

UC SANTA BARBARA

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CANCER-PREVENTING GENE PROTECTS AGAINST STRESS AND EXTENDS LIFE SPAN IN WORMS

A gene that protects against cancer and environmental stress and promotes longevity has been identified in studies of a nematode worm, according to a report to appear in Science Magazine and published September 14 on the Science Express web site.

The discovery by a research team at the University of California, Santa Barbara provides scientists with a new means for identifying novel anti-cancer drugs and may lead to a better understanding of the effects of stress on longevity. It will make it possible to search for more potent and less harmful drugs that prevent or eliminate cancer using simple, easily cultured worms.

The human "p53" gene, the only gene to be featured on the cover of Newsweek, has been renowned for years as one of the most important genes in preventing cancer. In fact, most human tumors carry a defective p53 gene. However, Joel Rothman, professor of molecular biology and leader of the research team, notes, "We found that p53 plays a more fundamental role in worms. It protects against the deleterious effects of cancer-causing agents and is apparently a kingpin for supporting life under a variety of stress conditions."

Though the studies on worms led the researchers to learn about p53 function in a whole animal, scientists initially did not believe that such a simple creature contained this gene, which is so important in human medicine.

That changed when lead author William B. Derry, a post-doctoral fellow on Rothman's research team, discovered that worms carry the gene.

"Although it was initially hard to recognize, we found that the worm gene has all the essential parts of the human cancer-blocking gene," said Derry.

Mammals, including humans, contain three forms of the p53 gene, which have some overlapping functions. "Since the worm has only one, it is much easier to study its function in the context of a whole animal," said Derry. This feature made it possible for the researchers to reveal what is the likely basic function of the family of p53 genes in all animals.

Most relevant to cancer is the worm gene's ability to protect against "genotoxic" stress, such as exposure to carcinogens and radiation, which lead to cancer cell growth in humans. Like its human counterpart, which eliminates potential cancer cells, worm p53 eliminates such damaged cells by causing them to die, while sparing the rest of the animal.

However, the researchers also found that worm p53 is important for other aspects of the animal's biology. To their surprise they found that the gene extends the life span of worms that are starving. Following the discovery in recent years that there are both genes and drugs that can dramatically extend its longevity, the *C. elegans* worm has become the premier organism for studying life span. The researchers' discovery suggests that p53 may function to extend human life span both by blocking cancer and possibly by protecting against the effects of environmental stresses.

The scientists also found that p53 helps the worm to survive in low oxygen levels, or asphyxiation. In humans, a lack of oxygen is responsible for widespread tissue damage caused by heart attacks and stroke.

"The finding that p53 can protect worms against oxygen deprivation, starvation, and genotoxic stress indicate that it helps the animal react to quite different environmental stresses," said Rothman.

Further, "these discoveries have implications for understanding human biology and also allow us to avail of genetics and biotechnology in worms to search for drugs -- both therapeutic and preventive -- that inhibit cancer in humans."

The team of scientists responsible for this work, which includes Derry, Rothman, and graduate student Aaron Putzke, discovered the worm p53 gene three years ago and learned of its function in stress and life span only in the past year.

However, the biotechnology industry has already begun to use worms for these anti-cancer drug discovery approaches that emerge from these discoveries.

NOTE: Science Express is located at:

<http://www.sciencemag.org/feature/express/introduction.shl>

Graphics available on request.

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