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Protein-protein interactions: Methods, databases, and applications in virus-host study

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Abstract

Almost all the cellular processes in a living system are controlled by proteins: They regulate gene expression, catalyze chemical reactions, transport small molecules across membranes, and transmit signal across membranes. Even, a viral infection is often initiated through virus-host protein interactions. Protein-protein interactions (PPIs) are the physical contacts between two or more proteins and they represent complex biological functions. Nowadays, PPIs have been used to construct PPI networks to study complex pathways for revealing the functions of unknown proteins. Scientists have used PPIs to find the molecular basis of certain diseases and also some potential drug targets. In this review, we will discuss how PPI networks are essential to understand the molecular basis of virus-host relationships and several databases which are dedicated to virus-host interaction studies. Here, we present a short but comprehensive review on PPIs, including the experimental and computational methods of finding PPIs, the databases dedicated to virus-host PPIs, and the associated various applications in protein interaction networks of some lethal viruses with their hosts.

Key Words: Protein-protein interactions; Experimental and computational methods; Protein-protein interaction networks; Protein-protein interaction databases; Disease pathways; Protein-protein interaction applications

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Core Tip: This paper provides a comprehensive review on protein-protein interactions (PPIs), including the experimental and computational methods of finding PPIs, the

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databases dedicated to virus-host PPIs, and the associated applications in the studies of some lethal viruses with their hosts. PPIs can be mapped into networks and innumerable novel insights into the functional organization of proteomes can be gained by analyzing the networks. Many studies have used network biology to construct PPI networks of lethal pathogens with their host *Homo sapiens* to dig deep down into the molecular constitution of the disease pathways, and have successfully found multiple potential drug targets against the viruses.

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INTRODUCTION

Proteins have been declared as the chief representative of biological function[1]. It has been reported that more than 80% of proteins do not function alone[2], but instead often interact with each other or with other molecules like DNA or RNA to perform distinct cellular functions. Protein-protein interactions (PPIs) are thought to execute many biological processes including complex metabolic pathways and signaling cascades, and hence it is crucial to understand the particular nature of these associations[1,3].

De Las Rivas and Fontanillo[4] defined PPIs as “physical contacts with molecular docking between the proteins that occur in a cell or in a living organism *in vivo*”. The physical contacts between the proteins should be specific and intentional, *i.e.*, evolved for a particular function. Protein interacting with other proteins can be in any form, *i.e.*, in binary, multi-protein complexes or in the form of long chains[1,4]. Proteins involved in a certain cellular pathway or biological process are often found to interact with each other repeatedly, suggesting that the proteins with associated functions are more likely to interact with each other[2,5]. Conversely, researchers can reveal the functions of unidentified or uncharacterized proteins if the proteins with which they are interacting are known[6,7]. The outcome of most of the cellular processes can be deciphered by protein interactions. The information about PPIs can help scientists find out potential drug targets by investigating the pathogen-host interaction network[8,9]. Therefore, it is significant to study PPIs for understanding the functions of proteins within a cell or a living organism.

EXPERIMENTAL METHODS TO DETECT PPIs

PPIs can be determined by different high-throughput experimental and computational methods which yield different types of PPI data. The high-throughput experimental techniques either identify the interactions directly or infer them indirectly based on different approaches[1,4]. In the following, the two main experimental methods, yeast two-hybrid (Y2H) and tandem affinity purification-mass spectrometry (MS), will be introduced.

Y2H

Y2H, also known as a binary method initially reported in 1989, is the most widely and commonly used interaction detection approach that identifies direct physical interactions between two proteins *in vivo*[10]. It detects the interactions between the query protein of interest and the protein library. In this approach, the former fused with the binding domain of a particular transcription factor is known as the bait and the latter fused with the activation domain of the transcription factor is referred to as the prey. If the bait and prey can interact with each other, they will bring together the two halves of the transcription factor to activate the transcription complex (shown in Figure 1), which transcribes the downstream reporter gene leading to the expression of the reporter gene[1,4,11]. The availability of many full genomes with the advancement of next-generation sequencing techniques allows us to use protein interactions to help

