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In This Issue

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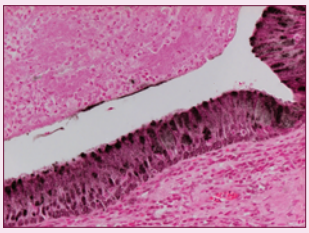
PPARα helps set apart females and males Many hepatic genes encoding proteins that control metabolic pathways are differentially expressed in males and females. Much of this hepatic sexual dimorphism is caused by differences in pituitary growth hormone secretion. However, in this issue (3138–3148), Leuenberger and colleagues report that the nuclear receptor PPARα represses the transcription of many hepatic genes encoding proteins involved in steroid metabolism and immunity only in female mice. One of the genes most strongly repressed in female mice by PPARα was oxysterol 7α-hydroxylase (Cyp7b1), which encodes a member of the cytochrome P450 superfamily of enzymes involved in drug metabolism and the synthesis of cholesterol, steroids, and other lipids. Detailed analysis of the mechanism by which PPARα repressed Cyp7b1 expression revealed that the ligand-binding domain of PPARα was sumoylated only in female mice and that this posttranslational modification enabled PPARα to interact with GA-binding protein α (GABPα) bound to the Cyp7b1 promoter. This complex recruited chromatin-modifying enzymes that functioned to prevent Sp1 transcription factor from binding to the Cyp7b1 promoter to stimulate transcription. As PPARα-mediated repression protected female mice from estrogen-induced intrahepatic cholestasis, the most common hepatic disease during pregnancy, the authors suggest that PPARα agonists might provide a new approach to prevent this disease. What happens when T cells just won't die? X-linked lymphoproliferative disease (XLP) is […]

The making of goblet cells



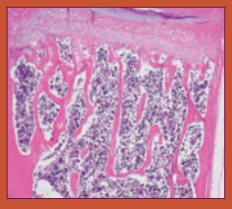
Goblet cells are mucus-producing epithelial cells normally found in only small numbers in the respiratory tract lining. However, many acute and chronic inflammatory stimuli increase the number and activity of pulmonary goblet cells, a response that contributes to the pathogenesis of chronic pulmonary disorders. In this issue (2914–2924), Chen and colleagues have identified the transcription factor SAM-pointed domain–containing Ets-like factor (SPDEF) as a regulator of pulmonary goblet cell differentiation and mucus production in mice. Lineage-tracing analysis identified epithelial cells known as Clara cells as the progenitors of goblet cells induced by pulmonary allergen exposure in vivo. Consistent with a role for SPDEF in this process, in vivo expression of SPDEF in Clara cells induced goblet cell differentiation, while the conducting airway epithelium of mice lacking SPDEF contained no goblet cells after pulmonary allergen exposure in vivo. Mechanistically, SPDEF induced expression of genes encoding proteins involved in goblet cell differentiation, mucus production, and allergen sensitization. As these proteins were expressed in goblet cells lining the airways of patients with chronic lung diseases, the authors suggest that SPDEF regulates a transcriptional network that controls the goblet cell differentiation and mucus hyperproduction associated with common pulmonary disorders, including asthma, chronic obstructive pulmonary disease, and cystic fibrosis.

PPARα helps set apart females and males

Many hepatic genes encoding proteins that control metabolic pathways are differentially expressed in males and females. Much of this hepatic sexual dimorphism is caused by differences in pituitary growth hormone secretion. However, in this issue (3138–3148), Leuenberger and colleagues report that the nuclear receptor PPARα represses the transcription of many hepatic genes encoding proteins involved in steroid metabolism and immunity only in female mice. One of the genes most strongly repressed in female mice by PPARα was oxysterol 7α-hydroxylase (*Cyp7b1*), which encodes a member of the cytochrome P450 superfamily of enzymes involved in drug metabolism and the synthesis of cholesterol, steroids, and other lipids. Detailed analysis of the mechanism by which PPARα repressed *Cyp7b1* expression revealed that the ligand-binding domain of PPARα was sumoylated only in female mice and that this posttranslational modification enabled PPARα to interact with GA-binding protein α (GABPα) bound to the *Cyp7b1* promoter. This complex recruited chromatin-modifying enzymes that functioned to prevent Sp1 transcription factor from binding to the *Cyp7b1* promoter to stimulate transcription. As PPARα-mediated repression protected female mice from estrogen-induced intrahepatic cholestasis, the most common hepatic disease during pregnancy, the authors suggest that PPARα agonists might provide a new approach to prevent this disease.

Bcl-xL: not just an antiapoptotic factor in osteoclasts

The B cell lymphoma 2 (Bcl-2) family member Bcl-xL is the major isoform produced following alternative splicing of the *Bcl-x* gene. Although its role as an antiapoptotic protein has been well characterized in several cell types, its function(s) in osteoclasts, bone-resorbing cells of hematopoietic origin, has not been determined. To address this issue, Iwasawa and colleagues generated mice with osteoclast-specific deletion of *Bcl-x* (*Bcl-x* cKO mice) (3149–3159). Perhaps unsurprisingly, given its antiapoptotic function in other cell types, Bcl-xL was shown to promote the survival of osteoclasts. Unexpectedly, however, *Bcl-x* cKO mice exhibited marked osteopenia at one year of age. Further analysis indicated that the reduced bone mass was caused by increased osteoclast-mediated bone resorption due, at least in part, to increased c-Src activity. Interactions between ECM proteins and cell surface integrins are known to activate c-Src. As Bcl-xL was found to decrease levels of the ECM proteins fibronectin and vitronectin, the authors suggest that Bcl-xL attenuates osteoclast c-Src activity, and thereby osteoclast bone-resorbing activity, through the decreased production of ECM proteins. Thus Bcl-xL functions in osteoclasts as both an antiapoptotic factor and a negative regulator of bone resorption.



What happens when T cells just won't die?

X-linked lymphoproliferative disease (XLP) is a rare inherited immunodeficiency most commonly caused by deficiency in SLAM-associated protein (SAP). Following primary infection with EBV, boys with XLP often develop an extreme, usually fatal accumulation of activated cytotoxic T lymphocytes, but the mechanistic link between this and SAP deficiency has not been determined. However, Snow and colleagues have found that T cells from individuals with XLP are resistant to apoptosis mediated by TCR restimulation, a process that normally constrains T cell expansion during immune responses, and propose that this makes the T cells susceptible to uncontrolled expansion upon infection (2976–2989). How SAP deficiency leads T cells to become resistant to apoptosis mediated by TCR restimulation was determined in a series of additional experiments. Specifically, SAP was shown to be required for TCR-induced upregulation of pro-apoptotic molecules, interacting with the SLAM family receptor NK, T, and B cell antigen (NTB-A) after TCR restimulation to augment the strength of the proximal TCR signal and achieve the threshold required for apoptosis.