Expanding drug development horizons: Receptor behaviors observed in living cell membranes

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Unprecedented single molecule imaging movies of living cell membranes, taken by a research team based at Kyoto University and the University of New Mexico, have clarified a decades-old enigma surrounding receptor molecule behaviors. The results, appearing in the latest issue of the *Journal of Cell Biology*, promise to open the door to new possibilities for drug development.

The work focuses on G protein-coupled receptors (GPCRs), a class of molecules in cell membranes that comprise the largest superfamily in the human genome. In spite of being the focus of roughly half of modern drug development due to their key role in signaling across the membrane, until now it has not been well understood how GPCRs relay signals from the outside world into cells' interiors.

For over 15 years, debate regarding GPCRs' signaling mechanisms has centered on whether these molecules work alone (as monomers) or in pairs (dimers). Using formyl-peptide receptors (FPRs) as a model GPCR, the research team found that the two views are both partially correct.

"By developing a super-quantitation single-molecule imaging method, in which GPCR molecules are inspected one by one in living cell membranes," explained Rinshi Kasai of Kyoto University's Institute for Integrated Cell-Material Sciences (iCeMS) and lead author of the paper,

"we are now able to actually 'see' that each individual FPR molecule moves around in the cell membrane, endlessly interconverting between monomers and dimers with different partners, completing each cycle within a quarter of a second."

According to iCeMS Professor Akihiro Kusumi, "We obtained a parameter called the dissociation constant, which will allow us to predict numbers of monomers and dimers if the total number of GPCRs in a cell is known. The ability of scientists to obtain such key numbers will be essential for understanding GPCR signaling, as well as defects leading to diseases from the neuronal to the immune systems. The implications for drug design, blocking signal amplification by monomer-dimer interconversion, are profoundly important."

The research team, funded in part by the Japan Science and Technology Agency (JST) and the Japanese education ministry MEXT, anticipates that their findings will have a broad impact on the further study of signal transduction in the cell membrane and conceptual and methodological development for drug discovery.

More information: The article, "Full characterization of GPCR monomer–dimer dynamic equilibrium by single molecule imaging" by Rinshi S. Kasai, Kenichi G. N. Suzuki, Eric R. Prossnitz, Ikuko Koyama-Honda, Chieko Nakada, Takahiro K. Fujiwara, and Akihiro Kusumi, was published online in the February 7, 2011 issue of the *Journal of Cell Biology*.

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