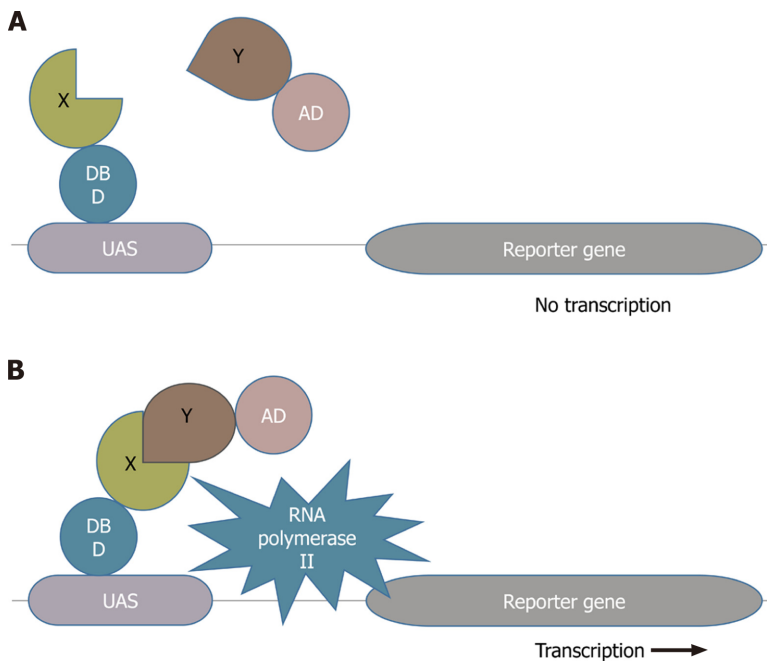


Figure 1 Yeast two-hybrid technique. A: There is no transcription of the reporter gene because the transcriptional factor is broken down into two halves; B: The reporter gene is being transcribed because the two halves of the transcription factor are brought together by the interaction between bait (X) and prey (Y) proteins[10]. DBD: DNA binding domain; AD: Activation domain; UAS: Upstream activation domain.

understand the functions of their gene products. Y2H has outranked the other experimental techniques and has become the system of choice for researchers in large-scale, high-throughput, and comprehensive investigations of PPIs. The complete proteomes of several pathogens including hepatitis C virus (HCV), bacteriophage T7, and vaccinia have been analyzed using the Y2H screen[12-14]. Several scientists have performed the comprehensive two-hybrid analysis of the yeast protein interactome, including the construction and analysis of PPI map of all possible associations between the yeast proteins[15-17].

Y2H has been used massively by scientists to infer physical interactions between macromolecules. It is advantageous because of its simple organization and easy detection for the transient interactions. However, despite its importance, there are certain disadvantages[10,18] which will be discussed in the section of experimental errors in PPI detection.

Tandem affinity purification-MS

MS is a powerful *in vitro* tool for the detection of macromolecular interactions. The principle of MS was explained extensively in one of our previous reviews[19]. MS allows us to identify polypeptide sequences by ionizing them and then detecting analyte ions based on their mass-to-charge ratios[20,21]. To interpret the mass spectra and detect PPIs, various MS-based methods have been developed so far. The MS-based detection of PPIs has become significant in the recent era especially for the large-scale investigations, through which high-throughput and high confidence PPIs can be identified[22,23]. These MS-based technologies include cross-linking MS (CLMS)[24], tandem affinity purification MS (TAP-MS)[25,26], and several others.

TAP-MS is a conventional MS-based qualitative method to study protein functions and interactions. Sinz[27] and Yugandhar *et al*[28] have extensively reviewed CLMS, which is a more recent and advanced MS technique for interpreting protein interaction networks. Many scientists have been working on the techniques using MS for finding potential interactors where true positives are segregated and prioritized from false positives. Gavin *et al*[29] and Collins *et al*[30] developed score-based methods to infer high-accuracy physical interactions.

According to the EMBL-EBI statistics (<https://www.ebi.ac.uk/intact/about/statistics?conversationContext=2>), TAP-MS has overtaken Y2H as a major source of generating PPI data.

