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In This Issue

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By John Ashkenas, Science Editor

Treating metastatic disease with a modified herpesvirus

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Using bacteria or viruses to control tumors is an old idea, and many such biotherapeutic agents have been designed and tested in cell and animal models. Safety concerns are paramount in this work, and most candidates with oncolytic properties have remained sidelined at the preclinical stage because, despite a general tropism towards cancer cells, they retain some ability to infect normal host cells or to cause systemic disease. Here, Nakamura and colleagues describe a second-generation derivative of the herpes simplex virus (HSV-1) that, they suggest, may be ready to clear this hurdle. A previously engineered form of HSV-1, deficient in the viral gene for the enzyme ribonucleotide reductase, replicated preferentially in liver tumors. Unlike healthy hepatocytes, liver tumor cells divide rapidly and possess sufficient pools of deoxynucleotides to support efficient viral replication. The newer recombinant virus, Myb34.5, has this same defect but also carries an engineered form of the *$\gamma_1$34.5* gene. The product of this gene allows the virus to circumvent a host cell defense mechanism that would otherwise shut down protein synthesis in infected cells. In Myb34.5, $\gamma_1$34.5 is expressed under control of the *Myb* promoter, which is active in cycling cells, leaving the virus with extremely limited ability to proliferate in healthy host tissues. Nakamura et al. show that injection of Myb34.5 into mice carrying a high load of metastatic liver cells affords these animals considerable protection and significantly extends their survival. Even when provided at doses 10-fold higher than a rapidly fatal dose of wild-type HSV-1, Myb34.5 did not kill or paralyze treated mice. The authors caution, however, that neither mice nor other experimental animals provide fully adequate models for HSV-1 infection. Hence, viral toxicity in humans remains a possibility.

Control of intestinal inflammation by PGE_2 and its receptor

(See article on pages 883–893.)

Nonsteroidal anti-inflammatory drugs (NSAIDs) have as a common side effect the ability to damage the lining of the intestine. Since NSAIDs inhibit prostanoid biosynthesis, it is accepted that these complications reflect a protective role of some prostaglandins in suppressing intestinal inflammation and damage. Still, the identity of the relevant prostaglandins has not been known, and the involvement of multiple prostaglandin receptors in this beneficial response could not be excluded. Now, however, Kabashima et al. provide a surprisingly simple answer. Taking advantage of the many mouse knockout strains available that lack one or another of the prostaglandin receptors, they show that the prostaglandin PGE_2, acting through a single receptor, EP4, is largely if not single-handedly responsible for maintaining the integrity of the intestinal mucosa. While EP4-deficient mice do not ordinarily show symptoms of colitis, the authors find that they are hypersensitive to damage by low doses of the proinflammatory compound dextran sodium sulfate — doses that are well tolerated by wild-type mice and by animals with mutations in the other receptor genes. Conversely, NSAID treatment, coupled with low-dose DSS, can cause acute disease even in wild-type mice, but treatment with a specific EP4 agonist prevents this response. Hence, this class of agonist might be useful in protecting humans from NSAID gastrotoxicity and might also prove beneficial for ulcerative colitis and Crohn disease, conditions where the intestinal mucosa is prone to inflammation and tissue damage.

Forging a link between brain and bone

(See article on pages 915–921.)

The adipose-derived hormone leptin is well known for its influence on feeding behavior. Animals with genetic defects in leptin signaling become obese when supplied unlimited food. However, even when food supply is limited to prevent obesity, leptin still exerts profound effects on various organs, including the bones. These effects are mediated by the central nervous system, specifically hypothalamic neurons that respond to signals from neuropeptide Y (NPY), and, as Baldock and colleagues now show, they can be mimicked by defects in the NPY receptor Y2. The accelerated bone deposition in animals lacking leptin signaling might be thought to occur as a consequence of hormonal imbalance, possibly mediated by changes in corticosteroids or plasma calcium levels. However, Baldock et al. find no evidence for such a mechanism, and they suggest instead that rapid bone deposition and high trabecular bone volume result from direct neural control of bone growth. The absence of Y2, either specifically in the hypothalamus or throughout the body, yields the same increase in mineralized bone formation that was previously seen in leptin deficient animals. Double knockout animals, lacking both Y2 and leptin, show an identical bone phenotype, as expected if NPY signaling in the hypothalamus acts solely downstream of leptin. Baldock et al. speculate that autonomic nerves within the bone mediate the effects of hypothalamic signaling. How osteoblasts might recognize and respond to such stimuli remains an open question. Still, the emerging model of central control of bone metabolism casts the genesis and control of osteoporosis in an entirely new light.