Article

Network pharmacology: A further description

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Abstract
Network pharmacology devotes to understand the pharmacological mechanism of drug action in the network perspective. Based on previous studies, in present article I further outlined and defined the aims, scope, theory and methodology of network pharmacology.

Keywords network pharmacology; methodology; theory; scientific discipline.

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1 Introduction

During the past twenty years, the successful cases of drug design have been dropping significantly. The failure cases in clinical trials, due to lack of drug efficacy and unexpected toxicity, have accounted for more than half of the failure cases of drug design (Kola and Landis, 2004). The main cause was strongly attributed to the wrong guiding ideology for drug design in traditional pharmacology based on the view of a drug - a target - a disease.

Complex diseases, such as cancer and diabetes, etc., do not usually attributed to mutation or dysfunction of a single molecule, but are usually caused by dysfunction of related whole regulation network. In a network, a single molecule is a network node. So even a single molecule changes insignificantly, they will collectively lead to a substantial change in the whole signal path. For example, research has founded that the 10% increase of a single molecule expression level in metabolic pathways can lead to 100% of final metabolite production. The research on cancer genome project has revealed that the vast majority of mutations exist only in a few samples, and to find the same genetic mutation is almost impossible. At the level of network, however, cancer-related mutations will mostly appear in the genes of specific signaling pathways. Thus, for diagnosis and treatment of cancer and other complex diseases, the target is not surely a single gene, but may be a specific pathway or network. The analysis of molecular mechanisms of diseases based on biological networks is thus imperative. As a concequence, Hopkins (2007, 2008) put forward the concept of network pharmacology. Network pharmacology devotes to understand drug's pharmacological mechanism in the network perspective.

In a sense, it is also a branch of network biology (Zhang, 2011a, 2011b, 2012a, 2016d; Budovsky and Fraifeld, 2012; Huang and Zhang, 2012; Zeitoun et al., 2012; Li and Zhang, 2013; Iqbal et al., 2014; Shams and Khansari, 2014; Jesmin et al., 2016; see more details of network biology at http://www.iaees.org/publications/journals/nb/nb.asp).

Network pharmacology aims to understand diseases at the systematic level, and to know the interaction between the drug and the body on the basis of equilibrium theory of biological networks. It is substantially bringing the significant changes of theory and methodology in drug design (Gertsch, 2011; Li and Zhang, 2013; Zhang et al., 2013; Zheng et al., 2013; Hao and Xiao, 2014; Shi et al., 2014).

2 Aims and Scope

Network pharmacology is an interdisciplinary science based on pharmacology, network biology, systems biology, bioinformatics, computational science, and other related scientific disciplines. In particular, it is a network-based science, just like other new proposed sciences (Zhang, 2016c). Network pharmacology aims to understand the network interactions between a living organism and drugs that affect normal or abnormal biochemical function. It tries to exploit the pharmacological mechanism of drug action in the biological network, and helps to find drug targets and enhance the drug's efficacy. The scope of network pharmacology covers but not limits to: (1) theories, algorithms, models and software of network pharmacology; (2) network construction and interactions prediction; (3) theories and methods on dynamics, optimization and control of pharmacological networks (here generally refer to disease network, disease - disease, disease - drug, drug - drug, drug - target network, network targets - disease, and drug targets - disease network, etc.); (4) network analysis of pharmacological networks, including flow (flux) balance analysis, topological analysis, network stability, etc.; (5) various pharmacological networks and interactions; (6) factors that affect drug metabolism; (7) network approach for searching targets and discovering medicines (including medicinal plants, etc); (8) big data analytics of network pharmacology, etc.

3 Theoretical Fundamentals

3.1 Scientific foundation

3.1.1 Pharmacology

Pharmacology is the branch of medicine and biology on drug action where a drug can be broadly defined as any man-made, natural, or endogenous molecule which exerts a biochemical and/or physiological effect on the cell, tissue, organ, or organism (Vallance and Smart, 2006; Wikipedia. 2016b). It aims to study the interactions between a living organism and chemicals that affect normal or abnormal biochemical function.

