that are involved in controlling the apoptotic, cell cycle arrest and senescence functions of p53. Cells and tissues from mice expressing this mutated p53 showed that the mutations abrogated these cellular functions in response to DNA damage, but, surprisingly, the animals were protected from lymphoma development. The expression of genes involved in modulating mitochondrial respiration and limiting glycolysis and oxidative damage were still induced by p53 in these mice, suggesting that p53 may prevent tumorigenesis by regulating metabolism.

Other, as yet unknown, p53 functions may be also involved in cancer suppression, and future research should aim to elucidate the exact antitumor effect of p53-mediated metabolic and antioxidant functions before new therapeutic approaches can be designed to modulate these tumor suppressor pathways.—CP

■ METABOLIC DISORDERS

A route to leanness

A population of hypothalamic neurons expressing the Agouti-related peptide (AgRP) has been shown to be important in the induction of feeding. Although the hormones leptin and insulin act on these neurons, knocking out either leptin or insulin signaling in AgRP neurons does not seem to affect energy homeostasis. Now, Hongxia Ren et al. show that disabling both these pathways in mice by knocking out a central transcriptional mediator, FoxO1, in AgRP neurons can improve metabolism, resulting in lean mice that eat less (Cell 149, 1314–1326).

The researchers then performed microarray analyses of the AgRP hypothalamic neurons with or without FoxO1 and found that the G-coupled protein receptor Gpr17 was downregulated in FoxO1-deficient neurons. In cell culture studies, they found that FoxO1 directly bound the Gpr17 gene and increased its expression. When they administered Gpr17 agonists into the brain ventricles of mice, this increased feeding. A Gpr17 antagonist decreased feeding, suggesting that targeting this pathway could be used to treat obesity in humans.—EC

■ INFECTION DISEASES

Turning the tide against TB

Multidrug-resistant tuberculosis, accounting for nearly 5% of cases, is difficult and expensive to treat. A recent clinical trial reports positive results for a new drug, delamanid, in people with this form of tuberculosis (N. Engl. J. Med. 366, 2151–2160).

Delamanid, an inhibitor of mycolic acid synthesis, has previously been shown to have antituberculosis activity in both in vitro and in vivo preclinical studies. Gier et al. tested delamanid at two doses in a randomized, placebo-controlled trial. A total of 321 patients with multidrug-resistant tuberculosis were treated with delamanid, as compared to 160 patients treated with placebo, with all patients receiving a background drug regimen. After 2 months of treatment, the two delamanid-treated groups had a higher proportion of sputum cultures that were negative for mycobacterial growth. However, a dose response was not observed. The drug seemed to be well tolerated, although it was associated with an effect on cardiac electrical activity—QT interval prolongation.

Effects on sputum culture growth have previously been associated with long-term outcomes of tuberculosis treatments, but longer clinical trials of delamanid will be needed. In addition, it will be important to determine how delamanid can be used most effectively in combination with other antituberculosis agents.—MB

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