Research News

Mutant presenilins strike again

A recent study sheds light on the mysterious mechanism by which mutations in presenilin proteins (PS) disrupt neuronal Ca^{2+} homeostasis and suggest a new therapeutic approach to treating Familial Alzheimer Disease (FAD). PS are required for processing of amyloid precursor protein into the amyloid β (Aβ) peptide, which accumulates in senile plaques, and inherited mutations in the genes encoding PS 1 and 2 account for almost 40% of early-onset cases of (FAD). Cells harboring FAD mutant PS exhibit altered Ca^{2+} homeostasis, although little is known about PS contribution to the Ca^{2+} signaling pathway. In the September issue of *Neuron*, Yoo *et al.* report that in neurons, FAD-associated mutations in PS1 and PS2 downregulate capacitative calcium entry (CCE), the mechanism by which intracellular Ca^{2+} stores are replenished after IP_3-mediated release from the endoplasmic reticulum (ER). They also observed that mutant PS-mediated CCE inhibition led to increased Aβ generation. Although the authors do not identify the mechanism by which diminished luminal Ca^{2+} concentrations increase Aβ levels, they suggest that the imbalance in Ca^{2+} homeostasis may lead to some of the other molecular phenotypes associated with mutant PS, such as altered protein folding and increased vulnerability to apoptotic stimuli.

Genetic cause for fetal loss

Mutations in genes encoding coagulation factors lead to venous thrombosis, and may also underlie complications that occur during the late stages of pregnancy. Although fetal loss in the first trimester of pregnancy is a common occurrence that has many possible explanations, fetal loss in the second and third trimesters is often associated with thrombotic conditions. Point mutations in genes encoding coagulation factor V and prothrombin have been previously associated with thrombophilia. In the 5 October issue of *The New England Journal of Medicine*, Martinelli *et al.* report that carriers of specific factor V or prothrombin mutations also have a three-fold higher risk of late fetal loss. Since at least one of these mutations is found in at least 16 percent of women with unexplained late fetal loss, the authors suggest that genetic screening and anticoagulant therapy may useful in preventing pregnancy complications.

That's disgusting!

A specialized brain system may be required to recognize disgust on another person's face, and also to experience it firsthand. In the November issue of *Nature Neuroscience*, Calder *et al.* describe a patient shown by magnetic resonance imaging to have lesions in the insula and putamen, brain regions involved in taste and motor control, respectively. The patient could recognize happiness, fear, anger, sadness or surprise in facial expressions or in nonverbal sounds, and reacted normally to scenarios evoking anger or fear. He understood the concept of disgust intellectually and could correctly identify disgusting visual scenes. However, his emotional response to a variety of disgusting scenarios was impaired, and he was unable to recognize facial or vocal expressions of disgust. These results support previous suggestions that the insula and putamen may be involved in experiencing particular emotions and recognizing those emotions in others. Huntington disease patients, who have damage to the same brain regions, also have difficulty recognizing facial expression of disgust. The insula is activated by unpleasant tastes, so its involvement in disgust supports the idea that this emotion may have evolved as a response to offensive foods.

AIDS vaccine advance

A cytokine-augmented DNA vaccine can control viremia and prevent clinical AIDS in rhesus monkeys, suggesting a new approach to improve the quality of life and lifespan of HIV-1 infected people. In the 20 October issue of *Science*, Barouch *et al.* demonstrate the protective efficacy of a vaccine-elicited immune response against a highly pathogenic simian/human immunodeficiency virus (SHIV). The vaccine included a plasmid encoding an SIV Gag and HIV-1 Env proteins, as well as an IL-2/IgG fusion protein to enhance the immune response. Monkeys that received the vaccine combo did become infected with SHIV, but maintained stable $CD4^+$ T cell counts, low to undetectable viral loads, and no evidence of clinical disease by 140 days after challenge. Previous studies have suggested that cytolytic T cells (CTL) play a crucial role in controlling HIV-1 replication, and the development of a vaccine that elicits a potent CTL response has been a primary goal of HIV vaccine researchers. Barouch *et al.* observed that the monkeys in their study did indeed develop a potent Gag-specific CTL response, as well as a virus-specific $CD4^+$ T cell response. The IL-2/IgG fusion is believed to provide the secondary signal needed to drive the T cell proliferation and differentiation. Additional studies are required to determine if the vaccine will have a similar effect in people, as rhesus monkeys do not have the prolonged asymptomatic period characteristic of human HIV-1 infection. However, although the vaccine is not able to prevent viral infection, a vaccine that can slow disease progression could be useful in countries where antiviral drugs are not readily available.

Stem cells find their niche

Stem cell division in the ovaries and testes of *Drosophila* is regulated by the somatic support cells that form a 'stem cell niche', rather than intrinsic properties of stem cells themselves. In the 12 October issue of *Nature*, Kiger *et al.* and Tran *et al.* show that signals from somatic cells in the tip of the testis proliferation center are required for stem cell differentiation during spermatogenesis. Loss of function experiments reveal that the epidermal growth factor receptor and its downstream effector Raf are part of the somatic cell signal transduction mechanism. In the 13 October issue of *Science*, Xie and Spradling describe a complementary system found in *Drosophila* ovaries. Again, somatic cells in the tip of the egg-producing area are involved in setting up a niche involving the signaling protein Dpp to regulate stem cell self-renewal. Mammalian stem cell niches have yet to be reported, but the authors suggest that these findings have implications for stem cell tumors, which could be caused by defects in somatic control cells rather than stem cells themselves. They also suggest that the efficacy of stem cell transplants may depend upon inclusion of appropriate somatic control mechanisms.

By Kristine Novak, John MacFarlane, and Sandra Aamodt