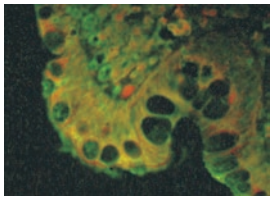
Spot the difference in proteasome composition

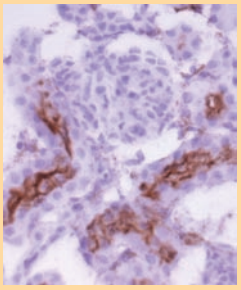


Excessive activation of NF-κB is associated with the pathogenesis of both Crohn disease (CD) and ulcerative colitis (UC). Although CD and UC have many common features, the inflammatory mechanisms underlying these disorders differ — CD is characterized by a Th1 response and UC by a Th2 response. So, Visekruna and colleagues set out to determine whether NF-κB activation mediated by the proteasome (an enzymatic complex that degrades proteins) differed in these two diseases (pages 3195–3203). Proteasomes in the inflamed mucosa of patients with CD differed markedly from those in the mucosa of healthy individuals, with high levels of immunoproteasome subunits being detected in CD tissues and none in healthy tissues. By contrast, only low levels of immunoproteasome subunits were detected in the inflamed mucosa of patients with UC. These differences meant that proteasomes from individuals with CD were more efficient at degrading the inhibitor of NF-κB, IκBα, and processing the NF-κB p50 precursor p105 than proteasomes from individuals with UC, providing a potential molecular explanation for the different inflammatory responses underlying these two disorders. Because the NF-κB family member c-Rel was expressed at higher levels in the inflamed mucosa of patients with CD than in that of patients with UC, the authors suggest that p50/c-Rel NF-κB heterodimers initiate a Th1 response in the CD mucosa that leads to the production of IFN-γ, a trigger of immunoproteasome subunit expression.

Ghrelin seeks out reward center in the brain

Ghrelin is a hormone produced by the stomach that targets the brain to trigger food intake and energy homeostasis. As the ghrelin receptor growth hormone secretagogue 1 receptor (GHSR) is expressed in regions of the hypothalamus that control energy homeostasis, it had been thought that the effects of ghrelin on appetite and energy homeostasis were mediated through this region of the brain. However, Abizaid and colleagues show that in mice and rats, ghrelin triggers dopamine production by neurons in the ventral tegmental area (VTA) of the brain and that this promotes food intake (pages 3229–3239). Ghrelin was shown to bind neurons in the VTA and to trigger their production of dopamine, as well as to modify their input synapses. Importantly, infusion of ghrelin into the VTA of rats increased their food intake, whereas infusion of GHSR inhibitors decreased the amount they consumed after a 24-hour fast. The dopaminergic neurons activated by ghrelin are also activated by pleasurable stimuli and form part of the reward-seeking neural circuit. So, the authors suggest that ghrelin stimulation of the VTA might be involved in diseases of food abuse.

Two new roles for the VDR in bone metabolism



Vitamin D is required for normal bone metabolism, mainly because, through the vitamin D receptor (VDR), it regulates calcium uptake by the intestines and kidney. The VDR is also expressed by other cell types, including chondrocytes, but whether this is important for bone metabolism has not been determined. To analyze this, Masuyama and colleagues generated mice with a chondrocyte-specific deletion of the gene encoding the VDR (pages 3150–3159). Trabecular bone volume of young mice with chondrocytes lacking the VDR was increased compared with that in control mice because they had decreased numbers of osteoclasts. Chondrocyte VDR signaling in vitro induced upregulation of receptor activator of NF-κB ligand (RANKL), which is required for osteoclastogenesis, providing an explanation for the decreased number of osteoclasts in mice with chondrocytes lacking the VDR. Further analysis showed that chondrocyte VDR signaling also modified osteoblast expression of FGF23, which regulates phosphate homeostasis. However, further analysis is required to identify the factor secreted by chondrocytes in response to VDR signaling that induces osteoblasts to express FGF23.

Repair, not destruction: a new approach to treating retinopathy

Many diseases of the eye (such as retinopathy of prematurity [ROP] and diabetic retinopathy) that result in loss of vision are the result of the growth of abnormal blood vessels that leak and bleed, causing retinal edema and hemorrhage. Current treatments are designed to prevent the growth of these abnormal blood vessels. But a new study, in mice, indicates that an alternative treatment strategy might be to repair these blood vessels so that they do not leak and bleed (pages 3266–3276). Using an oxygen-induced mouse model of retinopathy, Ritter and colleagues showed that retinal neovascularization could be normalized by transplantation of adult BM–derived myeloid progenitor cells and that the transplanted cells had to express hypoxia-inducible factor 1α (HIF-1α) to mediate vascular repair. Further analysis showed that the transplanted cells differentiated into microglia in the eye and that endogenous microglia are involved in retinal vascularization. This study suggests that transplantation of autologous BM-derived progenitor cells might be a viable therapy for the treatment of human diseases that resemble this mouse model of retinopathy, such as ROP.