RESEARCH HIGHLIGHT

In silico study of polypharmacology with protein-ligand interacting fingerprint

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Received: August 18, 2015
Published online: November 09, 2015

The past years have witnessed the versatile applications of interaction fingerprint method, including three-dimensional structure analysis, docking-pose clustering and filtering, scoring function improvement and enhancing enrichment of virtual screening. However, it's still unclear whether it's possible to study the polypharmacology with such a strategy. We have explored this important question by assessing the performance of ligand-based interaction fingerprint (LIFt), a new approach providing insights into the target profiles for the selected small drug. According to our results, it's found that LIFt could recognize most of the native targets for the promiscuous kinase inhibitor staurosporine on the basis of experimental determined complex structures. In addition, with assistance of physics-based docking and sampling techniques, LIFt can predict the kinase-selectivity profile as well as the unexpected off-targets for the clinical drug or experimental candidates with appreciated accuracy. More encouragingly, a prospective prediction of new target for the established synthetic anti-tumor drug TN-16 was experimentally validated, which suggests the promise of LIFt in practical use of polypharmacology study.

Keywords: Ligand-based interaction fingerprint; polypharmacology; off-target; Tanimoto coefficient; docking and sampling

To cite this article: Ran Cao, *et al*. *In silico* study of polypharmacology with protein-ligand interacting fingerprint. Receptor Clin Invest 2015; 2: e976. doi: 10.14800/rci.976.

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Accumulating evidences suggest that small-molecule drug tends to interact with multiple targets, which is coined as polypharmacology [1-3]. Multi-targeted drugs own advantage in treating complicated disease which involves multiple signaling pathways, as exemplified by the dozens of kinase inhibitors for cancer treatment in the clinic [2, 4]. In contrast, just like a double-edged sword, it also caused problem as to the unexpected off-target which could result in side effects or even toxicity [1, 5]. On this basis, it's of necessity to elaborate the potential target-profiles for the selected drugs. However, exhaustive profiling all the target-drug pairs with experiments is expensive and laborious. In contrast, *in silico* study of polypharmacology holds great promise for the much less expense. For instance, the chemo-centric methods such as SEA (Similarity Ensemble Approach) [6], could generate the most promising drug-target associations from large-scale

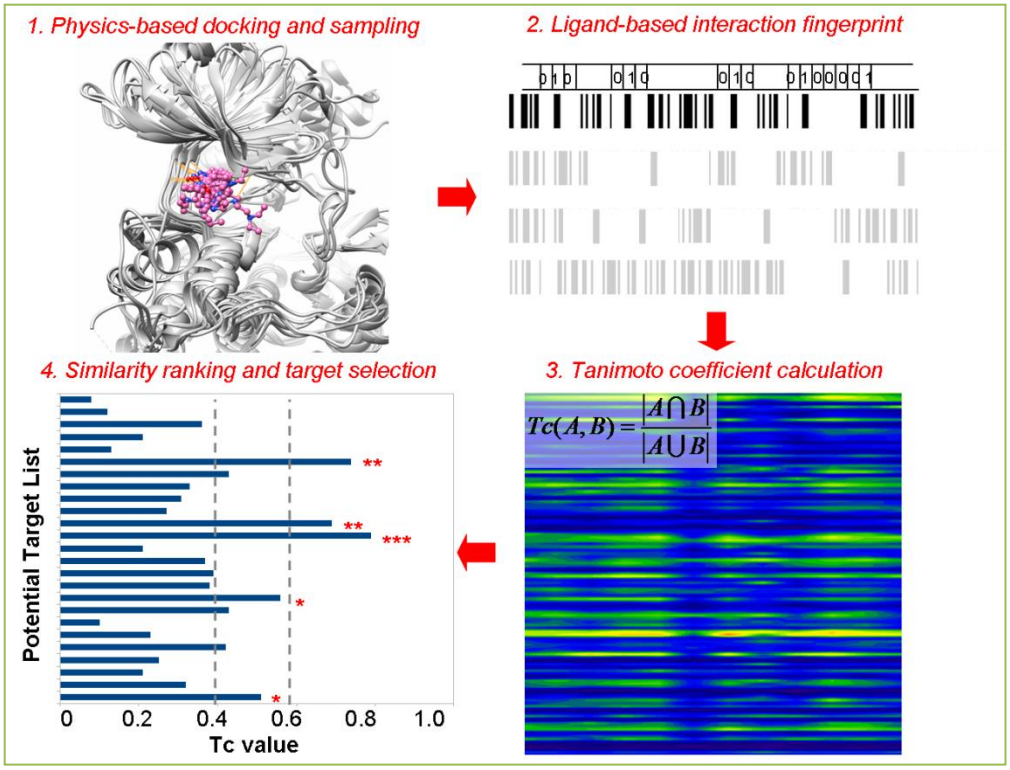

Figure 1. The workflow of predicting target profiles for the selected drug with proposed LIFt approach.

profiling with appreciated accuracy [5, 7]. Nonetheless, there's intrinsic limitation as to the lack of ligand binding information, which is essential to the structural modifications.

