Taking the conversation inside: Enhancing signals in cell interior

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Scientists used to think most of the exchange of information between cells was conducted at the surface, where cell receptors receive signals from other cells.

Now Yale researchers report in the March 20 issue of the journal *Cell* how a switching station beneath the cell surface is crucial to processing signals from outside the cell. They also describe a key molecular switch that terminates signaling from this station.

The findings portray a much more "complex and fluid system of cellular information processing than previously envisioned", said Derek K. Toomre, assistant professor of cell biology at Yale and co-author of the study.

The Yale team was led by Pietro De Camilli, M.D., the Eugene Higgins Professor of Cell Biology and Neurobiology. De Camilli is also an investigator in the Howard Hughes Medical Institute, a member of the Kavli Institute for Neuroscience and a director of the Yale Program in Cellular Neuroscience, Neurodegeneration and Repair.

When information arrives at the cell surface, receptors that decode this information are internalized by a process called endocytosis. Typically endocytosis was viewed primarily as a mechanism to turn off signaling within the cell. However, recent research has shown signaling continues after internalization and that its strength and quality is strongly influenced by molecular interactions within the cell.

The signaling location characterized in the study, referred to as an APPL1 endosome, plays a key role early in this signaling process. The Yale team identified a molecular switch: the generation of a fatty component (a phosphoinositide) in the endosome membrane that triggers progression of receptors and other cargo from APPL1 endosomes to other intracellular destinations. Turning off this switch jams traffic in the APPL1 endosomes and enhances signaling.

De Camilli first became interested in this novel endocytic compartment when studying a protein that binds to the APPL1 endosome and is involved in Dent disease, a rare genetic disease of the kidneys, and in Lowe syndrome, a rare genetic disease of the eyes, the kidneys and the brain.

"We expect that studies of APPL1 endosomes will not only advance our understanding of basic mechanisms in cell physiology, but also give us new insight about pathogenetic mechanisms and potential therapeutic strategies in Lowe syndrome," De Camilli said.

Source: Yale University (news : web)