In This Issue

A lean and mean VEGF for cancer cells

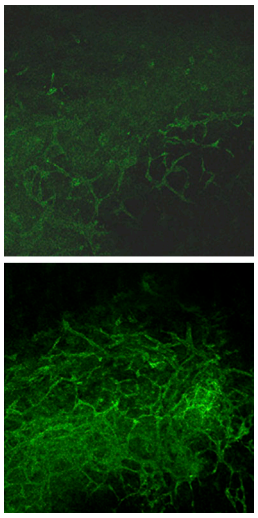
Cells that suffer DNA damage start pumping out a previously undiscovered version of the angiogenesis promoter VEGF, as Mineur et al. report. The variant, which is tough and mobile, might help cancer cells tap new sources of blood.

Researchers have already nabbed about 10 versions of VEGF, which many cancer cells overproduce to feed their need for blood. Mineur et al. were studying the effects of UV light on cells when they stumbled across another variant that lacks three of the eight standard VEGF exons. The new version, which the researchers dubbed VEGF111, forms in cells exposed to UV radiation or DNA-breaking compounds such as camptothecin. Those results suggest that the VEGF111 results from DNA damage.

VEGF111 is short but sturdy; it lacks the region that's vulnerable to protein-slicing enzymes such as plasmin, making it harder to break down. The variant is also missing the VEGF section that interacts with the extracellular matrix (ECM). That loss might boost VEGF111's mobility because it wouldn't get snared as it diffuses through the ECM.

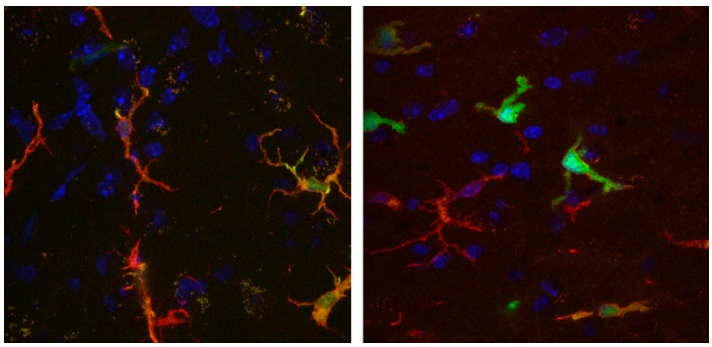
The researchers didn't detect the new variant in cells from healthy mice and people, or in animals dosed with UV light or camptothecin, perhaps because the variant is rare. But tumor cells transplanted into mice that received camptothecin did manufacture VEGF111. To gauge the molecule's effects on angiogenesis, the team injected mice with tumor cells that fashioned one of three VEGF versions, including VEGF111. All three types of the growth factor spurred formation of new blood vessels. These vessels covered the tumors that made the two other VEGF isoforms, but they sprouted a short distance away from growths that produced VEGF111. The reason for this difference isn't clear.

Because it's durable and forms in response to DNA damage, such as that caused by chemotherapy, VEGF111 could be a formidable foe. It might help cancer cells resist drugs, for instance. On the other hand, the molecule could spur new treatments for conditions in which angiogenesis is desperately needed, such as heart attacks and nonhealing wounds. JCB



More blood vessels sprout on cell clusters that fashion VEGF111 (bottom).

Reference: Mineur, P., et al. 2007. *J. Cell Biol.* 179:1261–1273.



In two strains of mice with SOD1 mutations, the brain teems with microglia from the bone marrow (yellow).

Microglia to the rescue

Immune cells fight a losing battle against a harmful abnormal protein found in some cases of amyotrophic lateral sclerosis (ALS), as Kang and Rivest report. The findings support the hypothesis that extracellular accumulations of faulty proteins trigger the disease's neural damage.

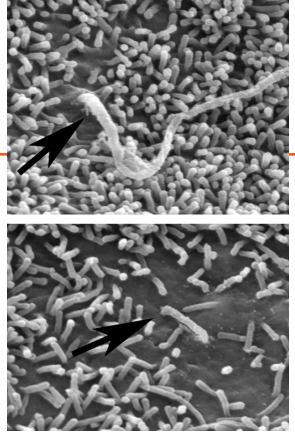
Researchers aren't sure why muscle-controlling motor neurons deteriorate in ALS. Patients with the inherited form of the disease carry mutations in the gene for the antioxidant enzyme SOD1. But how defective SOD1 causes neurodegeneration remains uncertain. One possibility is that the altered SOD1 builds up outside neurons and eventually kills them. Several studies suggest that some neighboring cells can shield neurons from the protein's ill effects. Kang and Rivest tested whether microglia, the main infection-combating cells in the brain, were protective.

The researchers transplanted bone marrow with labeled cells into two mouse strains that manufacture different forms of mutant human SOD1. In both strains, the cells swarmed from the marrow to the brain, presumably to attack the SOD1. Injecting defective SOD1 into the brains of normal animals also drew a crowd of microglia. The team found that SOD1 activated microglia, but not if the cells lacked an adapter protein called MyD88.

To probe MyD88's role, the researchers implanted bone marrow lacking the protein into mice from the two strains. In one strain, MyD88-deficiency caused the animals to develop symptoms sooner and to die nearly two months earlier. In the other stain, however, losing MyD88 signaling had no effect on survival. It's possible that the SOD1 variant in this strain kills the animals so quickly that the transplants didn't have time to help.

