Published in final edited form as:

Circulation. 2015 July 14; 132(2): e16. doi:10.1161/CIRCULATIONAHA.114.012494.

Letter to the Editors regarding: “The ERG-APLNR Axis Controls Pulmonary Venule Endothelial Proliferation in Pulmonary Venous Occlusive Disease” by Lathen, et.al:

Papangelis, Pulmonary Arteriolar Endothelium Express Aplnr

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We have read with great interest the manuscript by Lathen and colleagues titled “The ERG-APLNR Axis Controls Pulmonary Venule Endothelial Proliferation in Pulmonary Venous Occlusive Disease,” and congratulate the authors for their thorough approach using human samples and modern genetic techniques.¹ However, there are two key points, which in our opinion deserve attention.

First, following a literature review the authors conclude that “*These studies point to the concept that Aplnr signaling has direct and unique effects on the venous circulation.*” However, the majority of the cited studies do not describe venous specific mechanisms. Cheng et al. demonstrated that apelin administration decreased both the mean arterial pressure and the mean circulatory filling pressure in rats, summarizing that “apelin is an arterial and venous dilator in vivo.”² Cox and colleagues³ employed a bead chemotaxis model on frog embryos; although apelin soaked beads induced sprouting from the cardinal vein region, the response to apelin was comparable to VEGF soaked beads, and did not exclude non-venous endothelial cells responding to apelin. Lastly, the authors invoke work by Eyries and colleagues⁴ that utilized the zebrafish caudal fin amputation model to study the apelin contribution on regenerative angiogenesis. This model is not specific to venous regeneration, nor is a venous specific angiogenic effect of apelin towards vascular regeneration discussed in this manuscript.⁴ More importantly, we have evaluated Aplnr expression in the adult mouse lung, using Microfil injected into the right ventricle to effectively delineate the pulmonary arterial tree. We found robust expression of Aplnr in the pulmonary arteriolar endothelium using two independent approaches: 1) in situ hybridization (given the paucity of a robust Aplnr antibody) and 2) green fluorescent protein (GFP) expression from the recently developed AplnrCreER:RosamTmG mice.⁵ The larger pulmonary arteries did not express Aplnr, as reported by Lathen and colleagues. Although we cannot fully exclude the possibility of a secondary, yet unidentified apelin receptor that

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Disclosures: None

may be mediating the effects of apelin in pulmonary arterial hypertension (PAH), our findings provide strong evidence that Aplnr, given its robust expression in the pulmonary arterioles, can certainly be the key receptor that mediates the effects of apelin in PAH.

Second, the selective induction of Aplnr in response to adenoviral Erg expression in the pulmonary venous endothelial cells, but not any of the other validated Erg transcriptional targets, and the disparate pattern of Erg and Aplnr expression in vivo, highlight the limitations in understanding how Erg activity is regulated, and selectively induce some transcriptional targets but not others, in the arterial and venous endothelial cells.

The referenced work by Lathen and colleagues¹ provides interesting insights into a novel mechanism of pulmonary veno-occlusive disease; nevertheless, we believe that the roles of Aplnr in the pulmonary vasculature extend beyond the pulmonary venous system, and would like to ensure the pulmonary arteriole expression of Aplnr is not understated.

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