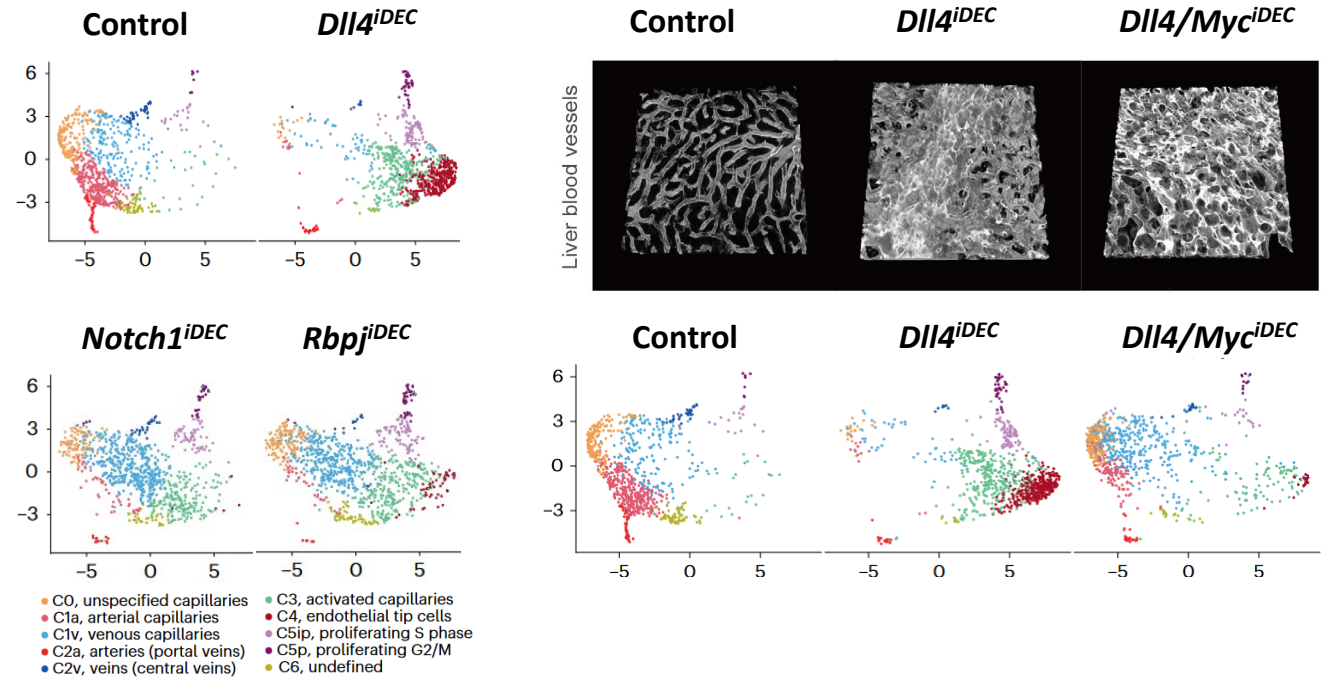
Incongruence between transcriptional and vascular pathophysiological cell states

Fernández-Chacón M, Mühleder S, Regano A, Garcia-Ortega L, Rocha SF, Torroja C, Sanchez-Muñoz MS, Lytvyn M, , Casquero-Garcia V, De Andrés-Laguillo M, Muhl L, Orlich MM, Gaengel K, Camafeita E, Vazquez J, Benguría A, Iruela-Arispe ML, Dopazo A, Sánchez-Cabo F, Carter H, Benedito R.

Nat Cardiovasc Res (2023). May 29 doi: 10.1038/s44161-023-00272-4



Key findings:

- Genetic deletion or blocking antibodies against the ligand Dll4 do not phenocopy the deletion or blockade of Notch receptors.
- Loss of Dll4 triggers a milder loss of Notch signalling that results in a Myc-driven transcriptional switch toward cell proliferation and sprouting and major liver vascular abnormalization and pathology.
- Loss of Notch receptors or Rbpj leads to a greater loss of Notch signalling, which drives hypermitogenic cell-cycle arrest and senescence of ECs without a major impact on liver vascular architecture or pathology.
- Genetic deletion of Myc prevents the appearance of angiogenic transcriptional states, such as states related to cell proliferation or tip cells, but does not prevent vascular abnormalization.
- Inhibition of MAPK/mTor/Rac1/NO signalling did not affect the vascular abnormalization induced by Dll4 loss. Only anti-VEGFA treatment prevented it, but without fully suppressing the transcriptional deregulation.
- This study shows significant incongruence between single-cell transcriptional states, vascular phenotypes, and related pathophysiology.
- The vascular structure abnormalization induced by Dll4 blockade correlates with angiogenic states and neoplasms, but is not caused by them.