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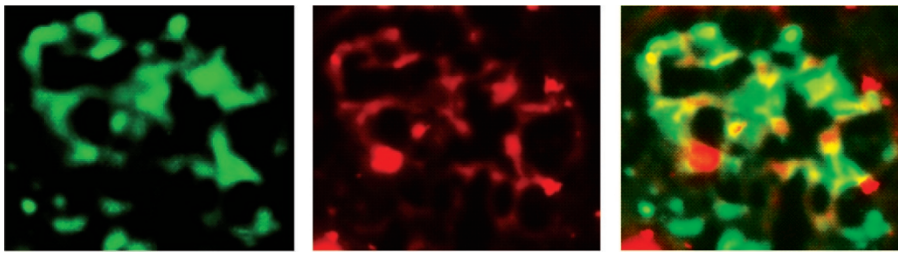


New inflammatory pathway involved in hypercholesterolemic nephropathy

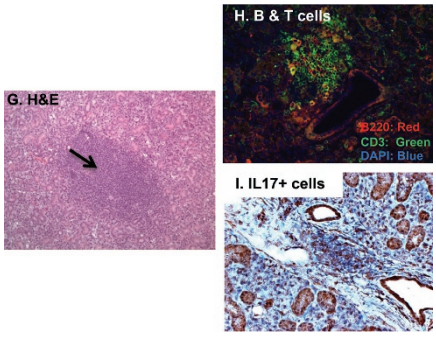
See page 106

Obesity has reached epidemic proportions in the United States, resulting in a major public health problem. Chronic obesity may result in extensive end-organ damage. Recent studies have shown that hyperlipidemia—in particular, hypercholesterolemia—is associated with renal macrophage–mediated inflammation, resulting in mesangial and epithelial cell injury and subsequent fibrosis and glomerulosclerosis. Urokinase plasminogen activator (uPA) is abundant in the kidney and has been implicated in various inflammatory–fibrotic disorders through its classic receptor, uPAR. The muscle-type nicotinic acetylcholine receptor α1 (nAChRα1) has recently been identified as an alternative urokinase receptor. Zhang *et al* reported that nAChRα1 played a role in the pathogenesis of an obstructive uropathy model of chronic kidney disease (CKD). In a study described in this issue, they investigated whether nAChRα1 was involved in the pathogenesis of hyperlipidemia-associated CKD.

Using a mouse model of hyperlipidemia-associated CKD, they demonstrated that renal nAChRα1 expression was strong and was associated with an increase in calcium and calpain-1, a cytosolic calcium–dependent cysteine protease known to be a pro-inflammatory protein. Downregulation of nAChRα1 resulted in decreased renal calcium, attenuation of calpain-1 activation, and decreased renal pathological changes, whereas upregulation of calpain-1 exacerbated the pathological changes and renal impairment. Identification of this pathway and its role in hyperlipidemia-associated CKD highlights the potential for therapeutic targeting. The authors point out that this novel nAChRα1–calpain-1 activation pathway may also be involved in other inflammatory disorders.

The role of IL17 in Sjögren's syndrome

See page 54



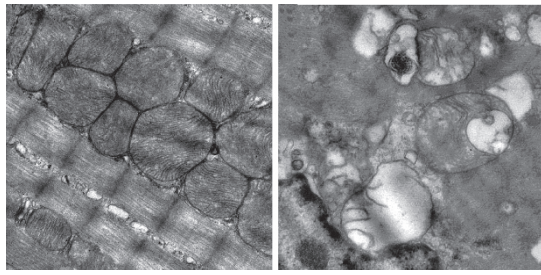
Sjögren's syndrome (SS) is a chronic, systemic autoimmune disease characterized by inflammation of the lacrimal and salivary glands, resulting in characteristic dry eyes and mouth. Recently, $CD4^+T_H17$ memory cells were identified within the lymphocytic foci of lacrimal and salivary glands in a mouse model of SS as well as in the minor salivary glands of human SS patients. While T_H17 effector cells can secrete any of six IL17 family cytokines, IL17A (IL17) has received the most attention in studies of autoimmune diseases. IL17 has been identified in the salivary glands of SS patients, and high levels have been detected in the sera and saliva of SS patients. On the basis of this data, Nguyen *et al* asked whether blocking IL17 might inhibit SS in a mouse model.

By directly inoculating salivary glands with an adenovirus vector expressing IL17R:Fc, which blocks IL17, the authors were able to demonstrate that inhibiting IL17 at an early disease stage could prevent the development of SS. More importantly, blocking IL17 at later stages led to disease regression and improved salivary gland function. Furthermore, even though the investigators inoculated only salivary glands, they demonstrated that IL17 blockade extended beyond the salivary glands to other organs. Further studies are required to determine the long-term effects of IL17 blockade by adenovirus expressing IL17R:Fc. Nevertheless, these promising studies point to a pronounced therapeutic effect of IL17 blockade and suggest that this therapeutic strategy might also be useful in the treatment of other autoimmune diseases.

Endogenous SO_2 protects against myocardial injury by increasing antioxidant capacity

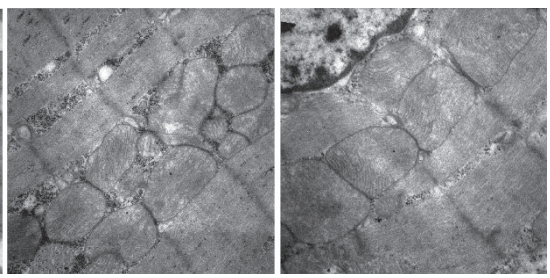
See page `12

Sulfur dioxide (SO_2) is generally recognized as an air pollutant with potential for toxicity after long-term exposure. However, there is mounting evidence that SO_2 may have beneficial



effects. Endogenous SO_2 is probably generated through metabolism of sulfur-containing amino acids and has recently been identified in vascular tissues. The highest concentrations of SO_2 were identified in the aorta, prompting Du and colleagues to ask whether SO_2 might have a role in protecting cardiac tissue from injury.

