Branching out requires VEGF

Not all isoforms are created equal. New results from Christiana Ruhrberg, David Shima (Cancer Research UK, London, UK), and colleagues reveal that the stickiness of vascular endothelial growth factor (VEGF) can make all the difference between blood vessels growing larger or finding new territory.

VEGF initiates the formation and expansion of the vascular system. VEGF isoforms differ in their ability to bind to the extracellular matrix (ECM), but, in vitro, endothelial cell proliferation is stimulated by VEGF regardless of its ECM-binding ability.

In the new study, Shima’s group examined mice engineered to make only single VEGF isoforms. These mice reveal that VEGF isoforms have opposing effects on growing vessel networks. Although all forms stimulated cell growth in vivo, mice that expressed only soluble VEGF had expanded microvessels with fewer branches. In contrast, microvessels in mice with only ECM-binding VEGF were narrow and branched excessively.

“Our results indicate that growth is integrated with tissues, because the tissue provides localized cues by depositing VEGF in precise spatial patterns,” says Ruhrberg. The road map is provided by ECM-bound VEGF, which attracted filopodia extending from the tip of a new vessel branch. Soluble VEGF did not remain where it was secreted, but rather traveled further away, thus stimulating expansion of existing vessels from a distance. The authors hope to raise awareness of isoform-specific effects for those considering the use of VEGF for therapy to increase or block angiogenesis.

Reference: Ruhrberg, C., et al. 2002. Genes Dev. 16:2684–2698.

An amidation a day keeps apoptosis away

Rapidly dividing cells such as tumor cells are susceptible to DNA damage that then induces apoptosis. As a result, DNA-damaging chemicals such as cisplatin are used as anticancer treatments. How the majority of nontumor cells survive chemotherapy has been mysterious. The trivial explanation is that the cells are growth-arrested and thus less susceptible to DNA-damaging agents. But a more precise explanation is put forth in a new article by Benjamin Deverman, Steven Weintraub (Washington University, St. Louis, MO), and colleagues, who have identified an antiapoptotic activity necessary to keep damaged but nondividing cells alive.

The proapoptotic activity that allows tumor cells to die is an unusual modification of the antiapoptotic protein Bcl-xL caused by DNA-damaging agents. This modification, deamidation of two asparagine residues, inactivated Bcl-xL, thereby allowing cell death to proceed. Growth-arrested cells escaped apoptosis by blocking deamidation. To prevent deamidation, cells needed Rb, a tumor suppressor protein that inhibits cell cycle progression. Because tumor cells lack Rb, and cycling cells down-regulate Rb, they are more sensitive to DNA-damaging agents. “Deamidation is like a checkpoint,” says Weintraub. “If you undergo DNA damage in the absence of Rb, then cells are susceptible to death.”

Reference: Deverman, B., et al. 2002. Cell. 111:51–62.

Arrested cells are Mad as Hec

The spindle checkpoint works even when on the move, according to new results from Silvia Martin-Lluesma, Volker Stucke, and Erich Nigg (Max-Planck Institute of Biochemistry, Martinsried, Germany). Against all that has been sacred in the field, these researchers find that mitosis can be arrested when checkpoint proteins leave the kinetochore.

The checkpoint is activated by Mad1 and Mad2 proteins, which bind to kinetochores that are not attached to the spindle microtubules. The prevailing theory has been that release of Mad1/Mad2 inactivates the checkpoint and allows mitosis to proceed.

Nigg and colleagues looked for human Mad1-interacting proteins and found Hec1, which recruited Mad1 and Mad2 to kinetochores. Given this function, the group was surprised to find that reducing Hec1 prevented cells from dividing, despite the fact that Mad1/Mad2 were not on the kinetochores. “This is different from all that has been shown so far,” says Stucke. “The components are depleted [from kinetochores], but you still get arrest and an active checkpoint.” Hec1-depleted cells that also lacked Mad2 continued through mitosis and ended in mitotic catastrophe. Thus, checkpoint components can signal from the cytoplasm.

According to one model of Mad function, the Mad proteins make a brief visit to kinetochores to sample the environment, but then propagate their inhibitory signal in the cytoplasm. Hec1 may regulate this process, but for now the details of Hec1 action remain obscure.

Reference: Martin-Lluesma, S., et al. 2002. Science. 297:226–270.