GRIFFIN:
GPCR - G-Protein Coupling Selectivity Prediction System

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G-Protein-Coupled Receptors (GPCRs) with seven transmembrane helices are the major membrane proteins which play a role of signaling to the inner cell. An external ligand stimulus to a GPCR induces the coupling with G-proteins, (Gi/o, Gq/11, Gs and G12/13), followed by different kinds of signal transduction (Fig.1). Since about half of all drugs distributed throughout the world are designed to control these mechanisms, GPCRs are important targets in the development of effective drugs. From the viewpoint of drug design, it is important to screen the drug that can effectively control activation of a specific G-protein, by monitoring them when they are stimulated by different ligands. In general, it is quite difficult to develop such a high throughput experimental system, however, the G-protein activity prediction made by using bioinformatics techniques contributes to the design of an effective experimental system.

Therefore our purpose is to develop a program to predict the GPCR - G-protein binding selectivity when both GPCR sequence and ligand information are submitted. Our work is unique because we consider not only the information of GPCR- G protein binding surface regions but also the overall structure of GPCR. Indeed, it seems natural approach because the entire complex consisting of ligand, GPCR and G-protein is expected to function as a whole, and it is also natural to assume that the G-protein coupling selectivity is largely determined by several features including physicochemical properties and structural information of the system.

Quantities representing the features of ligands, GPCRs and G-proteins are obtained, and some of these features are selected to represent GPCR as an N-dimensional vector. Plotting the vector in N-dimensional space and assigning it to the position of the GPCR that is known to bind a specific ligand and G-protein enables us to perform a prediction. We relegated the task of selecting N feature quantities and discriminant hyper-plane of Support Vector Machine (SVM), a machine-learning method, and subsequent discriminant analysis using SVM-optimized conditions yielded successful predictions for each G-protein with nearly 90% sensitivity and selectivity.

This system "GRIFFIN" (http://griffin.cbrc.jp, Fig.2) predicts the coupling selectivity of G-protein by submitting information of both ligand molecular weight and GPCR sequence. This is applicable for orphan GPCR with unknown ligand, by submitting a wide molecular weight range (for example, 100~30,000). The key feature of our research is to consider the complex entity as a whole including the ligand-binding regions which are located far from G-protein contact surface. A griffin is a creature from Greek myth with the body of a lion and head of an eagle, which is said to safeguard gold by catching hold of it with powerful limbs.This creature seems to change its posture at the moment its beak catches the held game and its power to grasp gold nugget dramatically changes, just analogous to the moment GPCR binds to a ligand and selectes a G-protein.

Reference

*1   Yabuki, Y., Muramatsu, T., Hirokawa, T., Mukai, H., Suwa, M.: "GRIFFIN: a system for predicting GPCR - G-protein couplingselectivity using a support vector machine and a hidden Markov Model", *Nucleic Acids Res.* **33** (Web Server issue), pp.W148- W153 (2005).
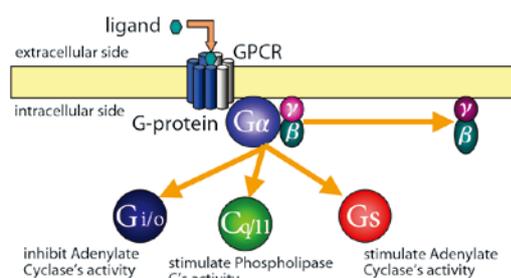
Fig.1 A scheme of the expression mechanism of GPCR functions
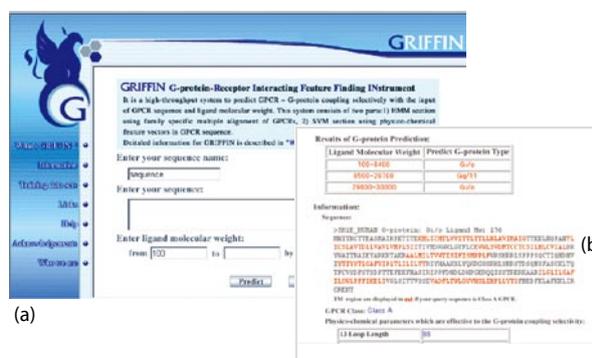
Fig.2 (a) Top page of "GRIFFIN"
(b) When you input a sequence and ligand molecular weight, it will predict the G-protein type.