There are a lot of branchs of pharmacology, clinical pharmacology, neuropharmacology, psychopharmacology, theoretical pharmacology, behavioral pharmacology, environmental pharmacology, biochemical and molecular pharmacology, cardiovascular pharmacology, gastrointestinal pharmacology, respiratory tract pharmacology, and urogenital pharmacology, etc.

3.1.2 Network biology

Network Biology was first proposed by Barabasi and Otlvai in 2004. Laterly, Zhang (2011b, 2012a) further defined the scope of network biology from cellular level to ecosystems and social networks. He also established the first and only journal on network biology (details can be found at http://www.iaees.org/publications/journals/nb/nb.asp). According to the journals' description, network biology focuses on (both dynamic and static) nodes (molecules, metabolites, cells, etc.) and between-node interactions in biological networks (pathways, ecosystems, etc.). It covers theories, algorithms and programs of network analysis; innovations and applications of biological networks; Dynamics, optimization and control of

biological networks; ecological networks, food webs and natural equilibrium; co-evolution, co-extinction, biodiversity conservation; metabolic networks, protein-protein interaction networks, biochemical reaction networks, gene networks, transcriptional regulatory networks, cell cycle networks, phylogenetic networks, network motifs; physiological networks; network regulation of metabolic processes, human diseases and ecological systems; social networks, and epidemiological networks, etc. In recent years, the theory and methodology of network biology have been establishing (Jiang and Zhang, 2015; Zhang, 2011a-b, 2012a-c, 2015a-c, 2016a-d; Zhang and Li, 2015). A lot of papers on biological networks of human diseases have been published also (Tacutu et al., 2011; Budovsky and Fraifeld, 2012; Huang and Zhang, 2012; Zeitoun et al., 2012; Li and Zhang, 2013; Iqbal et al., 2014; Shams and Khansari, 2014; Zhang and Li, 2015, Jesmin et al., 2016).

3.1.3 Systems biology

Hood (1998) first proposed the scientific discipline, sytems biology, and defined it as the science that studied all components and their interactions in biological systems. In the view of systems biology, the organism is a complex system containing many interactions between components (genes, proteins, mRNAs, small molecular metabolites, etc.) at multiple layers (cell, tissue, organ, and whole body) of the organism. Biological systems have such properties as emergency, complexity and robustness (Hood, 1998, 2002, 2003; Ideker et al., 2001; Schrattenholz et al., 2010; Zhang, 2012a, 2016d). Systems biology aims to exploit all components and their interactions under certain conditions (e.g., various genetic and environmental conditions), and to predict biological functions, phenotypes and their behaviors. According to systems biology, the drug target should be extended from the single molecule into molecular combination, a signal transduction pathway, or even a few of pathways (Frantz, 2005; Schrattenholz et al., 2010).

3.2 Basic principles

There are at least two basic principles in ideology of network pharmacology: (1) Schilling et al. (1999) held that throughout natural selection, the cellular metabolic activities always maintain a balance when no significant perturbation occurs, or regulatorily minimize the systematic bias from resting status. From the perspective of network biology, a biological network (human body) at steady state / natural equilibrium state is at the healthy state, i.e., a stable network with a specific topological structure and certain network properties. If the network equilibrium is disrupted or damaged, it will change to the pathological or disease state, i.e., an unstable network with different topological structure and network properties. A drug for disease treatment is to restore the biological network to the balance / equilibrium state, or reduce the degree of balance being destroyed (Yildirim et al., 2007; Janga and Tzakos, 2009). According to Le Chatelier's principle, if the balance (health state) of a system (network) has experienced a change (to a disease state), the role of an effective drug is to drive the balance to the direction that will weaken such change. (2) Due to biological redundancy (e.g., the redundancy of metabolites/molecules/reactions/interaction, etc.), which is the result of natural evolution, in my view, as an alternative solution, the role of an effective drug is to induce a somewhat different biological network that can guarantee the operation of basic functionality of the healthy biological network, if the normal balance is not easily achieved.

Network pharmacology is proposed based on the theory of network biology and biological balance, and it thus provides new ideas for drug discovery, as well as for understanding the mechanism of drug functioning. In the perspective of network pharmacology, we should try to perturb the pathogenic network using the drug rather than search for pathogenic genes only (Barabasi and Otlvai, 2004; Chen et al., 2008).

