Powerful Approach to the Analysis of Protein Motions

DXMS analysis provides novel tool for studying how movements allow proteins to perform their functions as molecular machines

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Researchers at the University of California, San Diego School of Medicine and the University of Texas Medical Branch (UTMB) in Galveston have concluded a study that offers a new understanding of the role that motions, or dynamics, play in the functioning of the protein Epac2. Their work provides information likely to help scientists design drugs to battle major diseases in which Epac2 plays a role, such as diabetes and cancer.

The study was selected "Paper of the Week" and will be the cover story of the *Journal of Biological Chemistry*, scheduled for publication on May 20 and now available online. The issue also contains a profile of the study's first author, project scientist Sheng Li of UCSD's Department of Medicine.

"This study offers a new understanding of the role that protein motions, or dynamics, play in the functioning of Epac2," said one of the principal investigators, Xiaodong Cheng, professor in the Department of Pharmacology and Toxicology at UTMB.

The cAMP molecule controls many physiological processes, ranging from learning and memory in the brain and contractility and relaxation in the heart to insulin secretion in the pancreas. cAMP exerts its action in cells by binding to and switching on specific receptor proteins, which, when activated by cAMP, turn on additional signaling pathways.

Errors in cell signaling are responsible for diseases such as diabetes, cancer and heart failure. Understanding cAMP-mediated cell signaling, in which Epac2 is a major player, likely will facilitate the development of new therapeutic strategies specifically targeting the cAMP-Epac2 signaling components, according to the researchers.

The project involved an ongoing collaboration between Cheng's research group at UTMB, experts in the study of cAMP signaling, and the other principal investigator, Virgil Woods Jr., MD, professor or medicine, and colleagues at UCSD School of Medicine, who are pioneers in the development and application of hydrogen/deuterium exchange mass spectrometry (DXMS) technology. Compared with other protein-analysis techniques, DXMS is especially good at studying the structural motions of proteins.

Using this novel approach, the investigators were able to reveal, in fine detail, that cAMP interacts with its two known binding sites on Epac2 in a sequential fashion, and that binding of cAMP changes the shape of the protein in a very specific way - switching on its activity by exposing further signaling interaction sites on Epac2.

"DXMS analysis has proved to be an amazingly powerful approach, alone or in combination with other techniques, in figuring out how proteins work as molecular machines, changing their shapes - or morphing - in the normal course of their function," said Woods. "This will be of great use in the identification and development of therapeutic drugs that target these protein motions."

Additional collaborators include Tamara Tsalkova and Fang Mei of the UTMB Department of Pharmacology and Toxicology; Mark A. White, associate professor in the UTMB Department of Biochemistry and Molecular Biology; and Tong Liu and Daphne Wang, both of the UCSD Department of Medicine and Biomedical Sciences Graduate Program.

The study was funded by the National Institutes of Health and the John Sealy Memorial Endowment Fund for Biomedical Research. Based on its success at applying DXMS to the analysis of a number of important proteins, UC San Diego was recently awarded an NIH grant to implement "next-generation" advanced DXMS analysis.

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