Compared with Y2H which detects only binary interactions, TAP-MS is a co-complex method which determines both direct and indirect associations between proteins *in vitro*. In this technique, a TAP tag is fused at the C- or N-terminus of a

protein of interest (the bait), which has two independent binding regions, allowing two successive affinity purification steps. The most common TAP tag consists of two immunoglobulin G binding repeats of Protein A from *Staphylococcus aureus* (ProtA) and a calmodulin-binding peptide which are separated by a tobacco etch virus protease cleavage site. In TAP, a group of protein complexes can be caught by a tagged bait protein in a pull-down assay, which are called prey proteins[2,4,31]. The prey proteins interacting with the bait are separated *via* sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and then identified by MS[18,32].

In addition to the tandem affinity purification, there is another co-complex method called co-immunoprecipitation (CoIP) for determining PPIs. The interaction data derived from co-complex methods cannot be used to infer binary interactions directly, and the related algorithms are needed to interpret the pairwise interactions from the experimental data[4].

Experimental errors in PPI detection

High-throughput experimental approaches for determining PPIs are very efficient, but they also have some limitations. They have a high possibility of false negative and false positive errors. False positives in an experimental system are those interactions that do not occur in the system naturally. One reason for the false positives in Y2H can be the auto-activation of transcription by the bait protein itself or sometimes the transient interactions that are not always specific, *i.e.*, the interactors can be the sticky prey proteins fused with the bait protein and chosen by Y2H analysis[4,10,33]. The precise percentage of the false-positive interactions in Y2H is not well known but the estimated rate of the inaccurate interactions is about 50%, which is quite a big percentage, yet still Y2H is one of the most powerful interaction determining methods [2,10]. Additionally, the experimental system for determining PPIs faces false negative errors too, *i.e.*, some interactions cannot be identified due to the flaws in the experimental system. In Y2H, most of the interactions between membrane proteins are undetectable. Hence, it is important to choose the Y2H design thoughtfully based on the type of cellular proteome. Sometimes in Y2H, very weak transient interactions escape from being identified by the method[10].

Co-complex methods also encounter errors in their interaction detection mechanisms. There can be sticky prey proteins in the TAP pull down assay that are detected by the method as interacting partners of the bait protein. The TAP is an *in vitro* technique, which means that it is not sure whether the interactions that occur *in vitro* will surely exist *in vivo*. Additionally in TAP, the very transient interactions often vanish due to the series of purification levels[1,2]. Another drawback of co-complex methods is that they might analyze all the elements of a protein complex which certainly may not have direct interactions with each other[10] (crossed links in Figure 2).

PPI studies do not just rely on Y2H or affinity purification methods, and due to the false positives and false negatives, several other methods have also been made into practice by researchers for PPI detection. Some of these *in vitro* techniques are CoIP [18], protein microarrays[34], protein-fragment complementation[35], X-ray crystallography, and nuclear magnetic resonance spectroscopy[36].

COMPUTATIONAL METHODS FOR PREDICTING PPIs

As discussed in the previous section, experimental methods for PPI detection have many limitations including a high percentage of false positives, high cost, and being significantly laborious and time-consuming. Besides, due to the completion of various genome sequencing projects, it is necessary to speed up to find the functional linkages between proteins. Thus, the computational prediction of PPIs seems to be very crucial. Now, computational methods are being practiced successfully to evaluate and analyze the interaction data generated by high-throughput experimental approaches as well as to predict novel PPIs by gaining insights from the already known interactions.

The computational methods are a quick and low-cost alternative to the traditional experimental techniques to predict PPIs. An important advantage of computational methods over the experimental ones is that we can study proteins by mapping the pairwise associations into a comprehensive network according to their distinct functional level[1,37]. Table 1 lists some of the important *in silico* methods of PPI prediction.

