

Math connects vascular network to the universe

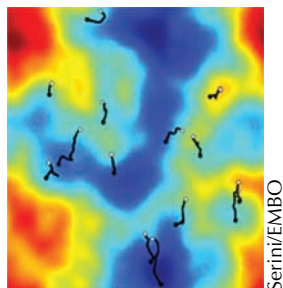
Endothelial cells (ECs) plated on a surface of Matrigel, a basement membrane matrix, spontaneously form a capillary network that is very similar to capillary beds formed in vivo. Now, Guido Serini, Federico Bussolino (University of Torino, Torino, Italy), Davide Ambrosi, Andrea Gamba (Polytechnic of Torino, Torino, Italy) and colleagues have used a combination of mathematical modeling and in vitro experiments to demonstrate that the key parameters in the pattern formation are the density of ECs and the biochemical properties of the chemoattractant.

The group found that if they disrupted either variable in the cell culture system then the capillary network formed was aberrant. For example, with fewer than 100 cells/mm², the cells form a continuous network, but more than 200 cells/mm² led to a Swiss cheese-like mat. And when the researchers swamped out the natural VEGF-A

chemoattractant gradient, which forms as a result of secretion from the ECs, the cells fail to aggregate.

All of the results could be accurately modeled using a non-linear diffusion equation, called the adhesion model, which implies that the behavior of ECs and the pattern follow simple mathematical laws. And by combining the two approaches, the group was able to define specific characteristics about the chemoattractant, such as its diffusion coefficient, that they otherwise would not have known. But perhaps most exciting, says Bussolino, is that the same type of equation can be used to describe the formation of many patterns in nature such as bacterial colony formation and *Dictyostelium* morphogenesis—and, oddly enough, the events that occurred just after the big bang that gave rise to the universe. ■

Reference: Serini, G., et al. 2003. *EMBO J.* 22:1771–1779.

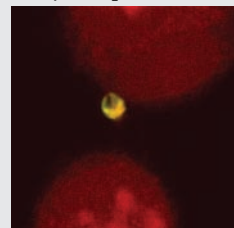


Endothelial cells move toward increasing concentrations (blue to red) of VEGF-A.

Serini/EMBO

Turning RacGAP into a RhoGAP

We already knew the players—MgcRacGAP, Aurora B, and RhoA—and that knocking out any one of them caused failure of cytokinesis; but it wasn't clear how they were connected. Now, it appears that Aurora B phosphorylates the GAP domain of MgcRacGAP, allowing it to turn its GAP activity toward RhoA, according to data from Yukinori Minoshima, Toshiyuki Kawashima, Toshio Kitamura (University of Tokyo, Tokyo, Japan), and colleagues.



Minoshima/Elsevier

MgcRacGAP and RhoA colocalize at the midbody during cytokinesis.

When they first isolated MgcRacGAP, the group found that most of its activity was directed toward Rac1 and Cdc42, but there were hints—although inconsistent ones—that it also had activity toward Rho proteins. In the new work, Kitamura and colleagues found that, late in mitosis, Aurora B, RhoA, and MgcRacGAP congregate at the midbody, where Aurora B phosphorylates a serine in the GAP domain of MgcRacGAP. The phosphorylated GAP protein then stimulates the GTPase activity of RhoA, converting GTP-bound active RhoA to GDP-bound inactive RhoA, and promotes the completion of cytokinesis and cell division. Overexpression of a phosphorylation-deficient mutant of MgcRacGAP blocks RhoA activity and results in polyploid cells.

“This is the first demonstration that a modification of a GAP changes its target specificity,” says Kitamura. “Biologically the interesting thing is that in the beginning of cell division MgcRacGAP probably works through Rac1 and Cdc42, which function in mitotic spindle formation. Then during the late stage of cell division and cytokinesis, MgcRacGAP converts itself to a RhoGAP and exerts itself through RhoA.” ■

Reference: Minoshima, Y., et al. 2003. *Dev. Cell.* 4:549–560.

Crml locks up replication factors

Limiting replication to a single round per division is critical for cells, but the proteins that control the process in metazoans have remained obscure. Now, Ryuji Yamaguchi and John Newport (University of California, San Diego, CA) find that Crm1 sequesters MCM helicase in the nucleus, preventing it from binding to the chromatin where it would initiate a new round of DNA synthesis.

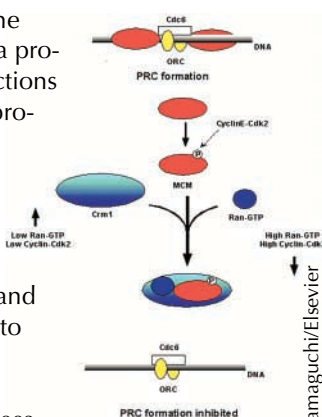
Working in *Xenopus* egg extracts, the team found that, although the prevention of rereplication is dependent on high concentrations of Ran-GTP and Cdk2 kinase activity, it does not require nuclear export of MCM. That means that Crm1 may have a new mechanism of action, since all of its previously known functions involved nuclear transport.

“We think this makes sense,” says Newport, “because it is an extremely rapid mechanism for inactivating MCM.” If the repression required transporting MCM out of the nucleus, the process would be considerably slower and more mistakes would occur in a process that can't tolerate errors.

The target of Cdk2 in the system is not yet clear, but the group thinks it may be MCM itself.

Given the observation that the inhibition requires Ran-GTP, a protein known to stabilize interactions between Crm1 and its target proteins, the authors hypothesize that Crm1, the phosphorylated MCM protein, and Ran-GTP form a heterotrimeric complex. But, says Newport, this is still a work in progress and it will take more experiments to unveil just how Crm1 blocks MCM activity. ■

Reference: Yamaguchi, R., et al. 2003. *Cell.* 113:115–125.



Yamaguchi/Elsevier

Crml in the cell cycle.