Seeing Forces in Flow: Label-Free 3D TFM of Endothelial Remodeling in Perfused Microvessels

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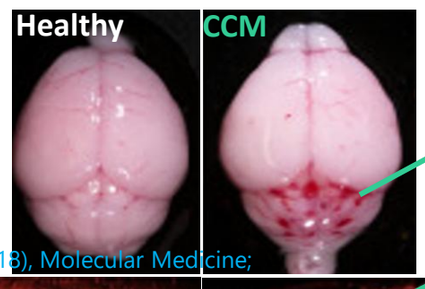
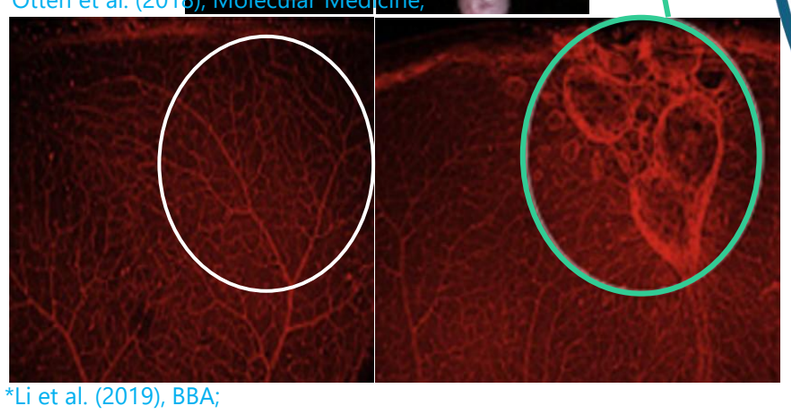
Endothelial remodeling in CCM

- CCM vessels are recognized as dilated, mulberry-like lesions in the low-shear vasculature of the human brain. These mosaic lesions comprise CCM1/2/3-mutant and wild-type endothelial cells.



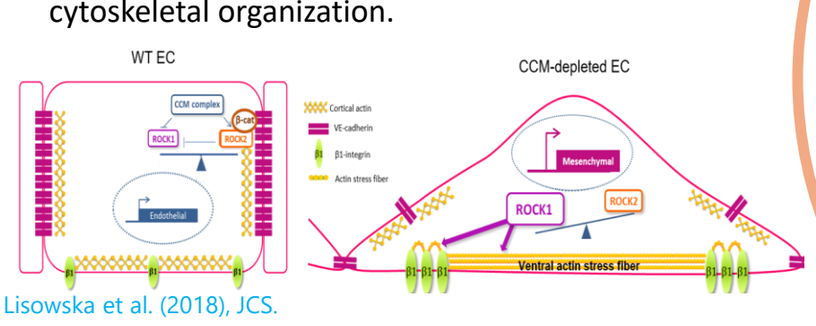
Otten et al. (2018), Molecular Medicine;



*Li et al. (2019), BBA;

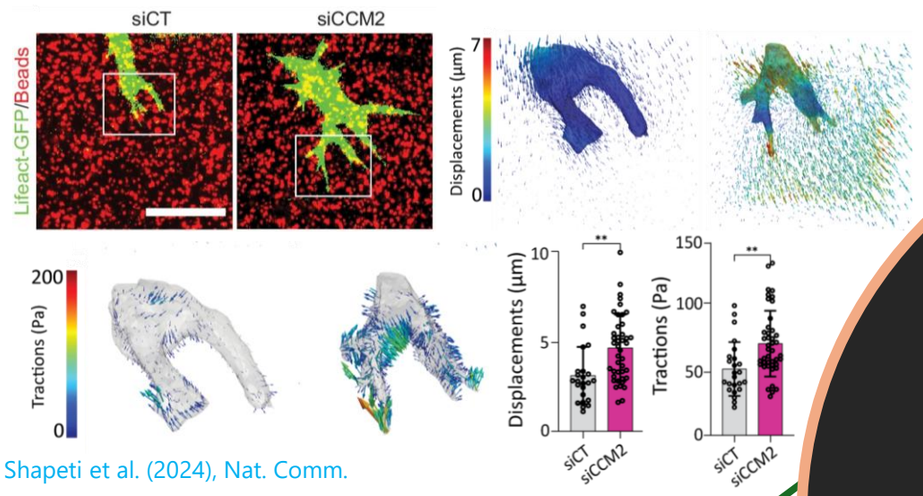
- Healthy ECs respond to fluid shear and ECM stiffness by generating traction forces that enable matrix remodeling and maintain junctional stability.