Using a rat model of isoproterenol (ISO)-induced acute myocardial injury, the authors demonstrated that ISO treatment led to reduced myocardial sulfite content, which correlated with reduced glutamate oxaloacetate transaminase (GOT) mRNA and protein activity. This is relevant because GOT has been implicated as playing an important role in production of endogenous SO_2. Administration of exogenous SO_2 resulted in increased myocardial sulfite and improved cardiac function after administration of ISO. Examination of ISO-treated cardiac tissue revealed extensive mitochondrial injury that was greatly ameliorated in rats co-treated with exogenous SO_2. ISO-treated cardiac tissue also demonstrated reduced antioxidant capacity, which was also reversed by supplementation with exogenous SO_2. Thus, diminished SO_2 in ISO-treated hearts appears to be responsible, at least in part, for a reduction in antioxidant capacity that results in mitochondrial damage and subsequent myocardial death. These results suggest that increasing myocardial SO_2 would be useful in the prevention of myocardial damage after ISO-induced myocardial injury. Further studies will be necessary to determine whether a decrease in SO_2 has a role in other types of myocardial injury.



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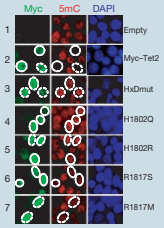
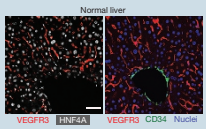
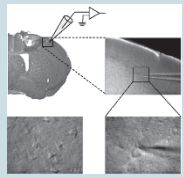


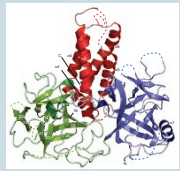
Loss-of-function TET2 mutations and myeloid tumorigenesis TET2 converts 5-methylcytosine to 5-hydroxymethylcytosine (5hmC) in DNA. Mutations in TET2 are frequently associated with myelodysplastic syndromes (MDS) and myeloid leukemias. In a recent letter in *Nature*, Ko *et al* report their study of the relationship between TET2 mutations and MDS and myeloid leukemias. They discovered that the TET2 mutations were loss-of-function mutations that impaired catalytic activity and resulted in loss of 5hmC. Depletion of Tet2 in mouse bone marrow stem/progenitor cells revealed a role for Tet2 in normal myelopoiesis, leading to increased numbers of monocytes and macrophages. Finally, they demonstrated that 5hmC levels correlated with global hypomethylation in human tumor samples, suggesting a mechanism for how loss-of-function TET2 mutations could lead to tumorigenesis. The authors suggested that 5hmC status could be used to predict which patients might respond to DNA methyltransferase inhibitor therapies.
Nature, published online 7 November 2010; doi:10.1038/nature09586



Crucial role of endothelial cells in liver regeneration At present, the only treatment for end-stage liver failure is liver transplantation, but the demand for donor livers far outstrips the supply. Understanding the mechanisms behind liver regeneration is therefore critical to designing therapies to regenerate damaged livers. As described in a recent letter in *Nature*, Rafii and colleagues sought to understand the role of liver sinusoidal endothelial cells (LSECs) in mediating hepatic regeneration. They demonstrated that an organ-specific $VEGFR3^+CD34^-VEGFR2^+VE\text{-}cadherin^+FactorVIII^+Prox1^-CD45^-$ LSEC orchestrates a biphasic liver-regeneration mechanism. In the early phase after partial hepatectomy, inductive angiogenic LSECs promote regeneration through release of angiogenic factors, whereas in the later phase, proliferative angiogenic LSECs vascularize and sustain the expanding liver mass. These results suggest that therapeutic strategies to regenerate liver tissue should combine endothelial progenitor cells or LSECs with hepatocytes.
Nature 2010;468:310–315; doi:10.1038/nature09493



GABA-mediated tonic inhibition suggests a therapeutic strategy for improving function after stroke Strokes often lead to permanent brain damage with devastating consequences for patients and their families. Recent studies have shown that stimulation of cerebral cortex surrounding the site of stroke damage can improve functional outcomes. GABAergic transmission in the peri-infarct cortex has been shown to dampen neuronal excitability. On the basis of these findings, Clarkson *et al*, in a recent letter in *Nature*, hypothesized that inhibition of GABAergic transmission subsequent to stroke would improve functional outcomes. They demonstrated that pharmacological inhibition of GABAergic transmission did indeed improve functional outcomes. However, the timing and duration of administration of GABAergic antagonists were critical. Administration of antagonists at the onset of a stroke actually increased the area affected by the stroke whereas administration 3 days after onset promoted functional recovery. Furthermore, prolonged antagonism of GABAergic transmission caused a progressive decrease in motor function.
Nature 2010;468:305–309; doi:10.1038/nature09511



Structural studies of ryanodine receptors provide insight into the mechanism of disease-associated mutations Ryanodine receptors (RyRs) are ion channels that control calcium release from endoplasmic and sarcoplasmic reticulum and are important in excitation–contraction coupling in muscle. RyR mutations are found in a variety of skeletal and cardiac muscle diseases. To understand how these mutations cause RyR dysfunction, Van Petegem and colleagues, as reported in a recent letter in *Nature*, obtained the crystal structure of the amino terminal portion of RyR type I. Based on the location of the disease-associated mutations within the crystal structure, they hypothesize that the disease-associated mutations destabilize the closed state of the receptors, resulting in leaky channels.
Nature, published online 3 November 2010; doi:10.1038/nature09471