In This Issue

Two ways VEGF-A builds a vessel

On page 1163, Gerhardt et al. present a mechanism to explain the function of VEGF in angiogenesis. Their findings implicate a specialized cell at the tips of vessels in guiding the growth of new sprouts, with cell mass provided by the division of different cells that lie further back.

The authors examined angiogenesis in mice retina. Retinal vessels grow by circular expansion and are thus convenient for examining newly sprouting vessels. Past images have suggested that the ends of growing vessels harbor an unusual tip structure. In this article, the authors show that this highly polarized tip cell is specialized to respond uniquely to VEGF-A isoforms. Tip cells extended long filopodia that followed along tracks of astrocyte cells. The filopodia used the VEGFR2 receptor to sense a gradient of VEGF-A, which is secreted by the astrocytes and thus guides the tip cells’ migration. Loss of the gradient, as found in knock-out mice that have only a uniformly expressed VEGF-A isoform, disturbed filopodial polarity. Misexpression of VEGF-A caused ectopic filopodial sprouting in transgenic mice.

Stalk cells (those growing behind the tip cells) also responded to VEGF-A isoforms. However, stalk cells were responsive to absolute concentrations of the growth factor, not gradients, and reacted by proliferating. In contrast, tip cells were non-proliferative and appear specialized for guidance and migration. The filopodia also express integrins, which could help to pull the cells along the matrix, perhaps by binding fibronectin, which is deposited by astrocytes. The authors have found similar tip cells throughout the developing central nervous system. Tumor vessels also have tip cells, but show signs of filopodial misguidance resembling transgenic mice overexpressing VEGF. That a specific pattern of VEGF deposition is required for vessel growth will present a challenge for those attempting to elicit angiogenesis for therapeutic purposes.

Catastrophe under pressure

Microtubules are geometry-sensing polymers that self-destruct under pressure, according to results on page 1029.

In the article, Janson et al. use an in vitro assay to show that force on microtubules leads to microtubule shortening. The group measured the time required for microtubules to reach catastrophe, the point at which growing polymers start to shorten. Microtubules that contacted a synthetic barrier experienced forces that hastened catastrophe. Stronger forces had increasingly larger effects on growth velocity, by lowering the rate of tubulin addition. The relationship between growth velocity and the time until catastrophe was the same in the presence or absence of force. Thus, force’s only contribution to shortening is to decrease growth velocity. A delay before addition of the next tubulin dimer could provide more time for structural changes (perhaps altered connections between protofilaments, for example) that might lead to catastrophe.

By sensing force, microtubules can respond to changes in cell shape. For instance, in fission yeast, the nucleus sits in the middle of the cell. Instability as microtubules contact the edges of cells may create the space necessary for nuclear repositioning; otherwise, the nucleus might get stuck somewhere in a corner of the cell. Forces exerted by centrosomes, kinetochores, or molecular motors may similarly affect microtubule dynamics during cell division. That microtubules themselves sense and respond to forces means no localized catastrophe-promoting factors are required. However, microtubules that persist for long periods of time, such as those at the kinetochore, may require stabilizing factors on their growing ends to resist force-induced catastrophes.