Scientists fixate on Ric-8 to understand trafficking of popular drug receptor targets

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Half the drugs used today target a single class of proteins – and now scientists have identified an important molecular player critical to the proper workings of those proteins critical to our health.

A protein known as Ric-8 plays a vital role, according to new results from a team led by Gregory Tall, Ph.D., assistant professor of Pharmacology and Physiology at the University of Rochester Medical Center. The work was published recently in *Science Signaling*.

What you see, what you smell, how you feel – molecules known as G-protein coupled receptors and their prime targets, G proteins, are key to those and many other processes that are ubiquitous in our bodies. These proteins serve as the targets of drugs used to treat conditions like cancer, diabetes, depression, allergies, and heart disease.

These receptors normally weave themselves throughout the cell membrane, with one part protruding from the outside of a cell, and the rest of the protein inside the cell. When a compound like a drug or a hormone attaches to a receptor on the cell surface, it affects the G protein bound to the portion of the receptor that is inside the cell, triggering a cascade of signals that make life possible – or improve health, in the case of a drug, or perhaps hurting health in the case of a toxin.

Previously, Tall discovered the existence of Ric-8 and learned that it binds to G proteins, which are made inside cells and have to make their

way to the cell's outer edge, the membrane, to work correctly. In the new work, his team found that Ric-8 is a chaperone that G proteins need to be transported to the cell membrane. When Ric-8 is knocked out, G proteins don't work as they should and are destroyed.

"G proteins are involved in many biological processes – how we see and taste, how our heart beats, even our mood," said Tall. "It's a very important class of proteins. Ric-8 is the chaperone that gets G proteins where they need to be, to the cell membrane. Without it, many of these proteins end up destroyed within the cell."

"Understanding more precisely how this important class of proteins operates in the body can perhaps make many of the drugs we use today more effective for patients," Tall added.

To do the study, Tall and colleagues had to devise a system where they could study the molecules in action. In living animals such as mice, when Ric-8 is knocked out completely, the animals die. So the team worked to identify a stem cell line in which the Ric-8 gene was knocked out, so they could study G protein function in the absence of Ric-8.

The first author was graduate student Meital Gabay. Other authors at the University include Mary Pinter, an undergraduate student now at the University of Colorado at Denver; technical associate Forrest Wright, now at SUNY Upstate Medical University; and graduate student PuiYee Chan. The team worked with scientists at Regeneron Pharmaceuticals who created the "knockout" mice used in the study.

Provided by University of Rochester Medical Center