Table 1 List of some important computational methods of protein-protein interaction prediction along with their brief descriptions		
Method	Description	Ref.
<i>In silico</i> two-hybrid (I2H)	The I2H method is based on the detection of direct physical associations between the interacting proteins and it relies on the presumption that in order to maintain the protein function reliable, the interacting proteins should go through coevolution	Pazos and Valencia[38]
Ortholog-based approach	It is a sequence-based approach that uses a pairwise local search algorithm to obtain the similarities between the query protein pairs and the known interaction pairs. It is dependent upon the homologous nature of the target proteins	Lee <i>et al</i> [39]
Gene fusion	Also known as Rosetta stone method. According to this method, some of the proteins with single domains fuse together in one organism and form a multi-domain protein in another organism	Enright <i>et al</i> [40]
Domain-pairs-based approach	This method predicts the interactions between proteins by the domain-domain interactions	Wojcik and Schächter[41]
Gene expression	An indirect way to predict PPIs. Based on the concept that the proteins translated from the genes that belong to the common expression profiling clusters more likely interact with each other than the proteins translated from the genes that belong to different clusters	Grigoriev[42]
Structure-based approaches	It predicts protein-protein interactions based on the structural similarity	Zhang <i>et al</i> [43]
Phylogenetic tree	This method predicts protein-protein interactions based on the concept that the interacting proteins show similarity in their evolution history	Sato <i>et al</i> [44]

PPI: Protein-protein interaction.

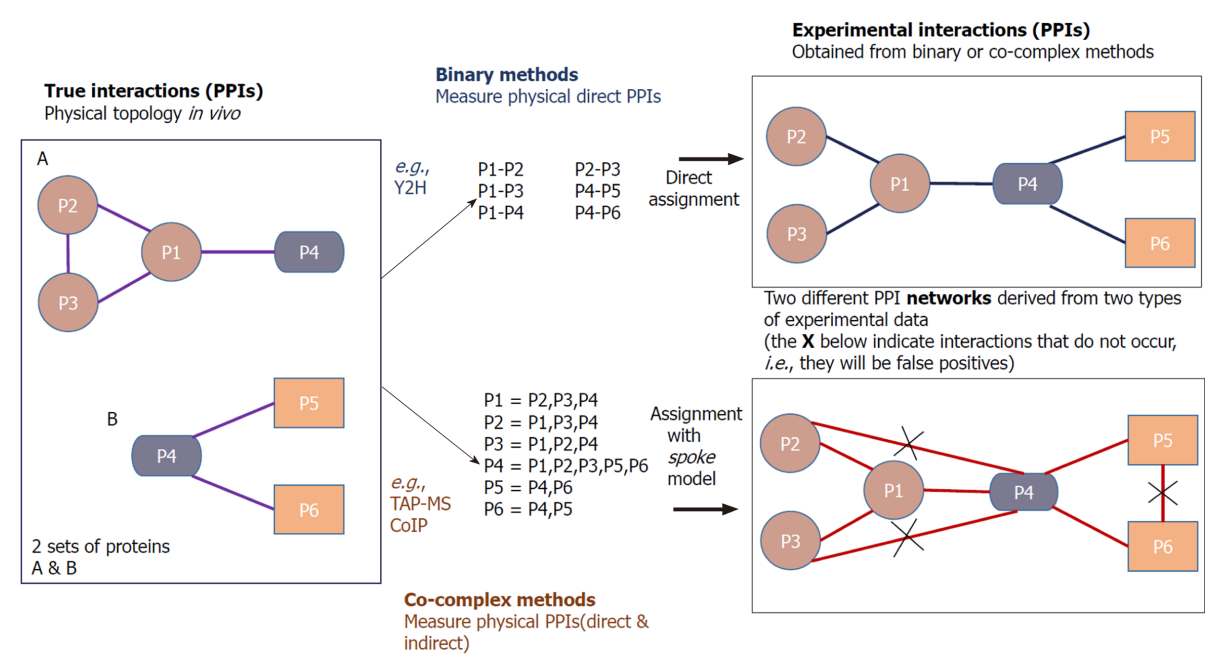


Figure 2 Binary and co-complex methods to determine protein-protein interactions. Yeast two-hybrid (Y2H) and tandem affinity purification mass spectrometry are the two most extensively used approaches for detecting protein-protein interactions. Given here are the two sets of proteins (4 proteins in set A while 3 proteins in set B) in the left panel and the connections show the genuine interactions between them. The right side shows the experimentally determined interaction network among the six proteins. The network in the upper right shows the interactions derived from Y2H, and the network in the lower right shows the interactions got from co-complex method, in which three of the interactions inferred do not exist[4]. PPI: Protein-protein interaction; TAP-MS: Tandem affinity purification mass spectrometry; CoIP: Co-immunoprecipitation.

