MedicalXpress

Scientists create 'fingerprints' for major drug development targets

December 2 2015

For the first time, scientists from the Florida campus of The Scripps Research Institute (TSRI) have created detailed "fingerprints" of a class of surface receptors that have proven highly useful for drug development.

These detailed "fingerprints" show the surprising complexity of how these receptors activate their binding partners to produce a wide range of signaling actions.

The study, which was published this week in the journal *Science Signaling*, focuses on interactions of G protein-coupled receptors (GPCRs) with their signaling mediators known as G proteins. GPCRs—currently accounting for about 40 percent of all prescription pharmaceuticals on the market—play key roles in many physiological functions because they transmit signals from outside the cell to the interior. When an outside substance binds to a GPCR, it activates a G protein inside the cell to release components and create a specific cellular response.

"Until now, it was generally believed that GPCRs are very selective, only activating few G proteins they were designed to work with," said TSRI Associate Professor Kirill Martemyanov, who led the study. "It turns out the reality is much more complex."

Ikuo Masuho, a senior research associate in the Martemyanov lab, added, "Our imaging technology opens a unique avenue of developing drugs

that would precisely control complex GPCR-G protein coupling, maximizing therapeutic potency by activating G proteins that contribute to therapeutic efficacy while inhibiting other G proteins that cause adverse side effects."

The study found that individual GPCRs engage multiple G proteins with varying efficacy and rates, much like a dance where the most desirable partner, the GPCR, is surrounded by 14 suitors all vying for attention. The results, as in any dance, depend on which G proteins bind to the receptor—and for how long. The same receptor changes G protein partners—and the signaling outcome—depending on the action of the signal received from outside of the cell.

This finding was made possible by novel imaging technology used by the Martemyanov lab to monitor G protein activation in live cells. Using a pair of light-emitting proteins, one attached to the G protein, the other attached to what's known as a reporter molecule, Martemyanov and his colleagues were able to measure simultaneously both the signal and activation rates of most G proteins present in the body.

"Our approach looks at 14 different types of G proteins at once—and we only have 16 in our bodies," he said. "This is as close as it can get to what is actually happening in real time."

In the accompanying commentary in *Science Signaling*, Alan Smrcka, a professor at University of Rochester Medical School and a prominent GPCR researcher, wrote, "[The findings] suggest the power of the GPCR fingerprinting approach, in that it could predict the G protein coupling specificity of a GPCR in a native system, which was previously undetected by conventional analysis. This could be very helpful for identifying previously unappreciated signaling pathways downstream of individual GPCRs that could be useful therapeutically or identified as potential side effects of GPCRs."

More information: A. V. Smrcka. Fingerprinting G protein-coupled receptor signaling, *Science Signaling* (2015). DOI: 10.1126/scisignal.aad8140