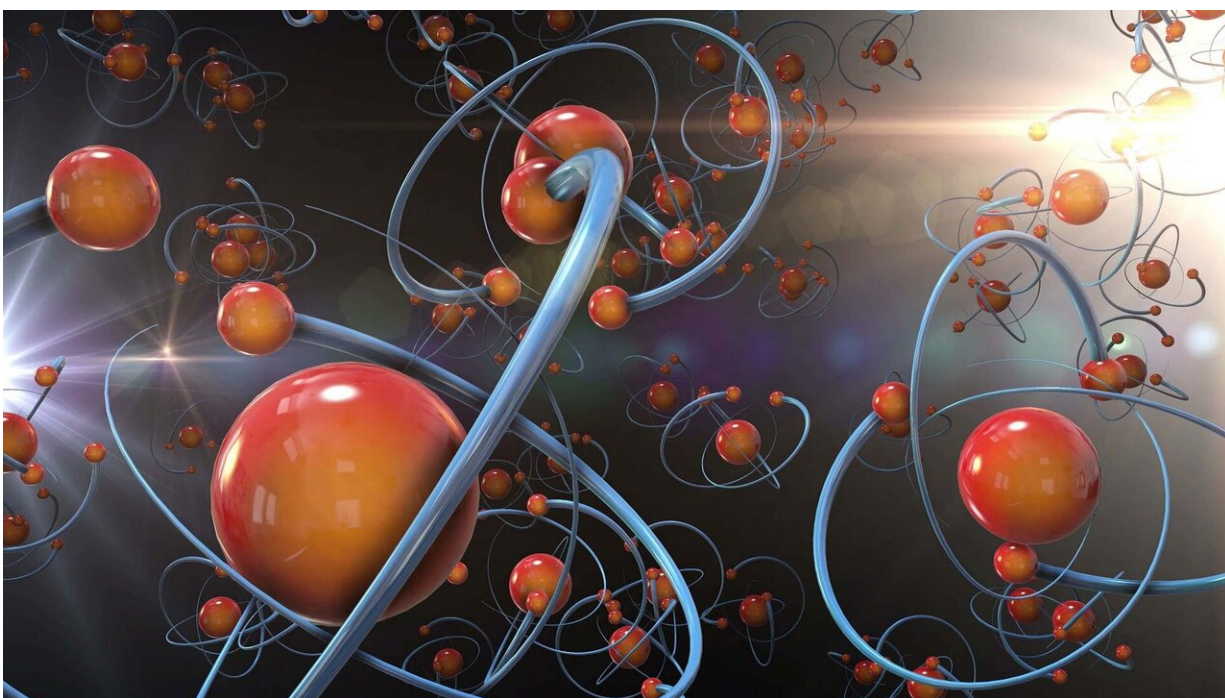


Single-molecule techniques illuminate mechanisms of GPCR activation

April 27 2022



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Scientists at St. Jude Children's Research Hospital and Columbia University/New York State Psychiatric Institute are studying G protein-coupled receptors (GPCRs), membrane proteins that are the target of one-third of approved drugs. Using single-molecule imaging techniques, researchers gained fresh insight into the process by which cellular signals are relayed by GPCRs. The work may aid the development of novel

drugs by manipulating the way they activate certain pathways. A paper on the work appeared today in *Cell*.

The [human genome](#) encodes roughly 800 GPCRs, which are expressed throughout the [human body](#) and control many physiological functions. GPCRs are important drug targets for a wide variety of disorders.

GPCRs transmit signals inside the cell when activated by agonists, (which are chemical signals such as neurotransmitters, hormones, cytokines or synthetic drugs). β -arrestins are proteins that bind GPCRs to stop G protein-mediated signaling and can also trigger a variety of other downstream signaling pathways.

The interaction of a GPCR with β -arrestin is mediated in part by a specific region of the GPCR, typically its tail. This tail undergoes activation-dependent phosphorylation. The phosphorylated GPCR tail docks into a groove on β -arrestin. But when β -arrestin is not engaged with a GPCR, this groove is occupied by β -arrestin's own C-terminal tail. Researchers wanted to understand how the β -arrestin C-terminal tail gets released to make room for the phosphorylated GPCR tail.

"We're trying to understand the process by which information is transmitted from the outside to the inside of the cell through GPCRs and, specifically, whether this information transfer occurs by way of detectable conformational [shape] changes in GPCRs and their binding partners," said co-corresponding author Scott Blanchard, Ph.D., St. Jude Department of Structural Biology. "Single-molecule imaging is a way to directly measure molecular-scale conformational changes that is very insightful and often more easily interpreted than other approaches."

A tale of two tails

Using single-molecule fluorescence resonance energy transfer

(smFRET), the researchers monitored the conformational dynamics (shape changes) of the β -arrestin C-terminal tail. Most work in this area has been done with ensemble methods that average hundreds of thousands of proteins. These averages can't show what a specific protein is doing. In contrast, the single-molecule approach can provide direct evidence about an individual protein's behavior and allow the researchers to study how it changes over time.

The group's findings show that the resting β -arrestin exists normally in a stable, autoinhibited state. In this state, the C-terminal tail is tightly bound to the groove. In order for the C-terminal tail to release and make room for the phosphorylated GPCR tail, an agonist must bind to the GPCR, which in turn "tickles" the β -arrestin to trigger the release. smFRET allowed the researchers to tease out the contributions of GPCR's phosphorylated state from its agonist-activated state, properties that can't be separated and studied in the cell. The ability to discern these states led to the discovery that the receptor tail itself also plays an autoinhibitory role that must be relieved by agonist binding.

The balance between the autoinhibited and activated states controls the intensity and duration of GPCR signaling, which in turn determines physiological responses. The findings may play a role in drug development as they allow for a systematic exploration of the outcomes from the pattern and extent of GPCR phosphorylation.

"Now that we know receptors can both activate G-proteins and mediate signaling through β -arrestin, the hope is that the field can develop more specific pharmacotherapies by finding [small molecules](#) that preferentially activate one pathway or the other," said co-corresponding author Jonathan Javitch, M.D., Ph.D., Columbia University and the New York State Psychiatric Institute.

More information: Wesley B. Asher et al, GPCR-mediated β -arrestin

activation deconvoluted with single-molecule precision, *Cell* (2022).
[DOI: 10.1016/j.cell.2022.03.042](https://doi.org/10.1016/j.cell.2022.03.042)

Provided by St. Jude Children's Research Hospital

Citation: Single-molecule techniques illuminate mechanisms of GPCR activation (2022, April 27) retrieved 5 June 2024 from <https://phys.org/news/2022-04-single-molecule-techniques-illuminate-mechanisms-gpcr.html>

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