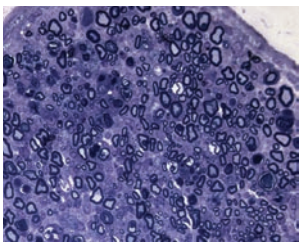
Appetite control requires PI3K signaling

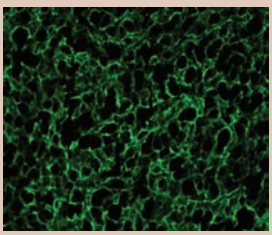
Obesity can result from abnormal action of the adipose-derived hormone leptin on hypothalamic proopiomelanocortin (POMC) neurons. Recent work suggests that leptin activates PI3K signaling in the hypothalamus, but the role of a central leptin-PI3K pathway in energy regulation remained to be established. In this issue (pages 1796–1805), Hill and colleagues have shown that POMC PI3K signaling is essential for leptin-induced activation of POMC cells in mice. Analysis of hypothalamic slices indicated that leptin caused rapid depolarization and increased the action potential frequency of POMC neurons. Mice with genetically disrupted PI3K signaling in POMC cells failed to undergo POMC depolarization or increase firing frequency in response to leptin, and targeted disruption of PI3K interfered with leptin-induced suppression of feeding. Despite these short-term physiological consequences, the absence of POMC PI3K signaling had no detectable impact on long-term body weight homeostasis. These data led the authors to propose that POMC PI3K signaling is essential for leptin-induced activation of POMC cells and suppression of food intake, but that PI3K signaling in POMC neurons is not the primary signaling pathway by which leptin regulates long-term energy homeostasis.

One regulator, opposite effects on neurodegenerative tauopathies

Intracellular aggregation of the protein tau is a defining neuropathological characteristic of neurodegenerative tauopathies, a group of heterogeneous dementias and movement disorders including Alzheimer disease (AD) and frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). Although mutations in the gene encoding tau have not been identified in individuals with AD, they have been identified in individuals with FTDP-17. In this issue, Lim and colleagues have determined that wild-type tau and one of the most frequent forms of mutant tau in individuals with FTDP-17 (P301L tau) are regulated in opposite ways by Pin1 (protein interacting with NIMA 1) (pages 1877–1889). Consistent with their earlier studies, knockdown and elimination of Pin1 expression in human cell lines and mice, respectively, enhanced the stability of wild-type tau protein, whereas overexpression of Pin1 decreased the stability of wild-type tau protein and suppressed tauopathy in mice transgenic for wild-type tau. By contrast, knockdown and elimination of Pin1 expression in human cell lines and mice, respectively, decreased the stability of P301L tau and suppressed tauopathy in mice transgenic for P301L tau, whereas overexpression of Pin1 enhanced tauopathy in mice transgenic for P301L tau. These data indicate the importance of using appropriate animal models for studying distinct neurodegenerative tauopathies and suggest divergent Pin1-targeted therapies for AD and FTP-17.



MicroRNAs dice with female infertility



Dicer is an RNAse III enzyme required for the generation of microRNAs (miRNAs), endogenously encoded small regulatory RNAs that can posttranscriptionally modulate gene expression. In mice, germline disruption of the gene encoding Dicer1 results in embryonic lethality, and little was known about the effects of global Dicer1 deficiency in adult mice until Otsuka and colleagues analyzed mice carrying a hypomorphic *Dicer1* mutation ($Dicer^{d/d}$ mice) (pages 1944–1954). The only defect observed in the $Dicer^{d/d}$ mice was female infertility caused by corpus luteum insufficiency. Further analysis indicated that the corpus luteum insufficiency was associated with decreased angiogenesis in the corpus luteum and that expression of the antiangiogenic factor tissue inhibitor of metalloproteinase 1 (TIMP1) was upregulated in the ovaries of $Dicer^{d/d}$ mice. As injection of the miRNAs miR17-5p and let7b into the ovaries of $Dicer^{d/d}$ mice decreased expression of TIMP1 and increased corpus luteum vascularity, the authors concluded that the development and function of the corpus luteum in mice is tightly regulated by miRNAs.

Unraveling how IFN-β helps patients with MS

Although IFN-β is a commonly used disease-modifying treatment for individuals with relapsing-remitting MS, the mechanisms underlying its therapeutic efficacy had not been described. However, Guo and colleagues have now delineated a mechanistic pathway by which IFN-β attenuates the development of autoimmune disease in the EAE mouse model of MS (pages 1680–1690). Mice expressing a nonfunctional form of the signaling molecule TRIF (Toll–IL-1 receptor domain–containing adaptor inducing IFN-β) were shown to develop more severe EAE than control littermates, and this was associated with increased infiltration into the CNS of $CD4^+$ Th cells producing IL-17 (Th17 cells). As similar observations were made following analysis of mice lacking the α subunit of the type I IFN receptor (IFNAR), these data indicated that TRIF-induced IFN-β initiates events that negatively regulate Th17-mediated disease. In vitro analysis indicated that IFN-β induced innate immune cells to produce IL-27 and that this cytokine inhibited the development of Th17 cells. These data were shown to have in vivo significance by the observation that administration of IL-27 to mice lacking IFNAR attenuated EAE, leading the authors to suggest that in individuals with MS, the therapeutic efficacy of treatment with IFN-β is likely to be mediated, at least in part, through its ability to induce the secretion of IL-27.