Response to Letter Regarding Article, “The ERG–APLNR Axis Controls Pulmonary Venule Endothelial Proliferation in Pulmonary Veno-Occlusive Disease”

We thank Dr Chun and colleagues for their interest in our recent work, in which we show that homozygous deletion of the Erg or Aplnr gene results in pulmonary veno-occlusive disease in mice.1 In our article, we cited 3 studies demonstrating that Aplnr signaling had direct effects on venous circulation, and we stand by this statement. In the first study, entitled “Venous dilator effect of apelin, an endogenous peptide ligand for the orphan APJ receptor, in conscious rats,” Cheng and colleagues2 showed that in rats, pretreated with mecamylamine to cause ganglionic blockade followed by noradrenaline to restore venomotor tone, apelin caused a dose-dependent decrease in mean circulatory filling pressure despite greater reduction in mean arterial pressure, with the authors concluding that “apelin has a prominent venodilator action” and “is a more efficacious venodilator than verapamil, flunarizine, and nifedipine.” In the second citation, Cox and colleagues3 reported that apelin stimulated outgrowth of endothelial cells from the posterior cardinal vein toward an apelin-impregnated bead in xenopus embryos. We agree that this does not exclude nonvenous cells sprouting in the same vicinity, although none were reported. In the third article, Eyries and colleagues4 studied the role of nonvenous cells sprouting in the same vicinity, although none were reported. In the third article, Eyries and colleagues5 studied the role of apelin in a zebrafish fin amputation model. Although the model is not specific to venous regeneration alone, endothelial cells in regenerated tissue formed a plexus characterized by immature thin-walled vessels that remodeled into new veins and arteries with arteriovenous anastomosis. The results of these articles demonstrate that modulation of apelin or Aplnr signaling had direct effects on venous circulation.

We realize that distinction between small pulmonary arteries and veins in the mouse may be difficult for vessels <200 μm in diameter, given the lack of biomarkers completely specific for each of these structures. Nonetheless, ß-gal–stained vessels in our global and endothelial-specific Aplnrf/f:nlacZ knock-in mice strains had the histological characteristics of veins (thin-walled, absence of medial layer), and stained positive for neuropilin-2 and Ephrin-B4 (vein-specific endothelial markers), as well, and had no staining using antibodies to neuropilin-1 and Ephrin-B2 (arterial-specific endothelial markers). We cannot comment on the finding of pulmonary arteriolar expression of Aplnr in AplnrCreER:RosamTmG mice, as you mention, because this work has not been published. When available, it will be interesting to compare Aplnr expression within all 3 gene knock-out animal models (Aplnr−/−:nlacZ, Aplnrf/f:nlacZ-Fli-1Cre, and AplnrCreER:RosamTmG).

It is well-known that Erg selectively regulates different genes depending on gestational age, cell type, organ specificity, and type of organism. Our findings that Erg selectively upregulates Aplnr in pulmonary venous endothelium, while not inducing genes specific to arterial endothelium or other cell types in veins, is itself a novel finding. Finally, within the adult mouse lung, the pattern of Erg and Aplnr expression is not disparate. Rather, Erg and Aplnr expression are tightly linked temporally and spatially to pulmonary venous endothelial cells during embryonic development and in the adult mouse. The fact that Erg is also seen in arterial endothelium within the adult lung simply suggests that it may control different genes and have other functions in cell types other than venous endothelium.

Disclosures

None.

References

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*Circulation*. 2015;132:e17
doi: 10.1161/CIRCULATIONAHA.114.014783

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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