SOUTHWESTERN NEWS

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DISCOVERY OF HOW PROTEIN CHANGES SHAPE COULD LEAD TO NEW CANCER-FIGHTING DRUGS

DALLAS – January 31, 2000 – By studying the crystal structure of a protein molecule, UT Southwestern Medical Center at Dallas scientists have discovered an important cell-regulation process that impacts cancer development and may lead to the development of new cancer-fighting drugs.

They found that a large protein called gelsolin begins the disassembling of the inner skeleton of most cells when its ball-like structure unfolds.

It was already known that lower gelsolin activity is a marker for breast, colon and bladder cancer.

Gelsolin breaks down the cytoskeleton of normal, nonmuscle cells. This layer beneath the cell membrane is composed of long filaments of actin molecules. For these cells to move, divide or go through apoptosis, or programmed cell death, the actin scaffolding must be dismantled.

"If you imagine a bowl of spaghetti when the noodles are long and intertwined, the mass is more stable. If you chop them all up, the mound of spaghetti changes and becomes more fluid," said Dr. Helen Yin, UT Southwestern professor of physiology. "Gelsolin severs the actin network and makes it less tangled; this changes the consistency of the cytoplasm so that the cells can move."

The researchers explained in a December issue of *Science* how the ball of gelsolin opens up -- when activated by calcium -- allowing one of its two halves, the C-terminal (carboxyl end), to bind to an actin filament.

In normal cells, this change in the gelsolin structure initiating the protein's severing of actin filaments is part of the cell cycle. But in cancer cells, this process is interrupted.

"Cancer cells can survive better because they don't undergo the apoptosis that will kill them," Yin said. "This may be partly because the cytoplasm doesn't rearrange as much because the gelsolin is down regulated in malignancies."

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Because gelsolin is important in both apoptosis and signal transduction, the researchers now are investigating how calcium activates gelsolin. The stimulating or blocking of this activation would be a likely basis for new drugs.

Yin first discovered that calcium activated gelsolin 20 years ago when she was doing postdoctoral research.

Her collaborators on her recent research were Dr. Marisan Mejillano, a postdoctoral fellow in physiology at UT Southwestern; Drs. Robert Robinson and Senyon Choe and researcher Vincent Le of the Salk Institute for Biological Studies in San Diego; and Dr. Leslie Burtnick of the University of British Columbia Faculty of Medicine.

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