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In This Issue

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Endothelial cytoskeletal rearrangements and the regulation of blood flow by eNOS (See article on pages 15–24.) Here, Laufs et al. investigate the control of cerebral blood flow, a major determinant of tissue damage during and after ischemic stroke. High blood flow, which can result from the activation of the endothelial NO synthase (eNOS), correlates with smaller infarcted regions following the induction of cerebral ischemia. Conversely, eNOS-/- mice develop unusually large infarcted areas under these conditions. Previously, this group showed that statins, drugs that inhibit biosynthesis of cholesterol precursors, increase blood flow by upregulating eNOS. Now Laufs et al show that the activation of eNOS is neuroprotective after ischemic stroke, and they offer a glimpse into the cellular events, occurring within the endothelium, that govern cerebral blood flow. RhoA activates rearrangement of the actin cytoskeleton, but it requires lipid modification to be localized properly to the plasma membrane. Laufs and coworkers show that treatments that interfere with RhoA function (including statins, which block the lipid modification of RhoA) elevate eNOS expression and help protect the CNS of wild-type mice. These treatments have no such protective effect in eNOS-/- mice. The authors further show that the effect of RhoA blockade on eNOS is strictly post-transcriptional, and they speculate that cytoskeleton-bound eNOS mRNA is specifically destabilized by rearrangement of intracellular stress fibers.Reduced cardiac […]

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By John Ashkenas, Science Editor

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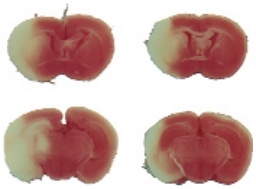
(See article on pages 15–24)



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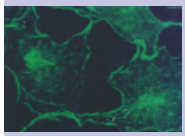
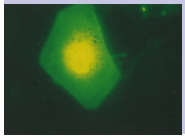
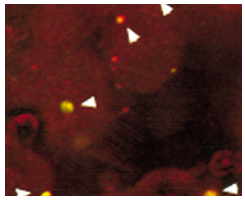




RhoA activates rearrangement of the actin cytoskeleton, but it requires lipid modification to be localized properly to the plasma membrane. Laufs and coworkers show that treatments that interfere with RhoA function (including statins, which block the lipid modification of RhoA) elevate eNOS expression and help protect the CNS of wild-type mice. These treatments have no such protective effect in *eNOS*$^{-/-}$ mice. The authors further show that the effect of RhoA blockade on eNOS is strictly post-transcriptional, and they speculate that cytoskeleton-bound eNOS mRNA is specifically destabilized by rearrangement of intracellular stress fibers.

Reduced cardiac scarring in MMP-9–deficient mice

(See article on pages 55–62)



Healing of injured tissue typically occurs in several stages, beginning with inflammation, in which collagen and other extracellular matrix (ECM) proteins are degraded, and continuing with synthesis and deposition of new tissue and remodeling of the local ECM. Matrix metalloproteinases (MMPs) may act at each of these stages, but precise roles for individual secreted proteinases are only now emerging. Ducharme and colleagues have followed the histological changes in the left ventricle following induced myocardial infarction (MI), comparing MMP-9–deficient mice with their wild-type littermates. The earliest phases of repair occurred normally in *MMP9*$^{-/-}$ mice, but later in the process, collagen deposits were poorly organized and relatively scarce in the absence of the proteinase. Because collagen I mRNA is present at wild-type levels, the authors suggest that collagen turns over more rapidly, perhaps as a result of increased expression of several other MMPs in infarcted hearts of *MMP9*$^{-/-}$ mice. Ducharme et al. suggest that inhibition of MMP-9 might prove useful in preventing scarring after MI.

HSP70 protects the pancreas from proteolytic injury

(See article on pages 81–89)

The exocrine pancreas is the source of trypsinogen and other latent digestive enzymes that can be activated once trypsinogen is cleaved to generate trypsin. The cells of the pancreas are normally protected from injury by maintaining this proenzyme in its uncleaved form. Working with rat pancreas fragments in organ culture, Bhagat et al. show that treatment with the secretogogue cerulein, which can cause pancreatitis in vivo, induces trypsinogen activation and cell damage. They also show that the stress response protein HSP70, a normal cell component that accumulates to high levels during the culture of pancreas fragments, helps protect these cells from secretogogue-induced injury. Antisense oligonucleotides targeted to HSP70 block this protective effect and allow trypsinogen to become colocalized with lysosomal hydrolases, which presumably mediate its activation. The flavonoid drug quercetin specifically inhibits transcriptional induction of HSP70, and it also induces activation of trypsinogen. How HSP70 might influence trypsinogen localization within the cell is not known.