Research News

Signaling bacterial death

Despite several decades of β -lactam use, the molecular mechanisms by which these antibiotics exert their bactericidal effects have not been clearly established. Drugs such as penicillins, cephalosporins and glycopeptides were originally believed to arrest cell growth by preventing expansion of the bacterial cell wall, but it is now known that these drugs also activate a bacterial autolytic signaling pathway. In the January issue of *Molecular Cell*, Novak *et al.* report that antibiotics induce cell lysis by activating the same signal transduction pathway that bacteria use to control their own density. *Streptococcus pneumoniae* continuously secrete a 27-amino-acid peptide, Pep²⁷, that acts as a cell death signal after reaching a critical concentration. This signal is sensed by the coupled response mechanism VncS-VncR, which in turn activates multiple death pathways, including activation of the autolysin LytA. Disruption of this cell death pathway has been seen in *S. pneumoniae* that are phenotypically tolerant and genetically resistant to antibiotics. The VncS-VncR pathway therefore provides a target for alternative antibiotic therapies to battle bacterial infections.

TV-triggered seizures

A study published in the March issue of *Nature Neuroscience* suggests that photosensitive epilepsy (PSE), a form of cortical hyperexcitability triggered by television and video games, may result from severely impaired contrast gain control in the visual cortex. In 1997, an episode of the Pokémon cartoon triggered seizures in 685 Japanese children, drawing public attention to this common disorder. PSE is caused by an unknown genetic defect, and the resulting brain dysfunction is poorly understood. Now Porciatti *et al.* report that whereas activity recorded from scalp electrodes in normal subjects saturates at a luminance (black-white) contrast of 20%, the response amplitude in PSE patients continued to increase up to a contrast of 90%. This abnormal response was found at frequencies of 4–10 Hz, the range known to trigger seizures, but not at higher frequencies. It is important to improve our understanding of the neurological basis of PSE, as it has a prevalence of 0.5–0.8% in children between ages 4 and 14.

No beer for baby

New data has elucidated the mechanisms by which alcohol intake during pregnancy causes neurotoxicity to the developing fetus. In the 11 February issue of *Science*, Ikonomidou *et al.* demonstrated that ethanol acts through a dual mechanism, as both an NMDA receptor antagonist and a GABA receptor agonist, to trigger an average 15-fold increase in neuronal apoptosis in developing rat forebrain. The areas in which the largest amount of neuronal cell death occurred within 24 hours after ethanol exposure included the hippocampus and the frontal, parietal, and cingulate cortices. The onset of apoptotic neurodegeneration required that blood ethanol concentrations be maintained above a

toxic threshold of 200 mg/dl for at least 4 consecutive hours during the period of embryonic day 19 through post-natal day 14, which coincides with synaptogenesis in the developing rat. This period corresponds to the last trimester of human pregnancy, and the authors suggest that heavy drinking, or treatment during this time period with other NMDA antagonists or GABA agonists, such as sedatives or anticonvulsants, may lead to neurological defects and may also be the basis of fetal alcohol syndrome.

Fat transplantation

Two new reports, both using the same mouse model, have revealed more information about the interplay between obesity and diabetes and the role of leptin in these metabolic disorders. The A-ZIP/F-1 mouse has no white adipose tissue and is the model for human lipodystrophic diabetes, a rare disorder characterized by a lack of fat, insulin resistance and hyperglycemia. This phenotype is unexpected, given the common association of diabetes with obesity. In the February issue of *The Journal of Clinical Investigation*, Reitman and colleagues showed that transplanting physiological amounts of donor fat from wild-type mice into A-

ZIP/F-1 mice reversed the pathology of lipodystrophic diabetes in a dose-dependent manner, indicating that a lack of fat causes the underlying metabolic abnormalities. And in the 24 February issue of *Nature*, Reitman's group refuted an earlier study showing that leptin deficiency accounts for insulin resistance in lipodystrophy, as its infusion into A-ZIP/F-1 mice did not reverse diabetes. Clearly these mice are missing a function provided by fat other than leptin secretion, and the studies indicate that fat transplantation studies could be a valuable approach to understanding adipose physiology and insulin resistance in diabetes.

Pumping iron

Two research groups have independently reported the isolation of a gene encoding what seems to be a long-sought-after iron transporter required for dietary iron absorption and a possible basis for hereditary hemochromatosis (HH). HH is common genetic disorder characterized by increased iron absorption, leading to liver cancer and cirrhosis, endocrine disorders and cardiovascular complications.

In an investigation into zebrafish development, Donovan *et al.* cloned *ferroportin1*, which, they reported in the 17 February issue of *Nature*, encodes a transmembrane protein required for the transport iron from yolk to the embryonic circulation. In another paper, published in the 25 February issue of *Molecular Cell*, McKie *et*

al. described the isolation of the mouse homolog of this transporter, *Ireg1*. Both studies reported that this gene product functions as an iron exporter *in vitro*, localizes to the basolateral membrane of polarized epithelial cells and is expressed in mouse liver and intestine (red stain in photo of mouse embryo). McKie *et al.* examined duodenal biopsies from HH patients, and found that *Ireg1* mRNA levels were increased up to 600%, suggesting that its overexpression contributes to increased iron transport into the circulation.

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