Biology

Cancer drug reveals unexpected partner

Taxol is one of the most potent anticancer drugs around, and researchers thought they had a good handle on how it works. The drug latches onto the cellular protein tubulin, preventing filamentous structures formed of the material from helping a tumor cell divide. The obstruction ultimately causes the cell to commit suicide.

Using a new technique that they hope will provide information on the safety and workings of potential drugs, scientists have now found that taxol may much more directly force a cell to self-destruct. The drug also appears to bind to and inactivate Bcl-2, a protein that normally serves to prevent cells from killing themselves.

This new interaction for taxol emerged from a study in which investigators genetically engineered viruses to display peptides, short chains of amino acids, on their surface. The viruses, which each bore their own random amino acid sequence, were then flowed over taxol-covered petri dishes. The researchers isolated the few viruses that stuck to the taxol molecules and determined what peptides adorned them.

A computerized search then matched those peptides to proteins with known amino acid sequences. One hit that popped up was Bcl-2, and further studies confirmed that taxol binds tightly to the protein, Diane J. Rodi of Florida State University in Tallahassee and her colleagues report in the Jan. 8 JOURNAL OF MOLECULAR BIOLOGY.

While their finding may help researchers design a more potent taxol—versions that better bind to Bcl-2, for example—Rodi's group also sees this study as vindication of their strategy for drug testing. As the human genome project characterizes more and more proteins, the scientists expect that large libraries of peptide-bearing viruses will help them identify any protein interactions a drug under development might have. This ability might head off side effects for some drugs.

"We think when you design a new drug that we can give you a list of all the potential targets of that drug in the human body, before any patient ever [sees] a drop of that drug," says study coauthor Lee Makowski, now at the National Science Foundation in Arlington, Va.

The researchers are also working with cancer investigators studying how tumor cells employ certain proteins to expel anticancer drugs. The peptide-bearing viruses may determine where exactly on those proteins the drugs attach and thereby help design drugs that avoid this resistance problem. —*J.T.*

Milking mice for mammary gland genes

The *Hox* family of genes helps sculpt the bodies of animals from head to toe—assuming the animal has toes, of course. These genes encode DNA-binding proteins that switch on arrays of other genes during an embryo's growth (SN: 8/20/94, p. 116). Some *Hox* genes might regulate arm-forming genes, for example, while others guide the growth of a head.

The myriad developmental roles of the *Hox* genes have obscured the fact that some of them also operate within the adult animal. Two scientists now report that at least three *Hox* genes are crucial to the pregnancy-related changes that occur in the mouse mammary gland. Female mice with mutations in all the genes can't raise their pups because they're unable to supply sufficient milk.

Until pregnancy, the mammary glands of these mutant mice appear normal, Feng Chen and Mario R. Capecchi of the Howard Hughes Medical Institute at the University of Utah School of Medicine in Salt Lake City report in the Jan. 19 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES. Their examinations of mammary tissue in pregnant mice with the *Hox* mutations revealed, however, that the animals had inadequate cell proliferation to form a proper network of milk-carrying ducts. —*J.T.*

Environment

Beluga whales' mercurial status

Beluga whales in the St. Lawrence River estuary have gained renown for their ill health. At autopsy, the animals' internal organs frequently show evidence of opportunistic diseases, suggesting immune damage—perhaps by environmental pollutants. Moreover, notes Julie M. Gauthier, a marine mammal toxicologist at the University of Quebec in Montreal, the cancer rate in this population of highly protected whales exceeds that in most human or animal populations: Each year, 1 in every 500 of these belugas develops a tumor.

A new study by Gauthier's team hints that mercury pollution might help foster the tumors.

The researchers examined cells derived from the skin of a beluga that had been harvested for consumption by Hudson Bay Inuits. The Quebec scientists incubated these cells with elemental or methyl mercury, pollutants found in the St. Lawrence and other North American waterways (SN: 3/9/91, p. 152).

After the treated cells divided once, the researchers looked for micronuclei: whole or fragmentary chromosomes that failed to become incorporated into the nuclei of newly formed cells. Micronuclei serve as markers of genetic damage and cancer risk.

In the December 1998 ENVIRONMENTAL TOXICOLOGY AND CHEMISTRY, Gauthier's group reports that about 15 percent of cells exposed to low concentrations of the mercury pollutants had micronuclei, twice the rate seen in unexposed cells. As concentrations of the pollutants climbed, so did micronuclei rates—eventually reaching a quadrupling of background values.

Moreover, Gauthier notes, the pollutant concentrations causing "significant DNA damage" in the new tests were comparable to what could be expected in the blood and skin of at least some St. Lawrence belugas. As such, she says, these pollutants—especially the methyl mercury discharged by plants along the river producing the chemical chloralkali—warrant further study as one possible factor underlying the high rate of cancers in these whales. —*J.R.*

Pesticides and breast cancer

About 14 percent of all Danish women develop breast cancer, a rate that has more than doubled since the late 1960s. A new study finds that exposure to a few chlorinated pesticides might be contributing to the cancer's rise.

Annette P. Høyer of the Copenhagen Center for Prospective Population Studies and her colleagues measured blood concentrations of chlorinated compounds commonly found stored in body fat: 18 pesticides (or their breakdown products) and 28 polychlorinated biphenyls. The blood samples came from 240 area women with breast cancer and some 480 others who remained cancerfree. All were participants in the Copenhagen City Heart Study, which had collected the blood 17 years earlier, before any cancers had appeared.

Even after accounting for well-known breast-cancer risks, such as a woman having no full-term pregnancies, blood concentrations of two pesticides emerged as independent risks for the malignancy, Høyer's group reports in the Dec. 5, 1998 LANCET.

A woman's chance of developing the cancer edged up slightly with increasing blood concentrations of beta-hexachlorocyclohexane, a constituent of the toxic pesticide lindane (SN: 3/15/97, p. 157). The persistent insecticide dieldrin, banned in the United States, provoked a more dramatic increase. Women with the highest blood concentrations of this estrogen-mimicking pollutant faced more than double the breast-cancer risk of those whose blood carried little or no dieldrin.

The good news: The researchers found no link between the cancer and any of the other pollutants in the study—including DDT, chlordane, and kepone—all of which accumulate in body fat. —*J.R.*