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In This Issue

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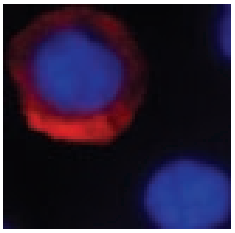
Coupling metabolism and immunology Ghrelin is a newly identified endogenous ligand for the growth hormone secretagogue receptor (GHS-R), a G protein–coupled receptor (GPCR), and is known to play a part in maintaining metabolic energy balance. Recently, a subtype of GHS-R was found in the lymphoid organs, suggesting a role for ghrelin in the immune response system, which Dennis Taub and colleagues have now investigated (pages 57–66). They found that ghrelin receptors are expressed in human T cells and monocytes and that expression is significantly increased upon cellular activation. Ligation of the receptor upon T cell exposure to ghrelin peptide was evidenced by induced calcium flux from inositol triphosphate production and actin cytoskeleton remodeling, hallmarks of GPCR ligation. The authors show that ghrelin inhibits inflammatory cytokines such as IL-1β and IL-6, which are induced by cellular activation and leptin stimulation. In an LPS-induced endotoxemia mouse model, ghrelin treatment inhibited IL-1β, IL-6, and TNF-α expression, exerting an anti-inflammatory effect. These results may further our understanding of anorexia and obesity, and support a role for ghrelin as a potential therapeutic target. See figure PPAR for the course Little is known about hepatic glycerol metabolism regulation. Sander Kersten and colleagues now begin to fill this void with a series of studies of the PPAR genes in mice (pages 94–103). To investigate the role of […]

Coupling metabolism and immunology

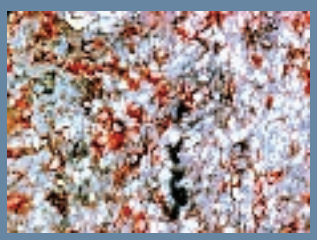


Ghrelin is a newly identified endogenous ligand for the growth hormone secretagogue receptor (GHS-R), a G protein–coupled receptor (GPCR), and is known to play a part in maintaining metabolic energy balance. Recently, a subtype of GHS-R was found in the lymphoid organs, suggesting a role for ghrelin in the immune response system, which Dennis Taub and colleagues have now investigated (pages 57–66). They found that ghrelin receptors are expressed in human T cells and monocytes and that expression is significantly increased upon cellular activation. Ligation of the receptor upon T cell exposure to ghrelin peptide was evidenced by induced calcium flux from inositol triphosphate production and actin cytoskeleton remodeling, hallmarks of GPCR ligation. The authors show that ghrelin inhibits inflammatory cytokines such as IL-1β and IL-6, which are induced by cellular activation and leptin stimulation. In an LPS-induced endotoxemia mouse model, ghrelin treatment inhibited IL-1β, IL-6, and TNF-α expression, exerting an anti-inflammatory effect. These results may further our understanding of anorexia and obesity, and support a role for ghrelin as a potential therapeutic target.

PPAR for the course

Little is known about hepatic glycerol metabolism regulation. Sander Kersten and colleagues now begin to fill this void with a series of studies of the *PPAR* genes in mice (pages 94–103). To investigate the role of *PPAR* genes in glycerol metabolism, the authors utilized array technology and found that, in contrast to *PPARα*$^{-/-}$, fasting wild-type mice had increased expression of several genes involved in hepatic glycerol metabolism. These same genes were also induced in response to a PPARα agonist. *PPARα*$^{-/-}$ mice had reduced glucose production even under fasting conditions and in the presence of a PPARα agonist. Mice that were deficient in *PPARγ* or *PPARβ/δ*, however, showed reduced expression of the glycerol metabolism gene mitochondrial glycerol 3-phosphate dehydrogenase (*mGPDH*) in adipocytes rather than hepatocytes. Interaction studies further showed that the cytosolic *GPDH* gene is a physical target of PPARα. Taken together, the data here indicate a direct role for PPARα in hepatic glycerol metabolism and show that PPARγ controls glycerol metabolism in adipose tissue.

Cancer patient, heal thyself



Tumor-specific T cells are found in cancer patients, but these cells fail to reject tumors. This failure could be due to anergy, limited stimulation during priming, or tumor-directed immunosuppression. Viktor Umansky and colleagues now provide a method to enable specific activation and tumor infiltration of T cells from cancer patients (pages 67–76). They show that patients' bone marrow is enriched for subsets of tumor-antigen–specific memory T cells. These cells were isolated from bone marrow and stimulated with tumor-antigen–presenting dendritic cells to become IFN-γ–producing and cytotoxic-effector cells. NOD/SCID mice previously implanted with primary tumors were intraperitoneally injected with activated memory or naive T cells. In contrast to naive cells, memory cells infiltrated the tumor transplants and reduced tumor size. The adhesion molecule P-selectin plays a role in homing these memory T cells to the tumors, as P-selectin glycoprotein 1 was induced in antigen-specific–activated T cells. These results present a potential immunotherapy strategy for cancer treatment with appropriately reactivated tumor-specific memory T cell subsets preexisting in patients' bone marrow.

PAF-way to bone loss

In postmenopausal osteoporosis, increased bone turnover leads to bone resorption and a higher risk of bone fracture. Platelet-activating factor (PAF) has been implicated in diseases associated with bone resorption. To investigate the role of PAF in postmenopausal osteoporosis, Satoshi Ishii and colleagues characterized bone loss in PAF receptor knockout (PAFR-KO) mice after ovariectomy (pages 85–93). They found that bone mineral density as well as bone volume was improved in ovariectomized knockout mice as compared with WT mice. By assaying acetyl-CoA:lyso-PAF acetyltransferase activity and PAFR mRNA expression level in cultured bone cells, the authors also showed that the osteoclasts are responsible for PAF's mechanism of action and that the cytokines TNF-α and IL-1β increased lyso-PAF acetyltransferase activity in osteoclasts. Resistance to bone resorption was also observed when cells were treated with WEB 2086, an antagonist of PAFR. These data indicate that PAF inhibition presents a possible strategy for treating osteoporosis and other diseases involving PAF activity.