The study suggests that microglia from the bone marrow protect neurons from toxic buildups of mutant SOD1. But if microglia are on the job, why do the animals still die? The researchers hypothesize that, although microglia can keep faulty SOD1 in check temporarily, the immune system eventually tires, allowing lethal amounts of the protein to accumulate. JCB

Reference: Kang, J., and S. Rivest. 2007. *J. Cell Biol.* 179:1219–1230.



A cell without Par3 (bottom) sports a petite cilium (arrow).

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For long, lush cilia, try Par3

A protein that induces cells to create tight junctions also helps the primary cilium grow, as Sfakianos et al. show. Although the details remain murky, the protein, Par3, helps lengthen the structures by connecting a molecular motor that travels along the cilium to proteins that are embedded in the cilia membrane.

Researchers know that Par3 teams up with three other proteins, but they don't know all of its effects. Some studies suggest that Par3 helps induce adhesive tight junctions between epithelial cells. Other work indicates it sets up cell polarity in neurons by defining the axon. Sfakianos et al. have identified yet another function for Par3.

The team used RNAi to quash the protein. Although cells lacking Par3 still established tight junctions, they took extra time to form. The cells seemed to polarize normally, suggesting that Par3 isn't necessary to complete this process. However, loss of Par3 fouled up construction of the cilium. Normal cells grew lengthy cilia, but cells lacking Par3 could only manage puny filaments.

Par3 hooks up with a molecular motor called Kif3a, which helps haul new cilium building blocks to the growing tip. Without this interaction, cilia were stumpy. But cilia were absent when cells were missing another protein called Crumbs3, which settles in the membrane along the cilium. The team showed that Par3 uses Crumbs3's PDZ-binding domain to maneuver Crumb3 into position. So Par3 might spur cilium elongation by tying the membrane protein to motor proteins that slide along the cilium. The next step for the researchers is to determine how these links guide fresh components to the end of the cilium. JCB

Reference: Sfakianos, J., et al. 2007. *J. Cell Biol.* 179:1133–1140.

Making room for muscle

A mysterious version of the protein calcineurin turns out to be a healer that helps refurbish damaged muscle, as Lara-Pezzi et al. report. The molecule promotes cell division and drives away immune cells that can obstruct repair.

Sparked by rising calcium levels, calcineurin flips on transcription factors that control everything from immune responses to heart development to muscle cell differentiation. The two halves of the protein, CnA and CnB, come in several forms. Scientists discovered a new version of CnA, known as CnAβ1, nearly 20 years ago, but they knew little about its function.

Now, the researchers show that, with CnAβ1, undifferentiated muscle cells divide more quickly and are less likely to specialize. Calcineurin usually exerts its influence by activating the NFAT transcription factors. CnAβ1, however, activated a different signaling pathway and blocked the transcription factor FoxO.

CnAβ1 also sped regrowth of damaged muscle, the team shows. In mice that had received an injection of a muscle-destroying poison, boosting CnAβ1 levels caused an increase in the number of active muscle stem cells and a thickening of regenerating muscle fibers. CnAβ1 also trimmed the number of macrophages at the injury site and limited accumulation of fresh extracellular matrix.

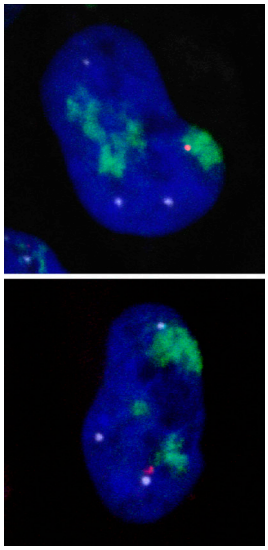
Thus CnAβ1 helps muscle heal by encouraging cell division, calming inflammation, and limiting scarring, leaving more room for new muscle cells. The next question, the scientists say, is whether the variant is important for other fast-dividing cells, such as stem cells and tumor cells. JCB

Reference: Lara-Pezzi, E., et al. 2007. *J. Cell Biol.* 179:1205–1218.

Hey, DNA, get over here

Active genes sidle up to Cajal bodies with help from actin, Dundr et al. report. The study is the first to show directed movement of mammalian genes that are being transcribed.

Interphase chromosomes jiggle, but they usually remain within so-called territories. Particular DNA segments, however, can travel substantial distances. One situation that might involve DNA movement is the liaison between active genes and Cajal bodies, which harbor small nuclear RNAs (snRNAs) for splicing. Cajal bodies often show up near working genes for snRNA and histone proteins, although researchers didn't know whether Cajal bodies form near these genes or whether the partners move toward each other.



A DNA stretch with active genes (red) closes in (top to bottom) on a Cajal body (white).

To find out, Dundr et al. inserted into HeLa cells an artificial chromosome carrying 16 copies of an snRNA gene. The team tracked the positions of the chromosome and Cajal bodies after the genes started transcription. The two components cozied up, the researchers found. The Cajal bodies were sluggish, remaining in roughly the same place. The DNA, by contrast, was responsible for most of the movement, particularly during a final lunge that began around six to seven hours after gene activation. In total, it traveled about two to three microns.

The researchers also found that a tether of RNA linked an active gene to the Cajal body, indicating that the newly made strand was feeding directly into the structure. Disrupting actin, Dundr et al. showed, prevented the movement, suggesting that actin helps haul certain active genes to Cajal bodies. The question of why this movement occurs remains unanswered. JCB

Reference: Dundr, M., et al. 2007. *J. Cell Biol.* 179:1095–1103.