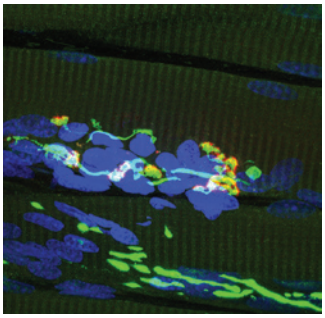
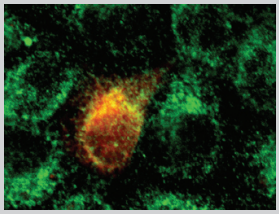
MuSK: the myasthenic perfume



Myasthenia gravis (MG) is an autoimmune disease characterized by the production of antibodies against AChR. AChR-specific antibodies are detected in 90% of nonimmunosuppressed MG patients; however, antibodies against a novel antigen, muscle-specific kinase (MuSK), have been found in approximately 70% of patients with generalized MG who lack detectable AChR autoantibodies. Shigemoto and colleagues demonstrate that MuSK autoantibodies are also pathogenic in MG (pages 1016–1024). Immunization of rabbits with MuSK ectodomain protein caused myasthenic weakness and produced electromyographic findings compatible with MG and consistent with a significant reduction in AChR clustering at the neuromuscular junction. MuSK antibodies specifically inhibited in vitro AChR clustering responses to all known stimuli. Thus, MuSK autoantibodies rigorously inhibit AChR clustering mediated by multiple pathways, an outcome that broadens our general comprehension of the pathogenesis of MG.

Cataloging Claudin mutations

Claudin-16 (Cldn16) is selectively expressed in the tight junctions of renal epithelial cells of the thick ascending limb of Henle's loop, where it regulates the reabsorption of divalent cations. More than 20 different mutations in *CLDN16* have been identified in patients with familial hypomagnesemia, hypercalciuria, and nephrocalcinosis, a disease of excessive renal Mg^{2+} and Ca^{2+} excretion. Kausalya and colleagues now show that the mutations are of 2 varieties: those that lead to the intracellular retention of Cldn16 and those that affect its capacity to facilitate paracellular Mg^{2+} transport (pages 878–891). Nine of the mutants are retained in the endoplasmic reticulum, where they undergo proteasomal degradation. Three mutants accumulate in the Golgi complex; 2 mutants are efficiently delivered to lysosomes. The remaining 7 mutants localize to tight junctions, and at least 4 of these are defective in paracellular Mg^{2+} transport. Pharmacologic chaperones were used to rescue surface expression of several retained Cldn16 mutants. Understanding the molecular defects associated with disease-causing Cldn16 mutations may lead to a therapeutic treatment.



Obesity: it's all in your head

Rats presented with a lard-supplemented diet double their caloric intake and develop severe hepatic insulin resistance within 3 days. Using this as a model of human obesity, Pocai and colleagues further investigate how to trick overfed rats into eating less (pages 1081–1091). They exploit the finding that hypothalamic metabolism of fatty acids can control feeding and glucose metabolism. Central administration of long-chain fatty acids (LCFAs) inhibits feeding in normal but not in overfed rats. Here the authors show that an increase in circulating lipids fails to increase the levels of esterified LCFAs in the mediobasal hypothalamus in overfed rats and that the activity of liver enzyme carnitine palmitoyltransferase-1 (CPT1) is selectively increased in the arcuate nuclei of overfed rats. Central inhibition of CPT1 decreased food intake and restored hypothalamic LCFA regulation. This work provides the first direct demonstration for impaired sensing of lipids in overfed rats and demonstrates that restoring the hypothalamic levels of esterified LCFAs via inhibition of CPT1 is sufficient to normalize food intake, body weight gain, and glucose homeostasis. A strategy designed to restore lipid sensing within the arcuate nuclei of the hypothalamus could potentially be an obesity treatment.

A tough Itch to scratch

Although extensive studies have been performed to understand the induction of T cell tolerance, the link between Th2 tolerance and control of allergic inflammation is not well understood. Here, Venuprasad and colleagues provide evidence that MEKK1/JNK signaling converges with the Itch-mediated protein ubiquitination pathway in the control of Th2 tolerance and allergic asthma (pages 1117–1126). The authors used a MEKK1 mutant and $JNK1^{-/-}$ mice to demonstrate that, like $Itch^{-/-}$ T cells, T cells from MEKK1 mutant or $JNK^{-/-}$ mice are also resistant to the induction of tolerance. The authors then linked Th2 tolerance to asthma by combining an in vivo tolerance protocol using high-dose soluble antigen with a mouse model of asthma. Although asthma could be prevented with high-dose soluble antigen pretreatment in control mice, mice lacking the Itch E3 ligase still developed an allergic reaction. Thus, these results highlight a novel genetic pathway linking MEKK1/JNK signaling to E3 ligase–mediated protein ubiquitination, which is critical in the induction of Th2 tolerance and airway inflammation.