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Predict Drug-Protein Interaction in Cellular Networking

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Abstract: Involved with many diseases such as cancer, diabetes, neurodegenerative, inflammatory and respiratory disorders, GPCRs (G-protein-coupled receptors) are the most frequent targets for drug development: over 50% of all prescription drugs currently on the market are actually acting by targeting GPCRs directly or indirectly. Found in every living thing and nearly all cells, ion channels play crucial roles for many vital functions in life, such as heartbeat, sensory transduction, and central nervous system response. Their dysfunction may have significant impact to human health, and hence ion channels are deemed as "the next GPCRs". To develop GPCR-targeting or ion-channel-targeting drugs, the first important step is to identify the interactions between potential drug compounds with the two kinds of protein receptors in the cellular networking. In this minireview, we are to introduce two predictors. One is called **iGPCR-Drug** accessible at http://www.jci-bioinfo.cn/iGPCR-Drug/; the other called **iCDI-PseFpt** at http://www.jci-bioinfo.cn/iCDI-PseFpt. The former is for identifying the interactions of drug compounds with GPCRs; while the latter for that with ion channels. In both predictors, the drug compound was formulated by the two-dimensional molecular fingerprint, and the protein receptor by the pseudo amino acid composition generated with the grey model theory, while the operation engine was the fuzzy K-nearest neighbor algorithm. For the convenience of most experimental pharmaceutical and medical scientists, a step-by-step guide is provided on how to use each of the two web-servers to get the desired results without the need to follow the complicated mathematics involved originally for their establishment.

Keywords: G-protein-couple receptors (GPCRs), protein channels, molecular fingerprints, pseudo amino acid composition, iGPCR-Drug, iCDI-PseFpt.

I. INTRODUCTION

An essential step in the drug discovery pipeline is identification of drug-target interaction in cellular networking [1, 2]. The completion of the human genome project and the emergence of molecular medicine have provided more opportunity to discover unknown target proteins for drugs. However, although many efforts have been made to discover new drugs in the past few years, the number of newly approved drugs remains quite low (around only 30 per year). This was partially due to the situation that many compounds or drug candidates had to be withdrawn because of unacceptable toxicity. A lot of money and time had been wasted owing to this kind of failures. Therefore, it would significantly stimulate the drug development and speed up its pace if we could develop some computational methods for predicting the sensitivity and toxicity before a drug candidate was synthesized [3-5]. To realize this, we need to deal with a number of problems. Firstly, a drug could have many different effects including positive and negative, and it is quite hard to identify and understand all its possible effects; secondly, different people might have completely different responses to a same drug [6-8]; thirdly, it is very difficult to trace the drug effects because the biological interaction pathways are extremely complicated in human beings. Accordingly, it would be very helpful to introduce computational methods for predicting the interactions between drugs and target proteins in cellular networking.

Many efforts were made in this regard for computationally analyzing and predicting drug-protein interactions. The most commonly used approaches are docking simulations (see, e.g., [9-12]), literature text mining [13], combining chemical structure, 3D (three-dimensional) structural information, and genomic sequence [14], structural bioinformatics [11], and protein cleavage site prediction [15-17] based on Chou's distorted key theory [18], among others (see, e.g., [19-21]).

In this minireview, we are to introduce two web-server predictors developed recently. One is for identifying the interactions between drugs and G-protein-coupled receptors (GPCRs) in cellular networking, and the other for the interactions between drugs and protein ion channels.

