MedicalXpress

Key protein interactions involved in neurodegenerative disease revealed

November 8 2012

Scientists from the Florida campus of The Scripps Research Institute (TSRI) have defined the molecular structure of an enzyme as it interacts with several proteins involved in outcomes that can influence neurodegenerative disease and insulin resistance. The enzymes in question, which play a critical role in nerve cell (neuron) survival, are among the most prized targets for drugs to treat brain disorders such as Parkinson's disease, Alzheimer's disease and amyotrophic lateral sclerosis (ALS).

The study was published online ahead of print on November 8, 2012, by the journal Structure.

The new study reveals the structure of a class of enzymes called c-jun-N-terminal kinases (JNK) when bound to three peptides from different protein families; JNK is an important contributor to stress-induced apoptosis (cell death), and several studies in animal models have shown that JNK inhibition protects against neurodegeneration.

"Our findings have long-range implications for drug discovery," said TSRI Professor Philip LoGrasso, who, along with TSRI Associate Professor Kendall Nettles, led the study. "Knowing the structure of JNK bound to these proteins will allow us to make novel substrate competitive inhibitors for this enzyme with even greater specificity and hopefully less toxicity."

The scientists used what they called structure class analysis, looking at

groups of structures, which revealed subtle differences not apparent looking at them individually.

"From a structural point of view, these different proteins appear to be very similar, but the biochemistry shows that the results of their binding to JNK were very different," he said.

LoGrasso and his colleagues were responsible for creating and solving the crystal structures of the three peptides (JIP1, SAB, and ATF-2) with JNK3 using a technique called x-ray crystallography, while Nettles handled much of the data analysis.

All three peptides have important effects, LoGrasso said, inducing two distinct inhibitory mechanisms—one where the peptide caused the activation loop to bind directly in the ATP pocket, and another with allosteric control (that is, using a location on the protein other than the active site). Because JNK signaling needs to be tightly controlled, even small changes in it can alter a cell's fate.

"Solving the crystal structures of these three bound peptides gives us a clearer idea of how we can block each of these mechanisms related to cell death and survival," LoGrasso said. "You have to know their structure to know how to deal with them."

More information: "Structural Mechanisms of Allostery and Autoinhibition in JNK Family Kinases," December 5, 2012 print edition of *Structure*.

Provided by Scripps Research Institute