PPI DATABASES

The continuous increase in PPI data produced by high-throughput technologies needs the formation of biological repositories where these data should be stored in an effective and organized way. The data in the publicly available PPI databases makes it much easier to analyze different types of interactions according to our concerns[37]. There are more than 100 repositories accessible online related to PPI data[45]. Here we will discuss the most popular databases (see Table 2) of PPI information that have

Table 2 List of popular protein-protein interaction databases with total numbers of interactions and last updated time

PPI database	URL	Total interactions	Last updated	Ref.
STRING	http://string-db.org/	> 2000 mio	2020	Szklarczyk <i>et al</i> [50]
BioGrid	http://thebiogrid.org/	1746922	2021	Oughtred <i>et al</i> [47]
HPIDB	https://hpidb.igbb.msstate.edu/index.html	69787	2019	Ammari <i>et al</i> [51]
MINT	https://mint.bio.uniroma2.it/	131695	2012	Zahiri <i>et al</i> [3] and Licata <i>et al</i> [55]
DIP	https://dip.doe-mbi.ucla.edu/dip/Main.cgi	81923	2017	Zahiri <i>et al</i> [3] and Salwinski <i>et al</i> [56]
IntAct	http://www.ebi.ac.uk/intact/	1130596	2020	Orchard <i>et al</i> [52]
HPRD	http://www.hprd.org/	41327	2010	Zahiri <i>et al</i> [3] and Keshava Prasad <i>et al</i> [57]

PPI: Protein-protein interaction; URL: Uniform resource locator.

been used by most of the researchers worldwide and contain experimentally verified virus-host PPIs.

Biological General Repository for Interaction Datasets

The Biological General Repository for Interaction Datasets (BioGRID) is a publicly retrievable and comprehensive database which stores experimentally determined PPI data of almost all important model organisms[3,46]. It has constantly being updated and according to the February 2021 release, it carries 1740000 non-redundant protein and genetic interactions collected from 70000+ publications[47]. The current version of BioGrid (v 4.3.194) themed curation projects focuses on curated interactions of different diseases including coronavirus disease 2019 (COVID-19), ubiquitin-proteasome system, fanconi anemia, glioblastoma, and autophagy.

Search Tool for Retrieval of Interacting Genes

Search Tool for Retrieval of Interacting Genes (STRING) is equipped with the complete information about the functional relationships between proteins. The current version STRING v11.0 contains interaction data of 5090 organisms that is the highest number of organisms covered by any PPI database. The major assets of STRING database are its exhaustive coverage, confidence scoring of the interactions, and its intuitive user interface[48,49]. Currently, the database covers 3123056667 PPIs which are the sum of high-confidence and low-confidence interactions. An important new feature in the current version of STRING is that users can perform Gene Ontology and KEGG analysis of their input which has provided ease in gene-set enrichment analysis[50].

HPIDB

HPIDB is a curated database that contains host-pathogen interaction data. Developed in 2010, it is updated yearly and presents new versions. Currently, it contains protein interaction data between 66 hosts and 668 infectious pathogen species. The number of unique interactions is 69787 according to the last update (July 29, 2019). The pathogenic species that can be found superabundantly in HPIDB are influenza virus, herpes virus, papillomaviruses, *Saccharomyces cerevisiae*, and several others[51].

IntAct

Developed in 2002, IntAct is a freely available molecular interaction data source and contains the data obtained from literature curation or deposited directly by the researchers. In 2013, IntAct and MINT joined their efforts and started the MINTACT project to maximize the coverage and curation output[52].

International Molecular Exchange Consortium databases

The International Molecular Exchange Consortium (IMEx) is an international consortium established by the joint efforts of prime public interaction databases including DIP, IntAct, HPIDB, MINT, BioGRID, MatrixDB, I2D, and some others. BIND and MPIDB which used to be large PPI databases are also members of IMEx but they no longer are active anymore. The data in IMEx is a comprehensive and integrated consortium of databases recording meta data for PPIs in a standard PSI-MS format and is available for all the researchers to re-use and re-analyze. Over the last two decades, there has been a massive increase in protein interaction data and out of

all the resources, IMEx is the only source which is providing up to the minute information regarding protein interactions and annotations[45,53,54].

