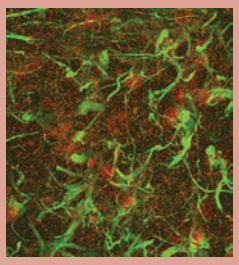
Keeping PPARα on the go leads to HCV-induced liver cancer

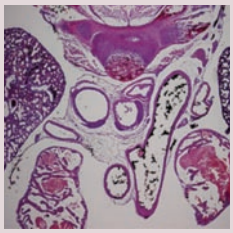
Individuals who are chronically infected with HCV are at increased risk of developing hepatocellular carcinoma (HCC). However, the mechanisms underlying this increased risk have not been determined. Mice engineered to express the HCV core protein (HCVcpTg mice) develop HCC that is preceded by hepatic steatosis, the accumulation of triglycerides in vacuoles in hepatocytes. In this issue (pages 683–694), Tanaka and colleagues have shown that persistent activation of PPARα is required for the development of hepatic steatosis and HCC induced by the HCV core protein. *Ppara*$^{+/+}$:HCVcpTg mice, but neither *Ppara*$^{+/-}$:HCVcpTg nor *Ppara*$^{-/-}$:HCVcpTg mice, developed severe hepatic steatosis as a result of increased hepatocyte uptake of fatty acids and decreased hepatocyte mitochondrial β-oxidation. Similarly, HCC developed only in *Ppara*$^{+/+}$:HCVcpTg mice, and this was observed after the onset of hepatic steatosis. Consistent with the idea that sustained activation of PPARα is required for hepatic steatosis and HCC, treatment of *Ppara*$^{+/-}$:HCVcpTg mice with a PPARα agonist induced hepatic steatosis and HCC characterized by hepatocyte mitochondrial abnormalities. These data have important clinical implications and led the authors to suggest that they might provide new avenues for the development of therapeutic and nutritional approaches to the treatment of individuals chronically infected with HCV.

ADK links epilepsy and brain pathology



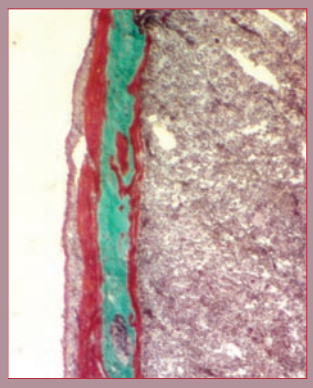
The brain of individuals who suffer from epilepsy is characterized by astrogliosis. Little is known about the mechanisms that link astrogliosis to neuronal dysfunction, but it is hoped that identifying these mechanisms could lead to new possibilities for therapeutic intervention. Using a mouse model of focal epileptogenesis whereby injection of the chemical kainic acid (KA) into the amygdala restricts astrogliosis and epileptogenesis to the CA3 region of the hippocampus, Li and colleagues have shown that adenosine kinase (ADK) expressed by astrocytes is a key molecular link between astrogliosis and neuronal dysfunction (pages 571–582). Expression of ADK was shown to be upregulated only in the CA3, and spontaneous focal electroencephalographic seizures were also restricted to this region of the brain. Consistent with a central role for ADK in neuronal dysfunction, transgenic expression of ADK in the CA3 induced spontaneous seizures in this region of the brain, and mice in which expression of ADK was reduced in the forebrain were resistant to KA-induced epileptogenesis. Furthermore, ADK-deficient ES cell–derived neural progenitor grafts suppressed astrogliosis, ADK upregulation, and seizures when implanted after KA administration. These data therefore led the authors to suggest that increased expression of ADK might predict epileptogenesis and that ADK-based therapeutic strategies might provide a new approach for the treatment of individuals with epilepsy.

Myocardin helps plug the ductus arteriosus



Patent ductus arteriosus (PDA) is one of the most common congenital heart defects. It occurs when the ductus arteriosus (DA), the muscular artery that acts as a shunt between the pulmonary artery and aorta in a fetus, fails to close after birth. Recent studies have indicated that in full-term infants PDA frequently has a genetic basis, and Huang and colleagues have now identified the gene encoding myocardin and myocardin-regulated genes as candidate genes that might have a role in the pathogenesis of PDA (pages 515–525). Mice in which the gene encoding myocardin was selectively inactivated in neural crest cells, which give rise to VSMCs, were born at the normal mendelian ratio but died of PDA before day 3 of life. Neural crest–derived SMCs in the DA of the mutant mice lacked expression of myocardin-regulated genes encoding SMC contractile proteins. Moreover, elimination of myocardin in primary aortic SMCs markedly reduced the expression of proteins responsible for the SMC contractile phenotype and induced the expression of genes encoding ECM. These data led the authors to suggest that myocardin has a central role in maintaining the SMC contractile phenotype and repressing the SMC synthetic phenotype.

Softly, softly: *Phex* mutation in osteoblast lineage cells causes rickets



X-linked hypophosphatemia (XLH) is the most common form of inherited rickets. It is caused by loss-of-function mutations in *PHEX* (phosphate-regulating gene with homologies to endopeptidases on the X chromosome). Mice with a mutation in *Phex* are known as *hyp*-mice and have symptoms similar to those in individuals with XLH. *PHEX*/*Phex* expression is not limited to bone cells of the osteoblast lineage, and there are conflicting reports as to whether defects in cells other than osteoblast lineage cells are involved in the disease that develops in individuals with XLH and *hyp*-mice. However, Yuan and colleagues have now shown that mice in which *Phex* was eliminated only in osteoblasts and osteocytes recapitulate the disease observed in *hyp*-mice (pages 722–734). Indeed, mice in which *Phex* was eliminated in all cells, mice in which *Phex* was eliminated only in osteoblasts and osteocytes, and *hyp*-mice showed similar decreases in serum phosphate levels, similar defects in kidney phosphate transport, and similar levels of osteomalacia. These data led the authors to conclude that loss of *Phex* in osteoblasts and/or osteocytes is sufficient to manifest the *hyp*-mouse phenotype.