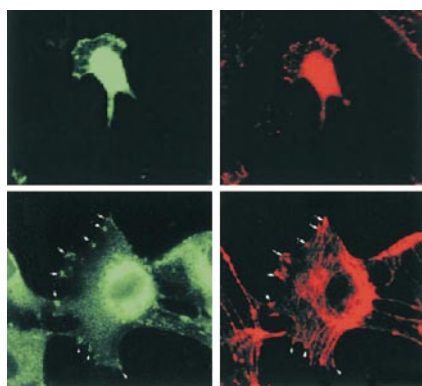


### Angiostatin Antagonizes Angiomotin

Work on angiogenesis inhibitors such as angiostatin has generated a lot of newspaper print, but rather less understanding about just how these molecules work. Now, Troyanovsky et al. report on their discovery of angiomotin, an angiostatin-binding protein that appears to be a target for angiostatin action (page 1247). Angiomotin is not a transmembrane protein, however, and does not appear to act as a traditional signal-transducing receptor for angiostatin.



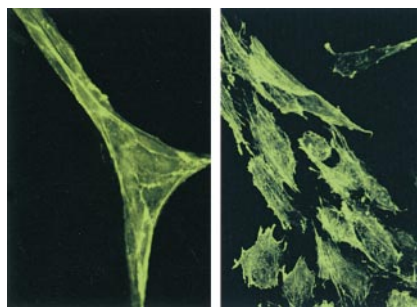
Only cells that contain, or are transfected with, angiomotin show the following responses to angiostatin: the internalization of angiostatin, an increase in FAK kinase activity, a reduction of both background and growth-factor induced migration rates, and an inhibition of tubulogenesis. As discussed in a comment by Zetter (page F35), angiomotin's localization at the leading edge of migrating cells suggests that it is normally involved in migration, and that the binding of angiostatin to angiomotin may disrupt this function. This would interfere with the migrations of endothelial cells involved in the initial clustering step of angiogenesis.

### Endostatin Antagonizes Itself, Trimerized

Endostatin, another angiogenesis inhibitor, is cleaved from the COOH terminus of collagen XVIII (c18). The longer of these cleavage products includes a trimerization motif, and in this issue, Kuo et al. report that

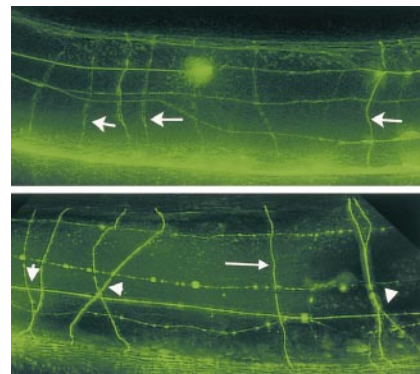
this trimerized form of endostatin (termed the noncollagenous domain 1, or NC1) has promigratory activity that is antagonized by monomeric endostatin (page 1233). Ackley et al. find support for a similar phenomenon in the nervous system of *Caenorhabditis elegans* (page 1219).

Kuo et al. report that addition of c18 NC1 prevents endothelial cells from aggregating into tubules in matrigel, and stimulates migration of cells away from preformed tubules. Similar migration and dissolution events may be necessary to initiate new tubule formation during angiogenesis. Dimerized endostatin domains have the same effects on motility, but endostatin monomers are inactive and can actually inhibit motility induced by c18 NC1.



Ackley et al. perform a similar experiment in worms mutant for CLE-1, the worm homologue of c18. These worms, which lack only the NC1 domain of CLE-1, show defects in cell migration and axon guidance. Although expression of CLE-1 NC1 in the mutant worms rescues these defects, expression of monomeric endostatin does not result in rescue. Instead, it prevents rescue by coexpressed CLE-1 NC1 and causes dominant migration defects in a wild-type background. The presence of c18 in nematodes, which are avascular and have no endothelial cells, indicates that c18 and endostatin are clearly important for functions other than those associated with endothelial cell and angiogenic functions.

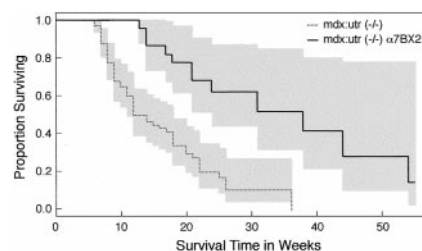
Unlike other scatter factors, NC1 requires the presence of extracellular matrix (ECM) for its in vitro activity. There are two possible explanations for this. NC1 may act by oligomerizing a cell surface receptor, which then



signals to interfere with an adhesive signal from the ECM. Alternatively, NC1 may associate with or oligomerize an ECM component, thus modulating the ECM's ability to stimulate migration via cell surface receptors. An analysis of NC1-binding proteins should allow differentiation between these two models.

### Integrins to the Rescue

Correcting myopathies by gene therapy is a formidable task, given the extent of muscle as a target tissue. Results reported by Burkin et al. (page 1207) suggest an alternative strategy: by increasing the production from an endogenous gene unrelated to the mutated gene, a genetic defect may be at least partially corrected.



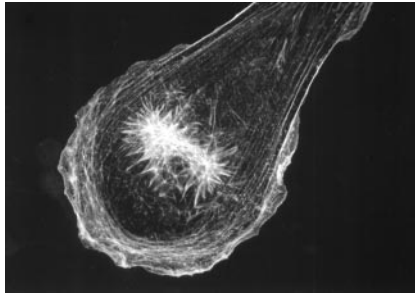
Burkin et al. start with mice that lack both dystrophin and utrophin. Humans with Duchenne muscular dystrophy (DMD) have mutations only in dystrophin, but the doubly mutant mice are the best mimic of this situation, as utrophin tends to substitute for dystrophin function in singly mutant mice. When Burkin et al. use transgenesis to overproduce the  $\alpha 7$  integrin in the muscles of the doubly mutant mice, they find that lifespan increases threefold and there is improvement in other phenotypes asso-

ciated with muscle degeneration. This is consistent with overlapping roles of dystrophin and integrins in connecting extracellular matrix to cytoskeleton. The activity of integrin  $\alpha 7$  at the neuromuscular junction and in calcium homeostasis may also be important.

Based on these results, gene therapy with the smaller, more manageable integrin gene could be considered for treating DMD. However, if a method could be found to increase production from endogenous integrin genes, gene therapy might be avoided altogether.

### ***HMG1 and Atherosclerosis***

HMG1 is a small protein that binds to and bends DNA. But HMG1 is also known as an extracellular mediator of endotoxin lethality and an inducer of neurite outgrowth. Degryse et al. add



to this list on page 1197 with their report on HMG1's ability to induce chemotaxis of rat smooth muscle cells (SMCs) via binding to the receptor for advanced glycation endproducts (RAGE), suggesting a possible connection to atherosclerosis.

SMCs contain little or no HMG1, but they respond to exogenous HMG1 with membrane ruffling, a reduction in the number of stress fibers,

cell polarization, and directed cell migration. Detergent-permeabilized and necrotic cells release sufficient HMG1 to induce these effects. During atherosclerosis, HMG1 may be released from the early macrophage infiltrate and from the damaged and necrotic endothelial cells that flank the SMCs and are rich in HMG1.

Previously, RAGE had been implicated in certain forms of atherosclerosis associated with diabetes. The work of Degryse et al. suggests that HMG1 may be an even more important ligand for this receptor than the advanced glycation endproducts that are produced during hyperglycemia.

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