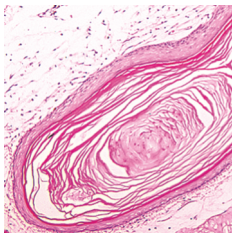
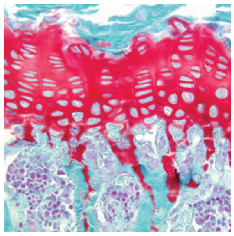
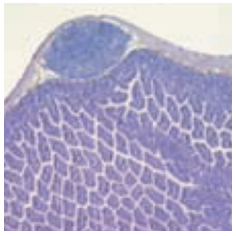


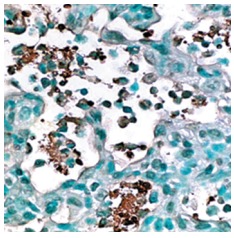
Skin regeneration is easy. The epidermal layer of the skin is a rapidly renewing tissue and relies on the regenerative capacity of keratinocytes. As a result, skin transplants using cultured epidermis have been successful in treating patients with severe skin wounds. To determine the cells responsible for rapid epidermal regeneration, Pritinder Kaur and colleagues separated epidermal stem cells from their progeny by FACS techniques and assayed their abilities to regenerate epidermal tissue in both in vitro and in vivo settings (pages 390–400). As expected, keratinocyte stem cells displayed robust regenerative capabilities, but transit-amplifying cells and early differentiating cells, which are more committed progenitor cells, could also form a fully stratified epidermis under appropriate microenvironmental conditions. This work presents important new considerations for the development of cellular therapies for clinical applications.



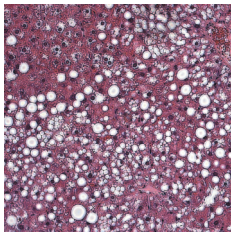
gp130: one pathway with multiple outcomes. Mammalian skeletal growth and maintenance involves cooperation among bone formation, resorption, and remodeling. Cytokines such as IL-6 are known to signal through a receptor complex containing the common gp130 coreceptor signaling subunit. Both the STAT1/3 and SHP2/ras/MAPK pathways are initiated by gp130 signaling, but the distinct downstream effects of these two pathways on bone development were previously unknown. Natalie Sims and colleagues now resolve the effects of these signaling pathways by targeted mutagenesis of gp130 in mice, which renders them deficient in either STAT1/3 activation or SHP2/ras/MAPK activation (pages 379–389). The authors report that STAT1/3 activation is involved in chondrocyte proliferation and osteoblastogenesis, whereas SHP2/ras/MAPK activation plays a key role in inhibiting osteoclastogenesis. These insights may provide new therapeutic targets for improving bone growth and bone density in mammals.



Cancer immunotherapy with low-affinity epitope vaccination. Antitumor immunotherapy is a challenging endeavor since most human tumor–associated antigens are nonmutated self-proteins expressed on normal tissues. The ideal vaccination approach requires self-tolerance while eliciting an effective antitumor response. In an effort to design the ideal vaccine, David Gross and colleagues examined epitopes derived from murine telomerase reverse transcriptase (mTERT) as potential immunogenic anticancer vaccines (pages 425–433). They found that epitopes with a low affinity for HLA class I molecules could be modified to generate an antitumor immune response without stimulating an autoimmune response. In vivo, mice vaccinated with the modified low-affinity epitopes maintained tumor immunity, while mice vaccinated with high-affinity epitopes died after challenge with tumor cells. These studies highlight the importance of rational epitope selection for cancer vaccines.



TNF-α keeps the type 1 immune response in check. TNF-α is a cytokine produced by innate immune and Th1 cells known to be involved in protective (type 1) antimicrobial immunity. Zhou Xing and colleagues sought to elucidate the role of this cytokine in the type 1 immune response by characterizing TNF-α–deficient mice upon challenge with microbial infection (pages 401–413). They observed that mice deficient in TNF-α died upon pulmonary infection with myobacteria and suffered from an overactivation of the type 1 immune response as evidenced by expansion of CD4 and CD8 cells, increased frequency of antigen-specific T cells, overproduction of proimmune cytokines IFN-γ and IL-12, and severe lung injury. Establishing TNF-α as a negative regulator of type 1 immunity has important implications for the development of therapeutic strategies that aim to block TNF-α.



Leptin aims for the central nervous system. Leptin administration has been highly successful in treating the diabetes, insulin resistance, and hepatic steatosis associated with lipodystrophy. This adipocyte hormone acts on a variety of tissues including the brain, skeletal muscles, heart, and pancreatic β cells. Jeffrey Friedman and colleagues have identified the CNS as the primary site of action for leptin's effects on metabolic improvement in lipodystrophy (pages 414–424). Using a congenital mouse model of lipodystrophy, the authors observed that subcutaneous administration of leptin was not as potent as lower doses administered directly to the CNS. Furthermore, using microarray technology, the authors identified repression of the enzyme SCD-1 as a mechanism of leptin action to improve hepatic steatosis. These findings may have profound effects on the progression of leptin treatment strategies for metabolic diseases.