Some protein interaction databases are dedicated to a specific viral pathogen for example HCVPro[58] containing the data on PPIs between HCV and human. VirHostNet[59] covers an extensive range of human specific viruses and contains nearly 22000 virus-human PPIs.

APPLICATIONS OF PPIS IN DISEASE NETWORKS AND IN VIRUS-HOST RELATIONSHIP

Bacteria and viruses are the major pathogens affecting humans on earth. Bacterial infections can be eradicated by using antibiotics, and viruses not easy to be eliminated can only be inhibited in their growth. Viruses depend entirely on their hosts and infect hosts often by virus-host protein interactions[54]. PPIs can be mapped into networks and innumerable novel insights into the functional organization of proteomes can be gained by analyzing the networks. Several protein interaction network construction and visualization tools are available, including Cytoscape[60], BioLayout[61], and VisANT[62]. Analyzed by these tools, PPI networks can provide the differences between normal and the diseased states, and thus the fundamental knowledge about the disease can be obtained based on the related pathways revealed through the analyses of PPI network, *i.e.*, by looking into the subnetworks constructed by the proteins involved in the disease[1,63]. Protein interaction networks can help find new disease-related genes by the presumption that the neighboring genes of the disease-causing gene are expected to be causing the same disease or involved in causing some similar diseases (Figure 3)[64]. Various researchers have been using network biology to study pathogen-host relationship at the molecular level, which ultimately helps in identifying key viral proteins and their human targets and helps scientists in further biological investigations.

The quickly developing knowledge of human interactome map and the availability of different host-pathogen networks have paved us the way for a better understanding of diseases. Viral genomes code for a very small number of proteins, which makes it easy to understand the mechanisms of the infections by viruses[64,65]. The network-based study on the infection of host with viral pathogenesis is progressing over time. In one of our previous studies, we constructed a comprehensive protein interaction network of HCV with its host *Homo sapiens*[66] and found out many crucial insights into finding potential targets against HCV and some other disease pathways, such as cancer pathways (Figure 4). In fact, certain viruses such as papilloma and herpesvirus have been reported to be causing up to 20% of the cancers[67]. Additionally, virus-host relationship was also studied by us for human papillomavirus[68], influenza A virus (IAV)[69], and dengue virus with *Homo sapiens*. Interestingly, in a study performed by Navratil *et al*[70], they compared a set of virus targets with a list of 1729 human genetic disease-related proteins, and found that 13% of human virus targets are also linked with at least one human genetic disease. In short, there are so many types of viruses causing a wide variety of infections worldwide. From Ebola virus outbreak in Africa to Middle East respiratory syndrome coronavirus outbreak, viruses have killed thousands of people with no specific effective treatment. Every viral infection involves PPIs between the virus and its host including the viral entry to the host cell and hijacking the host transcription machinery. Identification of PPIs between the viruses and their hosts lets us understand the infection mechanisms of the viruses and find a way to combat the infections using antiviral drugs or vaccines[71].

When we talk about human interactome, more than 645000 PPIs are reported to be disease-associated while only 2% of these proteins are targeted by drugs[72]. The reason for most of the proteins considered to be undruggable is because of the absence of detectable pockets for binding ligands[73]. Researchers have been significantly investigating PPI inhibitors and stabilizers and have succeeded in developing new technologies that have enabled the systematic discovery of drugs focused on PPIs[74, 75]. Zhang *et al*[76] and Robertson and Spring[77] have extensively explained the use of peptidomimetics to find the 'hot spots' on the protein surfaces for drug design. Targeting PPIs for designing therapeutics was once considered a difficult and impossible task. However, during the past two decades, the concept has changed and PPI drug targets have gained considerable interest from the scientific community. Some researchers have been conducting drug target studies in both wet and dry labs, hoping to find potential hot spot regions in PPIs' binding interfaces for designing therapeutic drugs. The discovery of small molecule PPI modulators by the emergence

