Physics vs. asthma

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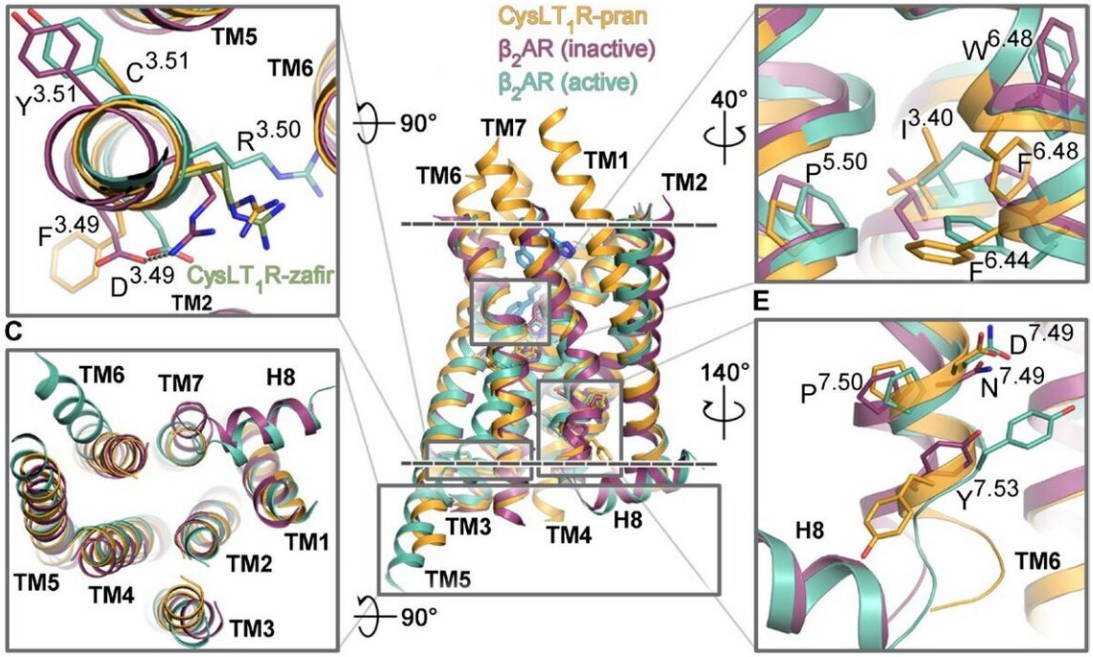

The segments of the CysLT1 receptor responsible for its activation are shown in orange, next to other G protein-coupled receptors. Credit: Luginina et al./Science Advances

A research team from the MIPT Center for Molecular Mechanisms of Aging and Age-Related Diseases has collaborated with colleagues from the U.S., Canada, France, and Germany to determine the spatial structure of the CysLT1 receptor. The paper was published in *Science Advances* .

G protein-coupled receptors, or GPCRs, are molecular machines incorporated into cell membranes. These receptors pick up specific signals on the outside of a cell and transmit them into the cell. The signals come from various sources, including photons of light, fat molecules, small proteins, and DNA fragments. A GPCR can trigger diverse events in the cell, such as division, relocation, or even death.

The GPCR-mediated cellular "communication" is crucial for the functioning of an organism. No wonder that these receptors are in some way involved in all processes in our bodies. They are the targets of about 40% of existing medications, too. Thus, it is interesting for structural biologists to understand the functioning mechanism of these biological machines and find a way of affecting them, by developing new drugs that possess more specificity and fewer side effects.

Structural biology is a cross-disciplinary field at the interface of physics and biology, concerned with studying the 3-D arrangement of biological macromolecules, such as proteins. Structural studies involve genetic engineering, artificial protein production, purification, and crystallization. Once the protein crystal has been obtained, the physics comes in: Researchers expose the protein crystal to powerful X-rays to generate diffraction patterns. The resulting data can be mathematically processed to recover a detailed 3-D atomic structure of a given protein molecule, with a precision of up to several angstroms.

Structural studies rely on powerful X-ray sources. These typically come in two kinds: synchrotrons and the more recently developed free electron lasers. In both cases, electrons are accelerated to nearly the speed of light. They are then forced to change their speed or direction of motion, leading to X-ray emission. In a synchrotron, the electrons move along a curved, almost circular trajectory. In a free electron laser, they travel through a passage between two rows of alternating oppositely directed magnets, known as an undulator.

While structural biologists have used synchrotrons since the 1970s, free electron lasers are a relatively recent addition to the protein crystallography toolkit. Introduced in the early 2010s, they generate extremely powerful radiation and enable X-ray diffraction analysis of minuscule 1-micrometer crystals. This new instrument has already brought about the discovery of several hundred structures.

Researchers from MIPT have investigated the structure of a GPCR known as CysLT1. It is involved in inflammatory processes and plays an important role in allergic diseases, including asthma, which affects about 10% of the global population. The team of biophysicists obtained the detailed 3-D structure of the receptor with the molecules of zafirlukast and pranlukast. These are two drugs prescribed to patients with asthma, allergic rhinitis, and urticaria.

While relatively large, 0.3-millimeter crystals with pranlukast were grown in the study, the crystals with zafirlukast only reached the size of several micrometers. The former samples were investigated at the ESRF synchrotron in Grenoble, France. The latter were examined using the Stanford University-operated Linac Coherent Light Source, a free electron laser. The researchers' colleagues from Canada helped to explore the mechanisms of signal transmission via CysLT1.

"These are no doubt unique structures, and we've grown quite fond of them," said study co-author Aleksandra Luginina from the MIPT Laboratory of Structural Biology of G Protein-Coupled Receptors. "The CysLT1 receptor's mechanism of operation updates how we see the functioning of GPCR protein subgroups. Also, by identifying the binding sites for the zafirlukast and pranlukast molecules, we lay the basis for improving asthma medications—increasing their efficiency and reducing side effects."

GPCRs are notoriously difficult objects for structural studies. Only a

handful of labs worldwide have managed to complete research projects of this kind. The MIPT team is glad that an Institute laboratory is now among them.

More information: Structure-Based Mechanism of Cysteinyl Leukotriene Receptor Inhibition by Antiasthmatic Drugs. *Science Advances* 2019. DOI: 10.1126/sciadv.aax2518

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