Structural characterization of inactive GPR84

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GPR84 is an orphan G-protein coupled receptor (GPCR) which belongs to class A GPCRs and is highly expressed in immune cells, including macrophages, neophiles, monocytes and microglia in the central nervous system (1). GPR84 can be activated by endogenous medium-chain fatty acids and the activation of GPR84 is crucial to inflammatory processes, with increased expression of GPR84 observed in diabetes, arthrosclerosis, inflammatory bowel disease and neuroinflammatory diseases (2, 3). Therefore, GPR84 is a potential drug target of anti-inflammation therapy, but there are no existing clinical drugs targeting GPR84 currently. Furthermore, the structure of GPR84 with antagonists would help to find different binding sites of the receptor, including orthosteric and allosteric binding sites, and design antagonists with potent binding affinity and high selectivity of GPR84 to reduce side effects.

There are two publications which show the structures of GPR84 with agonists and its activation mechanism (4, 5), but no structures of inactive-state GPR84. This project aims to structurally characterize inactivated GPR84 with synthesized compounds with high binding affinity that potently inhibit its activation, which could be potential drugs to treat inflammation. This is to promote structure-based drug design of antagonists for GPR84 or GPCRs. Currently, wide-type human GPR84 has been successfully expressed in a yeast expression system and purification optimization of GPR84 for structural studies is ongoing. We have seen monodisperse peak with size exclusion chromatography and the concentration and purity of GPR84 were enough for electron microscopy. Unfortunately, the protein shows some aggregation with negative staining, and we are setting up HEK cell expression system to improve the expression quality.

Reference

1. Marsango S, Barki N, Jenkins L, Tobin AB, Milligan G. Therapeutic validation of an orphan G protein-coupled receptor: The case of GPR84. Br J Pharmacol. 2022;179(14):3529-41.
2. Gaidarov I, Anthony T, Gatlin J, Chen X, Mills D, Solomon M, et al. Embelin and its derivatives unravel the signaling, proinflammatory and antiatherogenic properties of GPR84 receptor. Pharmacol Res. 2018;131:185-98.
3. Recio C, Lucy D, Purvis GSD, Iveson P, Zeboudj L, Iqbal AJ, et al. Activation of the Immune-Metabolic Receptor GPR84 Enhances Inflammation and Phagocytosis in Macrophages. Front Immunol. 2018;9:1419.
4. Liu H, Zhang Q, He X, Jiang M, Wang S, Yan X, et al. Structural insights into ligand recognition and activation of the medium-chain fatty acid-sensing receptor GPR84. Nat Commun. 2023;14(1):3271.
5. Zhang X, Wang Y, Supekar S, Cao X, Zhou J, Dang J, et al. Pro-phagocytic function and structural basis of GPR84 signaling. Nat Commun. 2023;14(1):5706.