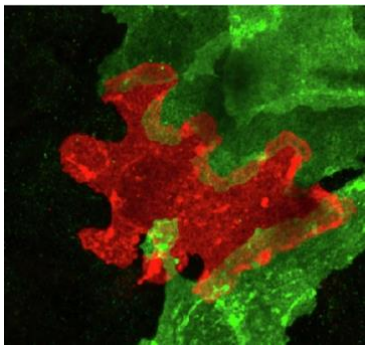
March 2025 EVBO Paper of the month

Hans Schoofs, Nina Daubel, Sarah Schnabellehner, Max L. B. Grönloh, Sebastián Palacios Martínez, Aleksi Halme, Amanda M. Marks, Marie Jeansson, Sara Barcos, Cord Brakebusch, Rui Benedito, Britta Engelhardt, Dietmar Vestweber, Konstantin Gaengel, Fabian Linsenmeier, Sebastian Schürmann, Pipsa Saharinen, Jaap D. van Buul, Oliver Friedrich, Richard S. Smith, Mateusz Majda and Taija Mäkinen.

Dynamic cytoskeletal regulation of cell shape supports resilience of lymphatic endothelium

Nature (2025). https://doi.org/10.1038/s41586-025-08724-6

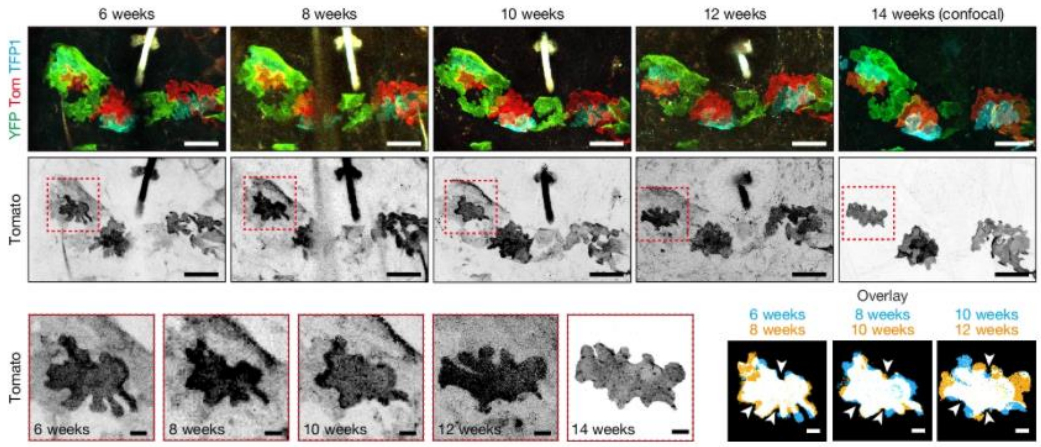


Mosaic labelling highlights the intercellular overlaps between LECs

The lymphatic vasculature is responsible for the uptake of interstitial fluid, immune cell trafficking and lipid absorption in the gut. Uptake of extravasated fluid is mediated by so called lymphatic capillaries. These blunt ended vessels have discontinuous junctions, and lack structural support by mural cells or a thick basement membrane. Yet, lymphatic capillaries must stay open under high interstitial fluid pressure and dynamically adjust their caliper in response to fluid alterations.

The study by Schoofs, Daubel *et al* from the lab of Taija Mäkinen made use of whole mount imaging techniques, intravital microscopy, mathematical modeling and in vitro mechanical assays to identify the mechanisms underlying the resilience of lymphatic capillaries. Using genetic reporters, immunohistochemistry and classical histology approaches to investigate junctional morphology in lymphatic endothelial cells (LECs) revealed not only classical button junctions, but also highlighted a broader spectrum of junctional organizations – suggesting dynamic junctional remodeling. To observe the remodeling events in LECs, they made use of a multicolour labelling strategy, enabling the visualization of individual LEC in distinct colours. This approach highlighted the unique oak-leaf LEC cell shape and revealed that cellular overlaps between neighbouring LECs shrink in response to increased fluid volume. Moreover, intravital imaging of individual dermal LECs over several hours and weeks revealed that LECs continuously remodel their lobular interfaces, resulting in drastic cell shape changes even during homeostasis. These dynamics were driven by actin remodeling as LEC-specific deletion of the RhoGTPase CDC42 led to loss of capillary LEC shape and monolayer integrity, ultimately leading to reduced lymphatic function. Interestingly, the intriguing oak leaf-shaped morphology is not unique to LECs, but also found in plant epidermal cells, called puzzle cells, which cover the outermost layer of leaves. Mathematical modeling of a virtual lymphatic vessel showed that the unique lobate shape, like in plants, aids in providing structural support. The authors next evaluated what triggers LECs to adopt such a lobate shape and found that subjecting cultured LECs to isotropic stretch could promote several aspects of capillary LECs observed in vivo. Specifically, the cells showed increase in the curvature of cell-cell contacts and cellular overlaps. Interestingly, this response was dependent on CDC42, as inhibition or silencing of the protein disrupted monolayer integrity, like in vivo.

Taken together, the study shows, for the first time, the dynamic remodeling continuously occurring in lymphatic capillaries as they respond to fluid alterations, and sheds light on the mechanisms that ensure resilience and stability of the LEC monolayer.



Longitudinal intravital imaging of individual LECs shows the extensive remodeling of their cell shape during homeostasis