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the hormone relied on the sympathetic nervous system, the branch that pumps out adrenaline during emergencies but at other times emits a hormonal trickle to maintain a low level of stimulation. This baseline activity was lower in mice lacking the leptin receptor, indicating a connection between leptin and the sympathetic nervous system. When that connection was broken by deleting the adrenaline receptor from mice osteoblasts, insulin levels shot up.

The researchers then dosed mice with a sympathetic stimulator. Rodents lacking leptin or the adrenaline receptor on their osteoblasts turned out normal amounts of osteocalcin, but much of it was in an inert form. That result suggests leptin affects insulin release by indirectly inactivating osteocalcin. The work boosts researchers' hopes of using osteocalcin to treat diabetes—a possibility some drug companies have already started to investigate.

Hinoi, E., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200809113.

Matrix fragments trigger fatal excitement

Shredded extracellular matrix (ECM) is toxic to neurons. Chen et al. reveal a new mechanism for how ECM demolition causes brain damage.

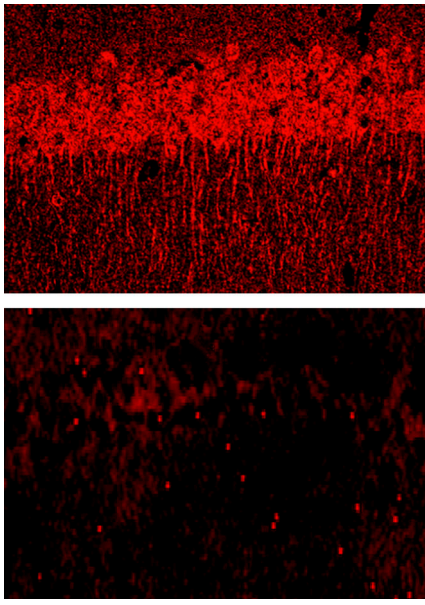
A stroke or head injury kills large numbers of neurons through a process called excitotoxicity. A surge of the neurotransmitter glutamate jolts receptors such as the kainate receptor and stimulates cell death. Enzymes add to the death toll by chopping up ECM near the injury site. How ECM breakdown takes out neurons was mysterious. The standard view was that neurons perished because they got separated from the ECM as it dissolved.

Chen et al. found otherwise when they engineered mice to lack the ECM component laminin in the hippocampus, a brain region often damaged by stroke or injury. If cells languished after parting from the ECM, the researchers reasoned that mice missing laminin would suffer more damage from excitotoxicity. But when excitotoxicity was spurred with an injection of kainate—a molecule that, like glutamate, activates the kainate receptor—the laminin-lacking mice showed less brain damage. After a dose of diced laminin, however, the mutant mice were vulnerable to kainate, indicating that the fragments are the culprit in cell death.

The researchers discovered that chopped-up ECM kills cells by ramping up production of one subunit of the kainate receptor, known as KA1. They speculate that hiking the amount of KA1 subunits might make the receptor more sensitive and thus more likely to trigger an overreaction by the cell.

Although drugs that obstruct the glutamate receptor slow brain cell death, they can lead to serious cognitive impairment and even coma. The study suggests that drugs that block KA1 might provide an alternative way to save brain cells after stroke or head trauma.

Chen, Z.-L., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200803107.



The extracellular matrix thins in mice lacking laminin in the hippocampus (bottom).

Slow down, enzymes at work

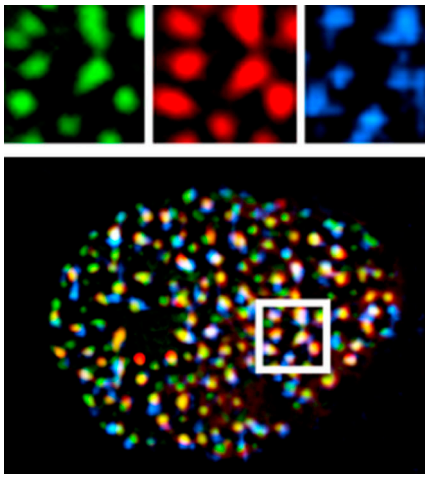
DNA replication lags when the molecule is undergoing repairs. Sugimura et al. reveal that one DNA-fixing protein helps create this delay by fending off another DNA repair enzyme.

Damage that severs both strands of a DNA molecule creates what's called a double-stranded break, or DSB. When the cell is copying its DNA, DSBs can cause trouble for replication forks, the spots where the double helix unzips so enzymes can copy the two strands. If a replication fork runs into a double-stranded break, researchers think that DNA duplication usually slows or stops. Previous work has revealed that the protein PARP-1 helps correct single-stranded DNA breaks. But whether it helps heal the DSBs that arise during replication was unclear.

Sugimura et al. tested whether PARP-1 inhibits the movement of replication forks along the DNA molecule. In vitro studies suggested that it did, but in vivo evidence was lacking. In human cells, replication fork speed doubled after addition of RNAi that targeted PARP-1, the scientists found. A PARP-1 inhibitor had a similar effect.

Cells deploy two mechanisms for mending DSBs—non-homologous end-joining (NHEJ) and homologous recombination (HR). The team found that the replication forks decelerate in cells that can't perform NHEJ, but not in cells where HR is defective. That result suggests that replication fork slowing occurs because HR is at work repairing the break. PARP-1 helps delay the fork's progress, the researchers determined, by allowing HR proteins access to the DNA but obstructing the protein Ku70, which is necessary for NHEJ and can block HR.

Sugimura, K., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200806068.



PARP-1 (green) associates with replicating regions of the genome (red and blue) and will slow fork progression during double-strand break repair.