GPCRs and Drug Discovery

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In drug discovery, G protein-coupled receptors (GPCRs) are one of the most important drug targets. In the current drugs, 60% of drug target molecules are located at the cell surface, and half of them are GPCRs (Overington *et al., Nat. Drug Discov.*, **5**, 993-996, 2006). In search for low molecular weight compounds acting on ligand-known GPCRs, initial screening is usually conducted to examine interaction between compounds and GPCRs. If in this screening some candidate compounds are found, optimization will be started to synthesize compounds that show excellent properties as drugs. In this optimization, trial and error approach is usually employed in GPCR agonists and antagonists under examining directly the interaction between the compounds and GPCRs. However, if the information concerning the structure of each GPCR is available, the optimization could be processed more efficiently. To find proper compounds interacting with target molecules on the basis of structural information are currently a routine work in the case of soluble proteins. However, as to membrane proteins in particular in mammals, it has been very difficult to obtain structural information. From this viewpoint, the research on the crystal structure of bovine rodopsine by Dr Miyano's group opened the way to deal GPCRs on the basis of structural data.

Another issue of GPCRs in drug discovery is orphan (ligand-unknown) GPCRs (oGPCRs). There still remain about 120 oGPCRs in human genome. We have developed a method applicable to identify ligands for oGPCRs by detecting specific intracellular signal transductions [1,2]. Although we have identified some ligands of oGPCRs by this method, it seems to have limitations to apply for all GPCRs. Therefore, it is hoped that structural research on GPCRs will contribute to resolve the issues of oGPCRs including the prediction of their lignads in the future.

[1] Fukusumi, S., Fujii, R., and Hinuma, S., Recent advances in mammalian RFamide peptides: the discovery and functional analyses of PrRP, RFRPs and QRFP. (2006) *Peptides*, **27**, 1073-1086.

[2] Itoh, Y., *et al.* Free fatty acids regulate insulin secretion from pancreatic beta cells through GPR40. (2003) *Nature*, **422**, 173-176.