Thinking on building the network cardiovasology of Chinese medicine

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ABSTRACT: With advances in complex network theory, the thinking and methods regarding complex systems have changed revolutionarily. Network biology and network pharmacology were built by applying network-based approaches in biomedical research. The cardiovascular system may be regarded as a complex network, and cardiovascular diseases may be taken as the damage of structure and function of the cardiovascular network. Although Chinese medicine (CM) is effective in treating cardiovascular diseases, its mechanisms are still unclear. With the guidance of complex network theory, network biology and network pharmacology, network-based approaches could be used in the study of CM in preventing and treating cardiovascular diseases. A new discipline — network cardiovasology of CM was, therefore, developed. In this paper, complex network theory, network biology and network pharmacology were introduced and the correlation of “disease-syndrome-formula-herb” was illustrated from the network angle. Network biology could be used to analyze cardiovascular diseases and syndromes and network pharmacology could be used to analyze CM formulas and herbs. The “network-network-based approaches could provide a new view for elucidating the mechanisms of CM treatment.

KEYWORDS: complex network; cardiovascular diseases; Chinese medicine; network cardiovasology

Chinese medicine (CM) has been used to treat cardiovascular diseases for more than 1,000 years. It has formed its own unique theoretical system and is the result of the accumulation of abundant clinical practice. Even in the era of percutaneous coronary intervention (PCI), CM could improve the quality of life and prognosis of patients with cardiovascular disorders¹,². The reductionist methods¹ of dissecting biological systems into their constituent parts have been the main way for investigating the mechanisms of CM in preventing and treating cardiovascular diseases. It is becoming increasingly clear that these approaches have reached their limits. They can reduce complex systems to the interactions of their parts, but do not explain the holistic characteristics of complex systems, such as emergence³ which means that properties are not possessed by the individual

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components of a system but "emerge" in the assembled system. Since Watts and Strogatz\textsuperscript{2} discovered the "small-world" effects of complex networks in 1998, remarkable progress has been made in the research of complex network theory. These theories have greatly enhanced our understanding of complex networks. When network-based approaches were applied to research of biology and pharmacology, network biology and network pharmacology were the result\textsuperscript{6,7}. The establishment of the two new disciplines is an important breakthrough in the research methods of life sciences, and also provides a new method and conceptual framework for the research of CM.

Network-based approaches have attracted much attention in the research of CM\textsuperscript{8,9} and there are a number of pilot studies that underlie the mechanisms of CM in treating cardiovascular diseases by using such methods\textsuperscript{10-13}. In this article, complex network theory, network biology and network pharmacology will be simply introduced. Combined with current research models of CM, the connotation of "disease-syndrome-formula-herb" is illustrated from the network angle. A new discipline — network cardivasology of CM is proposed and its research contents are illustrated. Contrary to the reductive method, the network-based integrative approach is put forward. Network biology may be used to analyze CM syndromes corresponding with cardiovascular diseases, while network pharmacology could be used in resolving CM formulas and herbs. The "network-network" research model may provide a new view of the mechanisms of CM.

1 Complex network theory, network biology and network pharmacology

Since all complex systems have many interconnected components, complex networks may be an intuitive and practical way for modeling and simulating complex systems. Generally speaking, the cardiovascular system and CM are both considered to be complex systems, so complex networks could be a bridge connecting them. Learning from complex network theory may facilitate effective study of these systems. When the components of a complex system were regarded as nodes and the interactions among the components were regarded as edges, any complex system could be regarded as a complex network. Research on networks of earthquakes\textsuperscript{12} and networks of citation\textsuperscript{13} has revealed that different kinds of complex networks have been shown to share some common topological attributes. Such attributes of complex networks are usually described by degree distribution, small-world effects, robustness, network motifs and so on\textsuperscript{14}.

Complex network may be represented as a graph that is composed of nodes and edges. The degree of a node in a network is the number of edges the node has with other nodes, and the degree distribution\textsuperscript{15} is the probability of the distribution of these degrees over the whole network. If a node has a high degree, it is known as a "hub" which means it has many connections. Small-world effects\textsuperscript{1} mean that there is a relatively short path between any two nodes in a network. Robustness\textsuperscript{16} is a property that allows a network to maintain its functions against internal and external perturbations. Network motifs\textsuperscript{31} are small recurring sub-networks from which the networks are built.

Complex network theory has become a very powerful protocol for biological research. Barabási and Oltvai\textsuperscript{4} first proposed using network-based approaches for biological research and proposed the idea of "network biology". Researchers can, in this way, represent and analyze the essence of biology's layers as computable networks. By analyzing the topology of the biological networks, the key nodes (hubs) and motifs which perform certain tasks can be found. Thus we will gain a deeper understanding of biological systems. Hopkins\textsuperscript{2} proposed the idea of "network pharmacology". Network analysis suggests that due to the network structure and robustness of biological systems, partial inhibition of a surprisingly small number of targets can be more efficient than the complete inhibition of a single target\textsuperscript{18}. It indicates that systematic drug-design strategies should be directed against multiple targets. It has become an important
way of drug-design paradigm by using network analysis to find the optimal drug target combination.

