Cell protein interactions favor fats

March 22 2012

For cells to signal each other to carry out their vital work, could the cell membrane's lipids -- or fats -- play a role in buttering-up the process? A research group led by University of Illinois at Chicago chemistry professor Wonhwa Cho thinks so, and presents detailed findings in the April 27 issue of *Molecular Cell*, online March 22.

Proteins -- molecular machines that process signals critical for cell function and regulation -- perform their work by forming complex and tightly regulated interaction networks. Until recently, most scientists thought cellular protein interactions were very tight and specific. But research now indicates that is not the case.

Cho has studied cell membranes for more than two decades and has long hypothesized that membrane lipids play a critical role in regulating cellular protein interactions. To convince skeptics, he and his team conducted a genomic-scale investigation into if, and how, lipids play this role.

"Cellular protein interactions are mediated by so-called protein interaction domains, or PIDs. These are small molecular structural units within large proteins that specialize in recognizing interaction partners," he said.

"We decided to characterize PIDs in the whole genome and determine how many are regulated, by which membrane lipids, and how it's done."

For their pilot study they selected the PDZ domain, one of the most

abundant in human cells and a target for drug development. Developing therapies based on protein interactions is a major field of biomedical research, but a better understanding of protein interaction networks is needed.

Due to the large number of PDZ domains, it was impractical to characterize all of them experimentally. So Cho, working with UIC computational scientist and associate professor of bioengineering Hui Lu, his graduate student Morten Kallberg, Columbia University colleague Barry Honig and Honig's postdoctoral assistant Antonina Silkov, performed bioinformatics computations to predict and classify the functions of all lipid-regulating PDZ domains using an experimental database collected by Cho's postdoctoral assistant Yong Chen and graduate student Ren Sheng.

Cho said the group found that "an unexpectedly large number" of PDZ domains -- more than 30 percent -- interact with various membrane lipids, and that lipids control their cellular location and interaction with other protein partners.

"Furthermore, different PDZ domains are regulated by different lipids in different mechanisms, which open new avenues for drug development for specific control of cellular activity of PDZ domains implicated in major human diseases," he said.

The findings will be available online in a searchable format for other researchers working on PDZ domains.

Cho and his group have since used their PDZ approach to study the other major protein interaction domains. He said they've collected substantial data and will soon report findings showing that lipids control cellular location and function in the other domains as well.

Cho said his next major step is to develop a new and novel class of small molecules that specifically modulate lipid binding activity of protein interaction domains to control diverse, dysfunctional cellular signaling pathways which cause cancer, diabetes and other inflammatory and metabolic diseases.

Provided by University of Illinois at Chicago