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G PROTEIN-COUPLED RECEPTORS

Pioneering Frizzled family receptor structure solved

A crystal structure of the human Smoothened (SMO) receptor — an essential component of the Hedgehog signalling pathway — bound to an antitumour compound is reported for the first time. Remarkable differences in the SMO receptor (which is a member of the class F G protein-coupled receptors (GPCRs) and is transcription-factor-coupled) were observed compared to class A GPCRs (the largest class of GPCRs that includes the histamine and chemokine receptors), reflecting the less than 10% sequence similarity between the two classes.

The engineered construct of the human SMO receptor was expressed and crystallized with LY2940680 — a SMO receptor antagonist that is currently being evaluated in early clinical trials for small-cell lung cancer — and resolved at 2.5 Å resolution. The crystal structure showed that the SMO receptor has the canonical GPCR seven-transmembrane (7TM) bundle, but an overlay of the receptor with previously solved class A GPCR structures indicated many distinct features that are specific to the SMO receptor.

The most important differences seen were in helices V, VI and VII, in which the SMO receptor lacked the most conserved proline residues that are pivotal in the activation process of class A GPCRs. Instead, a large number of glycine residues was observed in these helices, which the authors suggest facilitates the 7TM bundle to adopt various conformational changes during receptor activation.

Looking at the other regions, the binding pocket of the SMO receptor is long and narrow and connected to the extracellular environment through an entrance formed by the extracellular domain (ECD) linker domain as well as extracellular loop 2 (ECL2) and ECL3. The contact residues for LY2940680 were in helices I, II, V and VII, as well as in the ECD linker domain and the ECLs.

Interestingly, the ECLs of the SMO receptor were unusually long compared to most class A GPCRs. Notably, although the β-hairpin region structure of ECL2 is shared with class A GPCRs, its function differed. In the SMO receptor, the ECL2 forms a major part of the ligand binding pocket and has extensive contacts with LY2940680. By contrast, for most class A peptide GPCRs, the ECL2 points outward from the ligand binding pocket, whereas the rhodopsin ECL2 covers the top of the ligand.

Together, this crystal structure adds to the growing body of information being generated through the crystallization of different members of the GPCR classes. It also demonstrates the remarkable utility of the 7TM bundle, despite the low sequence similarity, among these receptors.

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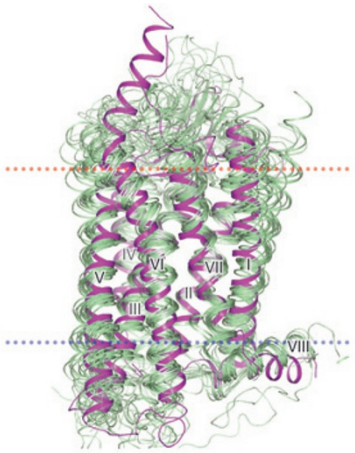
ORIGINAL RESEARCH PAPER Wang, C. *et al.* Structure of the human smoothened receptor 7TM bound to an antitumour agent. *Nature* **497**, 338–343 (2013)



Superimposed structures of the SMO receptor (magenta) and class A GPCRs (light green) from the side. Image is reproduced, with permission, from Wang, C. *et al.* © (2013) Macmillan Publishers Ltd. All rights reserved.