Research News

Painkiller killer

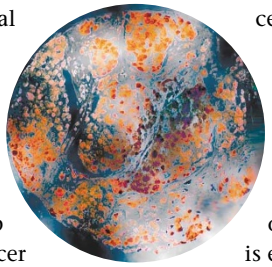
Ingestion of only two to three times the maximum daily recommended dose of acetaminophen can cause liver toxicity. The drug's damaging effects result from the activity of a liver protein, the constitutive androstane receptor (CAR), according to a study in the October 11 *Science*. The results could lead to treatment for acetaminophen overdoses, which account for the majority of hospital admissions for acute liver failure in the United States. Zhang *et al*. report that mice null for the gene encoding CAR do not succumb to acetaminophen toxicity. CAR normally protects the liver by promoting the clearance of foreign compounds. But the authors found that CAR also enhances the production of enzymes that help convert acetaminophen to a highly toxic form. They went on to examine the potential therapeutic value of androstanol, a compound that inhibits CAR activity. Androstanol decreased expression of CAR target genes and prevented liver toxicity when given to mice one hour after acetaminophen overdose.

Stem–cell enabler

Only a few genes are known to be involved in keeping embryonic stem cells in an undifferentiated state. In the October 15 *Genes and Development*, Hanna *et al*. add one to the short list. The gene, *Foxd3*, encodes a POU-family transcription factor that is expressed in embryonic stem cells, and has been implicated as a negative regulator of differentiation. For example, overexpression of *Foxd3* in a myeloid cell line prevents appropriate maturation of these cells into granulocytes. The authors showed that *Foxd3* is required for the maintenance of pluripotent cells in the mouse embryo. Embryos lacking *Foxd3* died by age 7 and could not be used to form embryonic stem cells. The authors also created chimeric embryos composed of wild-type embryonic stem cells mixed with *Foxd3*-mutant cells. These embryos developed normally, suggesting that Foxd3 acts through an intercellular signaling pathway. Identification of this pathway could perhaps lead to ways of maintaining the pluripotency of embryonic stem cells in culture.

Prostate cancer prognosticator

Researchers have identified a protein that could serve as a prognostic marker for the most lethal prostate cancers. In the 10 October *Nature*, Varambally *et al*. find that a protein first identified in flies is overexpressed in hormone-refractory, metastatic prostate cancer. The polycomb group protein EZH2 (enhancer of zeste homolog 2), appears to act as a gene silencer in cultured prostate cancer cells, consistent with its function in other systems. Furthermore, removing EZH2 activity in cultured cancer cells resulted in inhibition of cell proliferation. Currently, blood levels of the prostate-specific antigen (PSA) can allow physicians to diagnose prostate cancer, but the test is not good at distinguishing different types of tumors. EZH2, in contrast, is expressed in tumors with the poorest prognosis (shown here in orange, staining prostate cancer cell nuclei).



Vasudeva Mahavisno

Bad skin defense

Breaches in the skin normally activate the production of microbe-fighting compounds by skin cells. In skin disorders such as psoriasis, the natural antibiotics are expressed to a particularly high degree. Now it seems that the situation may be reversed in one major skin disorder, atopic dermatitis, often referred to as eczema. In the October 10 *NEJM*, Ong *et al.* took a look at two antimicrobial peptides, LL-37 and HBD-2. Individuals with atopic dermatitis severely underproduced these peptides. Such individuals are also highly susceptible to infection, in particular by the bacterium *Staphylococcus aureus*. The authors tested the microbe-killing ability of the two peptides at concentrations found in skin lesions of patients with atopic dermatitis. These concentrations failed to kill *S. aureus* in a test tube, whereas the concentrations typically found in psoriatic lesions did kill the bacteria. Skin from individuals with atopic dermatitis is known to have amplified levels of two cytokines, interleukin-4 and interleukin-13. The investigators found that these cytokines inhibited production of the antimicrobial peptide in skin cells in culture. The authors conclude that underproduction of antimicrobial peptides could underlie some of the symptoms of atopic dermatitis, which affects 15 million people in the United States.

Cancer survival rates

Long-term survival rates for many cancers are higher than previously thought, according to a study by Hermann Brenner in the October 12 *Lancet*. Long-term survival rates have traditionally been estimated by following a cohort of patients diagnosed many years ago. This method, called cohort analysis, fails to take into account recent advances in treatment and detection that can save lives. Brenner took a different approach. He used a method called period analysis that examines survival data from patients chosen during a specific recent time period, in this case the year 1998. In this analysis, the year of diagnosis is not fixed, as it is in cohort analysis. Using cancer registry data from the National Cancer Institute he estimated 5, 10, 15 and 20-year estimated survival rates. He compared these rates with those derived from cohort analysis of patients diagnosed from 1978 to 1993. Estimates of overall relative survival rates for all years were higher with the new analysis. For example, the 10 year and 15 year estimates were 57% and 53%, 7% and 11% higher, respectively, than corresponding estimates based on cohort analysis. The gap was higher for some types of cancer. Both analyses showed similar survival rates for cancers that have resisted medical advances, such as lung cancer.

15-year relative survival rates

	Cohort estimates	period estimates
Breast	58.1	71.3
Stomach	13.7	19.0
Testis	86.4	91.1
Ovary	36.7	49.9
Brain/nervous system	19.5	27.6
Hodgkin's disease	66.2	73.8
Melanomas	79.3	83.5
Lung and bronchus	8.2	8.1

By Charlotte Schubert