As increasing deposits of complex structure in PDB database,[8] we have deepen our knowledge about the mechanism of molecular recognition, which leads to numerous success of structure-based drug discovery [9]. Physics-based docking and sampling techniques facilitate such efforts by providing near-native binding poses for interested small molecules [10, 11]. However, in contrast with achievements in identifying novel ligands for the specific protein [12-14], there are few reports with respect to the other side of the coin, which means explore new targets for the specific small-molecule drug [15, 16]. This could be partially attributed to the inability of current scoring functions in estimating the entropy contribution as well as desolvation effects, which becomes more severe when estimating the absolute binding free energy for a given drug in context of distinct targets [16].

The interaction fingerprint (IF) method [17] provides an alternative solution for the above problem. However, whether it is suitable for the study of potential targets needs to be comprehensively assessed and experimentally tested. We addressed this question by introducing a new ligand-based interaction fingerprint (LIFt) approach and systematically assessing the performance in prediction of polypharmacology for 12 well-established small-molecule kinase inhibitors [18]. On the basis of complex structure, either experimental result or theoretical model, we can extract three-dimensional (3D) binding information according to well-established geometric criteria for a series of important interactions, such as H-bond, ionic interaction, π-π stacking, non-polar contact [17, 19]. The essential knowledge is routinely explored in the practice of structure-based drug discovery [20]. By translating the above 3D interactions into one-dimensional (1D) binary string, we can obtain the representative IF profile for drug-target complex (Figure 1), which could be compared in a pair-wise manner to determine the Tanimoto coefficient (Tc). Tc value can be used to quantify the interaction similarity and suggest the promising target(s) for a given drug (Figure 1).

Our results indicate that LIFt can recognize 52 of 54 native kinase targets for the nonselective inhibitor staurosporine on the basis of experimentally determined complex structures, with mean Tc values above 0.46. It's noted that the two outliers (Tc value of 0.13 and 0.34), whose structure deviates from electron density map, could be corrected with physics-based optimization of binding site, where LIFt gives largely improved results (Tc value increased to 0.48 and 0.65).

We also showed LIFt could be extended to the study of kinase selectivity profiles with the aid of "state-of-the-art" molecular simulation techniques, such as physics-based docking and sampling. With sunitinib as an example, we found LIFt can distinguish 54 of 60 inactive kinases (IC_{50}>10 μM) with Tc value lower than 0.4, while 56 of 127 active kinases (IC_{50}<10 μM) with Tc value higher than 0.50. We also proved that the unsatisfied result is primarily, if not exclusively, owing to the single-conformation limitation for protein target in the present strategy. Series of structural simulation on the binding pocket (e.g. 4.5 Å within the ligand) could alleviate the problem of undersampling, however it is far from taking into account the whole protein flexibility, especially considering the loop region where large-scale conformational change exists. The inference can be supported by the observation of top-ranked inactive kinase TIE2. By collecting 6 ligand-present (holo) crystal structures, we obtained consistently low Tc values (<0.4) which forms a contrast to the high Tc value (0.55) for the ligand-free (apo) conformational state (PDBID: 1FVR). It's also suggested that long MD simulation may help to alleviate the problem to some extent. In our opinion, a variety of simulations only serve as the means for providing reasonable theoretical model. The key point to obtain a reliable complex structure in the absence of crystallography assistance is relying on the elaborate experimental results on the ligand binding characteristics, such as structure-activity relationships (SAR).

We further extended the assessment by modeling the cross-activity of 10 different kinase inhibitors against BRD4 protein with *in silico* methods. According to our results, it's revealed that there's great similarity in the ligand action modes among different targets, including the conserved H-bonds as well as the nonpolar contact, which are consistent with a previous report [21]. More encouragingly, we proved the power of LIFt in exploring novel targets with a prospective study which focused on the synthetic anti-tumor drug TN-16, generally recognized as the colchicine-site binder. According to our study, it's shown that 29% (54 of 187) of kinases present Tc value greater than 0.4. Among them, the highest ranked candidate p38α MAP kinase (Tc=0.68) was experimentally validated with an IC_{50} value of 9.8±0.4 μM.

In summary, we have introduced a new approach of ligand-based interaction fingerprint with the aim of profiling potential targets for selected small drugs or drug candidates. Our data demonstrate that LIFt could compete with physics-based scoring functions in both retrospective and prospective studies. We are currently developing the enhanced LIFt to provide more general application and accurate prediction, which means incorporating ligand similarity as well as target diversity into the current approach.

Conflicting interests

The authors have declared that no competing interests exist.

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