4 Methodology

Based on high-throughput -omics data, network database retrievals and other biological information, network pharmacology stresses construction of pharmacological networks, topological analysis of pharmacological

networks, network flow analysis, structural optimization and optimal control of pharmacological networks, etc. Other experiment and observation based methods are also included (Li and Zhang, 2013).

4.1 Data source

There are two sources of foundamental data for research in network pharmacology, public databases and experimental verification. First, we can use public databases, i.e., the existing public data and published data, to construct network models of the specific disease and drug target, to predict the drug target (Budovsky and Fraifeld, 2012); further, to construct drug-target-disease network and analyze pharmacological mechanism of the drug, and finally validate the mechanism through experiments (Zhou et al., 2012). Second, we may use -omics technologies and high -throughput technologies to investigate the interactions between the drug and network model, to construct and analyze drug-target-disease network based on the generated data, and to analyze pharmacological mechanism of drug action.

4.2 Big data analytics

Big data is the data sets so large or complex that conventional data processing tecgniques are inadequate. Challenges include analysis, capture, data curation, search, sharing, storage, transfer, visualization, querying and information privacy (Wikipedia, 2016c).

Big data analytics is the process of examining big data to uncover hidden patterns, unknown correlations and other useful information. With big data analytics, e.g., high-performance data mining, predictive analytics, text mining, forecasting and optimization, we can analyze huge volumes of data that conventional analytics can not handle. In addition, machine learning techaniques are ideally suited to addressing big data needs (Zhang, 2007b, 2010; Zhang and Qi, 2014; SAS, 2016). Many problems in network pharmacology, network construction, interactions prediction, etc. are also expected to be addressed by using big data analytics.

4.3 Network construction and interactions prediction

For a disease and the corresponding drug, the pharmacological network is the most important basis for further phamarcetical studies. However, most pharmacological networks are unknown or imperfect. Therefore, how to construct a pharmacological network is a prerequisite for such diseases. Among them, the networks of disease related protein interactions are the most important. The most used methods to find such interactions and construct pharmacological networks include phylogenetic profile (Gaasterland and Ragan, 1998; Pellegrini et al., 1999), gene neighborhood (Dandekar et al., 1998), gene fusion event (Marrcotte et al., 1999), mirror tree (Fryxell. 1996), correlated mutation (Gobel et al., 1994), correlated evolutionary rate (Fraser et al., 2002), prediction from primary structure (Bock and Gough, 2001), and homologus structural complexies (Aloy and Russell, 2003), etc. Among them, phylogenetic profile method is considered to be particularly useful for construction of networks and prediction of large scale interactions. Tu (2006) used Pearson correlation between proteins, which is based on phylogenetic profile method, to construct the networks of small-cell lung cancer and non-small-cell lung cancer and predict potential interactions. Zhang (2011a, 2012a, 2012b) has proposed a series of correlation methods to construct networks. Pearson correlation measure will lead to a false result (Zhang and Li, 2015). Thus, Zhang (2015c) used partial linear correlation and proposed some partial correlation measures, and used them to jointly predict interactions (Zhang, 2015b). Moreover, there are a lot of other studies on construction and prediction of biological networks (Goh et al., 2000; Pazos and Valencia, 2001; Guimera and Sales-Pardo, 2009).

We may use an incomplete network to predict missing interactions (links) (Clauset et al., 2008; Guimera and Sales-Pardo, 2009; Barzel and Barabási, 2013; Lü et al., 2015; Zhang, 2015d, 2016a, 2016d; Zhang and Li, 2015).

Generally, network evolution based (Zhang, 2012a, 2015a, 2016b), node similarity based (Zhang, 2015d; based on prediction from primary structure), and correlation based (Zhang, 2007a, 2011a, 2012a, 2012b,

2015d, 2016d; Zhang and Li, 2015) methods are expected to be the most promising in the future.

4.4 Network analysis

Network analysis covers a variety of areas and methods (Zhang, 2012a). Main contents of network analysis, used in network pharmarcology, include the following aspects.