- Loss of CCM2 disrupts mechanosensing and junctional structure by altering cell contractility and cytoskeletal organization.



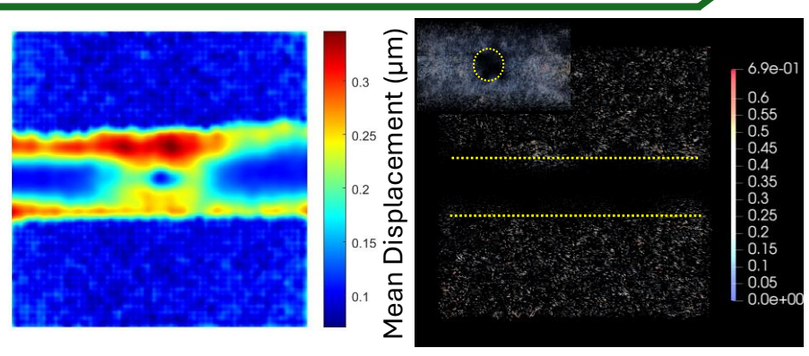
Lisowska et al. (2018), JCS.

- CCM2-silenced cells feature high actin fibers, invade more, and exert high traction forces.

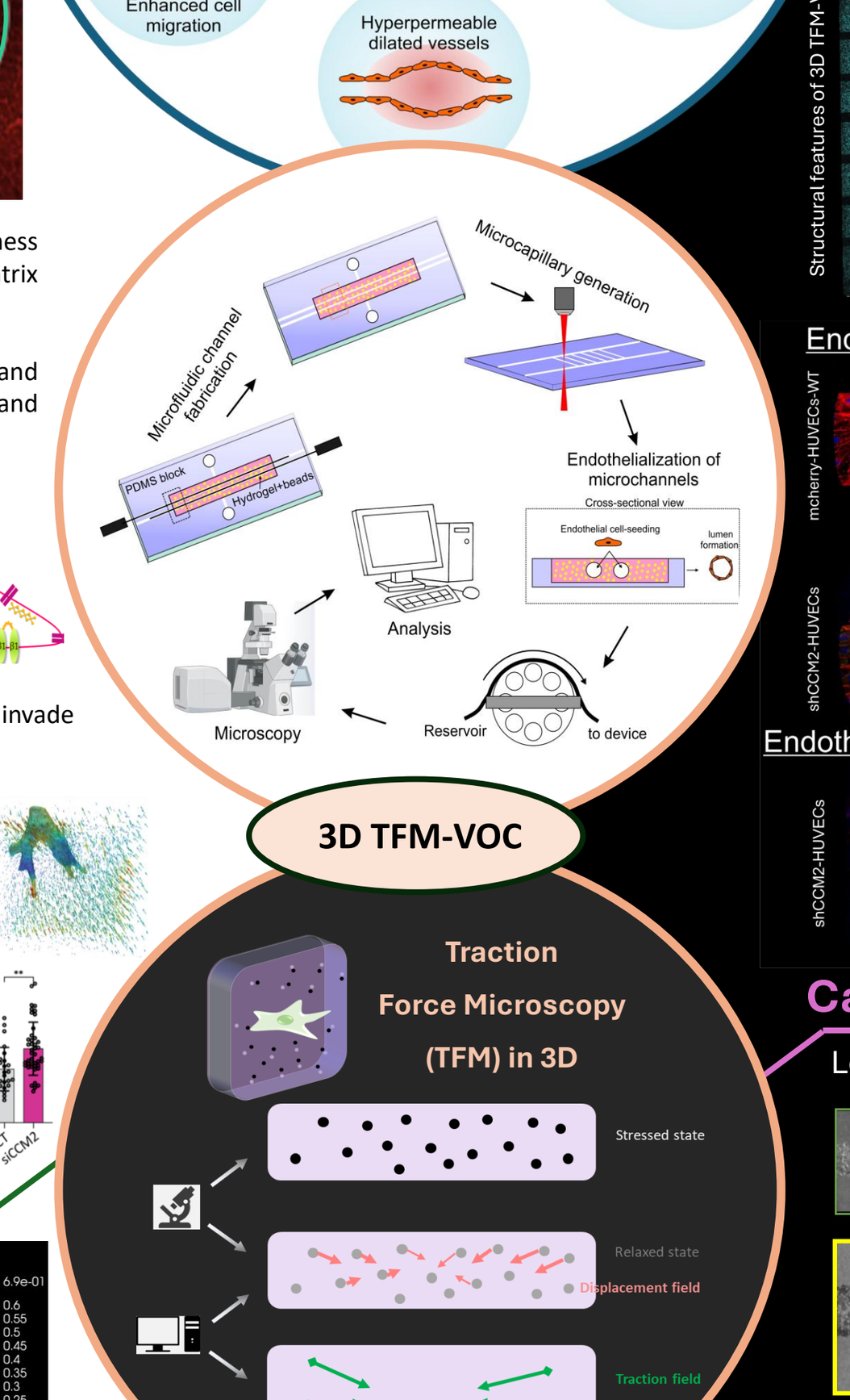


Shapeti et al. (2024), Nat. Comm.

