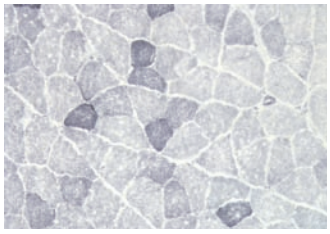
Peroxynitrite tolerates pain

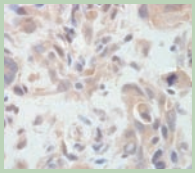
Individuals using opiates chronically to relieve pain must take higher and higher doses of the drug to achieve equivalent pain relief (i.e., they exhibit antinociceptive tolerance). Muscoli and colleagues have now provided some insight into the molecular mechanisms behind antinociceptive tolerance in mice, demonstrating a crucial role for peroxynitrite ($ONOO^-$) in this process (pages 3530–3539). Antinociceptive tolerance in mice repeatedly administered morphine was associated with the accumulation of tyrosine-nitrated proteins in the dorsal horn of the spinal cord, increased production of proinflammatory cytokines, oxidative DNA damage, and activation of the nuclear protein poly(ADP-ribose) polymerase. These changes were inhibited, as was the induction of antinociceptive tolerance, if the morphine was administered together with a pharmacological inhibitor of nitric oxide synthesis, a pharmacological scavenger of superoxide, or a pharmacological catalyst for $ONOO^-$ decomposition. The identification of $ONOO^-$ as a mediator of morphine-induced antinociceptive tolerance in mice led the authors to suggest that the development of drugs targeting $ONOO^-$ might provide an adjunct therapy for individuals using opiates to relieve chronic pain.

PGC-1α helps skeletal muscle and pancreatic islets communicate



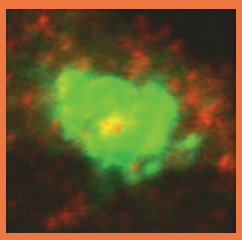
Expression of the regulator of transcription PPARγ coactivator 1α (PGC-1α) is reduced in the skeletal muscle of individuals with type 2 diabetes compared with healthy individuals. By generating mice lacking PGC-1α only in skeletal muscle (MKO mice), Handschin and colleagues have shown that loss of glucose homeostasis is caused, in part, by decreased expression of PGC-1α, rather than the decreased expression of PGC-1α being a downstream effect of loss of glucose homeostasis (pages 3463–3474). When fed either a normal or high-fat diet, MKO mice had much higher blood glucose and much lower blood insulin levels than wild-type mice. Higher levels of proinflammatory cytokines such as IL-6 and TNF-α were found in the skeletal muscle of MKO compared with wild-type mice. Higher levels of circulating IL-6 were also detected. As IL-6 treatment decreased insulin secretion by wild-type and MKO pancreatic islets, the authors suggested that PGC-1α mediates crosstalk between skeletal muscle and pancreatic islets through IL-6.

The origin of the sarcoma



Malignant fibrous histiocytoma (MFH) is a soft tissue sarcoma commonly diagnosed in late adult life, but little is known about the molecular mechanisms of tumorigenesis. However, Matushansky and colleagues have now identified mesenchymal stem cells (MSCs) as the apparent cells of origin of MFH (pages 3248–3257). When compared with a panel of cell lines derived from different sarcomas, the genetic and immunohistochemical profiles of undifferentiated human MSCs were most similar to those of the MFH cell line. Further analysis revealed that proliferating MSCs and the MFH cell line expressed high levels of DKK1, an inhibitor of Wnt signaling. DKK1 inhibition of Wnt2 canonical signaling was shown to prevent MSCs from differentiating. Activation of Wnt2 canonical signaling was not detected in MFH cell lines, and inhibition of Wnt2 canonical signaling in MSCs induced their spontaneous transformation. When these cells were transplanted into immunocompromised mice, tumors with a morphology similar to that of MFH developed. Wnt5a noncanonical signaling through JNK was also not detected in MFH cell lines, and restoring Wnt2 and Wnt5a signaling in MFH cells caused them to differentiate. These data led the authors to suggest that reprogramming MFH cells to differentiate might provide a therapeutic strategy for the treatment of MFH.

New links in the cystic fibrosis chain



The mutations in the gene encoding cystic fibrosis transmembrane conductance regulator (CFTR) that cause cystic fibrosis (CF) have pleiotropic effects. One effect of these mutations is that the pH of the *trans*-Golgi network (TGN) is lower than normal. In in vitro studies reported in this issue (pages 3489–3497), Ornatowski and colleagues identified new links between this cellular change and the pathology and complications of CF. Hyperacidification of the TGN in CF bronchial epithelial cell lines and primary cells from individuals with CF was shown to cause increased activity of the proprotein convertase furin. This, in turn, was found to be responsible for the increased TGF-β produced by the cell line compared with CFTR-corrected cells. The increased levels of TGF-β augmented collagen production (which in situ is associated with tissue fibrosis) and suppressed the ability of human macrophages to kill *Pseudomonas aeruginosa*, infection with which is a major complication for individuals with CF. Furthermore, increased furin activity resulted in increased activation of the *P. aeruginosa* toxin exotoxin A (ExoA) and thereby increased ExoA-mediated cytotoxicity. This study provides strong support for the use of chloroquine (which raises the pH of intracellular organelles) to treat CF, something that is currently being tested in clinical trials, and identifies furin inhibitors as potential new therapeutics.