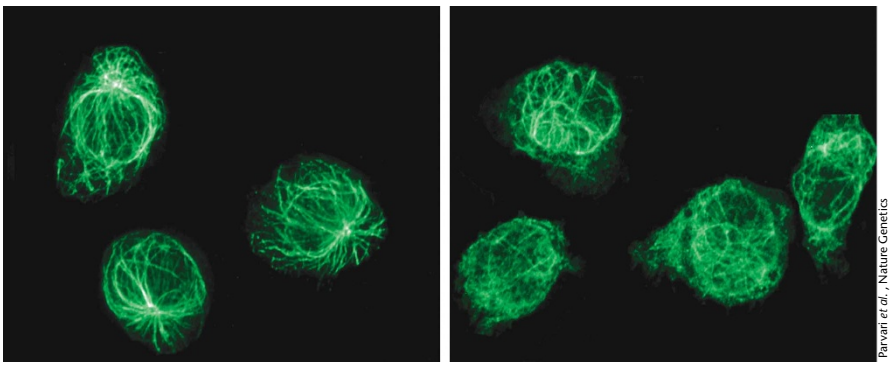

Fig. 2 Individuals with Kenney-Caffey syndrome have cells with abnormal tubulin architecture. ***a***, Organized tubulin in lymphoblastoid cells of a healthy individual. ***b***, Disorganized tubulin in cells from an affected individual.

gene results in a very different genetic disease in mice homozygous for the mutation[2].

The mouse mutation results in an alteration in the last encoded amino acid of murine chaperone E, which the authors show destabilizes the protein. The mice suffer from a progressive degeneration of their motor neurons, resulting in their death 4–6 weeks after birth. These mutant mice were thought to be a model for the human genetic disease spinal muscular atrophy, but the authors have shown that the latter disease is in fact caused by mutations in a different gene. When a construct expressing wild-type chaperone E was inserted into the mouse germline, the phenotype was reversed in homozygous mutant offspring carrying this construct. Although they have very different manifestations, the mouse and human diseases have several features in common. Both result in loss and disorganization of microtubules, and both result in growth retardation, small brains and defective spermatogenesis.

Tubulin protein sequences are highly conserved in all multicellular organisms, suggesting that almost any mutation in these essential building blocks is not tolerated. However, mutations in microtubule-associated proteins are the causes of several inherited human diseases, including frontal-lobe dementia with parkinsonism and lissencephaly (tau mutations)[8], Charcot–Marie–Tooth (*KIF1B* mutation) and Opitz syndrome (*MIDI* mutation). All of these diseases cause major brain impairment, consistent with the important role of microtubules in neuronal architecture and axonal transport. Several diseases, in addition to the tubulin-specific chaperone diseases discussed here, are caused by mutations in chaperones or putative chaperones, for example McKusick–Kaufman syndrome (mutations in the putative chaperonin, MKKS), spastic ataxia of Charlevoix–Saguenay (mutations in SACS, which is similar to hsp90) and desmin-related myopathy (mutations in human β-crystallin, a small heat-shock protein)[9]. In addition, as chaperones deal with misfolded proteins, they are involved in many diseases in which abnormal proteins are deposited as aggregates such as Huntington and Alzheimer disease[9]. Thus chaperones are considered potential therapeutic targets because of their ability to disaggregate and dispose of misfolded proteins.

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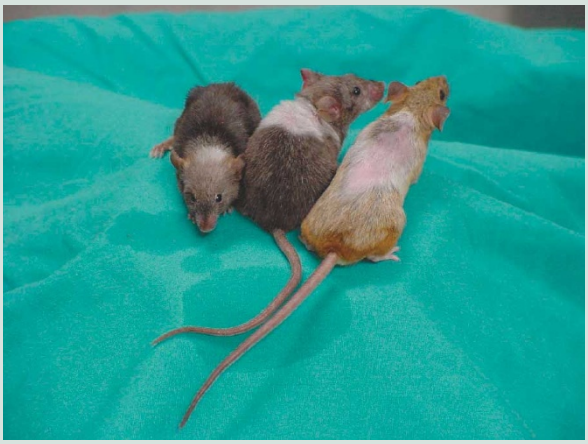
Circadian rhythm beats back cancer



The *Per2* gene helps measure the pace of the circadian rhythm—and now it appears that it also helps keep cancer at bay, according to a study in the October 4 Cell. Fu *et al.* suspected a connection to cancer when they found hyperplasia in the salivary glands of relatively young *Per2*-mutant mice. They next tested the animals' sensitivity to radiation, an indication of cancer susceptibility. Irradiation can damage the cells responsible for hair color. Indeed, after irradiation all of the *Per2* mutant mice developed prematurely gray hair (shown here) and a high frequency of lymphomas as compared to wild-type mice. Mutant mice also had aberrant temporal expression of genes involved in cell cycle regulation and tumor suppression. The researchers honed in on a mechanism for circadian control of one such gene, the p53 regulator c-*myc*. Its transcription is controlled directly by two PER2-controlled clock proteins. The results jibe with previous findings hinting at a link between circadian cycles and cancer; for example, women working the night shift appear to have an increased risk of breast cancer.

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