2 Network-based approaches for illustrating the association of “disease-syndrome-formula-herb”

Cardiovascular disease is a kind of complex disorder that is associated with the effects of multiple genes in combination with lifestyle and environmental factors. It is challenging to study and treat these conditions because the specific factors that cause them have not yet been identified. It is helpful for clarifying their roles in diseases respectively by examining single gene or protein functions. However, such studies are insufficient for attaining a whole picture of the coordination among genes and proteins under different conditions. The advantage of CM in treating cardiovascular diseases is that it uses systematic and holistic approaches for understanding and treating diseases, while its disadvantage is that it is limited to using CM terms to explain its mechanisms. It is hard for physicians of other fields to understand CM, so the mechanisms of CM need to be clarified by modern scientific terminology and data model.

From the perspective of network biology, the cardiovascular system could be taken as a complex network. It is a multilayered network including genesis and development networks, differentiation and proliferation networks, repair and regeneration networks and so on. All the activities of the cardiovascular system rely on the structure and function of these networks. The risk factors continue to perturb the cardiovascular network, while the network resists perturbation. The interaction between risk factors and the cardiovascular network eventually result in disorders of many nodes and pathways. The mechanism of cardiovascular diseases is the damage to structure and function of the cardiovascular network. In CM, syndrome refers to the pathophysiological status of the body under certain conditions that are inferred by correlation of all four examinations of CM, including inspection, listening and smelling, inquiry and palpation. Syndrome reflects the integrative dynamic changes in the body. The syndromes of cardiovascular diseases could be regarded as the phenotypes of damaged cardiovascular networks. In cardiovascular diseases, the mechanism of the same disease with different syndromes may be seen as the different phenotypes caused by the damage of different cardiovascular network motifs, while the essence of the same syndrome for different diseases could be the same phenotypes caused by the damage of same cardiovascular network motifs.

Networks related to cardiovascular diseases and syndromes could be built by high-throughput comparing analysis of both normal and ill cardiovascular systems under different conditions. The hubs can be found by analyzing the degree distribution of the nodes in the network. The network motif can be found by search algorithm. The key hubs and network motifs may be used for diagnostic biomarkers for cardiovascular diseases and syndromes. These biomarkers could be used to evaluate changes in a variety of network motifs involving cardiovascular diseases and syndromes, so pertinent drugs could be selected to adjust and repair the balance of the network. Furthermore, these biomarkers may be used in developing new drugs and therapeutic evaluation.

From the perspective of network pharmacology, CM formulas for treating cardiovascular diseases could be regarded as a complex network. The effective materials of CM formulas include small molecular compounds, such as inorganic components, volatile oils, alkaloids, flavonoids and saponins, and biological macromolecules, such as peptides, proteins and polysaccharides. A CM formula is comprised of four kinds of ingredients constituting different roles: sovereign ingredients, minister ingredients, adjuvant ingredients and courier ingredients. Through the interaction of seven combinations in compatibility, the effective materials of CM formulas either cooperate or antagonize and then emerge as the holistic therapeutic effect.

The effective materials of CM formulas can be taken as nodes and the interactions among these materials taken as edges. A CM formula could, in this way, be represented by a complex network. A CM formula is composed of several herbs. A single herb could contain tens or even hundreds of components, this could therefore be taken as a minor formula represented by a minor network.

From the perspective of the network, the effective mechanisms of a CM formula in treating cardiovascular diseases are simultaneously fine tuned disordered nodes in cardiovascular networks to regain the dynamic balance of cardiovascular system. After building networks related to diseases, syndromes, formulas and herbs, with the guidance of complex network theory, the interactions among these networks can be analyzed. The therapeutic effect and toxicology of CM formulas and herbs could be evaluated by the changes in the key nodes and network motifs in the networks. The optimal dosage and compatibility of CM formulas and herbs could be determined by network analysis. Network-based approaches could bring a new perspective for the study of dose-effect and composition-activity of CM formulas and herbs in preventing and treating cardiovascular diseases. A new discipline — network cardiovasology of CM would therefore be established.

3 Approaches for building cardiovascular networks

Learning from research methods of systems biology, the research process of network cardiovasology of CM could be divided into four steps. First, the components of the studied network should be identified and relationships among the
components could be discovered by data mining, literature mining, experiment or even prediction. With all the relevant information, a primary network model could be built. Second, the components of the network or the environment should be selected to perturb the network, predict the changes in structure and function of the network based on the primary network model and observe the actual experimental results. Next, the experimental results should be compared with the prediction. According to the difference, the primary network model could be improved. Last, new experiments to perturb the network and predict changes in the network based on the improved network model could be conducted. Steps 2 and 3 would be repeated, so as to provide new experimental data to improve the network model with the aim that data predicted by the network model are consistent with the experimental model. A reasonable network model would be built to explain and predict biological activities and disorders.

