Have you seen?

Jostling for position in angiogenic sprouts: continuous rearrangement of cells explained by differential adhesion dynamics

Colin K Choi1,2 & Christopher S Chen1,2

Endothelial sprouting during angiogenesis is a highly coordinated morphogenetic process that involves polarized tip cells leading stalk cells to form new capillaries. While tip and stalk cells previously were thought to be stable and have static phenotypes within the sprout, it is becoming increasingly clear that endothelial cells undergo dynamic rearrangements. A new study using computer simulations, validated by in vitro and in vivo experimental data, now provides an explanation for these rearrangements, showing that sprouting cells are in a continuum of migratory states, regulated by differential cell-cell adhesions and protrusive activities to drive proper vascular organization.

See also: K Bentley et al (May 2014)

During angiogenesis, gradients of proangiogenic cues such as vascular endothelial growth factor (VEGF) induce a subset of endothelial cells to polarize and become tips cells, and lateral inhibition via delta-like 4 (Dll4)-Notch signaling converts neighboring cells to stalk cells and leads to differential VEGF receptor (VEGFR) expression in the sprout (Hellstrom et al., 2007; Lobov et al., 2007; Potente et al., 2011). Surprisingly, recent studies have found that tip and stalk cells change positions frequently during sprouting, revealing dynamic changes in Notch activity, tip–stalk fates, and cell motility within developing blood vessels (Bentley et al., 2009; Jakobsson et al., 2010; Arima et al., 2011). However, the mechanisms by which individual cells compete for positions remained unclear. Using an elegant, interdisciplinary approach that combined computer simulations with in vitro and in vivo experimental validations, Bentley et al now report in the journal Nature Cell Biology two cooperating mechanisms responsible for generating these endothelial rearrangements (Bentley et al., 2014). The authors show a feedback system between VEGF and Notch signaling that regulates vascular endothelial (VE)-cadherin to generate spatial differentials in cell-cell adhesions and polarized junctional protrusions. Both (adhesions and protrusions) in turn cooperated to change the local integrity of vessels, facilitate cellular intercalation and lengthening of the stalk, and enable endothelial cells to compete for the tip cell position (Fig 1).

A recent study reported that VE-cadherin was necessary for cellular organization during anastomosis, indicating a key role of cell-cell junctions in physically rearranging endothelial cells (Lenard et al., 2013). Differential adhesion via adherens junctions is well recognized in epithelial systems, but additional mechanisms involving cortical reorganization by Dia and myosin-II have also been reported (Levayer et al., 2011). To examine whether the endothelial rearrangements during angiogenic sprouting might be regulated by either differential adhesions or junctional-cortex-mediated processes, the authors tested these mechanisms in silico. Differential VE-cadherin engagement and cell-cell adhesion strengths, regulated by Notch and VEGF-2 activities, predicted that cells with high level of VEGF-2 (and low level of Notch signaling) will have weak adhesion with neighboring cells. Separately, modulations in notch activity between cells predicted serrated VE-cadherin junctions and differentially polarized cortical protrusions that will facilitate cell movements within the sprout. Testing the contribution of these two mechanisms to endothelial cell rearrangement, the authors found that the computational model matched the in vitro observations of cellular rearrangement and tip cell competition (Jakobsson et al., 2010) only when both differential adhesions and protrusions were present in the model. That is, the simulations predicted that spatial differentials in both VE-cadherin-mediated junctional adhesion strength and protrusions are required for dynamic cellular shuffling and intercalation, and when all cells either have high or weak adhesion/protrusions (tested with DAPT, high VEGF, and Dll4 or VEGFR antibody blocking), proper tip cell selection and endothelial cell rearrangement are inhibited.

Experimental studies further validated these predictions, in which embryoid body and mouse retina assays showed that endothelial junctions within sprouts exhibit a range of VE-cadherin organization. Relatively straight and immobile VE-cadherin boundaries correlated with “inhibited junctions” of high cell-cell adhesion and low protrusive activity, whereas serrated boundaries with endocytic VE-cadherin

1 Wyss Institute for Biologically Inspired Engineering, Harvard University, Boston, MA, USA
2 Department of Biomedical Engineering, Boston University, Boston, MA, USA E-mail: chencs@bu.edu
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vesicles and higher Dll4 presence correlated with “active junctions” of low adhesion and high protrusion. Furthermore, pathologically high VEGF conditions, such as occurs in glioblastoma and diabetic retinopathy, led to clusters of all-or-none VE-cadherin-mediated junction activities that resulted in minimal cellular rearrangements. Thus, the spatial control and fine-tuning of vessel permeability at the individual cell level, induced by VEGF, appears to be critical to normal sprouting (Siekmann et al, 2013).

The implications of this study extend beyond the boundaries of angiogenesis, suggesting both a fundamental mechanism responsible for dynamic rearrangements among cells as well as the importance of such rearrangements in executing multicellular morphogenetic programs. It is easy to imagine how additional variations on these themes could lead to the emergence of other tissue structures. The comprehensive interdisciplinary approach utilized in this study provides a powerful platform for future investigation.

Conflict of interest
The authors declare that they have no conflict of interest.

References