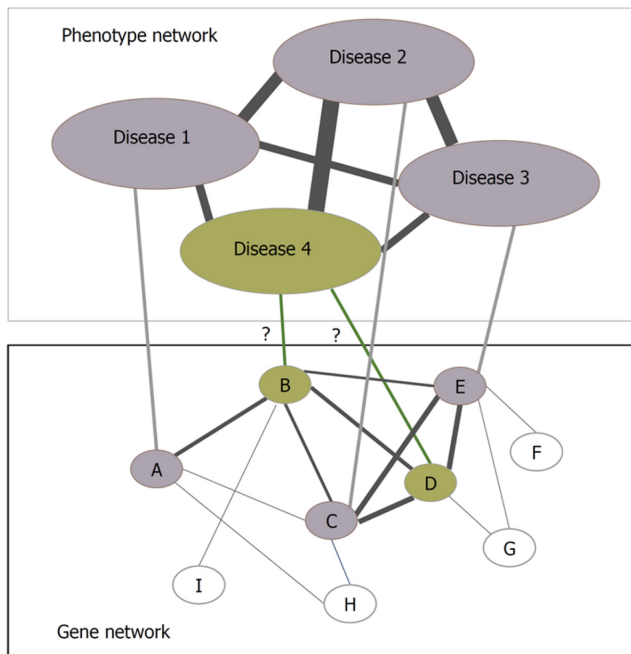


Figure 3 Protein interaction networks can help find new disease-related genes. The concept depicts that diseases 1, 2, and 3 are caused subsequently by genes A, C, and E, and the genes causing disease 4 are unknown but disease 4 is phenotypically associated with diseases 1, 2, and 3. If the known genes, *i.e.*, A, C, and E are closely associated functionally, it can be hypothesized that genes B and D are the cause of disease 4[86].

of new technologies has made the PPIs significant drug targets[72,78]. Until now, three databases have been dedicated to modulators of PPIs: (1) 2P2I database[79]; (2) TIMBAL[80]; and (3) iPPI-DB[81], and more than 40 PPIs have been targeted successfully[82]. To our knowledge, some of the druggable hotspots for well-studied PPI targets identified by various studies are: MDM2/p53, IL-2/IL-2Ra, HPV-11 E2/HPV-11 E1, TNF- α /TNFR1, and several others[83].

Currently, much focus has been diverted towards the recent COVID-19 pandemic, and many studies have been carried out to combat the deadly virus experimentally and computationally. Gordon *et al*[84] performed affinity purification-MS and identified 332 physical interactions between human proteins and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) proteins. The study helped researchers to dig deep down into the host molecular machineries and identify potential hotspots for developing therapeutic compounds to treat COVID-19. PPI identification will also help in predicting the behavior of the virus and the biological processes targeted by the virus. Khorsand *et al*[85] developed a three-layered network model to predict SARS-CoV-2-human PPIs and reported the most central human proteins in the network by investigating host proteins that are targeted by the viral proteins.

In summary, network biology has become the focus of attention in the recent era by scientists for understanding diseases and the biological processes targeted by the disease. Interaction networks are playing a significant role in understanding virus-host relationship and drug discovery.

CONCLUSION

The study on PPIs is not just a new field, but a new era in study of virus-host relationships, and we can say that PPIs are at the core of any viral infection. Scientists can use PPIs to gain innumerable novel insights into the functional constitution of a proteome by analyzing all kinds of network parameters. Network biology can help scientists find many potential drug targets that might be involved in certain viral pathways. Many studies have used network biology to construct protein interaction networks of lethal pathogens such as HCV, IAV, dengue virus, and human papilloma virus with their host *Homo sapiens* to dig deep down into the molecular constitution of the disease pathways, and have successfully found multiple potential drug targets against the viruses. In short, the future of PPI-induced network biology is quite clear and scientists can perform plenty of useful studies against any disease or pathway.

