New advances in structural discovery of human G protein-coupled receptors: the 826 project and importance of ligand stabilization

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G protein-coupled receptors (GPCRs) constitute the largest membrane protein family in the human genome, mediating over 80% human cell signaling. Dysregulation of GPCRs could lead to numerous human diseases, including cancer, immune diseases, diabetes, neurodegeneration, cardiovascular disorder, and so on. Structural determination of the receptor in complex with its native or synthetic ligands is the key to understand the ligand recognition and signaling mechanism for GPCRs, and to guide rational drug design. Yet, despite their importance as therapeutic targets, detailed molecular structures of only 30 GPCRs have been determined to date. One of the key challenges to their structure determination is adequate protein expression. On the other hand, recent GPCR structure–function breakthroughs have all required ligand stabilization of the receptor in some manner, highlighting the natural instability of GPCRs. Here we report the quantification of protein expression for all 826 human GPCRs using two different fusion construct sets. Analysis of these data can be used to identify trends related to GPCR expression between different fusion frames and between different GPCR families, and to prioritize lead candidates for future structure determination feasibility. We also initiated a new era of discovery that highlights the importance of ligand–receptor interactions beyond the traditional mindset. We propose that receptor stability is related to receptor folding and residence in the cell membrane, affording a new dimension that should be considered when studying receptor function. Combining the new advances in receptor expression and ligand stabilization, we show some successful case studies at the end.