4.4.1 Attribute analysis

Attribute analysis aims to screen node attributes (e.g., protein attributes, etc.) based on their contribution to topological structure of the network (Zhang, 2016e).

4.4.2 Topological analysis

Topological analysis of networks mainly includes the following

Find trees in the network: DFS algorithm, Minty's algorithm, etc (Minty, 1965; Zhang, 2012a).

Find circuits (closed paths, loops) (Paton, 1969; Zhang, 2012a, 2016e).

Finf the maximal flow: Ford—Fulkerson algorithm (Ford and Fulkerson , 1956; Zhang, 2012a).

Find the shortest path: Dijkstra algorithm, Floyd algorithm (Dijkstra, 1959; Zhang, 2012a; Zhang, 2016e).

Find the shortest tree: Kruskal algorithm (Zhang, 2012a).

Calculate network connectedness (connectivity), blocks, cut vertices, and bridges (Zhang, 2012a).

Calculate node centrality (Zhang, 2012a, 2012c; Shams and Khansari, 2014; Jesmin et al., 2016).

Find modules, mosaics, and sub-networks (Kondoh, 2008; Bascompte, 2009; Zhang, 2016f; Zhang and Li, 2016).

Analyze degree distribution (Huang and Zhang, 2012; Zhang, 2011a, 2012a, 2012c; Zhang and Zhan, 2011; Rahman et al., 2013).

For example, degree distribution and crucial metabolites/reactions of tumor pathways have been conducted (Huang and Zhang, 2012; Li and Zhang, 2013; Zhang, 2012c). In addition to the methods above, other statistical methods, e.g., PCA, etc., are also useful in network analysis.

4.4.3 Network structure and stability

Stability of biological networks has been studied in the past (Din, 2014). These studies have been focused on ecosystems and the methods can be used in the phamarceutical studies. Pinnegar et al. (2005) used a detailed Ecopath with Ecosim (EwE) model to test the impacts of food web aggregation and the removal of weak linkages. They found that aggregation of a 41-compartment food web to 27 and 16 compartment systems greatly affected system properties (e.g. connectance, system omnivory, and ascendancy) and influenced dynamic stability (Zhang, 2012a).

The most developed theory is that there is a relationship between network connectance and different types of ecosystem stability. Some models suggest that lower connectance involve higher local (May, 1973; Pimm, 1991; Chen and Cohen, 2001) and global (Cohen et al., 1990; Chen and Cohen, 2001) stability, i.e., the system recovers faster after a disturbance. However, another theory suggests that a food web with higher connectance has more numerous reassembly pathways and can thus recover faster from perturbation (Law and Blackford, 1992).

4.4.4 Flow (flux) balance analysis

Network flow is determined by topological structure and properties of the network (Borgatti, 2005). Flow balance analysis aims to analyze network flows at the steady state. Differential equations and other equations are usually used to describe network dynamics (Chen et al., 2010; Schellenberger et al., 2011). As an example, Jain et al. (2011) used mathematical models to decipher balance between cell survival and cell death using insulin.

Some standardized indices and matrices can be used in flow balance analysis (Latham, 2006; Fath et al., 2007; Zhang, 2012a). They include Average Mutual Information (AMI) (Rutledge et al., 1976). Ascendency

(A) index of a system was developed by Ulanowicz (1983, 1997). Compartmentalization index is used to measure the degree of well-connected subsystems within a network (Pimm and Lawton, 1980). Constraint efficiency is a measure of a total of constraints that govern flow out of individual compartments (Latham and Scully, 2002). Zorach and Ulanowicz (2003) have presented effective measures (effective connectivity, effective flows, effective nodes, effective rules) for weighted networks. Fath and Patten (1999a) developed a measure (measures the evenness of flow in a network) for network homogenization. In addition, Higashi and Patten (1986, 1989) and Fath and Patten (1999b) presented an index for describing the dominance of indirect effects.

