Research News

Resistin arrest prevents diabetes

A new hormone, resistin, provides a long-sought link between obesity to type II diabetes. Type II diabetes is characterized by insulin resistance and elevated blood glucose levels. Anti-diabetic drugs called thiazolidinediones (TZDs) enhance insulin sensitivity and lower glucose levels. TZDs are high-affinity ligands for the nuclear receptor PPAR-γ, although the gene targets of TZD-bound PPAR-γ are unknown. Steppan *et al.* performed a screen for genes that are downregulated in response to TZD treatment, and in the 18 January issue of *Nature* they report the discovery of a gene called resistin. Serum levels of resistin, expressed by adipocytes, increase during diet-induced obesity as well as in models of insulin resistance. Resistin-neutralizing antibodies enhanced insulin-stimulated glucose uptake and reduced hyperglycemia in obese mice. Treatment with recombinant resistin, however, impaired glucose tolerance and decreased insulin sensitivity. The authors propose resistin to be a new link among obesity, diabetes and TZDs. If the properties of human resistin are similar to those of mouse, inhibitors of this hormone may be developed as anti-diabetic drugs

Predicting statin responsiveness

Despite the ability of cholesterol-lowering drugs to slow the progression of atherosclerosis and reduce the risk of heart attack, these drugs have no effect in a large number of patients. In a search for genetic factors that underlie this unresponsiveness, researchers looked for polymorphisms in the gene encoding the cholesterol ester transfer protein (CETP), an enzyme that increases the content of low-density cholesterol and promotes atherosclerosis. In the 8 January issue of the *NEJM*, Kuivenhoven *et al.* report a genetic analysis of 807 atherosclerosis patients. They observed that a *CETP* polymorphism known as *TaqIB* was associated with higher plasma CETP concentrations and an increased progression of coronary atherosclerosis. The authors also found that men carrying this polymorphism benefited most from treatment with the cholesterol-lowering drug pravastatin. However, patients without this allele did not appear to benefit from the treatment. *TaqIB* may eventually be used as a marker that will allow physicians to identify patients who best respond to cholesterol-lowering therapies.

Faulty alarm clock gene

Scientists have identified the genetic basis of familial advanced sleep phase syndrome (FASPS), an autosomal dominant circadian rhythm variant that causes people to become early birds. FASPS sufferers wake at 4:00 a.m. (most people's sleepiest time) and go back to bed at 7:30 p.m. (most people's active social time). In the 11 January issue of *Science*, Toh *et al.* describe a linkage analysis on a large FASPS family, reporting a candidate gene, human *PER2*, which has homology to the *Drosophila period* circadian rhythm gene. The authors discovered that FASPS sufferers harbor a point mutation in a region of *PER2* that encodes a casein kinase Iε (CKIε) binding site, and propose that this mutation leads to decreased PER2 phosphorylation. The cellular concentration of PER and other circadian rhythm proteins accumulate and decline during the normal 24-hour cycle, and phosphorylation status is believed to regulate this process. The *hPER2* mutation may disrupt this normal cyclical accumulation and degradation, and shorten the normal sleep-wake period in FASPS individuals. Previous studies have shown that mutations that affect CKIε function disrupt circadian rhythm in hamsters and *Drosophila*, but this study constitutes one of the first linkages between a single gene and a complex human behavior.

A new leukemia mouse model

Researchers have discovered a transcription factor required for the carefully regulated coordination of hematopoietic stem-cell proliferation, survival and differentiation that occurs during myelopoiesis. Errors in this developmental program can cause leukemia. A number of growth factors have been shown to control this process, but little is known about transcription factors that regulate myeloid-cell proliferation and death. JunB, a component of the AP-1 transcription factor, is a known negative regulator of cell proliferation that is expressed during myeloid differentiation. Passegue *et al.* created transgenic mice that lacked JunB expression only in the myeloid lineage. In the 12 January issue of *Cell*, they report that these mice develop a transplantable myeloproliferative disease that resembles human chronic leukemia. JunB appears to control the numbers of granulocyte progenitors by inhibiting proliferation and promoting apoptosis. Deletion of JunB caused these progenitors to upregulate expression of the GM-CSF-α receptor, the anti-apoptotic proteins Bcl-2 and Bcl-xl, as well as the cell cycle regulators p16INK4a and c-Jun. The myeloproliferative disease progressed to blast crisis, making this one of the only mouse models to recapitulate the natural course of human chronic myeloid leukemia.

A relaxation break for heart research

A new gene therapy strategy may improve treatment of diastolic dysfunction, a condition in which the heart relaxes too slowly after each contraction, compromising the ability of the cardiac chambers to refill with blood. The normal cardiac contraction/relaxation cycle depends on intracellular calcium transients governed by the sarcoplasmic reticulum. During relaxation, Ca^{++} ions are sequestered in the sarcoplasmic reticulum via ATP-dependent calcium pumps, and the time required to remove Ca^{++} from the muscle fiber is prolonged in cardiac tissue samples from heart-failure patients. Parvalbumin, a small intracellular calcium-binding protein expressed in striated muscle, is a Ca^{++} sink that speeds the rate of decline in intracellular calcium. In the January issue of *Journal of Clinical Investigation*, Szatkowski *et al.* report a parvalbumin gene transfer approach to speeding heart relaxation. Using an adenoviral vector, the authors were able to express high levels of human parvalbumin in the left ventricle of rats. This caused a physiologically relevant acceleration of heart relaxation, and also enhanced relaxation performance in the hypothyroid rat model of slowed cardiac muscle relaxation. Parvalbumin's ability to directly buffer intracellular calcium in cardiac myocytes may also protect the heart and other organs from damage arising from cellular disturbances in Ca^{++} signaling pathways.

By Kristine Novak