II. GPCR

Besides G-protein-coupled receptors, GPCRs are also known as G protein-linked receptors (GPLR), serpentine receptor, seven-transmembrane domain receptors, and 7 TM (transmembrane). Forming the largest family of cell surface receptors, GPCRs share a common global topology that consists of seven transmembrane alpha helices, intracellular C-

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terminal, an extracellular N-terminal, three intracellular loops and three extracellular loops [22] (Fig. **1**). GPCR-associated proteins [23] may play at least the following four distinct roles in receptor signaling: **(1)** directly mediate receptor signaling, as in the case of G proteins; **(2)** regulate receptor signaling through controlling receptor localization and/or trafficking; **(3)** act as a scaffold, physically linking the receptor to various effectors; **(4)** act as an allosteric modulator of receptor conformation, altering receptor pharmacology and/or other aspects of receptor function [24-26]. Owing to their involvement in many diseases such as cancer, diabetes, neurodegenerative, inflammatory and respiratory disorders, GPCRs are among the most frequent targets of therapeutic drugs. More than half of all prescription drugs currently on the market are actually functioning by targeting GPCRs directly or indirectly [27, 28]. Tremendous efforts have been invested for studying GPCRs in both academic institutions and pharmaceutical industries. In developing drugs by targeting GPCRs, the first and essential step is to identify the interaction between drugs and GPCRs in the cellular networking.

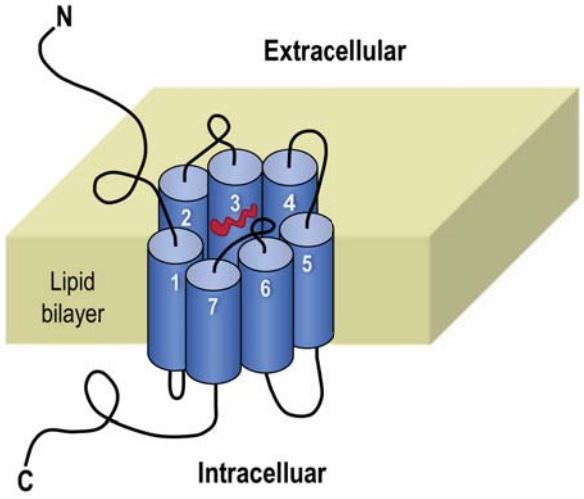

Fig. (1). Schematic drawing of a GPCR. It consists of seven transmembrane alpha helices, intracellular C-terminal, an extracellular N-terminal, three intracellular loops and three extracellular loops. Reproduced from Chou [22] with permission.

III. PROTEIN CHANNEL

Many crucial functions in life, such as heartbeat, sensory transduction and central nervous system response, are controlled by cell signalings via various ion channels. Ion channels represent a class of membrane spanning protein pores [29] that mediate the flux of ions in a variety of cell types (Fig. **2**). The pore-forming ion channel subunits are proteins. For example, the M2 proton channel is formed by four helices [30] (Fig. **3a**), while the p7 channel from Hepatitis C virus formed by six helices [31] (Fig. **3b**). Ion channels mediate and regulate crucial functions via controlling cell signalling [32, 33] in organ and cellular physiology, including the heart beat [34], sensory transduction and central nervous system function [29], and there are over 300 types of ion channels in a living cell [35]. Proper function of ion channels is crucial for all living cells. Ion channel dysfunction may lead to a number of diseases, the so-called channelopathies, such as epilepsy, arrhythmia, and type II diabetes [36]. This kind of diseases are primarily treated with the drugs that modulate ion channels, and hence ion channels are deemed by many as the drug targets next to GPCRs [37].

Likewise, in developing channel-targeting drugs, the first and essential step is also to identify the interaction between drugs and protein ion channels in the cellular networking.

