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TITLE

Molecular basis of drug action at the glucagon-like peptide 1 receptor

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The glucagon-like peptide-1 (GLP-1) receptor is a member of the family B G protein-coupled receptors (GPCRs) that contains many important drug targets. Its natural ligand, GLP-1, is a gluco-incretin hormone that plays an important physiological role in maintaining blood glucose homeostasis and holds promise as an very effective therapeutic drug for the treatment of type 2 diabetes. Understanding the molecular basis of ligand binding and activation of these receptors will facilitate the rational design of receptor-active drugs. However, the mechanisms underlying binding and activation of this family of receptors are poorly understood and the development of small-molecule ligands is problematic. Insights into the structure of the predominant ligand binding amino-terminal domain have substantially advanced with the solution of three-dimensional structures of the ligand-bound amino terminus of the GLP-1 receptor and several other family members. However, how family B ligands bind and activate their intact receptors is not yet clear. Receptor mutagenesis studies have suggested a two-domain tethering mechanism for activation of family B GPCRs in which the carboxyl-terminal region of the peptide binds to the amino-terminal domain of the receptor, while the amino-terminal region of the peptide interacts with the receptor core. Insights from our photoaffinity labeling studies on the GLP-1 receptor are consistent with this mechanism, while also suggesting some variation in binding sites among family members. These findings should help the development and refinement of novel receptor-active therapeutics targeting the GLP-1 receptor and all other members in this family.

Biography

Maoqing Dong, M.D., Ph.D. has completed two fellowships from the French National Center for Scientific Research (CNRS) and Mayo Clinic. He currently works as an Associate Professor of Medicine at Mayo Clinic College of Medicine. He is interested in drug actions at their receptor targets, mainly focusing on understanding ligand binding of G protein-coupled receptors. He has published more than 70 papers in peer-reviewed journals and presented 76 times in national and international scientific meetings. He is a reviewer of a number of journals and currently serves as an editorial board member of Journal of Diabetes and Metabolism.