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Researchers Identify Enzyme that Regulates Degradation of Damaged Proteins

A study by scientists at the University of California, San Diego and UC Irvine has identified an enzyme called a proteasome phosphatase that appears to regulate removal of damaged proteins from a cell. The understanding of how this process works could have important implications for numerous diseases, including cancer and Parkinson's disease.

The study – led by Jack E. Dixon, PhD, professor of Pharmacology, Cellular & Molecular Medicine, and Chemistry/Biochemistry at the University of California, San Diego and Vice President and chief scientific officer of the Howard Hughes Medical Institute – appears this week in the online edition of *Proceedings of the National Academy of Sciences* (PNAS).

Proteasomes are very large protein complexes found in all eukaryote cells, in archaea (a group of single-celled microorganisms) and in some bacteria. These basket-like chambers are essential for removing damaged or misfolded proteins from the cell. The inability of a defective proteasome to destroy misfolded or damaged proteins can be cataclysmic.

Scientists have known for some time that the proteasome can be regulated by a process called phosphorylation – a chemical process by which a phosphate is added to a protein in order to activate or deactivate it, and which plays a crucial role in biological functions, controlling nearly every cellular process, including metabolism, gene transcription and translation, cell movement, and cell death. However, researchers had a poor understanding of the kinases that put the phosphate residues on the proteasome and almost no understanding of the phosphatases that remove the phosphates.

Now researchers have described for the first time how a eukaryotic phosphatase known as ubiquitin-like domain-containing C-terminal phosphatase (UBLCP1) regulates nuclear proteasome activity, revealing that UBLCP1 decreases proteasome activity by selectively dephosphorylating the proteasome.

“So far, UBLCP1 is the only proteasome-specific phosphatase identified to exist in mammalian cells,” said Dixon. “We are just beginning to understand how it alters proteasome activity, but one can anticipate that defects in the phosphatase activity are likely to result in major alterations in the ability of the cell to remove damaged protein.”

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