SOUTHWESTERN NEWS

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UT SOUTHWESTERN SCIENTISTS UNCOVER NEW MECHANISM BY WHICH CELLS RID THEMSELVES OF DAMAGED PROTEINS

DALLAS – Dec. 13, 2002 – Scientists at UT Southwestern Medical Center at Dallas have identified a new and surprising mechanism by which a class of enzymes responsible for the breakdown of proteins operates.

The process of degrading proteins no longer needed by cells is essential in the normal growth, development and regulation of cells, and the study's findings have implications for understanding diseases like Parkinson's and several forms of cancer.

"Many diseases involve the inappropriate accumulation of unneeded or damaged proteins,'' said Dr. Philip Thomas, associate professor of physiology and the study's senior author. "Cells normally utilize an enzyme called the proteasome to remove these proteins by cutting them into small pieces."

The researchers found that the proteasome independently degrades substrates (substances acted upon by an enzyme) involved in Parkinson's disease and some types of cancer. The findings appear in this week's online Web version of *Science*.

"For some time, people thought that the proteasome could not work by itself," said Dr. George DeMartino, professor of physiology and a study author. "The study showed that it has the capability of doing something by itself with known, important substrates."

These findings may have implications for development of future drugs to treat diseases like cancer. "The progression through the cell cycle is normally controlled by degrading certain proteins at certain times in the cell cycle," said DeMartino. "In cancer cells, that process goes faster, and it doesn't turn off. If you can somehow inhibit proteasome function, you can prevent cells from going through the cell cycle and cell growth and, therefore, prevent cancer."

The proteasome, which is present in all higher cells, contains its active sites inside a

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cylinder-like shape with a gate that prevents the entry of normal cellular proteins, thereby protecting them from destruction. For years, scientists believed that proteasome only degraded proteins tagged by a "death marker" named polyubiquitin, which directed damaged proteins to a complex that opened the gate. The new findings reveal that some important substrates do not need to be marked with polyubiquitin, but can open the gate themselves, enter the active cylinder and be degraded.

The scientists conducted the research by performing biochemical assays using purified proteins involved in disease. Included were *α-synuclein* – a protein that is not normally degraded in Parkinson's disease – and a cell-cycle regulator important to the progression of cancer. Accumulation of the degradation-resistant *α-synuclein* is thought to play a causative role in Parkinson's disease.

Dr. Changwei Liu, postdoctoral research fellow in physiology and lead author of the study, said, "We found that the proteasome can cut in the middle of these substrates. This was totally unexpected. Interestingly, cutting *α-synuclein* in this manner produces fragments that are reminiscent of the products found in the pathological deposits in the brains of Parkinson's patients."

Dr. Michael Corboy, postdoctoral physiology research fellow, also helped author the study, which was supported by grants from the Welch Foundation and the National Institutes of Health.