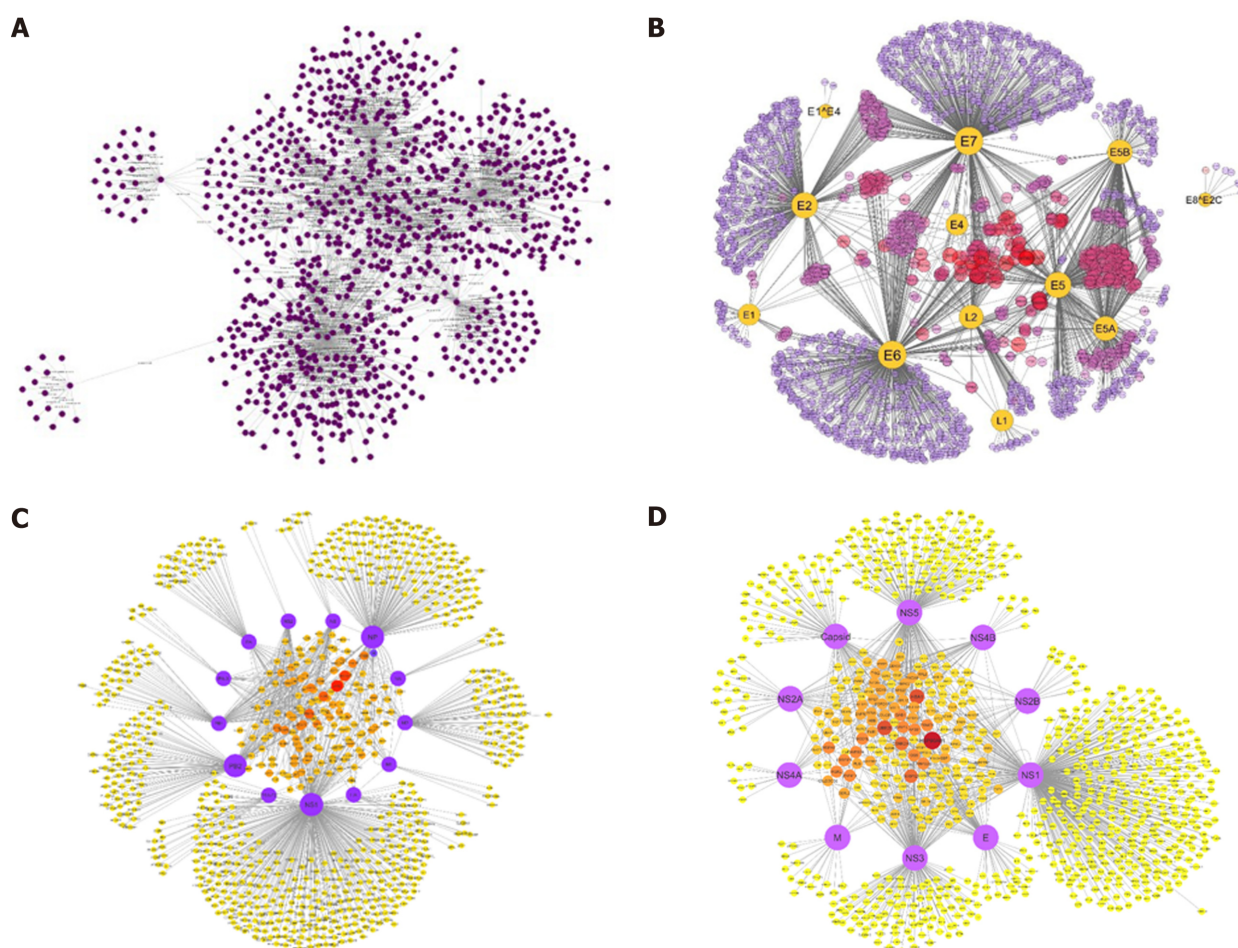


Figure 4 Comprehensive protein interaction networks of hepatitis C virus, human papillomavirus, influenza A virus, and dengue virus with host *Homo sapiens* constructed in Cytoscape by literature curated experimentally verified and computationally predicted protein-protein interactions. The network explains virus-host relationship between the infectious agents and host factors which contribute to disease pathways in human body. A: Hepatitis C virus; B: Human papillomavirus; C: Influenza A virus; D: Dengue virus.

Computational prediction of PPIs has become a mandatory tool for finding out the functionalities of unknown proteins.

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