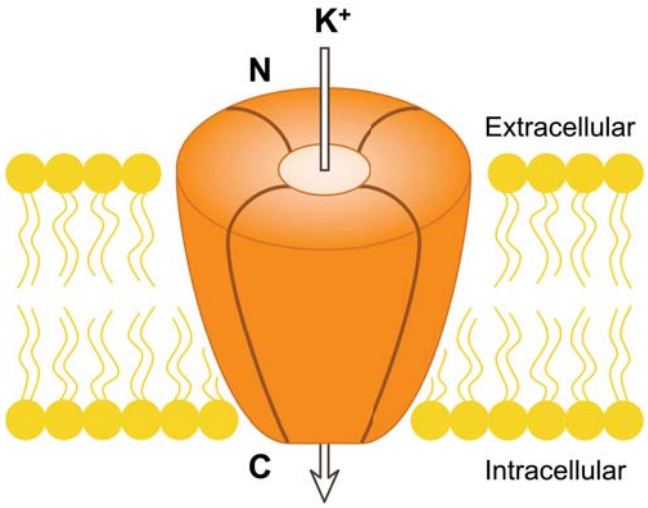

Fig. (2). Schematic drawing to show the membrane-spanning potassium channel consisting of four identical subunits. Reproduced from Chou [29] with permission.

IV. iGPCR-DRUG AND iCDI-PseFpt

With the avalanche of protein sequences generated in the post genomic age, to help pharmaceutical scientists and medicinal chemists to conduct the large-scale identification on drug-GPCR interaction and drug-channel interaction, two powerful sequence-based predictors were developed recently. One is called **iGPCR-Drug**, specialized for identifying the interaction between drugs and GPCRs [38]; the other called **iCDI-PseFpt,** specialized for identifying the interaction between drugs and ion channels [39]. Both of the two predictors were developed according to the five fundamental procedures summarized in [40]. In the two prediction systems, the part of drug compound was formulated by the 2D (two-dimensional) molecular fingerprint, and its counterpart of protein (GPCR or ion-channel) formulated by the pseudo amino acid composition [41, 42] (PseAAC) generated with the grey model theory [43], while the operation engine was the fuzzy K-nearest neighbor algorithm [38]. The anticipated success rates achieved by **iGPCR-Drug** and **iCDI-PseFpt** were 85.5% and 87.27%, respectively, remarkably higher than those by any of their peer predictors in this area.

Since user-friendly and publicly accessible web-servers represent the future direction for developing practically more useful models, simulated methods, or predictors [44, 45], a user-friendly web-server was established for each of the two that is freely accessible to the public.

Below, let us give a step-by-step guide to show how the users can easily get the desired result by means of the two web-servers without the need to follow the complicated mathematics involved during their development.

