Tick, tock, enzyme rewinds cellular clock

Dubbed the immortality enzyme, telomerase is living up to its reputation. By forcing cells to make the enzyme, investigators have bestowed upon them a seemingly infinite capacity to divide.

The test-tube experiments on human cells, reported in the Jan. 16 SCIENCE, solidify a hypothesis of cellular aging according to which telomerase's absence leads to a gradual destruction of chromosomes that ultimately stops cell division.

The new work will probably fuel further investigation into whether telomerase's presence or absence is crucial to cancer and the aging of animals. Moreover, the ability to create immortal but otherwise normal cells may offer new therapeutic options, particularly in the field of cell transplantation.

"It's opening a toy chest of possibilities," says study coauthor Woodring E. Wright of the University of Texas Southwestern Medical Center at Dallas.

A complex enzyme composed of several proteins and a strand of ribonucleic acid (RNA), telomerase affixes brief DNA sequences to the ends of chromosomes. This added genetic material, known as a telomere, provides a protective cap for the chromosomes (SN: 11/25/95, p. 362).

Each time a cell divides, however, it shaves off a portion of this chromosomal DNA. When grown in test tubes, cells usually stop doubling after a finite number of divisions and enter a state called senescence (SN: 1/3/98, p. 7). Since most adult cells do not use telomerase to rebuild their telomeres, scientists have long thought that the dwindling of telomeres pushes cells into senescence.

Wright and his colleagues recently added copies of the gene for a protein component of telomerase to human skin and retinal cells devoid of the enzyme. The new ability to produce this component enabled the cells to add telomeric DNA to their chromosomes. While skin cells normally senesce after about 60 doublings, some of the altered cells continue to have long telomeres after having divided nearly 120 times, with no sign of stopping.

"This is very strong evidence for the telomere-shortening hypothesis of senescence," says Judith Campisi of Lawrence Berkeley (Calif.) National Laboratory.

The buildup of senescent cells may contribute to aspects of human aging such as skin wrinkling and atherosclerosis, but these cellular experiments do not address that issue directly, notes Campisi.

While scientists will race to create mice that make telomerase continuously in all cells, they warn that the enzyme offers no guarantee of eternal health. "It's unlikely to extend life span," says Campisi. "There's a good chance one will end up with a tumor-prone animal. Cell senescence is a double-edged sword."

Indeed, most cancer cells seem to depend upon telomerase to bypass senescence and continue dividing. Some researchers have therefore suggested that telomerase inhibition should stop many tumors in their tracks.

"Immortality is an extremely common step in tumorigenesis, which provides a huge advantage to the tumor cell, but there's no evidence that it's required," cautions Campisi.

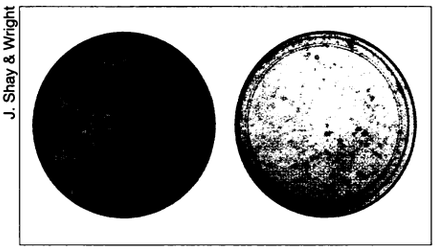
Furthermore, some animal experiments indicate that cancer cell immortality does not require telomerase (SN: 10/11/97, p. 228). About 10 percent of human cancer cells also maintain their telomeres without telomerase, which suggests that tumors can, if forced to, use another method to bypass senescence.

While many scientists remain firm proponents of telomerase inhibition as an anticancer strategy, Huber Warner of the National Institute on Aging in Bethesda, Md., says that both camps will have to await the development of inhibitors and their testing in animals. "Then you will have a much clearer answer," he says.

More immediately, investigators may immortalize cells from many tissues by adding the gene for the telomerase component. At present, they must study cells made immortal by adding cancer genes, which cause subtle changes in the cells.

Immortalized normal cells, adds Wright, could also aid cell transplant research. To treat muscular dystrophy, for example, physicians might obtain a patient's muscle cells, correct their genetic flaw, immortalize the cells, and return them to make new muscle. *—J. Travis*

J. Shay & Wright



Cells (stained purple) making telomerase keep proliferating (left), while those without the enzyme stop (right).

Unsaturated fats play yin-yang cancer role

Five years ago, researchers at the Harvard School of Public Health in Boston proclaimed that dietary fat appears to play no direct role in breast cancer risk (SN: 10/24/92, p. 276). That was then.

This week, the same researchers, along with a group of Swedish colleagues, came to a different conclusion. When they distinguished between fats, they found that monounsaturated fats, characteristic of olive and canola oils, appear to protect against breast cancer, while polyunsaturated fats in vegetable oils seem to enhance risk. Saturated fats—a major risk factor for heart disease—had no effect.

After collecting detailed dietary data from more than 61,000 Swedish women between the ages of 40 and 76, the researchers followed the women for 4 years. During that time, 674 developed invasive breast cancer. To determine any influence of foods, the scientists compared the diets of the cancer patients to those of the cancerfree women.

Even after accounting for standard breast cancer risks, such as having a family history of the disease, the effects of unsaturated fats stood out, the researchers report in the Jan. 12 ARCHIVES OF INTERNAL MEDICINE. For each 10 grams of monounsaturates that a woman consumed daily, the risk of breast cancer fell by 55 percent. However, that risk increased by almost 70 percent for each 5 grams of polyunsaturates downed per day.

The take-home message, says study leader Alicja Wolk of the Karolinska Institute in Stockholm, "should not be to add monounsaturated fats to one's current diet, but rather to substitute them for another fat [already being eaten]." Indeed, her group found that as calorie consumption climbed, so did cancer risk, regardless of the types of fats eaten.

Studies over the past 4 years have shown that breast cancer rates are low among Mediterranean women who eat a lot of olive oil, but they haven't determined whether there is something unusual about this oil. Because the Swedish women derived most of their monounsaturates from dairy products and meat, Wolk says, "we can now say monounsaturates are protective—whatever their source." Such animal products, though rich in saturates, can be major sources of monounsaturates.

That monounsaturates might inhibit some cancers and polyunsaturates spur them has long been evident from studies by Leonard A. Cohen of the American Health Foundation in Valhalla, N.Y., and others. "But [because they were] done in animals, few people paid attention to them," he says. In fact, he had trouble getting a review published in 1990 outlining the mechanisms by which monounsaturates may prevent breast cancer. It was "too far out," he says.

Lenore Kohlmeier of the University of North Carolina at Chapel Hill and her colleagues have turned up evidence of another risky fat—the *trans* fatty acids in margarines and vegetable shortening (SN: 5/21/94, p. 325). In the September 1997 CANCER EPIDEMIOLOGY, BIOMARKERS & PREVENTION, the researchers report that these fats also appear to increase breast cancer risk. *—J. Raloff*