Big, big problem

The rapidly rising rate of obesity in children and adolescents is setting the stage for a massive future spike in cardiac disease, according to two reports in the *New England Journal of Medicine* (**357**, 2329–2337; 2371–2379).

Jennifer Baker *et al.* followed more than 276,000 Danish children, ages 7–13, as they matured into adults. Overweight children, even those with just a little heft, were much more likely to develop heart disease later in life. For example, a 5-foot-1-inch 13-year-old boy weighing 121 lbs. had a 34% greater risk compared with a boy of the same height and age of normal weight, 96.5 lbs. If the boy weighed 132.5 lbs., the risk was 51% higher.

Kirsten Bibbins-Domingo *et al.* projected that, given today's rate of adolescent obesity, up to 37% of men and 44% of women in the United States will be obese by 2020. As a result, by the time today's adolescents turn 50, in 2035, 100,000 extra cases of heart disease will occur.

There was one positive sign in the studies. Children who were overweight at age 7 but not 13 had only low risk of heart disease—suggesting that early weight-loss intervention can help keep kids healthy as they age.—*CS*

Keeping tumors down

Cancer researchers are closer to understanding how the immune system can hold a tiny tumor in check for years in a dormant state (*Nature*, doi:10.1038/nature06309).

Little is known about why some tumors seem to persist for years without blowing up into full-blown cancer, but suppression by the immune system has been proposed as one mechanism.

To examine the immune system's role, Catherine Koebel, William Vermi and their colleagues treated mice with a carcinogen at a dose that resulted in many of the mice developing tiny, stable lesions.

When the immune system in these mice was disabled, the stable lesions rapidly blew up into fast-growing cancers. A few stable lesions spontaneously became cancerous before immunodepletion. When transplanted, such tumors could grow in mice with an intact immune system, suggesting that the tumors had escaped immune suppression.

The researchers next asked which arm of the immune system might keep the tumor cells in check. The dormant lesions developed into progressive tumors only after depletion of T cells or neutralization of cytokines involved in adaptive, but not innate, immunity.

The findings draw attention to a potential downside of severe immunosuppressive chemotherapy or radiation, writes Cornelis Melief in an accompanying commentary. Such treatment could potentially weaken the ability of the immune system to keep dormant lesions in check.—*CS*

Outfoxing neurons

Stem cell researchers have identified a transcription factor that sustains dopamine neurons, the type of neuron affected in individuals with Parkinson's disease (*PLoS Biol.* 5, e325).

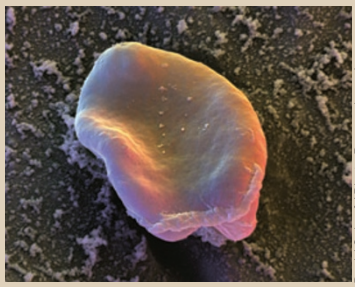
Raja Kittappa *et al.* examined mice over- and underexpressing the forkhead transcription factor Foxa2. Consistent with previous work, the researchers' findings showed that the transcription factor was required to generate dopamine neurons during fetal development and from embryonic stem cells. What's more, mice carrying only one copy of Foxa2 also showed a progressive loss of dopamine neurons in the same brain region affected in Parkinson's disease. The mice also showed abnormalities in motor behavior similar to those seen in Parkinson's disease.

Work in *Caenorhabditis elegans* and other systems suggests that *Fox* genes have a conserved role in regulating cell survival—consistent with the idea that Foxa2 controls a common effector pathway regulating stress responses in dopamine neurons.

These findings provide insight into why dopamine neurons die and suggest a new strategy to engineer cells for stem cell therapies. The heterozygous mice may also be useful for modeling Parkinson's disease, which is now mainly studied in mice through chemical induction of damage.—*CS*

Malaria vs. typhoid fever

Some gene variants that affect red blood cells can shield people from malaria infection—but they also increase susceptibility to infections with certain bacteria, such as *Salmonella typhimurium*, which causes typhoid fever. Findings in *The Journal of Experimental Medicine* (**204**, 2949–2961) hint at the reason for this susceptibility: excess iron loads in the liver may foster a bacteria-friendly environment.



David Scharf / Photo Researchers, Inc.

Malaria damage.

Marie-France Roy *et al.* examined mice known to be genetically susceptible to *Salmonella* infection. The likely culprit behind this susceptibility, they found, was a gene encoding a pyruvate kinase gene specific for red blood cells. Mutations in this gene resulted in a shortened lifespan for red blood cells, which can create an inhospitable environment for the malaria parasite. Not suprisingly, the mutation protected mice against infection by *Plasmodium chabaudi*, used to model human infection.

But how did the gene confer susceptibility to *Salmonella*? The researchers provide evidence that the mutant red blood cells spewed excess iron, which bacteria such as *Salmonella* thrive on. The iron also accumulated in the liver, a site of *Salmonella* infection. In sync with the idea that iron overload contributes to bacterial infection, mice fed a high-iron diet were also susceptible to *Salmonella* infection.

Whether iron overload may contribute to *Salmonella* susceptibility in people remains to be determined, as does the contribution of other factors such as anemia.—*CS*

Ageless NF-κB

The transcription factor NF-κB, known as a regulator of inflammation and the cell cycle, seems to have a key role in aging, according to a study in *Genes & Development* (**21**, 3244–3257).

Using a bioinformatics approach combined with microarray data from human and mouse tissues, Adam S. Adler *et al.* identified a broad set of genes that are regulated by NF-κB in an age-dependent manner.

Interfering with NF-κB function specifically in the adult epidermis, resulted in a return of a 'youthful' gene expression pattern and beneficial changes in histology—though the rejuvenation of the skin was only partial because NF-κB activity could only be blocked in the epidermis.

These results fit with previous findings that other longevity-related proteins, such as SIRT1 and FOXO3a, can directly inhibit NF-κB activity and that the gene for NF-κB resides within a chromosomal locus often associated with human longevity.—*RL*

Written by Randy Levinson and Charlotte Schubert