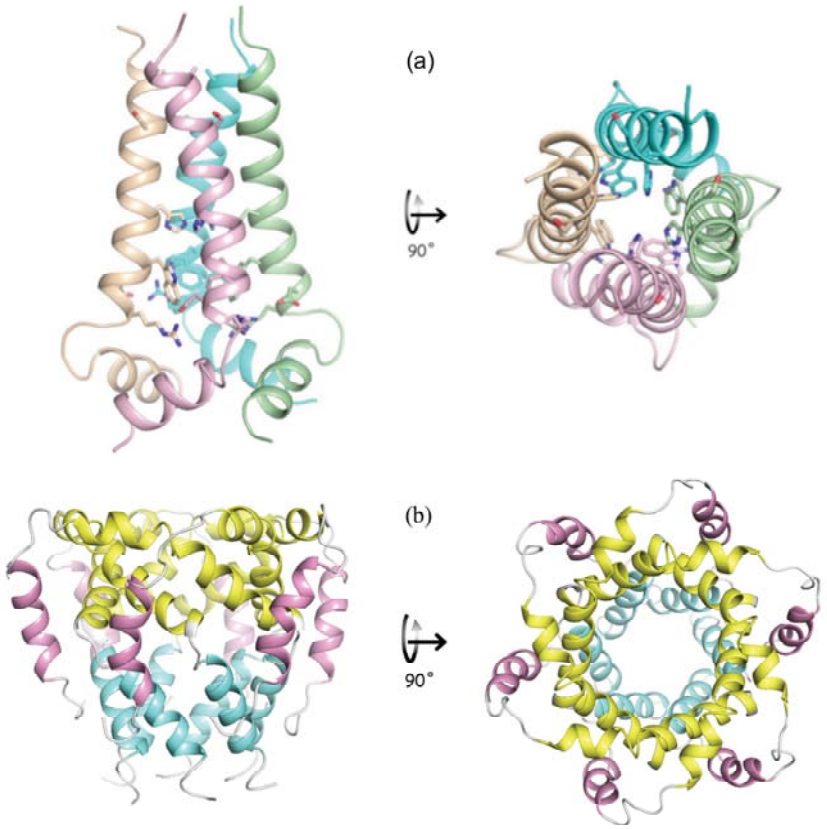

Fig. (3). Ribbon representation of the NMR structure as viewed from the side (left) and from the top (right) for (**a**) the M2 proton channel [30], and (**b**) the p7 channel from Hepatitis C virus [31]. Reproduced from [30] and [31] with permission.

1. iGPCR-Drug

Step 1. Open the web server at the site http://www.jci-bioinfo.cn/iGPCR-Drug/ and you will see the top page of the predictor on your computer screen, as shown in (Fig. **4**). Click on the Read Me button to see a brief introduction about **iGPCR-Drug** predictor and the caveat when using it.

Step 2. Either type or copy/paste the query pairs into the input box at the center of (Fig. **4**). Each query pair consists of two parts: one is for the protein sequence, and the other for the drug. The GPCR sequence should be in FASTA format, while the drug in the KEGG code. Examples for the query pairs input can be seen by clicking on the Example button right above the input box.

Step 3. Click on the Submit button to see the predicted result. For example, if you use the four query pairs in the Example window as the input, after clicking the Submit button, you will see on your screen that the "hsa:10161" GPCR and the "D00528" drug are an interactive pair, and that the "hsa:10800" GPCR and the "D00411" drug are also an interactive pair, but that the "hsa:1909" GPCR and the "D02566" drug are not an interactive pair, and that the "hsa:2913" GPCR and the "D01699" drug are not an interactive pair either. All these results are fully consistent with the experimental observations. It takes about 10 seconds before the results are shown on the screen.

Step 4. Click on the Citation button to find the relevant paper that documents the detailed development and algorithm of **iGPCR-Durg**.

Step 5. Click on the Data button to download the benchmark dataset used to train and test the **iGPCR-Durg** predictor.

Step 6. The program code is also available by clicking the button download on the lower panel of (Fig. **4**).

2. iCDI-PseFpt

Step 1. Open the web-server at the site http://www.jci-bioinfo.cn/iCDI-PseFpt and you will see the top page of the predictor on your computer screen, as shown in (Fig. **5**). Click on the Read Me button to see a brief introduction about **iCDI-PseFpt** predictor and the caveat when using it.

Step 2. See the above Step 2 for **iGPCR-Durg**.

Step 3. Click on the Submit button to see the predicted result. For example, if you use the three query pairs in the Example window as the input, after clicking the Submit button, you will see on your screen that the "hsa:1134" channel and the "D05453" drug are an interactive pair, and that the "hsa:10369" channel and the "D01295" drug are also an interactive pair, but that the "hsa:6531" channel and the "D00474" drug are not an interactive pair. All these results are fully consistent with the experimental observations.

Step 4. See the above Step 4 for **iGPCR-Durg**.

Step 5. See the above Step 5 for **iGPCR-Durg**.

Step 6. The program is also available by clicking the button download on the lower panel of (Fig. **5**).

