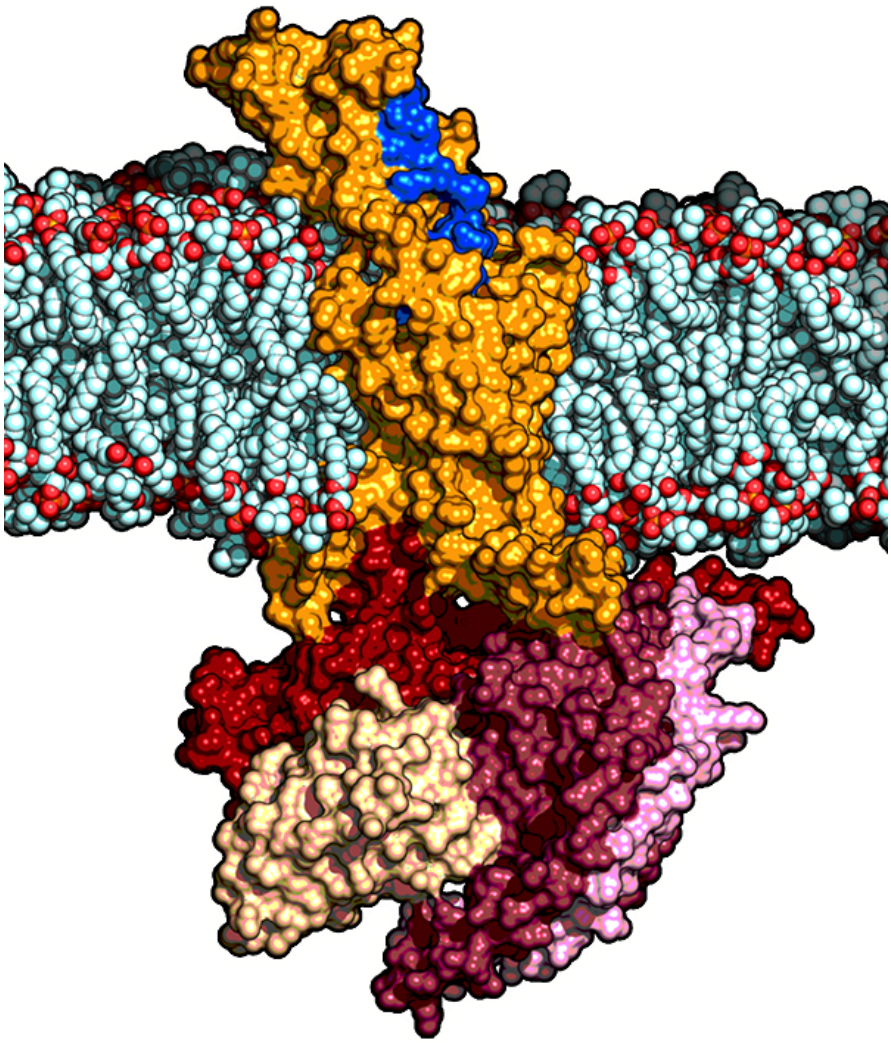
Biotech

Visualizing GPCR Activation Using Cryo-Electron Microscopy

Thu, 11/02/2017 - 10:15am by Steve Reyntjens, Ph.D., director product marketing, and Daniel Nemecek, Ph.D., applications development, life sciences, materials & structural analysis, Thermo Fisher Scientific, Inc.



3D structure of the calcitonin receptor with a bound ligand (salmon calcitonin -- blue) and embedded in a lipid bilayer representing the cellular membrane. Courtesy of Professor Patrick Sexton and Dr. Alisa Glukhova Monash University, Australia.

Researchers have recently used cryo-electron microscopy (cryo-EM) to determine the three-dimensional (3D) atomic structure of two class B G-protein coupled receptors (GPCRs) and revealed the structural basis of their activation and function.

GPCRs are a large family of membrane proteins that play crucial roles in intercellular signaling. They function as specific sensors, capable of distinguishing a vast array of different molecules, and triggering appropriate cellular responses. Ubiquitous and critical in a wide range of physiological processes, they have also been implicated in many diseases (e.g. diabetes or depression) and have become an important class of drug targets, accounting for over 30 percent of all drugs today.

The first atomic structure of a whole quaternary GPCR complex was determined using X-ray crystallography and described in *Nature* in 2011. This structure of the β2-adrenergic receptor (β2AR) in complex with its intracellular signaling partner yielded significant insights into the activation mechanism of class A GPCRs. Class A GPCRs are typically activated by a small-molecule chemical ligand (e.g. adrenaline), while class B GPCRs usually bind larger peptide hormones and are well-established targets for numerous chronic diseases, such as diabetes, bone diseases and obesity. Class B GPCRs are thus of major interest for drug discovery, but have proven to be particularly recalcitrant to crystallization (a requirement for structure determination using X-ray crystallography).

Recently, the structure of calcitonin receptor (CTR) was published in *Nature*, the first structure of a complete class B GPCR. The investigators used cryo-EM, a technique that has seen an impressive increase in the number and quality of structures published, due to important technological advances in recent years. Cryo-EM allowed them to use wildtype receptor without any modifications and the results showed the mechanism by which the receptor engages the peptide agonist and translates the signal to the G-protein subunits.

Another recent study in *Nature* presented the structure of the glucagon-like peptide 1 receptor and revealed the activation mechanism of class B GPCRs via hormone binding. Structures of complete, activated GPCRs like these are valuable for providing a fundamental understanding of underlying molecular mechanisms that will surely lead to new insights for drug development.

Cryo-EM has matured to become an important method in the structural biologist's toolkit. It overcomes some key bottlenecks of structure determination by crystallography. First, protein molecules are preserved in

near-native conditions in flash-frozen vitreous ice without cumbersome and sometimes impossible crystallization. This also eliminates uncertainty about the fidelity between the crystallized and natural states. Second, structural flexibility is preserved throughout the freezing and data collection process. This yields additional insights about conformational dynamics and variability that cannot be observed in a closely-packed, crystallized sample.

These recent reports of complete and activated GPCR structures herald a bright future for cryo-EM in the fundamental understanding of disease mechanisms and will ultimately lead to the development of impactful new drugs.

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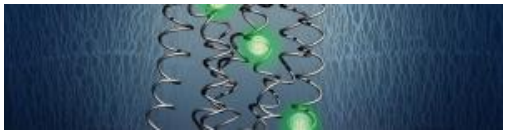

New Structure of Key Protein Holds Clues for Better Drug Design