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Structures and functions of seven-transmembrane helix receptors

The adiponectin receptors, AdipoR1 and AdipoR2, are key anti-diabetic molecules. AdipoR1 and AdipoR2 are seven transmembrane helix receptor proteins orienting their N- and C-termini on the intracellular and extracellular sides, respectively, which is opposite to G-protein coupled receptors (GPCRs). We determined the crystal structures of human AdipoR1 and AdipoR2, and found that they represent a novel class of receptor structure. The seven transmembrane helices form a large internal cavity, in which three conserved His residues coordinate a zinc ion. This zinc-coordinated structure indicates that AdipoR1 and AdipoR2 are hydrolytic enzymes. Both AdipoR1 and AdipoR2 assume the closed and open forms. The lipids bound in the closed and open forms were identified, which indicated that the zinc-coordinated structure is for lipid hydrolysis. We determined the crystal structure of a GPCR, leukotriene B_4 (LTB_4) receptor BLT1, bound with an antagonist. BLT1 exhibits the canonical seven transmembrane helix structure. The binding mode of the antagonist is characteristic, and is expected to be useful for further drug development. We applied the cell-free protein synthesis method to production of GPCRs. By adding a mixture of mammalian lipids in the cell-free reaction, GPCRs were synthesized and folded with lipids. This method is useful for large-scale production of high quality GPCR samples for structural and functional studies.

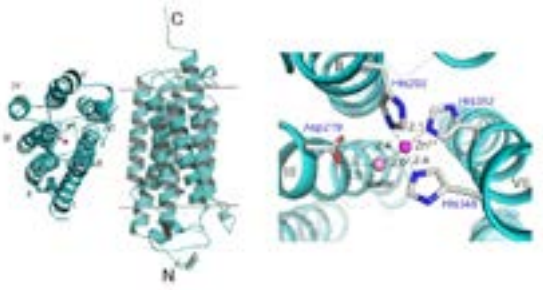

Figure 1: Crystal structure of human AdipoR2 (Tanabe et al., 2015)

Biography

Shigeyuki Yokoyama obtained his PhD degree from The University of Tokyo in 1981. He was an Associate Professor (1986–1991) and Professor (1991–2012) at the University of Tokyo, and now is Emeritus Professor. He was also appointed Director of the Cellular Signaling Laboratory (1993–2004), the Structural Molecular Biology Laboratory (2004-2006), the Protein Research Group (1998–2008), and the Systems and Structural Biology Center (2008–2013). He is a distinguished Senior Scientist and directing the Structural Biology Laboratory at RIKEN. He has published more than 800 papers, and has been serving as editorial board members of Nucleic Acids Research etc.

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