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SAR analysis of S1P5 receptor structure in complex with a selective inverse agonist

The sphingosine-1-phosphate (S1P) is a bioactive lysophospholipid that acts through five different subtypes of G protein coupled S1P receptors (S1PRs) - S1P1-5. S1P5 affects many cellular processes such as division, migration and survival. To date, several drugs (such as fingolimod [1], siponimod [2] and ozanimod [3]) have been developed for the treatment of multiple sclerosis, Crohn's disease and other autoimmune diseases that target S1P receptors, but they lack selectivity for receptor subtypes and mechanisms of action, which leads to adverse side effects.

Here we report the 2.2 Å crystal structure of the human S1P5 receptor in complex with its selective inverse agonist ONO-543060, obtained by room temperature serial femtosecond crystallography (SFX) data collection at the Pohang Accelerator Laboratory X-Ray Free Electron Laser (PAL-XFEL) using sub-10 μm crystals [4].

The structure displays a distinctive binding mode for the ligand, featuring an allosteric binding subpocket that does not only define the subtype specificity but also presents a template for rational drug design. Together with the previously published S1P receptor structures, the newly obtained inverse agonist-bound structure provides insights into the activation mechanism and uncovers molecular mechanisms responsible for inverse agonism in the S1P receptor family.

To lay out the groundwork for future personalized medicine approaches, we mapped the known missense Single Nucleotide Variations (SNVs) from gnomAD and COSMIC genome databases on the obtained S1P5 structure and annotated their potential functional roles.

Additionally, we compared the predictive performance of S1PR AlphaFold2 models for virtual ligand screening with experimental structures and found that, despite close structural similarity, the crystal structures better capture the full details of specific signaling states, while the S1PR AlphaFold2 models display mixing features of different functional states.

The high-resolution S1P5 structure provides a template for the structure based design of lead or tool compounds and our analysis provides insights into possible therapeutic strategies for the treatment of disorders related to the S1P family. The work was supported by the Russian Science Foundation (project no. 22-74-10036; https://rscf.ru/project/22-74-10036/).

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