4.4.5 Network models

Network models are the foundation to understand interactions within complex networks. Various random graph models produce network structures that may be used in comparison to real complex networks (Wikipedia, 2016a). Some network models have been developed for food webs (Zhang, 2012a), such as cascade model (Cohen et al., 1990), niche model (Williams and Martinez, 2000), multitrophicassembly model (Pimm 1980, Lockwood et al. 1997), MaxEnt models (Williams, 2010), and Ecopath model (Polovina, 1984; Christensen and Pauly, 1992; Libralato et al., 2006), etc. Ecosim is the dynamic program of the EwE (Walters et al., 1997, 2000). It is based on a set of differential equations derived from the Ecopath equation above, which allows a dynamic representationof the system variables, like biomasses, predation, and production (Libralato et al., 2006). They can be revised and improved to fit pharmacological networks. In addition, some dynamic evolution models are also network models (Zhang, 2016b).

4.5 Network dynamics, evolution and control

Theoretically, Ferrarini (2011a, 2011b, 2013a-d, 2014) have proposed a series of thoughts and methods on the dynamics, controllability and dynamic control of biological networks. Zhang (2015a) proposed a generalized network evolution model and self-organization theory on community assembly, in which the model is a series of differential (difference) equations with different number as the time. In addition, Zhang (2016b) developed a random network based, node attraction facilitated network evolution method. The two dynamic models are useful to study the network evolution, dynamics, and to predict interactions.

A network can be optimized to search for an optimal search plan, and achieve a topological structure so that the network possesses relative stability (Zhang, 2012a). The dynamic control of network means to change topological structure and key parameters of the network stage by stage so that the goal function of entire network achieves the optimum or suboptimum (Zhang, 2012a). Mathematical tools, like dynamic programming, decision-making analysis, game theory, etc., can be used to address these problems.

Luo (2007) conducted a constraint optimization on flux balance model in order to study cellular metabolic network (Fig. 1). First, a central carbon metabolism network model of the yeast cell was developed and metabolic flux analysis was conducted on it. Second, use the metabolic balance analysis to establish mathematical model (both differential equations and other flux balance equations) of cellular metabolic network, and use the growth capacity and Minimization of Metabolic Adjustment (MOMA) methods to optimize the model. Finally, compute the results, and make analysis. Optimization analysis on the model of cellular metabolic network can improve the efficiency and accuracy of the metabolic balance model. It will also enhance our understanding on cell metabolic regulation, help gain insight on the unknown metabolic fluxes, identify node’s rigid nature, help identify metabolic network of alternative channels, and thus calculate the theoretical maximum yield of metabolites. To study cell migration controlled by Rho GTPases, Kim et al. (2015) built a dynamic network model of Rho GTPases signal network, and developed a Boolean network model used to analyze various states and emergency reconstruction of Rho GTPases signal network. In order to reveal Epithelial Mesenchymal Transition (EMT) in the process of cancer metastasis from the dynamics

view, Tanaka and Ogishima (2015) defined the state space of a gene regulation network as all possible activation patterns for the network, and then introduced panorama into the state space, which showed a relatively stable distribution of three steady states or phases.

4.6 Network visualization

Network visualization aims to present users with the static/dynamic two- or three-dimensional illustrations and images of biological networks. There are a variety of such network software for doing it (Zhang, 2012a), for example, ABNNSim (Schoenharl, 2005), Topographica (Bednar et al., 2004), Pajek, NetDraw, NetLogo (Resnick, 1994), netGenerator (Zhang, 2012a, 2012d), Repast (Macal and North, 2005), Topographica (Bednar et al., 2004), Startlogo (Resnick, 1994), etc.

5 Application

Network pharmacology helps to better understand the influence of behaviors of cells and organs on functional phenotypes, to understand the mechanism of drug functioning, to provide theoretical basis and technical support for drug design and for rational clinical use of drugs. Moreover it helps to predict and explain drug interactions and optimize the use of drugs, to find the factors that affect drug efficacy and safety, and to quickly discover biomarkers and drug targets (Zhou et al., 2012).

