Missing Enzyme Incites Cancer Debate

Six generations of mutant mice have put a damper on one of the hottest areas in cancer research, although some scientists warn against a pessimistic rush to judgment.

The mice lack a component of telomerase, an enzyme that fastens short sequences of DNA to the ends of chromosomes. These so-called telomeres protect the tips and serve as buffers, since a bit of every chromosome tip is lost whenever cells divide (SN: 11/25/95, p. 362).

Except for the germ cells, which give rise to sperm and eggs, few adult human cells seem to produce telomerase. Yet most cancer cells do make the enzyme, prompting speculation that tumor cells need it to keep dividing. Consequently, many scientists have hailed the idea of inhibiting telomerase as a promising strategy for treating cancer.

That hypothesis is under fire now that a team of scientists has shown that cells from telomerase-deficient mice form tumors. Telomerase inhibition "may not be the phenomenal approach that we all hoped and prayed for," says Ronald A. DePinho of Albert Einstein College of Medicine in New York.

"It's a little confusing what the take-home message is," counters Jerry W. Shay of the University of Texas Southwestern Medical Center at Dallas. "The worst thing we can do is say that telomerase inhibition is dead on arrival."

DePinho and his colleagues, who describe their work in the Oct. 3 CELL, created telomerase-deficient mice by deactivating a gene that encodes an RNA sequence necessary for the enzyme's function. The scientists then bred the mice, producing five more generations lacking the enzyme.

With markers that label telomeres, the investigators found that this DNA grew shorter with each successive generation. Indeed, 5 percent of the chromosomes in cells from sixth-generation mice had no detectable telomeres.

As the telomeres shortened, more and more cells exhibited chromosomal instability, says DePinho. Some cells had extra or missing chromosomes; others contained chromosomes fused end to end.

Peter M. Lansdorp

Without the enzyme telomerase, telomeres (red) disappear from some chromosomes (arrow).

The scientists also added *ras*, a well-known cancer-causing gene, to cells from the mice. The resulting cells were able to divide indefinitely in test tubes and, when injected into mice, formed tumors. The investigators estimate that some of the tumor cells have undergone 360 doublings without telomerase.

Either cancer cells can tolerate the chromosomal instability brought on by a lack of telomerase, or they have an alternative telomere repair pathway, says DePinho, noting that neither choice supports telomerase inhibition as a cancer-fighting strategy.

Shay and other scientists argue that the differences between people and mice, especially in terms of cancer development, preclude such a conclusion.

"Our bottom line is that these initial studies do not support the mouse as a good model of human telomere biology and cancer," contends Calvin B. Harley of Geron Corp. in Menlo Park, Calif., a firm looking into telomerase inhibition as a cancer therapy.

Noting that the mice studied started out with unusually long telomeres, Harley suggests that these protective structures may not have eroded to the point where cancer cells die.

The sixth-generation mice are infertile, presumably because they have lost the telomeres in their germ cells, DePinho has reported at scientific meetings. He has also noted that other cells from these mice do not proliferate normally.

Declining to comment on the unpublished results, DePinho says that his group will soon report more findings on the telomerase-deficient mice. "This is a treasure trove of fantastic biology at every level—development, aging, cancer, genomics," he says. —*J. Travis*

Bursting bubbles break chemical bonds

Blasting two high-powered jets of liquid into each other is bound to mix things up, and a new study demonstrates just how much. The fast, turbulent flows created by such a collision are powerful enough to break chemical bonds, researchers have found.

The source of this power lies in bubbles, says Kenneth S. Suslick of the University of Illinois at Urbana-Champaign. He and his team used a laboratory device that smashes two fluid jets into each other. The device was originally designed to blend fine droplets of liquid, but Suslick's interest lay in its application to chemistry. He suspected that bubbles rapidly growing and collapsing in the turbulent collision would generate an intense local heating that could drive chemical reactions.

This cavitation process "provides a mechanism for [transforming] mechanical action in a liquid into chemical reaction," Suslick says. He and his colleagues describe their findings in the Oct. 1 JOURNAL OF THE AMERICAN CHEMICAL SOCIETY.

Cavitation also occurs when ultrasound waves pass through liquids, producing bubbles that grow rapidly and then collapse in a flash of light (SN: 4/29/95, p. 266). In their liquid jet experiments, Suslick's team charted the progress of a standard reaction used in ultrasound chemistry experiments—the formation of triiodide from iodide in a solution of water and carbon tetrachloride.

Fairly high jet pressures are needed, the team found. Below a threshold of about 148 times atmospheric pressure, no reactions occurred.

"I'd be very hard pressed to see how you could do that chemistry unless you had cavitation," says William R. Moser, a chemical engineer at Worcester (Mass.) Polytechnic Institute. "I think he's demonstrated something quite important that has general applications." Several years ago, Moser and his coworkers proposed using liquid jets as a way of breaking down chlorine compounds in contaminated groundwater.

Suslick and his group now plan to make the cavitation process more efficient, thus harnessing it for use in chemistry. This approach runs counter to the century-old idea that cavitation is always a problem. Naval engineers have known since the late 1800s that bubbles forming and collapsing on propeller blades make noise and erode the blades. High temperatures and shear forces produced by the bubbles contribute to that deterioration, Moser says.

"It's amusing to go back to it now and see that there are chemical consequences too," Suslick adds. —*C. Wu*