doi.org/10.1016/j.jacbt.2016.07.009>
8. Wenzel P et al (2011) Lysozyme M-positive monocytes mediate angiotensin II-induced arterial hypertension and vascular dysfunction. *Circulation* 124:1370–1381. <https://doi.org/10.1161/CIRCULATIONAHA.111.034470>

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.