3D TFM under flow



Displacement Measurements around vessels during flow



3D TFM-VOC

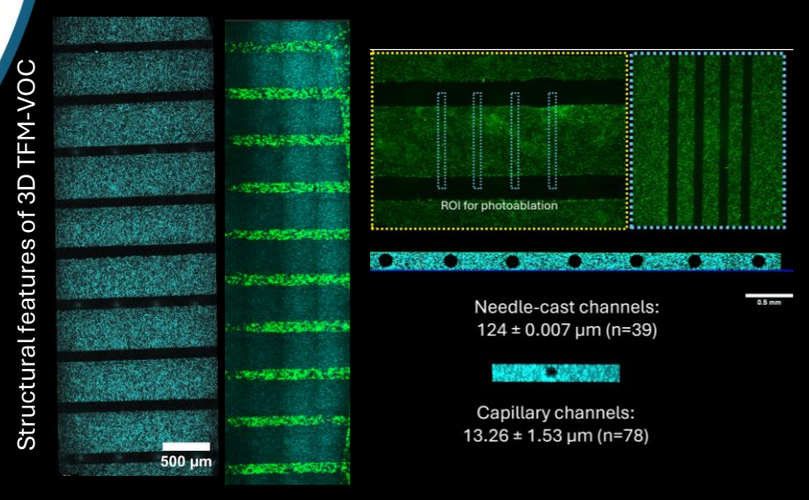
Traction Force Microscopy (TFM) in 3D

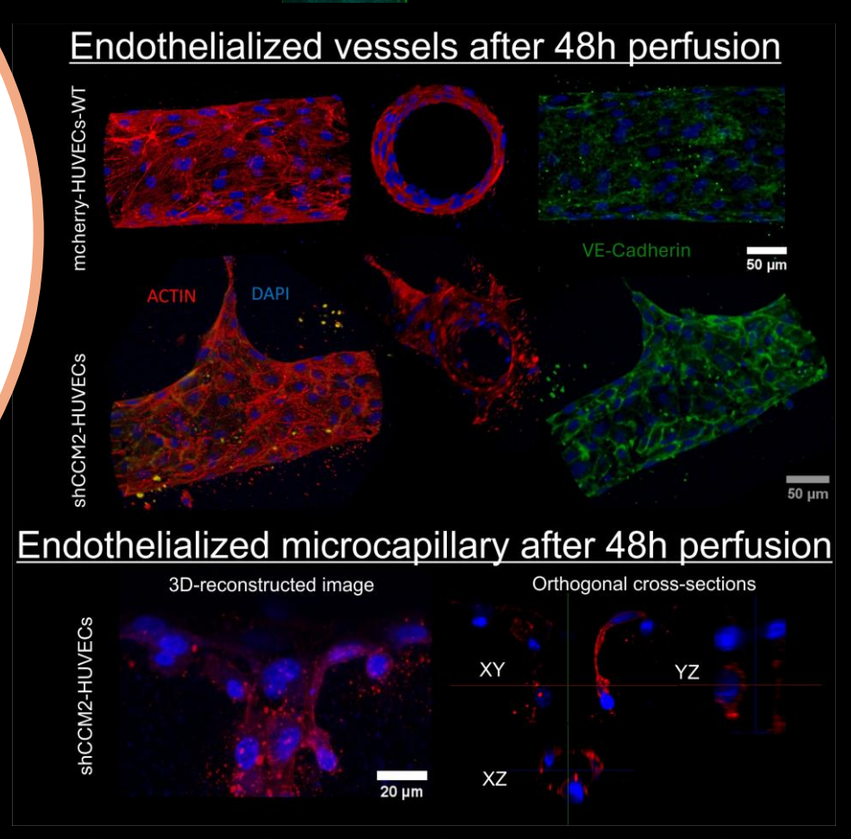
Barrasa-Fano et al. (2021), SoftwareX.

