STM JOURNALS

Research & Reviews: A Journal of
Drug Design & Discovery

ISSN: 2349-9036
Volume 10, Issue 2, 2023
DOI (Journal): 10.37591/RRJoDDD

http://pharmajournals.stmjournals.in/index.php/RRJoDDD/index

Research RRJoDDD

A Comprehensive Study on Protein–Protein Interaction in Drug Development: Future Prospects and Challenges

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Abstract

Protein–protein interactions (PPIs) play important roles in various cellular processes and have become a major area in drug development. Most of the studies that are related to protein–protein interactions (PPIs) are correlated with different types of diseases, including infectious diseases, cancer, and neurodegenerative disorders. Therefore, targeting PPIs constitutes a therapeutic avenue for disease and an essential strategy for new drug development. In the last 10 years, PPI has been an emerging field in the study of drug intervention, and it's the most difficult task for drug discovery. In recent years, most PPI modulators have not only been developed, but clinical trials have also been carried out on them for their potential to treat a particular disease. Those that have been approved from an industrial point of view have been suggested by the experts, as they have a broad future in drug discovery. In this study, we focus on summarizing recent advances in the field of PPI, including computational analysis, its types, detection methods, andfuture perspectives for the design of type new drugs targeting PPIs in the future.

Keywords: Protein–protein interactions, computational analysis, detection methods, future design, drug development

INTRODUCTION

Proteins are organic molecules and the building blocks of living organisms, composed of amino acids. Protein–protein interactions (PPIs) play an important role in various biological processes and are often identified as biomarkers in diseases. Targeting PPIs has gained significant attention in drug development [1]. PPIs are involved in many cellular pathways and are often altered in disease states.

Inhibiting or modifying these interactions can be a good step for developing new therapeutic agents. Numerous biological processes, such as signal transmission, cell cycle progression, metabolic pathways, and cell-to-cell contacts, depend on protein–protein interactions [2, 3].

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Received Date: November 01, 2023
Accepted Date: November 21, 2023
Published Date: November 30, 2023

Citation: Pankaj Malhotra, Simran Rai, Deepika Yadav, Ankit. A Comprehensive Study on Protein-Protein Interaction in Drug Development: Future Prospects and Challenges. Research & Reviews: A Journal of Drug Design & Discovery. 2023; 10(2): 25–31p.

The Biological Impact of Protein–Protein Interaction

- PPIs have the ability to affect an enzyme's kinetic characteristics, which may have a subtle impact on substrate binding or allosteric effects.
- PPIs also play an important role in generic mechanisms because they have the potential to enable the substrate and its binding site.
- New binding sites can also be found with the help of PPIs, which can help small effector molecules.

- A PPI can inhibit or deactivate a protein. PPI interacts with several binding partners to modify a protein's specificity for its substrate.
- PPIs also have beneficial potential and play an important role in either an upstream or downstream event. Finding knowledge about protein–protein interactions aids in determining potential therapeutic targets.
- PPIs can help to find the new binding site for small drug-targeting components and effector compounds or molecules [4].

Application

- *Drug discovery:* PPI targeting may result in the creation of new treatments and also play an important role in the discovery of new molecules and their binding sites for any further interactions with that type of molecule.
- *Disease mechanisms:* disease mechanisms also depend on PPI dysregulation, which is linked to a number of disorders, including necrosis and neurological conditions. It also has modifying agents that will lead to a multi-protein complex that plays a central role in the cellular system of living organisms [5].
- *Biotechnology:* is used in the creation of protein complexes with specific functions for both industrial and medicinal applications. Interactions of protein molecules were also important for the regulation of most biological approaches.
- PPI networks are useful in systems biology to comprehend the intricacy of biological processes [6].

TYPES OF THE PROTEIN–PROTEIN INTERACTIONS

A protein–protein interaction can be divided into distinct categories based on a variety of criteria, such as composition, affinity, and longevity.

- These complexes are categorized into homo-oligomeric and hetero-oligomeric groups based on their compositions.
- Homo-oligomers are also formed by the initiation of PPIs and their identical changes, which are mainly occurring in the muscles. When we are studying the hetero-oligomers, it shows that they will also be involved in the non-identical polymers and will lead to the formation of cytochrome-free radicals. They will also play an important role as enzymes, transporter molecules of proteins, and in DNA or MRNA remodeling, that is why different factors also affect their roles.
- Affinity distinguishes obligatory and non-obligate complexes. An obligatory interaction occurs when the elements of a complex (protomers or monomers) interact. There are temporary and permanent interactions based on life. When we differentiate both of them, it will show that transient interactions temporarily occur in the in vivo remodeling; on the other hand, permanent interactions include the type of interaction that is very stable and cannot be changed. The IL-5 cytokine dimer, for example, is a persistent protein–protein connection. Based on the fold, PPIs will be divided into two categories based on their folds, which are known as only domain and peptide domain interactions. PPIs are also produced by the recognition of globular domains and small interfaces of the liner motif, which will be able to form the peptide domain complexes.

