Research News

New gene for epilepsy

Classical epilepsies, the most common epilepsies, affect 0.4% of the population, and heredity studies clearly show that they have a genetic component. But where are the genes? Variability of symptoms suggests that multiple genes may modify the symptoms, and has vexed gene hunters. In the June *Nature Genetics* Cossette *et al.* examined a unique family that has eight members with a similar set of symptoms of a common form of classical epilepsy, juvenile myoclonic epilepsy (JME). The researchers report the first example of a genetic lesion associated with JME or any classical epilepsy. All eight individuals in this family were heterozygous for mutations in a gene encoding a subunit of the GABA_A receptor, a chloride channel. Sixteen different subunits can contribute to GABA_A in the brain—and a different subunit has been implicated in another, rare form of epilepsy. The new results suggest that screens focusing on these subunits may yield new genetic relationships, and open the door to the development of drugs targeting mutant GABA_A subunits.

Zits and CRH

Breaking out in pimples before your big date is a fear of adolescence—and now it appears that it may be well founded. Researchers have found a link between stress and skin disorders mediated by the stress-related hormone corticotropin-releasing hormone (CRH). In the 14 May *Proceedings of the National Academy of Sciences*, Zouboulis *et al.* show that oil-secreting glands in the skin may produce the same stress signals normally found in the hypothalamus. They found that *in vitro*, human gland-containing skin cells expressed CRH, a CRH-binding protein and the two CRH receptors, CRH-R2 and CRH-R1. CRH induced lipid biosynthesis in these cells, which suggests that CRH may exacerbate acne *in vivo*. The authors provided a hint to relationships of skin problems with age and sex: Testosterone decreased the expression of both CRH receptors, whereas human growth hormone induced higher expression of CRH-R2 but decreased expression of CRH-R1. Understanding how CRH acts in the skin could lead to new treatments for acne and other disorders related to sebaceous glands.

Deleting sperm

A study in mice identifies a new gene required for sperm production. Ron Firestein *et al.* report in the 1 May *Journal of Clinical Investigation* that mice lacking the gene *Sbfl* fail to progress through spermatogenesis and show reduced testes size. Otherwise the mice appeared largely healthy and showed normal mating behavior. *Sbfl* encodes a pseudophosphatase, which is thought to contain catalytically inactive phosphate-binding domains that may sequester phosphorylated substrates. The specific function of *Sbfl* is unknown, but

Reprinted with permission from [C]

the authors report that *Sbfl* RNA and anti-Sbfl antibodies stained seminiferous tubules (RNA shown here). *Sbfl* was expressed in immature sperm and in sperm support cells (Sertoli cells), as well as at low levels in the brain and in the colon. The authors speculate that deficiencies in human *Sbfl* may account for some of the 40% of cases of male infertility that so far resist explanation—which would bring the list of known genes implicated in male fertility to four. *Sbfl* could also be a target for male contraception.

Keeping pace

In recent years organs such as the liver and heart have been shown to keep their own circadian rhythm. Now it's clear that about 10% of the genes in the heart, the liver and the circadian control center in the brain show 24-hour oscillations in expression, and for the most part, they aren't the same genes. That's the conclusion of three studies examining circadian patterns in mice using microarrays. In the 2 April *Current Biology*, Akhtar *et al.* report results for the liver, and in the 3 May *Cell*, Panda *et al.* compare genes in the liver and the suprachiasmatic nucleus, a region in the brain that coordinates circadian cycles. Storch *et al.* compare the heart and the liver in the 2 May *Nature*. The studies suggest that perhaps more than 10% of cell processes show circadian regulation, as many circadian genes in all three organs encode rate-limiting enzymes in key biochemical pathways. These include nutrient and drug metabolism pathways in the liver and neurotransmitter production in the suprachiasmatic nucleus. Some circadian genes in the heart and liver may control common processes, as some of these critical rate-limiting genes oscillated in both organs. Ultimately, clinicians may be able to correlate drug doses at certain times of day with circadian oscillations in the activity of the drug target. Collectively, these results may help point researchers at common cycling genes, perhaps as targets for future drugs to combat jet lag and other problems associated with circadian disruption.

Outcompeting p53

Loss of p53 function occurs in over 50% of cancers, yet which of the many effects of losing p53 has the greatest influence on carcinogenesis remains largely unexplored. Is it the consequent DNA damage, the loss of cell cycle checkpoints or the inability to prevent cell death that drives tumor progression? In the April issue of *Cancer Cell*, Schmitt *et al.* suggest that, at least for certain types of non-Hodgkin lymphoma, it's apoptosis that is key. The researchers examined mice with symptoms of non-Hodgkin lymphoma due to overexpression of the *c-myc* oncogene. Normally, loss of p53 in this background greatly exacerbates cancer progression. The researchers engineered

lymphoma cells to overexpress genes that prevent apoptosis—*Bcl2* and a dominant-negative caspase 9 gene—and then transplanted the cells back into mice. Disruption of apoptosis alleviated the selective pressure for p53 inactivation as the transgenic lymphomas did not develop p53 mutations. Furthermore, these tumors also had most of the hallmarks of p53-deficient lymphomas, including aggressive invasiveness. Whether disruption of p53-mediated apoptosis has a central role in the development of other types of tumors remains to be seen—but the answers may help target drug development to the specific functions of p53 relevant to different cancer types.

Charlotte Schubert and Paul Morin