JCI The Journal of Clinical Investigation

In This Issue

J Clin Invest. 2002;110(11):1577-1577. https://doi.org/10.1172/JCI119963.

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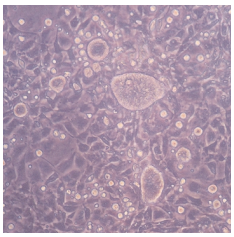
Epimorphin makes gut things happen. Epimorphin is a mesenchymal protein expressed in the fetal gastrointestinal tract during villus morphogenesis as well as in the adult intestine during villus repair after injury. To study the gene's function, Deborah Rubin and colleagues altered epimorphin expression in a myofibroblast cell line that expresses low levels of endogenous protein and examined the effects both on cocultured gut epithelial cells and in a graft model. The results (pages 1629–1641) suggest that epimorphin has a role in gut ontogeny, and that it exerts its function at least in part via secreted factors, including members of the bone morphogenetic protein family. This is consistent with epimorphin's putative cellular function as a member of the syntaxin family of vesicle docking proteins, and provides support to the growing notion that syntaxins affect specific developmental processes.Arresting cells without damaging DNA. Cellular senescence is a state of terminal arrest in which cells remain metabolically active for extended periods but can no longer respond to mitogenic stimulation. Several tumor suppressor genes are involved in induction and maintenance of senescence, suggesting that senescence prevents tumorigenesis. Hoping to find a new way to prevent or treat cancer, Heiko Hermeking and colleagues (pages 1717–1727) have searched for agents that induce senescence without inducing DNA damage. As expression profiling associated downregulation of cGMP signaling with senescence, […]



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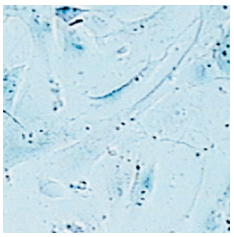
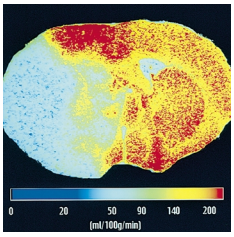
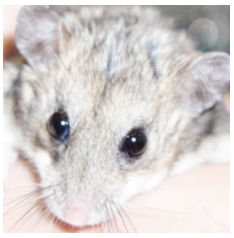


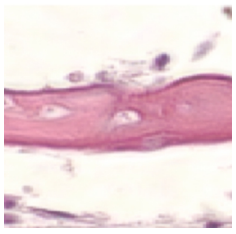
Arresting cells without damaging DNA. Cellular senescence is a state of terminal arrest in which cells remain metabolically active for extended periods but can no longer respond to mitogenic stimulation. Several tumor suppressor genes are involved in induction and maintenance of senescence, suggesting that senescence prevents tumorigenesis. Hoping to find a new way to prevent or treat cancer, Heiko Hermeking and colleagues (pages 1717–1727) have searched for agents that induce senescence without inducing DNA damage. As expression profiling associated downregulation of cGMP signaling with senescence, the researchers focused their screen on inhibitors of this pathway. One of them, an inhibitor of guanylate cyclase, induced cellular senescence. The effect was dependent on p21 (which was upregulated in response to the drug), but not on p53. The latter result suggests that the drug does not induce DNA damage, which is responsible for risks and side effects of most other chemotherapeutic agents.



Steroids, eNOS, and stroke protection. Corticosteroids reduce ischemic injury in myocardial infarction and reduce stroke size in focal cerebral ischemia. Having recently shown that nontranscriptional effects of the glucocorticoid receptor (GR) are responsible for the anti-inflammatory cardio-protective effects, James Liao and colleagues report now on the mechanisms of the anti-ischemic neuroprotective effects of corticosteroids. In an article beginning on page 1729, the researchers show that high doses of steroids, given within two hours of transient cerebral ischemia, trigger GR-association with phosphatidylinositol 3-kinase (PI3K) and activation of PI3K and Akt. This in turn activates endothelial nitric oxide synthase, thereby increasing cerebral blood flow by 40–50% and reducing cerebral infarct size by 30%. These effects were rapid and nontranscriptional, and while they required doses at least ten times as high as those required for a genomic response by the GR, they appeared specifically mediated by the receptor.



Hamster antibody stimulates thyrotropin receptor. Autoantibodies that activate the thyrotropin receptor and stimulate thyroid function cause Graves disease. Such antibodies would be valuable reagents in better understanding the complex molecular biology of receptor activation as well as potential therapeutic thyroid stimulators. An article in this issue (pages 1667–1674) now reports the successful isolation of an activating antibody. Using an Armenian hamster model of Graves disease, Takao Ando and colleagues isolated a monoclonal antibody that is a potent activator of the thyrotropin receptor. Like the autoantibodies, the monoclonal antibody is stimulatory at nanogram concentrations, but whereas binding of the endogenous hormone ligand promotes cleavage of the receptor into two subunits, binding of the antibody did not. This difference suggests a novel mechanism underlying the prolonged overstimulation of the thyroid gland in Graves disease.



How IL-7 uncouples bone formation and resorption. Postmenopausal drops in estrogen levels cause increased bone resorption without compensatory increase in bone formation — resulting in net bone loss and osteoporosis. The absence of estrogen leads to elevated levels of IL-7, and M. Neale Weitzmann and colleagues have examined the effects of this cytokine on bone metabolism in ovariectomized mice. Their findings (pages 1643–1650) suggest a critical role for IL-7 in the uncoupling of bone resorption from bone formation. High IL-7 levels promote osteoclastogenesis on one hand, and inhibit osteoblast differentiation and activity on the other. By affecting both pathways, IL-7 seems central to the altered bone turnover characteristic of estrogen deficiency.