Illuminating the path to hearing recovery: Structural insights into a receptor protein's role in auditory function

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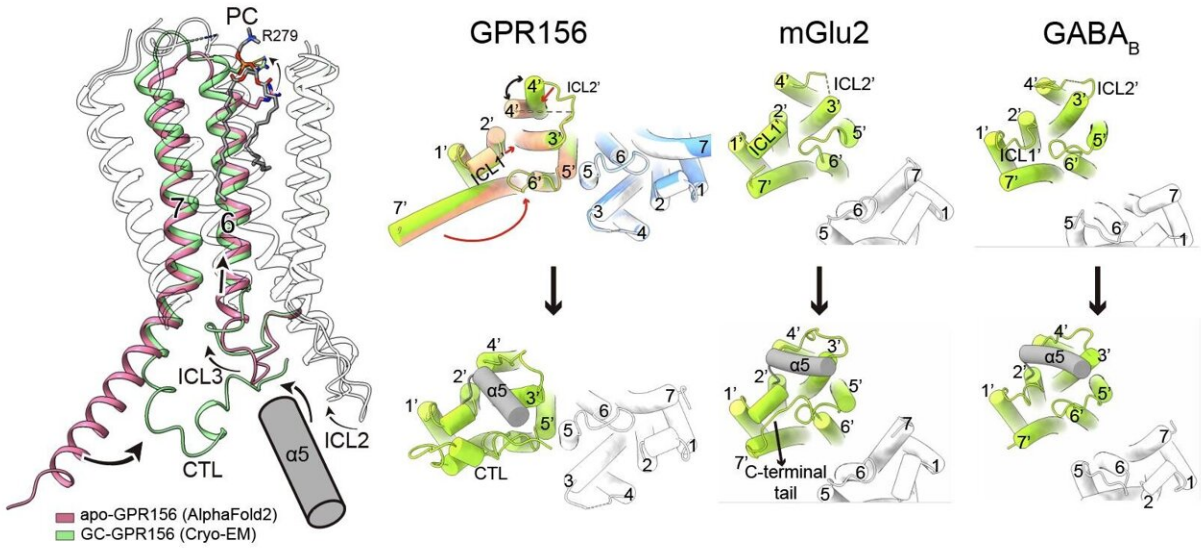

Schematic diagram illustrating the activation mechanism of GPR156 in comparison with representative class C GPCRs, mGlu2, and $GABA_B$ receptors. Credit: POSTECH

Researchers have worked to uncover the mysteries surrounding a specific receptor protein associated with hearing. Professor Yunje Cho's research team from the Department of Life Sciences at Pohang University of Science and Technology (POSTECH, Republic of Korea) has collaborated with Professor Kwang Pyo Kim's group from the

Department of Applied Chemistry at Kyung Hee University (KHU, ROK), Professor Vsevolod Katritch's team from the University of Southern California (USC, U.S.), and Professor Carol V. Robinson from the University of Oxford (UK).

Their findings have recently been published in the journal *Nature Structural & Molecular Biology*.

Deep within the inner ear lie the cochlea, responsible for sound detection, and the vestibular apparatus, which oversees balance. Cells within these regions harbor a class C orphan G-protein-coupled receptor (GPCR) called GPR156. When this receptor is activated, it binds with G-proteins inside the cell, facilitating signal transmission.

Unlike its counterparts, GPR156 exhibits sustained activity even in the absence of external stimuli, playing a pivotal role in upholding auditory and balance functions. Unveiling the structural and functional intricacies of GPR156 holds promise for devising interventions for individuals with congenital hearing impairments.

The research team employed cryo-electron microscopy (cryo-EM) analysis to delve into the GPR156 in the G_o-free and G_o-coupled states, achieving unprecedented resolution. Their investigation unearthed the mechanisms behind GPR156's ability to maintain heightened activity sans activators.

Their analysis confirmed that GPR156 activation hinges on its interaction with abundant lipids in the cell membrane, triggering structural shifts upon engagement with G-proteins in the cytoplasm. Notably, unlike conventional GPCRs, GPR156 exhibits flexibility in altering the structure of the seventh helix as it traverses the cell membrane, thereby facilitating binding with G-proteins and orchestrating signal activation to detect sound. This study represents a

crucial step forward in unraveling the structural dynamics and activation mechanisms of GPR156.

Professor Cho of POSTECH remarked, "Congenital hearing and balance impairments afflict numerous individuals. I am hopeful that our research will pave the way for groundbreaking treatments and drug discoveries to alleviate their suffering."

More information: Jinwoo Shin et al, Constitutive activation mechanism of a class C GPCR, *Nature Structural & Molecular Biology* (2024). DOI: 10.1038/s41594-024-01224-7

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