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Article

Network toxicology: A new science

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Abstract
Network toxicology is related to network biology. Based on my previous study (Zhang, 2016c), in present article I further outlined and defined the aims, scope, theory and methodology of network toxicology.

Keywords network toxicology; methodology; theory; scientific branch.

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1 Introduction

Toxicology studies the harmful effects of toxicants in biological systems (biological networks) that establish the extent of damage in living organisms. The effects of toxicants are influenced by network properties, network structure, and network dynamics, etc. Therefore, I first proposed the science concept, network toxicology (Zhang, 2016c). Network toxicology devotes to understand toxicological mechanism of harmful substances in the network perspective. In a sense, it is also a displine 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). In present study, I further outlined and defined the aims, scope, theory and methodology of network toxicology.

2 Aims and Scope

Network toxicology is an interdisciplinary science based on toxicology, pharmarcology, network biology, computational science, environmental sciences, and other related scientific branches. It is a network-based science, like other new proposed sciences (Zhang, 2016c). For in vivo toxicology, pharmacological networks are the focus. However, for in vitro toxicology, the environment-living organism networks are stressed (Rager and Fry, 2013; Fig.1). Network toxicology aims to understand toxicological mechanism of harmful substances in the network perspective. It devotes to analyze network interactions between living organisms and toxicants that affect normal or abnormal biological functions. The scope of network toxicology covers but not limits to:

(1) theories, algorithms and software of network toxicology; (2) mechanisms and rules of flow and diffusion of toxicants in the network; (3) network analysis of toxicological networks; (4) various toxicological networks and interactions; (5) factors that influence chemical toxicity, including the dosage; the route of exposure, the species, age, sex and environment; (6) toxicity assessment, i.e., identify adverse effects of a substance (Ottoboni and Alice, 1991); (7) control of toxicants, etc.

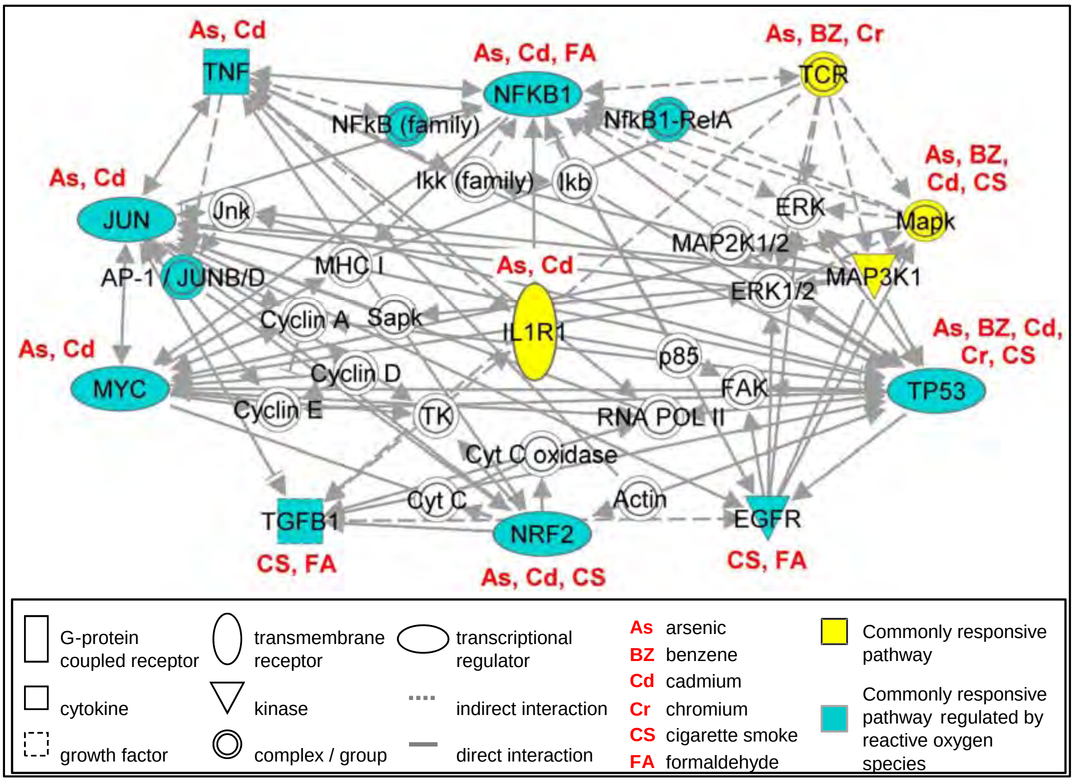

Fig. 1 The Environmental Toxicant Signalisome, a network containing pathway signaling commonly altered by environmental exposures (Rager and Fry, 2013).

