Study Unravels Detail of 'Most Important' Cellular Signal

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(PhysOrg.com) -- A new study provides crucial details that promise to help researchers better understand, and perhaps fine-tune with drugs, one of the most important signaling mechanisms in human cells, according to a study published online this week in the *Proceedings of the National Academy of Sciences*.

The newly published article is focused on G-protein coupled receptors (GPCRs), proteins at the heart of signaling cascades that make vision possible, carry nerve messages and set the timing of the heartbeat. Faulty GPCR signaling contributes to heart disease, cancer and diabetes to name a few. Many existing drugs work by attaching to GPCRs on the outside of cells in place of molecules that would otherwise occupy the same spot to drive disease. Researchers have been asking the question: what if, along with current drugs that interfere with disease on the outside, we could add drugs that interfere with the same disease again when the signal causing it has passed within the cell?

“The current study revealed new insights into how the structure of these signaling proteins makes possible their central role in life,” said Alan V. Smrcka, Ph.D., professor of Biochemistry and Biophysics at the University of Rochester Medical Center, and a study’s lead author. “It also promises to better guide efforts to design new drugs around them.”

Secret Handshake

The new publication is the latest in a nearly two-decade exploration by Medical Center researchers into the nature of the G protein-coupled receptor. Early work by the same team revealed the existence of a "hotspot" where the majority of a GPCR's interactions with other proteins take place inside of cells. This is the command center from which GPCRs exert control over myriad signaling pathways.

In an April 2006 article in the journal *Science*, Smrcka and colleagues identified a set of drug-like molecules that fit into, and bound tightly to, parts of the hotspot. At the time they postulated that this "hot spot" could adopt multiple shapes that would each represent potential targets for drug binding. In the new study the team applied a molecular imaging technique called nuclear magnetic resonance to directly investigate this possibility.

The field once believed that a given signaling molecule docked into the GPCR's hotspot like a key coming into a lock, two rigid shapes fitting together. The new study argues that their interaction may be more like a secret handshake: an interplay between flexible protein fingers capable of split-second shape changes that fit "the other hand" only under certain circumstances. This property, in part, enables the hotspot to act as a "master regulator" in many cells because it allows the protein to adopt different shapes to regulate multiple pathways.

Researchers found that, not only is the "hot spot" constantly in motion, exploring different shapes, but the entire G protein may also be doing the same thing. The finding may change the field's fundamental understanding of how these proteins behave, Smrcka said. The works supports the hypothesis that the hotspot quickly shifts its shape through a series of options. That way it is often the right shape to bind to any one of signaling molecules that might be standing by.

The team measured structural changes within the hotspot as it reacted to

several of its known signaling partners. Specifically, they tracked the movement of heavy nitrogen atoms that are part of the protein backbones making up the hotspot using a magnetic resonance imaging technique (NMR) that captures the each atom's energy signature. Researchers were surprised by how quickly and widely the shape of certain key protein building blocks could move around within the hotspot as it encountered its signaling partners. Parts of the protein skeleton shifted dramatically, for instance, when attached to phosducin, a signaling protein that binds to GPCR hotspots on cells in the retina to make vision possible.

Taken together, the new insights into the hotpot's structure and dynamics will guide new efforts to screen for drugs that might better interact with the hotspot as structural changes quickly expose it - then hide it - from potential partners. The hotspot's changeability actually increases the chance of finding a drug, Smrcka said, because it provides more shapes that a drug might fit into.

Provided by University of Rochester Medical Center (news : web)