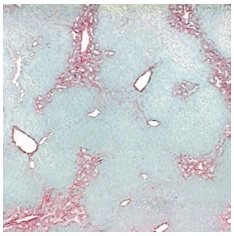
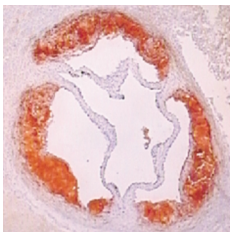
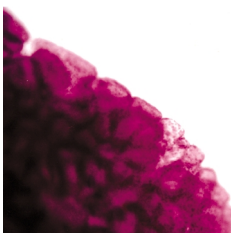


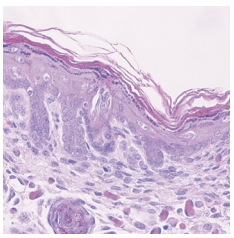
Revealed: a role for angiotensin II in liver fibrosis. While there is increasing evidence that the renin-angiotensin system plays an important role during liver fibrosis and that anti–angiotensin II (anti–Ang II) therapy is useful in chronic liver injury, the mechanisms by which Ang II facilitates these effects is unclear. In their study, David Brenner and colleagues provide evidence that NADPH oxidase mediates the effects of angiotensin II on hepatic stellate cells, major fibrogenic cells in the injured liver (pages 1383–1394). Ang II phosphorylated $p47^{phox}$, a key regulatory subunit of NADPH oxidase, and induced reactive oxygen species formation via NADPH oxidase activity. Ang II stimulated DNA synthesis, cell migration, procollagen α1(I) mRNA expression, and secretion of TGF-β1 and inflammatory cytokines. These effects are attenuated by an NADPH inhibitor and in NADPH knockout cells. Microarray analysis revealed that Ang II induces upregulation of genes involved in liver fibrogenesis. This study suggests a new pharmacologic target for the treatment of fibrosis.



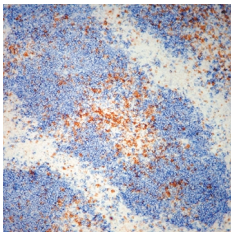
TGF-β keeps T cells in check in atherosclerosis. Increasing evidence suggests that atherosclerosis is an inflammatory disease promoted by hypercholesterolemia. However, the role of immune cells has been controversial. Göran Hansson and colleagues now show that TGF-β inhibits atherosclerosis by dampening T cell activation (pages 1342–1350). Atherosclerosis-prone *ApoE*$^{-/-}$ mice were crossed with transgenic mice carrying dominant-negative TGF-β receptor II in T cells. In the absence of functional TGF-β signaling in T cells, the authors observed a dramatic increase in atherosclerosis concomitant with increased T cell activation. These results show that abrogation of TGF-β signaling in T cells increases atherosclerosis and suggest that TGF-β reduces atherosclerosis by dampening T cell activation. Inhibition of T cell activation may therefore represent a strategy for anti-atherosclerotic therapy.



Stopping bone loss during lactation. Lactating mothers transfer large amounts of calcium to offspring via milk. This demand is associated with rapid bone loss in the mother; however, the mechanisms of bone loss during lactation are not completely understood. Parathyroid hormone–related protein (PTHrP) is secreted by the lactating mammary gland to regulate bone turnover during lactation. Because mammary development fails in $PTHrP^{-/-}$ mice, these mice cannot be used to address this possibility. As an alternative, John Wysolmerski and colleagues designed mice to delete PTHrP specifically in mammary epithelial cells during late pregnancy and lactation. Mammary gland PTHrP mRNA and milk PTHrP protein were almost completely absent (pages 1429–1436). Removal of PTHrP from the lactating mammary glands resulted in reductions in bone turnover and attenuated bone loss during lactation. This study suggests that during lactation, mammary epithelial cells are a source of circulating PTHrP, which promotes bone loss by increasing rates of bone resorption.



ARNT mice controlling skin function? Aryl hydrocarbon receptor nuclear translocator (ARNT), a transcription factor of the Per/AHR/ARNT/Sim family, regulates gene expression in response to environmental stimuli, including xenobiotics and hypoxia. To examine its role in the epidermis, Junji Takeda and colleagues used a *Cre-loxP* system to disrupt *Arnt* in keratinocytes (pages 1372–1382). The newborn *Arnt*$^{-/-}$ mice died within one day due to excessive trans-epidermal water loss. The authors show that architecture of the stratum corneum in these mice is similar to that in control mice, whereas the permeability barrier function and the composition of ceramides are significantly different. In particular, 4-desaturated and 4-hydroxylated ceramide species are diminished in the *Arnt*$^{-/-}$ mice, whereas 4-saturated ceramides are elevated. These data suggest that a direct or indirect interaction of ARNT with desaturase- or hydroxylase- species on the transcriptional or on the protein level is crucial for maintaining the epidermal barrier function.



Diversity is the spice of autoimmune life. A diverse T cell repertoire is required for the pathogenesis of organ-specific autoimmune diseases, such as experimental autoimmune encephalitis and diabetes mellitus. In contrast, the repertoire of autoreactive T cells that drives systemic autoimmune diseases such as lupus is poorly characterized. Whether help for autoantibody production comes from a finite number of T cells or a more diverse repertoire remains an unanswered question. Here, Terri Laufer and colleagues use a chronic graft-versus-host disease model of systemic autoimmunity to examine the diversity of the T cell repertoire required for antinuclear antibody formation (pages 1361–1371). The authors find that loss of B cell tolerance can be divided into two distinct components with different $CD4^+$ cell requirements. $CD4^+$ cell diversity is specifically required for the trafficking of $CD4^+$ cells into the B cell follicle and the production of isotype-switched IgG autoantibodies. This work provides new insight into the pathogenesis of lupus and suggests therapeutic targets.