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UC San Diego
University Archives. RSS 6020

Researcher at UCSD identifies cancer gene in regulatory mechanism of human cells

June 7, 1988

Contact: Yvonne Baskin, (619) 534-3120

UCSD RESEARCHER IDENTIFIES CANCER GENE IN REGULATORY MECHANISM OF HUMAN CELLS

A University of California, San Diego researcher has confirmed for the first time that the product of a cancer gene can bind to human DNA and directly control the activity of other cellular genes.

"People have long postulated that both growth and cancer require activation of new genes or a change in the activity level of genes," said Michael Karin, associate professor of pharmacology and member of the Center for Molecular Genetics at UCSD. "But only recently have we been able to get down to the biochemical details. What we've found is that every single stage in the process of growth control is a point where something can go wrong."

The proliferation of cells for growth or wound healing is guided by an elaborate hierarchy of genes and gene products (proteins) whose influence reaches from the cell surface through the cytoplasm and into the nucleus. Other researchers have found cancer genes (oncogenes) associated with the abnormal or excess production of growth factors, of cell membrane receptors that respond to these factors, and with the production of the signal chemicals that deliver the growth message to the nucleus.

"What was not known was what happens in the nucleus," said Karin. "And what we've found is that the proteins that switch on the transcription machinery of the genes inside the nucleus can be abnormally active, and this, too, can lead to cancer.

Karin reported on this work at the Third Chemical Congress of North America in Toronto Tuesday, June 7. Some of the work has also been published in recent issues of the journal Nature.

Starting with a human gene believed to be involved in the regulation of zinc metabolism, a trace metal ion essential for growth, Karin's lab defined a region of DNA that controls the gene's activity, then searched for proteins that bind with this DNA. Using this approach, he has identified several transcription factors that initiate gene transcription--the copying of the genetic message in a form needed for the cell machinery to make proteins.

When Karin isolated the gene coding for one of these transcription factors, called AP1, he found it was nearly identical (homologous) to a previously identified viral oncogene called Jun.

"This is the first case for a well-documented transcription factor that can also act as an oncogene," Karin said. "What it tells us is that the same basic mechanisms used to regulate the growth of cells in response to normal growth factors are also the site of action for powerful chemical agents that mimic the action of these growth regulators.

"When normal growth regulators stimulate AP1, the response is usually just a short burst of activity, then protein formation declines again," he said. "With chemical agents--tumor promotors--multiple exposures are required to cause cancer. But with each exposure, you get a stronger and longer response."

The team has identified other transcription factors and is now working on cloning the genes that code for them. These genes can then be compared to known oncogenes. "We believe every one of these may have the potential to act as an oncogene," Karin noted.

Another unanswered question is, which cellular genes get turned on when AP1 or related transcription factors are overproduced? And how does this promote tumor formation?

Karin's team identified these transcription factors because they bind to the control region from one of the human metallothionein (MT) genes. The MT genes code for small proteins that bind to heavy metals such as zinc and copper, and Karin believes they play an essential role in normal cell growth. On this basis he chose them as a model to study the cancer process.

The transcription factors that activate the MT genes, however, also stimulate other genes--some known, but most unknown-in the cell. One of the known genes codes for the enzyme collagenase, which by its ability to digest connective tissue could play an important role in tumor invasion of tissues (metastasis).

"What we predict is that these factors activate cellular genes that code for growth factors and other components of the pathway of growth control, which then stimulate even more AP1 production," Karin said. "We think what you get when something like AP1 is overproduced is a whole cycle feeding upon itself in a self-sustaining process that can somehow lead to cancer.

"The cell is like a clockworks if it loses control of the process at any single point, the whole mechanism will go awry."

(June 7, 1988)