There are some good cases supporting the use of network-based approaches in investigating mechanisms of CM in treating cardiovascular diseases. For example, increasing lines of evidence have demonstrated that heat-clearing herbs (HCB) are effective in treating coronary artery disease (CAD)\textsuperscript{[20]}. However, its mechanisms are still unclear. Wu et al\textsuperscript{[11]} revealed the molecular mechanism of the effective compounds of HCB by network analysis. They collected 1323 compounds of HCB. These compounds were put into Discovery Studio software for further process and cluster analysis. The result of cluster analysis was visualized by Pajek software. Then, 22 targets closely related to CAD were chosen and their three-dimensional structures were downloaded from PDB database. DS LigandFit software was used to dock the compounds of HCB with targets to screen active components. The active components of HCB and 22 targets were connected, so a drug-target network was built and visualized using Pajek software. The screened result indicated that HCB had interactions with 15 of 22 targets. Network analysis predicted that HCB could be effective in treating CAD and the possible mechanisms may be anticoagulant, anti-inflammatory, regulation of blood lipid profile and lowering of blood pressure. The anticoagulant effect of HCB may include inhibiting the activity of factors IX, VIII and XI and the aggregation of platelets. The anti-inflammatory effects of HCB may include inhibiting the activity of nitric oxide synthase, tumor necrosis factor-\(\alpha\) and cyclooxygenase-1. The hypolipidemic effects of HCB may include inhibiting the activity of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, squalene synthase and lanosterol synthase. The lowering blood pressure effect of HCB may include inhibiting the activity of angiotensin I converting enzyme 1 (ACE1), \(\beta\)-2 adrenergic receptor and SHE (Src homology 2 domain containing E) receptor. Besides that, network analysis was used to elucidate the mechanisms of herbal combination. For example, \textit{Salvia miltiorrhiza} (SM) and \textit{Panax notoginseng} (PN) in combination (SMPN) have been widely used for the treatment of CAD. SMPN is a classical herbal combination. However, why SMPN is more effective than SM or PN used alone is still unclear. Chen et al\textsuperscript{[10]} combined text mining with bioinformatics to analyze the difference among the functional networks of SM, PN and SMPN. Network analysis suggested that the therapeutic efficacy of SMPN should be the result of interaction between SM and PN in the multiple pathways and biological processes, including intracellular Ras signal transduction, apoptosis and proliferation of effector cells, and the regulation of immune effector process. In combination, SM may play a principal role and PN serves as an adjuvant to assist the effects during the treatment of CAD.

4 Perspective

CM has the characteristics of complex science and system science. That is an advantage of CM, but it also has some limits and needs to be further developed. Network-based approaches have triggered a revolution in biology. Building the network cardiovasology of CM means to bring network-based approaches to the study of CM formulas and herbs in preventing and treating cardiovascular diseases. It should link syndrome differentiation with biomedical diagnosis and focus on the application of advances of complex network theory in resolving the complexity of CM syndrome and formula. The development of network cardiovasology of CM needs multidisciplinary penetration and integration. The original CM concept of “disease-syndrome-formula-herb” would be illustrated from the angle of a complex network. All kinds of mathematical models could be used to analyze the data generated by high-throughput experiments to construct biological networks. It is closer to the essence of the reality from the perspective of the molecular network to study the effective mechanisms of CM diagnosis and treatment. It will bring new vitality to the field of CM and innovation to the treatment of cardiovascular conditions.

5 Competing interests

The authors declare that they have no competing interests.

REFERENCES

2. Shang QH, Xu H, Lu XY, Wen C, Shi DZ, Chen KJ. A multi-center randomized double-blind placebo-controlled
建立中医药网络心血管病学的思考

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摘要：随着复杂网络理论研究的进展，对于复杂系统认识和探索方法已经发生了革命性变化。基于网络方法应用在生命学科研究中，产生了网络生物学和网络药理学。心血管系统可以被看作是复杂的网络，而心脑血管疾病则可以看作是网络结构和功能的损伤所致。中医药治疗心脑血管疾病有良好的临床疗效。其相关机制至今仍未阐明。运用复杂网络理论和网络药理学指导，应用网络的方法来研究中西医防治心血管疾病，从而产生一门新的学科—中药网络心血管学。本文简要描述了复杂网络理论、网络生物学和网络药理学，从网络的角度阐释了“病-证-方-药”相关的实质。将网络生物学用于分析心血管疾病和证候，网络药理学用于分析复方和中药，这种基于“网络-网络”的研究方法可以为阐明中西医机制提供新的视角。

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