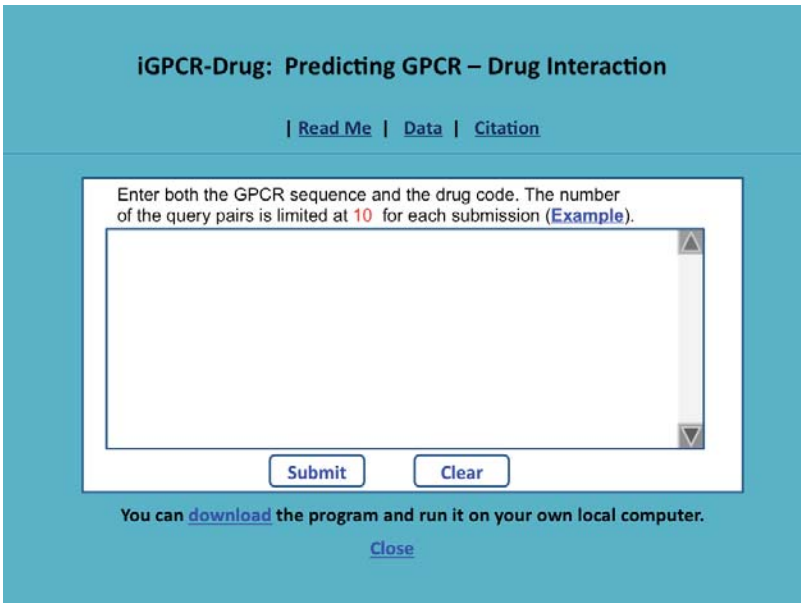

Fig. (4). A semi-screenshot to show the top page of the iGPCR-Drug web-server. Its web-site address is at http://www.jci-bioinfo.cn/iGPCR-Drug.

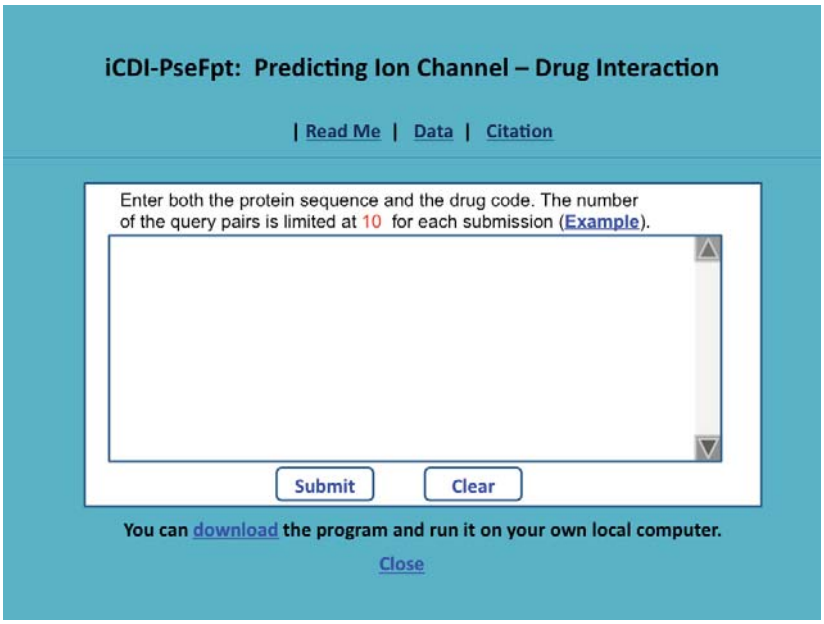

Fig. (5). A semi-screenshot to show the top page of the iCDI-SeqFpt web-server. Its web-site address is at http://www.jci-bioinfo.cn/iCDI-PseFpt.

V. CONCLUSION AND PERSPECTIVE

iGPCR-Drug and **iCDI-PseFpt** are two high throughput tools for system biomedicine, particularly for developing GPCR-targeting and ion channel-targeting drugs. It is an effective approach to formulate drug compounds with the 2D molecular fingerprint for identifying their interaction with proteins. To further enhance the success rate of prediction, one of the feasible avenues is to incorporate the informations of GO (gene ontology), functional domain, and sequential evolution into the protein samples concerned. Particularly, it is the GO information that has proved to be very effective in enhancing the quality for predicting protein subcellular localization. For a profound discussion in justifying the GO approach and analyzing the essence of why it is so powerful for protein subcellular location prediction, see Section VI of a recent review [46]. It is yet to be proved whether the GO information can be used to significantly enhance the prediction quality for the drug-protein interactions in cellular networking. Additional research work may be carrying out in the future to compare this method with other drug-target prediction techniques like those developed by González-Díaz *et al.* [47-64].

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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