Ghost Protein Leaves Fresh Tracks in the Cell

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Spectrin and ankyrin are two essential proteins acting like bricks and mortar to shape and fortify cell membranes. But distinguishing which protein is the brick and which is the mortar has turned out to be difficult. New evidence suggests that spectrin can do both jobs at once.

Ron Dubreuil, associate professor of biological sciences at the University of Illinois at Chicago, reports the finding in the Oct. 23 issue of the *Journal of Cell Biology*.

Spectrin was first discovered in red blood cells, where it forms a protein scaffold under the cell's membrane. It was named for its ability to maintain the shape of cell "ghosts," which have been emptied of their contents. Ankyrin serves as the mortar that attaches spectrin to the red blood cell membrane.

Dubreuil and his UIC co-workers have spent a decade looking at different types of cells -- mostly epithelial -- trying to learn what cues tell spectrin where to assemble in cells. They use the fruit fly as their test animal because its genetic makeup has many striking similarities to humans.

"In our study, we showed spectrin doesn't have to bind to ankyrin to do its job," said Dubreuil. "This hints at a complexity we never had any idea about in trying to understand how these molecules work."

Dubreuil and his colleagues initially assumed that ankyrin was the key to

targeting spectrin in all cells. But research in many laboratories had failed to find a cue for targeting that acted through ankyrin, so Dubreuil reworked his hypothesis.

"We decided to throw out our assumptions and start fresh," he said.

A laboratory fly was genetically engineered so that spectrin could no longer bind to ankyrin -- which, Dubreuil assumed, meant that spectrin should no longer attach to the membrane.

"We thought that was going to kill the function of the protein," he said, "but it didn't affect the ability of the protein to reach its destination at all. The molecule targeted correctly to the cell membrane." In fact, the genetically engineered flies often survived to adulthood, while mutants that lacked spectrin altogether died very early in development.

Meanwhile, Dubreuil discovered that another region of spectrin, called the PH domain, unexpectedly played an critical role. Removing the PH domain left spectrin unable to bind to the membrane in certain cells, and those flies died.

Dubreuil's research seeks to clarify how these proteins function in different cells. The hope is that researchers may one day create therapeutic molecules to compensate for genetic lesions in diseases such as hereditary anemia, Duchenne muscular dystrophy, cardiac arrhythmia and the degenerative brain disease spinocerebellar ataxia 5.

"As we learn more about mutations involving spectrin and their relationships to human diseases, we're going to have more and more questions about how these mutations affect specific functions of the molecule," he said.

Other participants in the study include UIC doctoral student Amlan Das

and laboratory technicians Christine Base and Srilakshmi Dhulipala.

Source: University of Illinois at Chicago