5.1 Exploit pharmacological mechanism of drug action and guide clinical application

In the view of network biology, network pharmacology helps to noly only understand the mechanism of drug functioning from the perspective of the whole network, but also guide drug's clinical use. In the conventional drug treatment, drug resistance has become a common phenomenon. Because the current drugs mostly point to a single target, thus the change of a single amino acid in the target may cause drug's resistance. As a result, many effective antibiotics work by acting on multiple targets at the same time rather than a single target (Lange et al., 2007; Shi et al., 2014).

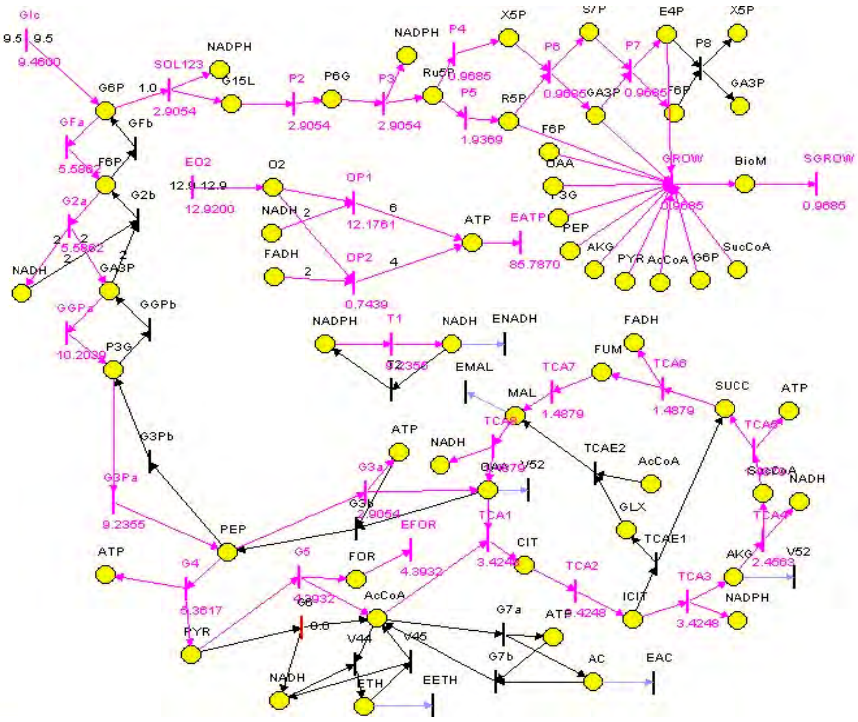

Fig. 1 Flux distribution map of *S. cerevisiae* cell's FBA model under the overgrow constraint when PDB gene was knocked out (Luo, 2007).

5.2 Discover and confirm drug targets

Tranditional research on single drug target focuses on the single molecule. Resultant drug usually fails to work due to some pharmacokinetic or toxic effects. Network pharmarcology stresses multiple targets, i.e., multiple molecules or even multiple sub-networks are used to adjust the biological network. The discovery and confirmation of drug targets will be accelerated due to the strong predictability based on the whole network (Apsel et al., 2008; Zheng et al., 2013).

As a case study, Budovsky and Fraifeld (2012) used network approach to search potential therapeutic targets in medicinal plants (Fig. 2). In this study, they used a list of the plants growing in the Judea region and suyveyed scientific literature and ethno-pharmacological data to identify medicinal applications of the local vegetation. The validated and potential human targets of the major compounds found in the medicinal plants were downloaded from the STITCH database (one of the largest repositories of chemical-protein interactions). Meanwhile, the NetAge database was applied to data mine association of the medicinal plants targets with the major human age-related diseases and associated processes. And protein-protein interaction data for the targets was extracted from the BioGRID database. With the focus on their medicinal applications, nearly 1300 plants growing in this region were identified and 25% of them have medicinal applications and were analyzed. It revealed that screening for chemical-protein interactions, together with the network-based analysis of potential targets, may facilitate discovery and therapeutic applications of medicinal plants.

