Chemists get grip on slippery lipids

August 30 2007

The ability of the body's cells to correctly receive and convey signals is crucial to good health. Lipids, or fats, play a critical role in this regulation by providing spaces for proteins to gather and network. They are helped in this process by protein molecules called lipid binding domains.

Understanding how these domains work may open up new targets of opportunity for drug development to treat illnesses such as cancer, diabetes and various inflammatory diseases.

Studying lipid binding domains is a specialty of Wonhwa Cho, distinguished professor of chemistry at the University of Illinois at Chicago. In two recently released papers appearing in the *EMBO Journal and the Journal of Biological Chemistry*, Cho and his associates describe mechanisms by which a particular binding domain -- the PX or "Phox" -- recognize specific lipids and interact with cell membranes to modulate functions.

"The PX domain can recognize and interact with a large number of lipid molecules and other proteins," said Cho. "We study how particular types of PX domains recognize specific lipids."

In the papers, Cho describes the structure and function PX domains from two proteins, KIF16B and Bem1p, which interact with a class of signaling lipids called phosphoinositides.

"KIF16B-PX domain is a critical component of the regulatory

mechanism to modulate the duration of receptor-mediated cell signaling pathways," Cho said. "That's important because both prolonged and shortened signaling pathways will cause problems."

"Bem1p-PX domain is a yeast scaffold protein that's critical for cell polarity. It serves as an excellent model system to study how a scaffold protein goes to the cell membrane in response to a particular lipid signal, and then modulates multiple protein-protein interactions."

Cho's research group pioneered a novel biophysical approach to explain the complex mechanisms by which cellular lipid signals specifically and divergently activate a wide array of lipid binding domains and the proteins harboring these domains during various cellular processes.

"This research may help in development of new types of small molecules and drugs that specifically modulate the signaling and trafficking processes," Cho said. "For example, if a cellular malfunction is caused by over-activation of a particular lipid-mediated pathway, then we can turn off that pathway by developing a compound that interferes with the interaction of the lipid with its binding protein."

Source: University of Illinois at Chicago