All obligatory PPIs are permanent, but not all permanent interactions are obligated. Non-obligate contacts are temporary; however, some non-obligate interactions, such as enzyme-inhibitor interactions, are permanent. Protein connections that change from free to weakly bound are classified as strong transients [7, 5].

PROTEIN AND PROTEIN INTERACTIONS IN DRUG DEVELOPMENT

Despite the important role of PPIs in cellular function, they have significant potential as therapeutic targets. There are more than fifty protein interaction modulations that are successfully targeted by small molecules and targeting with the help of PPIs with small molecule modulation is a new step in the field of drug targeting with PPIs [1]. These compounds have different modes of action on PPIs. A competitive

model also leads to managing the binding effects of the natural binding partner, which is known as a block of the binding partner, which will exhibit a completive effect on PPI interaction. The PPI approach is to bind the compound to a site that is not directly part of the PPI interface but to hold the protein in a low-affinity configuration, such that binding of the native binding portion is hindered. It is also possible to use a stable connection or isolation mode. Through the binding of a compound in an effector module stable mode, the protein can bind its main binding site in a high-affinity form to enhance PPI. Another form of stability is the active tethering mode, which is a direct connection at the edge of the interface with simultaneous contact between two protein partners [8].

CLASSIFICATION OF PPI DETECTION METHODS

In vitro, in vivo, and in silico methods are the three domains in which protein–protein interaction detection techniques exist. An operation is carried out in a controlled setting apart from a living being using in vitro procedures, which is also called an experimental approach.

In vitro methods (experimental methods) for PPI detection include tandem affinity purification, affinity chromatography, co-immunoprecipitation, protein arrays, complementation of protein fragments, phage screening, X-ray crystallography, and NMR spectroscopy. Using "in vivo" procedures, the entire living thing is subjected to a particular process. Synthetic lethality and yeast two-hybrid (Y2H, Y3H) are two in vivo techniques for PPI identification.

Computational methods, or in silico procedures, are carried out by computer simulation or a computer. Sequence-based, structure-based, chromosomal proximity, gene-fusion, in silico 2-hybrid, mirror tree, phylogenetic tree, and gene expression-based approaches are among the in silico techniques for PPI identification [9].

In Vitro Techniques to Predict Protein–protein Interactions

The TAP tag was developed to study PPI under intracellular conditions [10]. The two-step purification procedure that follows the twofold tagging of the targeted protein at its chromosomal locus constitutes the basis of this methodology [11]. In order to identify the PPI partner of the initial protein of interest, proteins that are still attached to the target protein can be probed and analyzed using mass spectrometry [12]. Using a whole-cell extract, co-immunoprecipitation improves interactions by presenting proteins in their native state as a complex combination of cellular components that may be necessary for a good interaction.

In addition, the use of eukaryotic cells allows for post-translational modifications that may be important for the interaction and are not present in prokaryotic expression systems. Protein microarrays are rapidly emerging as an efficient way to identify proteins, monitor their expression levels, and study protein interactions and functions. Protein microarrays are basically a piece of glass that has different protein molecules attached to it in different places. They've become really popular, and they're one of the most active fields of biotechnology right now. The aim of protein microarrays is to make them easier and more sensitive to proteins by using high-throughput machines that can analyze large amounts of protein at once [13–15].

In Vivo Techniques to Predict Protein–protein Interactions

The Y2H method is an in vivo method used to detect PPI [16]. The Y2H assay requires two protein domains with two specific functions:

1. A DNA-binding domain (DBD) that helps bind to DNA.
2. An activation domain (AD) that is responsible for activating DNA transcription.

Both domains are required for reporter gene transcription [17]. Y2H analysis allows PPI to be detected directly between protein pairs. However, the method can cause a large number of false-positive interactions [18].

In Silico Methods for the Prediction of Protein–protein Interactions

Large-scale development of effective tools for the detection of protein interactions between proteins PPI, which can be achieved in various combinations, has been initiated by a yeast-to-hybridization system and both in vitro and in vivo methods. However, the absence of PPIs may make it impossible for those methods to provide reliable data. To understand the overall landscape of potential interactions, it is best to develop methods that predict all possible interactions between proteins [19]. Various in silico processes have been developed to identify the interactions experimentally. Computational methods for in-silico prediction include sequence-based approaches, structure-based approaches, chromosome proximity, gene fusion, and in-silico 2 hybrid approaches [20].