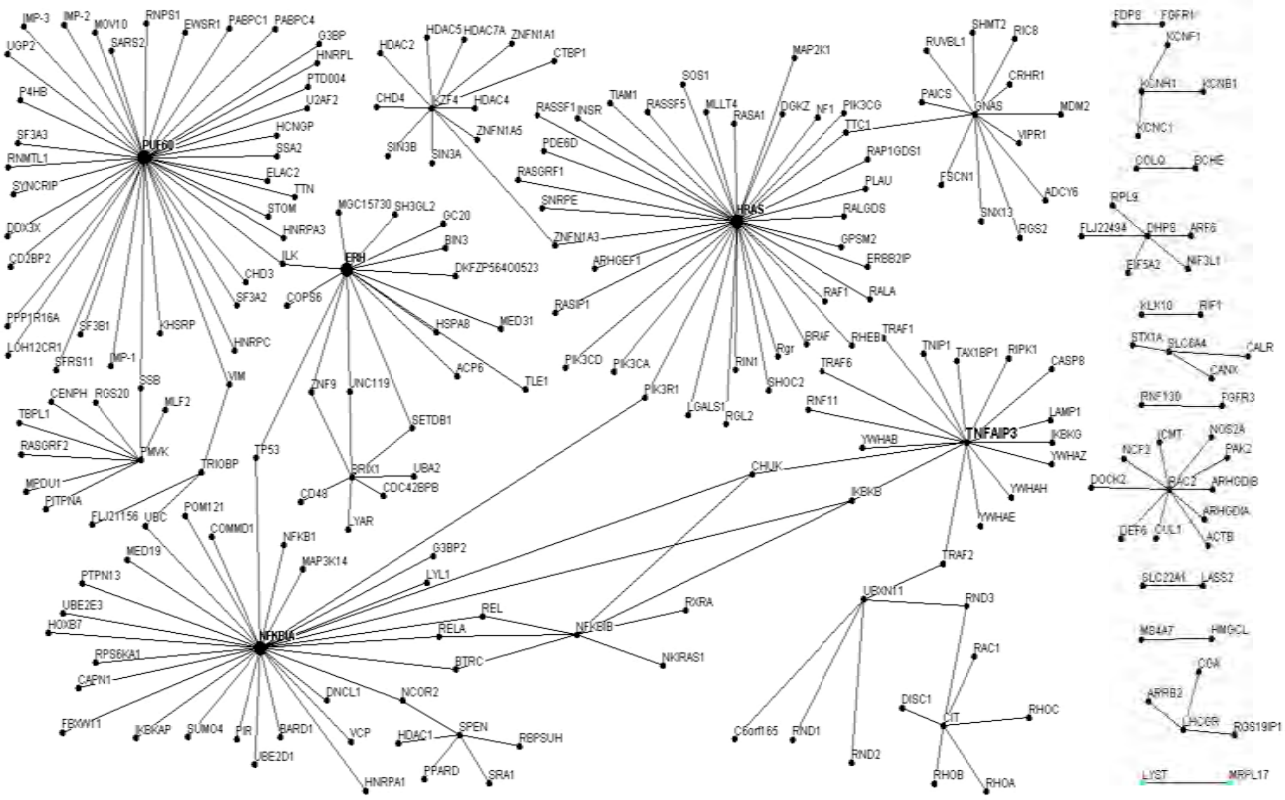

Fig. 2 Network of the direct protein-protein interactions between alpha-pinene targets including their first-order partners of the major compounds found in the *V. iphinoides* chemotypes (Budovsky and Fraifeld, 2012).

5.3 Guide research and design of new drugs

The selectivity of many approved drugs has proved to be worse than expected (Campillos, 2008). So far, some drugs of multiple targets are clinically successful, especially double or multiple enzyme inhibitors (Lange et al., 2007). Some medicine for treatment of tumors can be combined with multiple kinases (Frantz, 2005). Moreover, drug - target networks have scale-free properties (Campillos, 2008; Janga and Tzakos, 2009), therefore a single protein will show compensation mechanism for dysfunction, and the single target strategy thus fails to work.

6 Perspective

Besides being limited by deficient methodology of network biology and systems biology, network pharmacology will face such challenges as the limited knowledge and technology for identification of drug targets, fewer multi-target drugs, and poor database quality, etc. Nevertheless, network pharmacology is an emerging branch of pharmacology built on massive -omics data and multiple sciences. It is expected to greatly develop in the future.

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