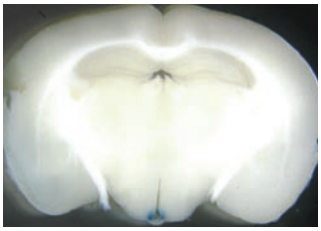
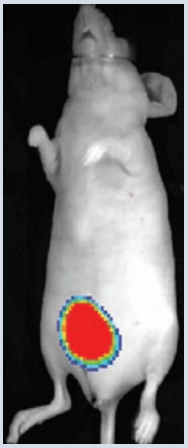
Leptin swings both ways to regulate energy balance



Activity of neurons in the hypothalamus that express neuropeptides proopiomelanocortin (POMC) or agouti-related peptide (Agrp) is controlled by insulin and also by leptin, a hormone made by fat cells that regulates feeding behavior. Leptin can reduce weight and food intake by inhibiting Agrp neurons and stimulating POMC neurons. The alternate paradigm — activating Agrp neurons and inhibiting POMC neurons — increases food intake and leads to obesity. In this issue, Gregory Barsh and colleagues examine how leptin regulates these neurons in opposite directions. The authors genetically engineered a reporter system and used 2-photon microscopy to monitor signal transduction by measuring PI3K activity in single hypothalamic neurons of mice (pages 951–958). PI3K was thought to lie downstream of leptin and insulin signaling. The researchers demonstrate that insulin and leptin can directly activate PI3K in POMC neurons. In Agrp neurons, leptin represses PI3K, while insulin maintains PI3K activation. This study advances our understanding of the mechanisms regulating critical POMC/Agrp circuits of the hypothalamus and provides experimental support for the hypothesis that PI3K signaling is required for the actions of leptin.

Blocking PLK-1 to beat bladder cancer

Bladder cancer is commonly treated by surgical removal of part of or the entire bladder, which causes loss of urinary and sexual functions. In this issue, Takeshi Yuasa and colleagues investigate the efficacy of intravesical polo-like kinase-1 (PLK-1) small interfering RNA (siRNA) against bladder cancer (pages 978–985). PLK-1 regulates cell division, and its expression is correlated with a variety of human tumors. The authors used an siRNA and cationic liposome complex to suppress the expression of endogenous PLK-1 in bladder cancer cells in a time- and dose-dependent fashion. Intravesical administration of PLK-1 inhibition reduced cell proliferation and induced apoptosis of cancer cells. To validate the efficacy of the siRNA/liposome complex in vivo, the authors implanted mice with bladder cancer cells, and transurethral administration of PLK-1 siRNA prevented the growth of bladder cancer in this mouse model. This interesting study shows that inhibition of PLK-1 through intravesical PLK-1 siRNA therapy could be an important strategy for the management of bladder cancer.



B cells cry for help in XLP

X-linked lymphoproliferative disease (XLP) is a rare and complex immune disorder caused by mutations in the gene that encodes the intracellular protein signaling lymphocytic activation molecule–associated protein (SAP). The mechanisms by which mutations in SAP cause the clinical manifestations of the disease —low levels of plasma proteins needed for immune responses, lymphoma formation, and often fatal mononucleosis infections — were unknown. Although mouse models of XLP have been generated, they have limitations in utility due to differences in how the disease develops in mice and humans. In this issue, Stuart Tangye and colleagues investigate defects in humoral immunity in 14 XLP patients from 9 different families (pages 1049–1059). They found that XLP patients have normal B cell development but a severe deficiency in the number of circulating memory B cells. This defect was due to impaired T cell help, as T cells from XLP patients had reduced production of the cytokine IL-10 and did not effectively stimulate B cell immunoglobulin production. The results identify IL-10 as a key contributor to impaired humoral immunity in XLP and offer potential therapeutic approaches for the treatment of this immunodeficiency.

Birthing a new mouse model to study aspirin therapy

Preeclampsia is a hypertensive disorder that occurs during pregnancy and can be detrimental to the health of the developing fetus and the mother. Low-dose aspirin therapy has been used to treat preeclampsia, but this strategy is controversial — some researchers believe that it prevents preeclampsia, while others find that it increases complications. In this issue of the *JCI*, Colin Funk and colleagues report the development of a new mouse model that mimics the effects of low-dose aspirin treatment to explore how such therapy would impact blood clotting and reproductive functions (pages 986–995). The mice generated have reduced PGH synthase 1 (PGHS1), a platelet protein that contributes to the cardioprotective effects of aspirin therapy. The authors found that in these mice, platelet aggregation was decreased, thrombosis was inhibited, and inflammatory responses were impaired. However, the uterine and ovarian environments were altered only slightly and allowed for normal induction of labor, normal litter size, and development of offspring similar to normal controls. This new mouse model will have significant value in the study of the role of low-dose aspirin treatment in several pathological conditions, such as preeclampsia, thrombosis, and inflammation.