Methods for discovering potential protein targets.

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Abstract

Drug repurposing is a clever and inventive method for utilising already-approved and readily-accessible medications to increase the number of therapies. It is difficult to find novel protein targets for medicines that have already received approval. Even if novel approaches to drug repurposing have been established, most experts feel that there is still potential for advancement. For medication repurposing applications, we cover protein-protein interaction (PPI) interface-targeting techniques in this chapter. We talk about specific characteristics, such hot spot residue and hot area prediction, and their significance in medication repurposing. We also provide examples of typical PPI network techniques for identifying drug off-targets. We also gather useful web resources for polypharmacology such as binding pocket identification, interface clustering, and hot spot prediction. We conclude by offering case studies that highlight the importance of protein interfaces and hot regions in medication repurposing. Typically bioactive small compounds are coupled onto solid supports and then used to separate target proteins from the entire proteome for target protein identification. High binding affinity between bioactive small molecules and their intended protein targets is necessary for this method. Additionally, when linkers are used to alter the structural makeup of bioactive compounds, the binding affinity can be severely impeded.

Keywords: Hot spots, Hot regions, Network-based approaches, Interface motifs, Protein interface clustering.

Introduction

Over the years, studies on drug development are accelerated both in the pharmaceutical industry and in academia; still the increasing demand for new drugs cannot be met. This situation underscores the need for innovative strategies and techniques. However, discovering new drugs and drug targets is challenging. Until recently, drug targets were largely limited to enzymes and receptors. Small molecules that target enzymes mostly mimic and compete with the substrates of the enzymes. The pressing demand for new drugs has led to an increase of investments of pharmaceutical companies in drug development. To address this challenge, one approach, which is discussed here, involves targeting protein-protein interactions (PPIs) [1].

Proteins typically execute their function by interacting with other proteins. These interactions transmit signaling cues, with the signaling cascading downstream through PPIs. The majority (or all) cellular processes, including cell proliferation, motility, and growth, depend on signalling, which takes place through temporary and long-lasting PPIs. Signal transduction may be affected by changes in PPI interfaces, which could result in malfunction and disease. For predicting protein-protein interactions, there are numerous computational and a few experimental methods. The potential for repurposing medications that target the interfaces seems great in theory given the prevalence of PPIs. Traditional PPI medication research, however, has proved difficult and hindered. Nevertheless, tiny compounds and fragment-based strategies have made progress [2].

In the search for new drugs, protein-protein interactions are receiving more and more attention. Finding possible drug candidates can be done by looking for similar binding sites on protein surfaces. Cholesteryl ester transfer protein (CETP) inhibitors were studied using protein-ligand binding profiles, and Xie discovered hitherto unidentified off-targets at the genome scale [3].

They found ligand binding sites in the network that were similar to the main target using SOIPPA to align the binding site structures. The putative off-targets of two CETP inhibitors are studied, and their biological pathways are delineated. According to their findings, CETP inhibitor side effects have a role in immunological response and stress management a variety of interrelated pathways. In order to identify the proteins in the human proteome that a ligand can bind, Frigola used the similarity of protein cavities. They looked into every human protein with a 3D structure using BioGPS in order to identify possible therapeutic targets based on similarities between cavities in the proteins. According to their findings,

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various unrelated proteins can be found to have comparable holes, and a protein typically has similar binding sites to seven additional proteins. They employed heat flow analysis to examine the impact of medication combinations on a network scale [4].

When compared to the use of a single drug in tumor-specific networks, they discovered that drug combinations might spread heat in the network. To get around these limitations, a number of strategies have been developed to record the fleeting and reversible binding interaction between bioactive small compounds and their intended protein targets. Covalent capture of the physical interaction of small molecules with their target proteins using photoactivatable moieties or electrophiles is one of the most effective strategies [5].

Conclusion

Due to the increased demand for new medications, drug repositioning research has lately accelerated, and experimental and computational repositioning methodologies are being developed. One of these tactics involves focusing on similar PPI interfaces, often known as hot spots and hot regions, using shared energetically significant residues. Using binding site similarities to simulate drug effects on a network scale has improved drug design. These techniques can reveal potential off-targets for newly developed pharmaceuticals as well as fresh uses for current medications.

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