Computational-aided Drug Discovery in Protein-Protein Interactions: Defining a simple protocol and testing it in Notch signaling

INTRODUCTION TO COMPUTATIONAL-AYIDED DRUG DISCOVERY:

Computational-aided drug discovery (CADD) is the implementation of computer technologies in the drug development cycle (Figure 1). Its role is mainly to improve and accelerate the hit discovery process, while it reduces the high costs associated with experimental methods. CADD also plays an important role in lead optimization and drug rational design. A widely used method in computational hit discovery is the structure-based approach, which is the implemented strategy in protein-protein interactions drug discovery.

Structure-based drug discovery relies on the knowledge of proteins structures and explicit modelling of both chemicals and biological entities. The standard approach is molecular docking. This methods sample ligand conformations from virtual compound libraries (chemicals or fragments) to dock them within the binding site of the biological structure and using scoring functions (empirical energetic functions) to predicted binding affinities. Among many strategies is the pharmacophore-based screening, in which pharmacophore hypotheses defines the virtual 3D arrangement of ligand’s key physicochemical properties for the interaction with its biological target. These features are used as a scaffold or map to screen compound libraries.

TARGETING PROTEIN-PROTEIN INTERACTIONS: PROMISING BUT CHALLENGING

Protein-protein interactions (PPIs) have a crucial role in cell signalling transduction and the execution of cellular functions, offering new therapeutic opportunities to treat pathologies such as cancer (2, 3, 20, 26) or immune disorders (27-29). PPIs have unique features and different chemical spaces from conventional targets.

C2-phospholipid-

The presence of small regions in the interaction surface called PPIs have singular features and different chemical spaces from conventional targets. Protein-protein interactions (PPIs)

4.

3.

2.

C2-phospholipid-

The fragment-based screening provides a more versatile screening for PPIs than docking small molecules, as it is based on docking small chemical fragments, covering wider chemical spaces than using small molecules. The application of CrystalDock offers an alternative approach for fragment-based screening to conventional free tools like DOCK or AutoDock.

Virtual Fragment-based screening and druggability

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RESULTS AND DISCUSSION:

PPIs target characterization

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CONCLUSIONS AND PERSPECTIVES:

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> Drug discovery in PPIs is currently an evolving field with a promising future for its notorious implications in human disease and drugable protein.

> Although several computational screenings strategies have been reported to trigger PPIs, there is still not a defined protocol procedure better than the others. It is probably a consequence of the PPIs complexity, challenging features and their still not completely clear chemical space.

> A simplified computational strategy to target PPIs using free and user-friendly software is proposed. The most important steps (pocket characterization, druggability, flexibility, fragment-based docking and pharmacophore generation) have been successfully tested in the case of Notch1 (Figure 2).

> The last steps proposed in the protocol are a crucial validation phase. The re-docking step using AutoDock Vina followed by the energy minimization of ligand-protein complex and discard possible steric clash. Finally, an ADME-tox filtering step using FAF-drug3 webserver is suggested to discard potential toxic compounds and select final hits with more optimal pharmacokinetic features.

> Although real concerns on Notch1 druggability exist, the strategy here reported applied in Jagged 1 could represent the first step for a future drug discovery research campaign to identify novel compounds triggering Notch(Jagged1) signaling in cancer.

REFERENCES:

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