How mechanical stimuli trigger cellular signaling

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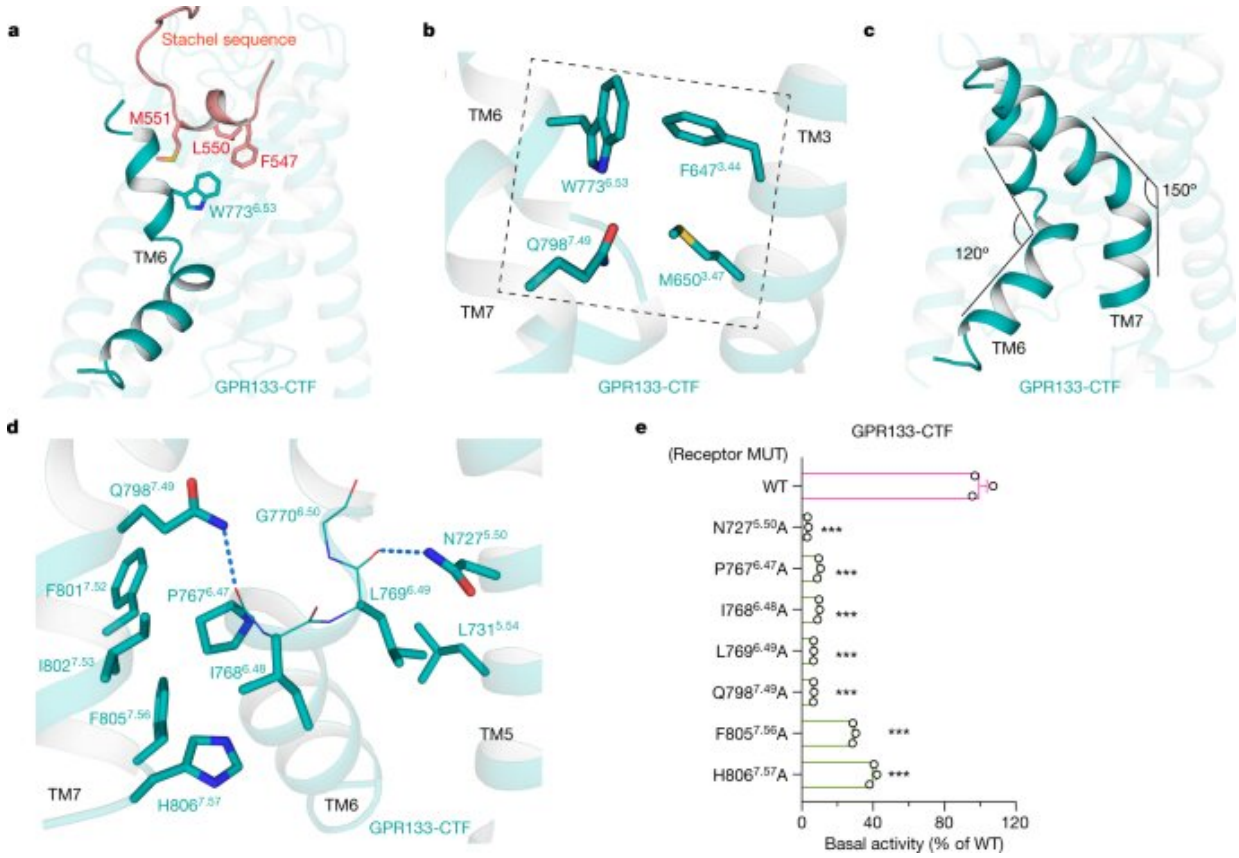

Active structures of GPR133-CTF and GPR114-CTF. Credit: *Nature* (2022).
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Breathing, seeing, hearing—the family of G protein-coupled receptors (GPCRs) is involved in a variety of physiological processes and is also

the cause of diverse diseases. As has now been discovered by a team of scientists led by Professor Ines Liebscher from Leipzig University, some members of the GPCR family respond to mechanical stimuli. In collaboration with Chinese research groups, they have achieved another milestone on the way to understanding the mechanism by which this receptor class is activated. For the first time, they were able to describe the structure of specific active receptors. Their findings have now been published in the journal *Nature*.

"GPCRs are involved in almost all physiological processes in the body. GPCRs allow humans to see, control their immune system, direct hormone balance," explained Professor Ines Liebscher from the Rudolf Schönheimer Institute of Biochemistry at the Faculty of Medicine, emphasizing that "they have been the focus of our research for many years now, and research on GPCRs is of such outstanding importance because the majority of approved drugs target this receptor family." GPCRs are receptors that transmit their signals via so-called G proteins, which is why they are also called G protein-coupled receptors—or GPCRs for short.

The researchers in Leipzig focus their work on a special class of receptors, known as adhesion GPCRs. In collaboration with several Chinese teams of scientists, the research groups led by Professor Ines Liebscher and Professor Torsten Schöneberg have now been able to describe the structure of special receptor molecules in their active state. This data supports findings from seven years ago at the Leipzig institute that these receptors are activated by a tethered agonist within the molecule. Furthermore, the Leipzig researchers showed that mechanical stimuli play a crucial role in the activation by the tethered agonist. It is still not fully understood how our body's own cells are able to interpret mechanics—in the form of vibration, gravitational forces, relative cell movement or swelling—as a signal. "Our research has established the basis for our partners from China to structurally elucidate a scenario of

how mechanical stimuli are recognized in the molecule and transmitted as signals," said Liebscher, a medical scientist and biochemist. "The results can be found in the current study."

Functional nature of mechanosensitive receptors elucidated

"About one-third of the GPCR family are still orphans, meaning that either their function or activation is unknown. With our current research, we have made a decisive contribution to better understanding GPCR structures," said co-author Schöneberg, director of the Rudolf Schönheimer Institute of Biochemistry. "The new study findings are of landmark importance when it comes to developing future forms of therapy," concluded Liebscher. She is a member of the steering committee in the EU-funded COST Action Adher´n Rise CA18240, which she successfully secured in 2019. This network of scientists from 28 European countries aims to promote, stimulate and implement research on adhesion G protein-coupled receptors (aGPCRs) "from bench to bedside". The latest findings and approaches to adhesion GPCR research will also be presented at the international conference 4GPCRnet, of which Professor Liebscher is co-organizer. This high-level meeting will be held on 26 to 29 September 2022 on Leipzig University's Augustusplatz campus.

More information: Yu-Qi Ping et al, Structural basis for the tethered peptide activation of adhesion GPCRs, *Nature* (2022). DOI: 10.1038/s41586-022-04619-y

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