In Silico Two-hybrid Method

The method is based on the computational method that interacting proteins should undergo co-evolution for protein function to be related to other molecules, which will lead to identifying the visualization steps in it. In other words, if parts of the essential amino acids of one protein are changed in another protein that interacts with the mutated counterpart, the corresponding amino acids should also undergo obligatory mutations. In the experimental studies or analysis step, gene sequencing containing two proteins is identified by multiple sequence alignment, and the similarities between them are calculated between each pair of residues in the same protein and the proteins [21].

Therefore, there are three different sets of pairs: two for intra-protein pairs and one for inter-protein pairs. Protein–protein interactions result from the distribution of correlations between interacting partners and individual proteins. Since the two-hybrid method is based on the prediction of the physical proximity of residue pairs of two individual proteins, the result of this method automatically indicates the possible physical interaction of the proteins [22].

Structure-based Prediction Approaches

When two proteins have comparable structures, the structure-based technique aims to predict protein–protein interactions. It was therefore proposed that if two proteins, A and B, can interact with one another, then there must be two other proteins, A and B, having structures that are comparable to those of proteins A and B. The initial stage in this procedure is to infer a protein's structure from its sequence, although most proteins may not have known structures. There are various methods for doing this. employing a method of multiple threading [23]. Hosur et al. have created a new algorithm that uses a structure-based method to infer protein–protein interactions. Three steps comprise the Coev2Net algorithm: binding interface prediction, interface compatibility with a model based on interface coevolution assessment, and interaction confidence score assessment [24]. An algorithm applied to binary protein interactions improved the performance of the algorithm compared to existing methods [25]. However, it used 3D structural data to predict PPI with accuracy and coverage better than predictions based on structural evidence. Protein–protein interaction (PPI) prediction:

- Protein–protein Docking: similar to molecular docking but focused on predicting the interactions between two protein molecules.
- PatchDock and ZDOCK: tools for protein–protein docking that predict the binding interface and complex structure [26, 27].

A COMPUTATIONAL ANALYSIS OF THE PPI NETWORK

The PPI is a connection of proteins connected by interactions in the different forms of the binding sides, which comes in the category of heterogeneous network. Computational studies, or in silico studies, are the main steps in the visualization of the PPI network.

The most basic sketch is in the form of a mathematical network with nodes and edges [28, 29]. In the protein study of that type of interaction, it will be represented as a node, or binding molecule, and the proteins that physically interact with it will be represented as neighboring nodes connected by a specific target site. An analysis of the network can produce a variety of results.

Accurate computational analysis of PPI networks is challenging, with major obstacles frequently encountered [30, 31].

1. Protein interactions are unstable.
2. Proteins can perform many different roles.
3. They can interact with each other when more than one protein is included with different functional groups or if they have different characteristics.

FUTURE PROSPECTS FOR PPIS IN DRUG DEVELOPMENT

- There are some Undesirable drug proteins that are also present, and PPIs will also lead to targeting these molecules in the future. The development of small compounds or biologics that disrupt or stabilize PPIs may offer new possibilities for illness treatment [32].
- Understanding PPI networks can aid in tailoring medication therapy to an individual's particular protein interactions, resulting in more effective and personalized treatments.
- Advances in structural biology: researchers can now visualize PPIs in atomic-level detail using structural biology techniques such as cryo-electron microscopy (Cryo-EM) and X-ray crystallography, which aid in drug creation.
- Machine learning and computational biology are increasingly being used to anticipate PPIs and build medications that target specific interactions, hence expediting drug discovery.
- Monoclonal antibodies and other biologics that target PPIs are gaining popularity in the treatment of disorders such as cancer [33–35].

CHALLENGES

- Many PPIs are fleeting and weak, making research challenging.
- Promiscuous interactions can result in incorrect results; therefore, specificity is essential.
- PPIs are strongly influenced by the cellular environment, necessitating careful experimental design [36, 4].

CONCLUSION

In conclusion, protein–protein interactions are fundamental to biological activities, providing various opportunities for scientific inquiry, medication discovery, and a better knowledge of biology and disease mechanisms. When we are checking the interaction of a particular substrate, there is no technique available to predict it accurately. Computational methods are available, and they can reduce most interactions. PPIs, with the help of these methods, can serve as a foundation for futuristic approaches to laboratory experiments and will help to identify numerous new molecules. When gene expression and protein interaction data are combined, they increase confidence in protein–protein interactions and the accompanying PPI network. Recent advancements in protein–protein interactions have resulted in identifying specific diseases and complex identifications with the help of computational methods, including molecular technologies like single transduction pathways and gene therapy techniques. In conclusion, the future of drug development incorporating protein–protein interactions looks promising, with the potential to open up new treatment options, improve therapeutic efficacy, and advance the field of personalized medicine.

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