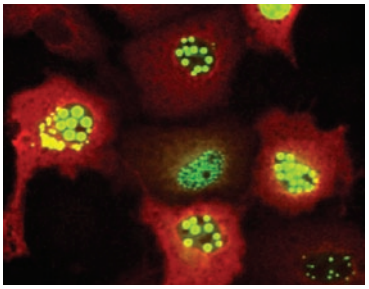
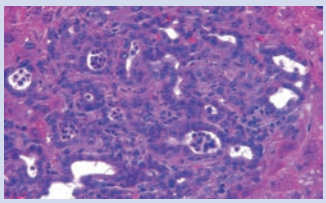
World-class IIa HDACs control cardiac growth



Nucleosomes package DNA into chromosomes inside the cell nucleus and help control gene expression. Enzymes known as class IIa histone deacetylases (HDACs) cause histone deacetylation, which constricts the nucleosome and represses gene activation. Many enzymes known as serine/threonine kinases control where HDACs are localized inside the cell, but whether certain class IIa HDACs respond selectively to specific kinases had not previously been determined. Backs and colleagues now show that the enzyme calcium/calmodulin-dependent kinase II (CaMKII) signals specifically to HDAC4 by binding to a unique docking site on this enzyme that is absent in other class II HDACs (pages 1853–1864). CaMKII-mediated phosphorylation of HDAC4 promotes the export of HDAC4 out of the cell nucleus and prevents its entry into the nucleus, thereby lifting the HDAC-mediated repression of specific genes. The authors also show that CaMKII-mediated phosphorylation of HDAC4 in cardiac cells results in cardiomyocyte enlargement. The study provides new insight into CaMKII and HDAC signaling pathways in the regulation of cardiac growth.

A mouse model of cholangiocellular carcinoma

Cholangiocellular carcinoma (CC) is a malignant epithelial neoplasm associated with bile duct epithelial differentiation and poor prognosis. The molecular mechanisms associated with CC initiation and progression are unclear, which is due in part to the lack of a proper mouse model. In this issue, Xu and colleagues describe a new mouse model of CC wherein the tumor suppressors SMAD4 and PTEN are specifically deleted in the liver (pages 1843–1852). In SMAD4 and PTEN liver-specific knockout mice, neoplastic foci emerged exclusively from bile ducts at 2–3 months of age, leading to tumor formation in all older animals. High levels of phosphorylated AKT, GSK-3β, mTOR, and ERK and abnormally increased nuclear levels of cyclin D1 were associated with tumor progression. The authors show that SMAD4 and PTEN regulate each other to maintain an expression balance and synergistically repress CC formation. The absence of either gene triggers the overexpression of the other, and conversely, as a part of a negative regulation loop, SMAD4 represses transcription of PTEN while PTEN promotes SMAD4 degradation, uncovering a molecular basis for the synergistic action between SMAD4 and PTEN in repressing CC formation.



Immunotherapy boosts the effectiveness of chemotherapy

The cellular components of the stroma of a tumor are more genetically stable than tumor cells, which makes them a more attractive target for cancer immunotherapy than the tumor cells themselves. Accordingly, Loeffler and colleagues generated an oral DNA vaccine targeting fibroblast activation protein (FAP), which is selectively overexpressed by tumor-associated fibroblasts (pages 1955–1962). In mice, oral administration of the vaccine induced a FAP-specific cytotoxic $CD8^+$ T cell response that suppressed the growth of both a colon and a breast carcinoma cell line and decreased their metastasis. Vaccination was associated with decreased expression of collagen type I in the remaining tumors and increased uptake of chemotherapeutic agents by the tumor cells. Consistent with this, when compared with administration of either agent alone, the combination of the vaccine with the chemotherapeutic agent doxorubicin markedly increased the suppression of tumor cell growth, induced tumor rejection in 50% of mice, and increased the lifespans of mice challenged with a breast carcinoma cell line. These data show that targeting a tumor-associated fibroblast–specific antigen is a valid cancer immunotherapy approach and will hopefully lead to new combination approaches for the treatment of cancer.

Antimicrobial (poly)peptides rise to the surface

The skin encounters many microorganisms, but human infections of this tissue are rare. This is mainly because the skin is a physical barrier to microorganisms. However, Sørensen and colleagues now show that antimicrobial (poly)peptides (AMPs), which are produced by epithelial cells in the skin during the innate immune response to infection, are produced in situations in which the risk of infection is high and can prevent infections from developing (pages 1878–1885). Large amounts of several AMPs, including human β-defensin–3 (hBD-3), were induced in an ex vivo model of sterile wounding and in in vivo human cutaneous wounds. Induction of AMPs was dependent on transactivation of the EGFR by heparin-binding EGF that was released from the cell membrane by a disintegrin and a metalloprotease–17 (ADAM-17). The concentration of hBD-3 produced by sterile wounding was estimated to be higher than that known to be required for killing *Streptococcus pyogenes*, and extracts of EGFR-activated epidermal cell cultures had substantially greater antibacterial activity against *Staphylococcus aureus* than did extracts of control cultures. Because expression of AMPs is also induced by sterile wounding in flies, the authors suggest that this response might be a common antibacterial mechanism associated with situations in which the risk of infection is high.