3 Theoretical Fundamentals

3.1 Scientific foundation

3.1.1 Toxicology

Toxicology is an interdisplinary science of pharmacology, biology, and chemistry, which concerns with the study of the adverse effects of chemicals on living organisms (Schrager, 2006). It also studies the harmful effects of chemical, biological and physical agents in biological systems that establish the extent of damage in living organisms (Ottoboni and Alice, 1991; Vallance and Smart, 2006; Wikipedia, 2016b). Toxicology includes some branches, aquatic toxicology, ecotoxicology, entomotoxicology, environmental toxicology, occupational toxicology, forensic toxicology, and in vitro toxicology, etc. Among them, computational toxicology is a branch that develops mathematical and computer-based models to better understand and predict adverse health effects caused by chemicals, such as environmental pollutants and pharmaceuticals (Reisfeld and Mayeno, 2012).

3.1.2 Pharmacology

Pharmacology is a branch of medicine and biology on drug action where a drug exerts a biochemical and/or physiological effect on the cell, tissue, organ, or organism (Vallance and Smart, 2006; Wikipedia. 2016a). It aims to study the interactions between a living organism and chemicals that affect normal or abnormal biochemical function (Zhang, 2016f). Pharmacology has some branches as clinical pharmacology, neuropharmacology, psychopharmacology, theoretical pharmacology, behavioral pharmacology, environmental pharmacology, biochemical and molecular pharmacology, cardiovascular pharmacology, gastrointestinal pharmacology, and urogenital pharmacology, etc. Toxicology is closely related to pharmacology. In a sense, it is also a branch of pharmacology.

3.1.3 Network biology

Network Biology was first proposed by Barabasi and Otlvai in 2004. Zhang (2011b, 2012a) further defined the scope of network biology from cellular level to ecosystems and social networks. 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).

3.2 Basic ideology

Toxicology studies the harmful effects of toxicants in biological systems (biological networks and the environment-living organism networks) that establish the extent of damage in living organisms. The toxicological effects are influenced by network properties, network structure, and network dynamics, etc. Therefore, to study toxicology in the network view is a necessity, as doing by network toxicology in the future.

4 Methodology

Based on high-throughput -omics data, network database retrievals and other information, network toxicology stresses construction of toxicological networks (i.e., biological networks, the environment-living organism networks, etc.), topological analysis of toxicological networks, network flow analysis, structural optimization and optimal control of toxicological networks, etc.

4.1 Data source

There are two sources of data for research in network toxicology, 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 toxicological network and analyze toxicological mechanism, and finally validate the mechanism through experiments (Zhou et al., 2012). Second, we may use various technologies to investigate the interactions between the toxicant and network model, to construct and analyze toxicologcal network based on the generated data, and to analyze toxicologcal mechanism of the toxicant.

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, 2016g, 2016h; Zhang and Qi, 2014; SAS, 2016). Many problems in network pharmacology are expected to be addressed by using big data analytics.

4.3 Network construction and interactions prediction

A toxicologcal network is the most important basis for further toxicologcal studies. How to find interactions and construct a toxicologcal network is a prerequisite. 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, to be used in network toxicology, 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 (Zhang, 2012a, 2016g, 2016h)

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

Flow balance analysis aims to analyze network flows at 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

Within the Toxicology in the 21st Century project (Hartung, 2009; Berg, et al., 2011), the best predictive models were identified to be Deep Neural Networks, Random Forest, and Support Vector Machines, which can reach the performance of in vitro experiments (Unterthiner et al., 2015). 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 toxicological networks.

4.5 Network dynamics, evolution and control

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.

Network is 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.

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.

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