Turning DNA into an antibiotic

Hoping to alleviate the desperate need for novel antibiotics, investigators are turning to DNA as a potential weapon in the ongoing war against bacteria. Paul F. Agris and his colleagues at North Carolina State University in Raleigh have successfully modified a small strand of DNA to mimic and interfere with a vital cog in the machinery that bacteria, yeast, and mammalian cells use to make proteins. "It could be the forerunner of a new type of antibiotic," says Agris.

The journey from a gene to the protein that the gene encodes starts when a cell's nucleus creates a molecule known as messenger RNA (mRNA) from the gene's DNA sequence. While DNA is composed of two intertwined strands of complex molecules called nucleotide bases, mRNA consists of a single string of such bases.

Completed mRNA molecules leave the nucleus for parts of the cell known as ribosomes. There, molecules of another form of RNA, short strands called transfer RNA (tRNA), briefly hook up to the ribosomes. They decode the sequence of bases in the mRNA and help chemically link the appropriate amino acids to form the gene's protein. The two tasks are carried out by different parts of the ribosome, however. "The large subunit is where the chemistry occurs. The small subunit is where the decoding occurs," says Agris.

As part of an effort to understand how tRNA attaches to the small subunit of a ribosome, Agris and his colleagues began to design DNA strands that resemble tRNAs in structure. "We chose DNA because it wasn't that far off from RNA," says Agris. To find a DNA sequence that would attach to ribosomes as a tRNA would, the investigators had to create an RNA-DNA chimera. For example, they added to their DNA a nucleotide base normally used by RNA but not by DNA.

Because these chimeras compete with tRNAs for binding sites on the small subunits of ribosomes, they interfere with protein assembly. In fact, adding these mimics to cells cut the protein production by 50 percent, Agris and his colleagues report in the January NATURE STRUCTURAL BIOLOGY.

If investigators can modify the tRNA mimics further, so that they shut down the protein construction only in fungi or bacteria and not in human cells, the molecules may provide an extremely useful antibiotic, says Agris. Many current antibiotics, he notes, interfere with the stringing together of amino acids by attacking the large subunit of ribosomes. Antibiotic resistance often develops, however, because the shape of the large subunit can mutate easily. "It denies the antibiotic a binding site," says Agris.

He and his colleagues suggest that their approach may prevent the development of antibiotic resistance. "By targeting the small subunit, we're probably at a location where resistance cannot occur," asserts Agris. "You can't change something so universal to the organism as the decoding process."

The investigators are also studying whether they can use liposomes, spherical globules of fat, to deliver their DNA-based tRNA mimic into cancer cells but not healthy cells. By halting protein assembly, the compounds would kill the cancer cells.

Examining skin reduces melanoma deaths

Taking the time to examine one's skin for potentially fatal skin cancer may reduce the risk of dying of the disease, concludes the first study of skin self-examination (SSE). Researchers from the Memorial Sloan-Kettering Cancer Center in New York City found that people who examined themselves—looking for moles that change color, shape, or size—were 44 percent less likely to die of melanoma than those who did not.

"It is very exciting," says study leader Marianne Berwick, an epidemiologist. "The results are very promising, but it is only a first study."

Approximately 35,000 people in the United States develop melanoma each year. When tumors are caught and removed early, 95 percent of patients survive. Nevertheless, the cancer can become very aggressive as it grows; every year, it kills 7,200 people.

The Sloan-Kettering team studied 1,199 white residents of Connecticut. Of those, 650 had just been diagnosed with melanoma that hadn't spread, and 549 were healthy controls. After asking all participants whether they practiced SSE, the researchers followed the health of the participants for 5 years.

After taking into account other known risk factors for skin cancer, such as light hair, eyes, and skin, a propensity to sunburn, and exposure to the sun, the team found that people practicing SSE were 44 percent less likely to die of the disease. They also found that SSE reduced the risk of getting melanoma by 34 percent. The researchers report their findings in the Jan. 3 JOURNAL OF THE NATIONAL CANCER INSTITUTE.

In order for SSE to actually reduce the occurrence of the cancer in the first place, Berwick notes, people must be noticing precancerous growths and having them removed before they progress to melanoma. Thirty-five percent of the control population reported having benign lesions removed.

J. Mark Elwood of the University of Otago in Dunedin, New Zealand, writes in the journal that while Berwick's results are important, they may not represent a cause-and-effect relationship. He suggests that the researchers test "whether the reduction in melanoma incidence is restricted to subjects whose SSE led to the removal of suspicious skin lesions."

Berwick agrees that the results need to be confirmed by other researchers, and she intends to continue to follow the participants.

Nervous system protein falsely accused

Swiss researchers have concluded that a protein accused of preventing the regeneration of nerves is innocent of the crime. This finding may eliminate one promising lead in the search for treatments for spinal cord injuries.

The adult human body has an amazing ability to repair wounds. Don't ask it to fix a severed spinal cord, however. The long nerve fibers, or axons, in the central nervous system (CNS) simply don't regenerate.

In the 1980s, investigators discovered that adult CNS axons can actually regrow if placed in the environment that normally surrounds peripheral nerves. They therefore concluded that something in the adult CNS actively prevents regeneration. Martin E. Schwab of the University of Zurich and his colleagues then found that myelin, the fatty insulation that surrounds nerves, stymies axon recovery. His group later identified a protein, IN-1, in CNS myelin that has proven to be partly responsible for this inhibition.

Last year, two other research groups suggested that they had found another important inhibitory molecule, myelin-associated glycoprotein (MAG). Schwab's team, in collaboration with a group led by Melitta Schachner of the Swiss Federal Institute of Technology in Zurich, now offers evidence that those experiments were misleading. Mice genetically manipulated not to make MAG have the same inability to regenerate damaged axons as normal mice, they report in the December 1995 NEURON.

"There is no evidence that MAG is a major inhibitor of regeneration in the CNS," says Schachner.

As a result, she adds, antibodies or other molecules that interfere with MAG are unlikely to be of much use in treating individuals paralyzed by spinal cord damage.