Rationale and model development

- Role of blood flow-generated shear and subsequent endothelial force transmission under physiologically-relevant mechanical cues is of key importance to explore in health and cerebrovascular disease.

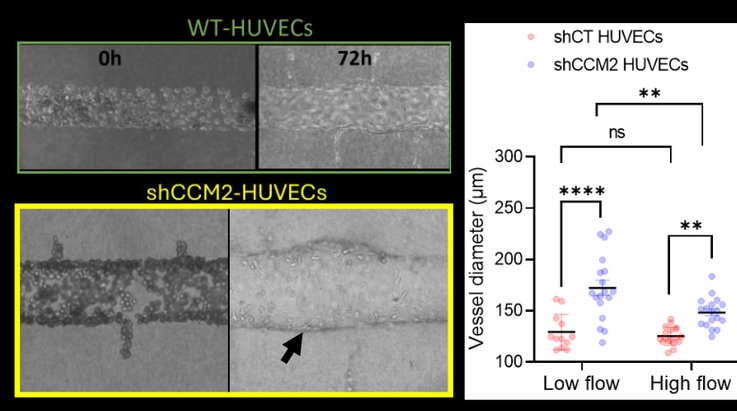
- To assess cellular force exertion by mutant endothelial cells during ECM invasion, the present research aims to develop a 3D Traction Force Microscopy - compatible vessel-on-a-chip (3D TFM-VOC) .



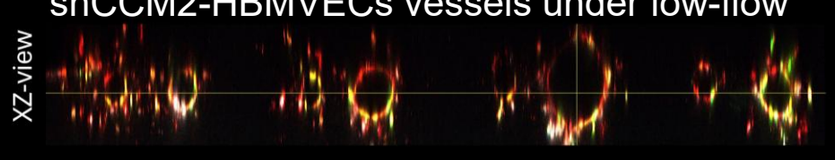


Capturing hallmarks of CCM

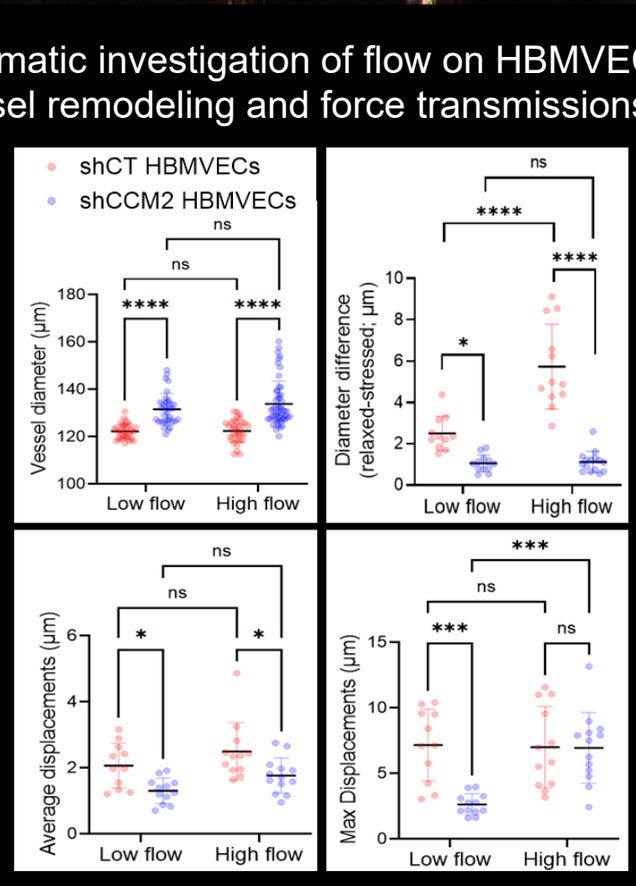
Low-flow mediates shCCM2-vessel dilation



shCCM2-HBMVECs vessels under low-flow



Systematic investigation of flow on HBMVECs vessel remodeling and force transmissions



Conclusion & Future Scope

- The microfluidic chips allow probing cell suspensions, flow rate modulation, and study of biophysical vascular transport processes, including barrier functions, with precise spatiotemporal control

- Control vessels generated inward radial displacements in the surrounding collagen matrix, indicating mechanical coupling between the endothelial monolayer and ECM under flow.

- CCM2-deficient vessels exhibited increased vessel diameter compared with controls and reduced average displacements under flow conditions. These findings suggest that CCM2 loss alters endothelial force transmission to the surrounding matrix in a flow-dependent manner.

- This model paves the path for further exploration of the dysfunctional mechanobiology in CCM2-affected vessels

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