SOUTHWESTERN NEWS

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UT Southwestern researchers discover master switch in cell death

DALLAS – June 30, 2005 – Researchers at UT Southwestern Medical Center have found an enzyme vital for controlling the early stages of cell death – a beneficial and normal process when it works right, but malignant in a variety of cancers when it malfunctions.

The researchers are now examining tissue from cancer patients to try to determine how mutations in the enzyme's gene may relate to cancer.

"We think this gene will really be a hot spot in research," said Dr. Qing Zhong, postdoctoral researcher in biochemistry at UT Southwestern and lead author of a paper to be published in the July 1 issue of the journal *Cell.*

The life and death of cells is a complex avalanche of reactions, controlled by a few molecules that sit atop a biochemical "pyramid."

The newly discovered enzyme, which the researchers have named Mule, destroys a key molecule at the top of the pyramid, thus leading to the cascading disintegration of the cell. Their findings also suggest a new drug target for controlling tumor formation.

Dr. Xiaodong Wang, professor of biochemistry at UT Southwestern and a researcher with the Howard Hughes Medical Institute, said the discovery of Mule will open up a whole field of research to study the enzyme's role in normal cell death and cancer.

"We think these findings are very significant," said Dr. Wang, senior author of the *Cell* study. "This is the first enzymatic step that regulates the degradation of proteins that control cell death."

The beneficial side of cell death – known as apoptosis – occurs when it kills cells at appropriate times, as is the case, for example, when it removes the webbing from the fingers of an embryo or shapes a developing brain. But the darker side of this complex process manifests itself in cancers when cells don't die when they're supposed to.

The key to the researchers' finding was the interaction between the Mule enzyme and a

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major player in cell death, the protein Mcl-1. Dr. Wang said that while there are many possible routes a cell may take toward apoptosis, this interaction serves as one of the "master switches" controlling whether or not those other pathways are triggered.

Normally, Mcl-1 keeps cells alive by protecting them against apoptosis. For a cell to die, Mcl-1 has to be disabled. "It's just like a guardian," Dr. Zhong said.

A healthy organism needs just the right amount of Mcl-1. Too little Mcl-1 can lead to a damaged immune system or even death. Too much, and cells stay alive when they shouldn't, leading to cancers such as lymphomas.

Using human cell extracts, the researchers found that Mule caused a protein called ubiquitin to bind to several sites on Mcl-1. When ubiquitin binds to a molecule, it serves as a flag for that molecule to be destroyed.

"If you have too much Mule in a cell, Mcl-1 will degrade tremendously," Dr. Zhong said.

The search for Mule took more than two years, as the UT Southwestern researchers specifically searched for an enzyme that controls Mcl-1.

The interaction between Mule and Mcl-1 might someday be manipulated to help cancer patients, Dr. Wang said. For instance, a tumor may contain cells with a deficit of Mule, making the tumor more likely to grow and perhaps be resistant to chemotherapy. Treatment might then focus on the biochemistry of Mule and Mcl-1, he said.

"We might be able to see if there's a problem with Mule, or perhaps we could screen beforehand," Dr. Wang said.

Other UT Southwestern researchers involved in the study were Wenhua Gao, student research assistant, and Dr. Fenghe Du, research specialist.

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