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In This Issue

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Leptin gives itself some negative feedback Leptin is a regulator of energy homeostasis that acts in the CNS to tell the body that energy stores have been restocked and that it can stop feeding. Many individuals who are obese exhibit leptin resistance (an inappropriately small response to high leptin levels), and one possible cause of this is that leptin might poorly activate its receptor (LRb). To gain insight into the physiologic function of a specific leptin-stimulated LRb signal, Björnholm and colleagues generated mice in which one of the LRb tyrosine residues (Tyr985) that is phosphorylated following leptin binding was mutated (pages 1354–1360). Female but not male mice expressing two mutant LRb molecules weighed less than normal mice, did not become obese when fed a high-fat diet, and exhibited decreased feeding and decreased production of neuropeptides that stimulate appetite. In addition, these female mice were more sensitive to leptin administration than wild-type female mice. These data indicate that leptin-mediated phosphorylation of Tyr985 inhibits leptin-mediated LRb signaling in female mice. The authors therefore propose that this negative-feedback pathway might contribute to leptin resistance in some obese individuals, in particular, femalesPlugging a Ca2+ leak may cause familial Alzheimer disease Familial Alzheimer disease (FAD) is an inherited early-onset form of Alzheimer disease. Mutations in the genes encoding presenilin-1 and presenilin-2 have been identified in […]

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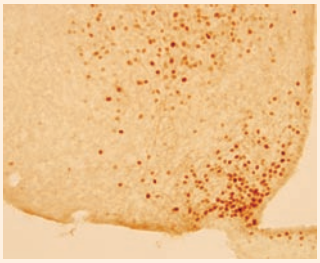

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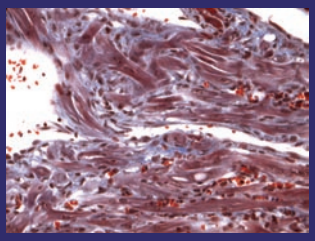
RyR2 mutants have big hearts



RyR2 is a Ca^{2+} release channel expressed by cardiac muscle cells that has an important role in cardiac excitation-contraction coupling. In vitro studies have shown that calmodulin (CaM) inhibits RyR2 function, but the physiological significance of this had not been determined. So Yamaguchi and colleagues generated mice expressing a mutant form of RyR2 that could not bind CaM (pages 1344–1353). Mice expressing only the mutant RyR2 showed signs of cardiac hypertrophy as early as one day after birth and died within 16 days of birth. Further analysis indicated that cardiac muscle cells from these mice showed abnormal release of Ca^{2+} from the sarcoplasmic reticulum and that the heart rates of these mice were substantially slower than the heart rates of wild-type mice. This study indicates that CaM inhibition of RyR2 is crucial for normal cardiac function in mice and might have clinical relevance because mutations in the gene encoding RyR2 have been associated with several forms of aberrant heart function in humans. However, it will first be important to determine whether impaired CaM inhibition of RyR2 is associated with human cardiac pathologies.

Plugging a Ca^{2+} leak may cause familial Alzheimer disease

Familial Alzheimer disease (FAD) is an inherited early-onset form of Alzheimer disease. Mutations in the genes encoding presenilin-1 and presenilin-2 have been identified in a substantial proportion of individuals with FAD, but the molecular effects of these mutations have not been clearly defined. In this issue (pages 1230–1239), Nelson and colleagues report on their use of in vitro assays to determine that, unlike wild-type presenilin-1, five of the six FAD-associated mutant forms of presenilin-1 analyzed do not allow Ca^{2+} to passively leak from the ER. For one mutant (A246E), the initial observations were corroborated by the observation that primary fibroblasts from an individual with FAD who expressed this mutant form of presenilin-1 did not passively leak Ca^{2+} from the ER. As mutations in the gene encoding presenilin-1 that are associated with a distinct neurological disorder, frontal temporal dementia, did not affect Ca^{2+} leakage from the ER, the authors concluded that the molecular effects of these mutations in the gene encoding presenilin-1 are disease specific. However, further studies are required to determine the connection between altered Ca^{2+} homeostasis and the pathogenesis of FAD.

Why don't mothers' bodies reject their fetuses?

The immune system is designed to attack anything that is not self, such as pathogens and genetically nonidentical organ transplants, so why does the maternal immune system not attack a developing fetus? In this issue (pages 1399–1411), Erlebacher and colleagues discuss their investigation of when, where, and how fetal antigens were presented to maternal T cells in pregnant mice. Female mice carrying fetuses expressing the antigen ovalbumin were transplanted with either $CD4^+$ or $CD8^+$ T cells expressing a TCR specific for ovalbumin. Both cell types were shown to recognize ovalbumin presented by maternal APCs but not ovalbumin presented by fetal cells. Presentation of ovalbumin by maternal APCs was detected from mid-gestation onward and did not prime the T cells to attack the fetuses; rather, it induced the deletion of the ovalbumin-reactive T cells. Furthermore, even when ovalbumin-specific T cells were provided with signals that primed them fully, they still did not attack the fetuses. This study therefore indicates that there are several mechanisms by which the developing fetus is protected from attack by maternal T cells. First, the T cells cannot recognize antigen presented by fetal cells; second, even when T cells recognize fetal antigen presented by maternal APCs, they are not primed and undergo clonal deletion; and third, even if the T cells were fully primed, they would not attack the fetus.