Sprouting angiogenesis relies on tip cell pulling forces

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Acto-myosin generated cellular forces are indispensable for angiogenesis, the formation of new blood vessels from preexisting ones. Up till now, one has speculated whether angiogenic sprout progression relies more on pulling forces exerted by tip cells, pushing forces originating from stalk cells, or both. Here, we provide evidence for the dominating role of pulling forces during early events of sprout progression. We adapted an in vitro model of endothelial cell invasion to make it compatible with 4D traction force microscopy. Detailed, spatially and temporally resolved matrix displacement fields were acquired around angiogenic sprouts that were invading in collagen hydrogels [1]. Matrix displacement patterns were consistent among a variety of sprout morphologies and suggested sprout mechanical activity that resembled that of a force dipole, with pulling forces concentrated at the sprout tip and base. Forces were estimated using a computational model of collagen mechanics and tip cell pulling forces were found to be of the order of only a few nN. We then zoomed in on single sprout protrusions to further unravel the nature of cell-matrix forces and found that extending protrusions were mainly building up pulling forces, while retracting protrusions were releasing pulling forces. Together, these data underline the importance of tip cell pulling for angiogenic sprout progression.

[1] Jorge Peñas et al., Biomaterials 136, 86 (2017)