

## In This Issue

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**Effecting T cell function** The erythropoietin-producing hepatocyte (Eph) kinases are the largest family of receptor tyrosine kinases in the immune system. The Eph kinases and their ligands are known to direct neural outgrowth, angiogenesis, and epithelial cell migration in the intestine. Jiangping Wu and colleagues now delve further into the role of Eph kinases in the immune system by [...]

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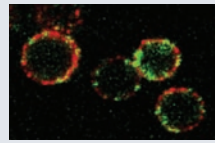




## Oxidants link obesity to diabetes

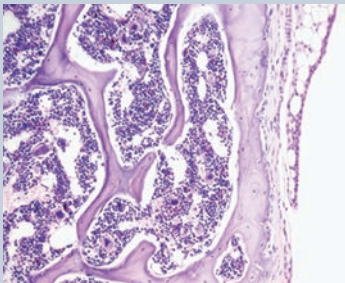
Obesity is associated with the development of diabetes, dyslipidemia, hypertension, and atherosclerosis. However, the mechanistic role of obesity in this syndrome has never been fully understood. Iichiro Shimomura and colleagues now show that increased oxidative stress in accumulated fat is an important pathogenic mechanism of obesity-associated metabolic syndrome (pages 1752–1761). Production of ROS increased significantly in adipose tissue of nondiabetic obese mice, and this was accompanied by augmented expression of NADPH oxidase and decreased antioxidative enzymes only in fat tissues. ROS production resulted in dysregulated local production of fat-derived hormones (adipocytokines) and systemic increases in oxidative stress in adipocytes and obesity models. Inhibition of ROS production attenuated the dysregulation of adipocytokines and improved insulin resistance, diabetes, hyperlipidemia, and hepatic steatosis. These results indicate that accumulated fat is a major source of ROS in obesity and that the redox state in adipose tissue is a potential therapeutic target for the prevention and treatment of obesity-associated metabolic syndromes.

## Ephecting T cell function



The erythropoietin-producing hepatocyte (Eph) kinases are the largest family of receptor tyrosine kinases in the immune system. The Eph kinases and their ligands are known to direct neural outgrowth, angiogenesis, and epithelial cell migration in the intestine. Jiangping Wu and colleagues now delve further into the role of Eph kinases in the immune system by showing that EphB6 modulates immune function in vivo (pages 1762–1773). The authors demonstrated that *EphB6*<sup>-/-</sup> mice were compromised in in vitro and in vivo T cell responses, in terms of lymphokine secretion and proliferation and the development of delayed-type skin hypersensitivity and experimental autoimmune encephalitis. On the other hand, humoral immune responses such as changes in serum Ig isotype levels and IgG response to tetanus toxoid were normal in the mutant mice. EphB6 was shown to migrate to the aggregated TCR and rafts after TCR activation. This study is the first to describe roles for an Eph kinase in in vivo immunological function.

## T bodies find their way home



Prostate cancer (PC) is one of the most frequently diagnosed noncutaneous malignancies in American men. PC usually metastasizes to the bone and is palliatively treated with androgen ablation; however, when the disease becomes

androgen independent, there is no effective therapy. Zelig Eshhar and colleagues investigate the use of adoptive transfer of tumor antigen-specific T lymphocytes as a PC therapy (pages 1774–1781). One of the obstacles in adoptive transfer has been the inefficient homing of the T cells to their tumor targets. Recently, it was demonstrated that “T bodies,” genetically reprogrammed T lymphocytes expressing anti-erbB2 chimeric receptor genes, can be directly applied to locally confined, well-established PC xenografts in SCID mice, resulting in retardation of tumor growth. The authors optimized the T body approach for the systemic therapy of advanced PC by preconditioning the cancer host using low-dose irradiation or cyclophosphamide in order to induce stromal cell-derived factor-1 (SDF-1) production within the bone marrow. SDF-1/CXCR-4 mediated homing of the adoptively transferred T bodies, resulting in decreased tumor growth and prostate-specific antigen secretion, prolongation of survival, and cure of the treated mice. The approach of patient preconditioning prior to the adoptive transfer of tumor-specific T cells offers great promise for the systemic cellular immunotherapy of metastatic PC and other malignant tumors.

## Caspase-3, the unfriendly ghost

Apoptosis plays an important role during skeletal development and bone remodeling. Excessive apoptosis of osteoblasts and osteocytes has been implicated as an important mechanism underlying osteoporosis. Songtao Shi and colleagues investigated the role of caspase 3-mediated apoptosis in maintaining bone mass (pages 1704–1713). The authors used 3 models, including caspase-3-knockout mice, caspase-3 inhibitor-treated osteoporotic mice, and caspase-3 inhibitor-treated human bone marrow stromal stem cells (BMSSCs) to reveal that caspase-3 is required for maintaining bone mass. The mechanism of bone defects in the caspase-3-deficient condition is due to attenuated differentiation of BMSSCs, in which overactivated TGF- $\beta$ /Smad2 signaling led to upregulated expression of p21/p53 and downregulated expression of Cdk2/Cdc2 and eventually replicative senescence of BMSSCs. Moreover, a caspase-3 inhibitor, a potent therapeutic agent for some degenerative diseases, was found to accelerate bone loss in osteoporotic mice and attenuate bone formation of human BMSSCs. This study offers a novel concept of how caspase-3 deficiency alters development and differentiation of stem cells leading to osteoporosis. Since the caspase-3 inhibitor was demonstrated to accelerate bone loss in a model for postmenopausal osteoporosis, these data suggest that caution should be exercised in the development of caspase-3 inhibitor for therapeutic purposes.

