Researchers gain insight into key protein linked to cancers, neurodegenerative disorders

May 30 2013

Virginia Commonwealth University researchers studying a key molecular player called Hsp70 that is responsible for protein homeostasis have uncovered how it binds together with another molecule responsible for intracellular energy transfer to enhance its overall activity and efficiency – details that have previously not been well understood.

Heat shock proteins, particularly the 70-kilodalton heat shock proteins, Hsp70, are important for cellular processes such as protein folding and protecting cells from stress. It is also involved with protein assembly, degradation and transport. Imbalances in protein homeostasis have been previously found to contribute to the onset of neurodegenerative diseases and cancers.

In the study, published this week in the Online First section of *Nature Structural & Molecular Biology*, a publication of the *Nature* journal family, researchers conducted a biochemical analysis of the structure to learn how ATP binding allosterically opens the polypeptide-binding site. In order for Hsp70 to do its job of regulating its binding to unfolded polypeptide substrates, it gains energy from the process of ATP hydrolysis. ATP is a molecule responsible for intracellular energy transfer.

The team found that when Hsp70 binds ATP it promotes the allosteric opening of the polypeptide binding site.

"Due to their essential roles in protein trafficking and proper folding since mis-folded proteins can disrupt cell function, Hsp70s are inextricably linked to the development of cancers, aging and neurodegenerative disorders," said Qinglian Liu, Ph.D., assistant professor in the Department of Physiology and Biophysics in the VCU School of Medicine.

"Understanding the structural properties at the atomic level and molecular working of Hsp70s will pave the foundation for designing efficient and potent small molecule drugs to specifically modulate the function of Hsp70s. The small molecule drugs may become novel and efficient treatments for cancers or neurodegenerative disorders," she said.

Liu said that the team's structural and biochemical analysis revealed how Hsp70s use ATP to open their peptide substrate binding site and thus regulate their ability in binding peptide substrates.

"These findings help us understand at the atomic level how Hsp70s function in maintaining the well-being of cellular proteins, such as folding, assembly, transport and degradation," said Liu.

According to Liu, future work will move the team in two directions. First, based on this published work, they aim to design specific and potent modulators for Hsp70s and test their potential in treating cancers or neurodegenerative disorders. A second focus will be to study how Hsp70s cooperate with their Hsp40 partners to achieve their optimum activity in maintaining protein homeostasis.

VCU collaborated with Brookhaven National Laboratory, the Department of Biochemistry and Molecular Biophysics at Columbia University in New York. All the work was conducted at VCU, with the exception of the X-ray diffraction data collection and analysis, which

was done at Brookhaven's National Synchrotron Light Source.

More information: The study is titled "Allosteric opening of the polypeptide-binding site when an Hsp70 binds ATP.

Provided by Virginia Commonwealth University