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Exploration of the mechanism of pattern-specific treatments in coronary heart disease with network pharmacology approach ☆

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ABSTRACT

Traditional Chinese medicine (TCM) pattern is a valuable classification method in the treatment of complex disease such as coronary heart disease (CHD). In accordance to TCM patterns, our ancestors created many pertinent TCM formulae, which have been used in China for thousands of years and are still playing an important role in China today. However, the biological mechanism of TCM pattern-specific formulae remains elusive. In this paper, we chose CHD patterns (Qi-stagnation induced blood-stasis syndrome, abbreviated as QSB; Qi-deficiency induced blood-stasis syndrome, abbreviated as QDB) as examples to illustrate the mechanism of their pattern-specific formulae. Using entity grammar systems (EGS) formalism, we built two pharmacologic networks of the formulae and obtained the intersection and difference networks by network comparison. Then we analyzed their common and different mechanisms for treating CHD by GO enrichment analysis. The results indicate that QDB-specific formula takes more special molecular paths to treat CHD, which contribute to more severe pathological changes in comparison with QSB. In this paper, we achieved a better understanding of the pharmacological characteristics of CHD patterns-specific formulae, which is beneficial to explore different therapies for a disease to enhance the effectiveness and pertinence of treatment.

1. Introduction

TCM pattern has been proven to be an effective classification method in patient stratification integrated with biomedical diagnostic method [1,2]. In accordance to TCM patterns, our ancestors created many pertinent TCM formulae, which have been used in China for thousands of years and are still playing an important role in China today especially in the treatment of chronic diseases [3] and miscellaneous diseases, such as coronary heart disease(CHD). According to the feature of the patterns, proper therapeutic strategies such as pertinent formulae are adopted in clinics. It is valuable to explore the mechanism of different pattern-specific formulae to enhance the effectiveness and pertinence of treatment for a disease, especially for the complex disease with personalized conditions.

Chinese medicine holds that blood-stasis syndrome is a common reason responsible for CHD in clinic of Chinese medicine due to Qi-stagnation (QSB) and Qi-deficiency (QDB). Modern TCM researches believe that QSB is the primary stage of CHD, while QDB is advanced [4]. In this work, we use QSB-specific formula (DS) and QSB-specific formula (BYHW) as the probe to explore the common and different mechanism of QSB and QDB treatments, respectively.

In the field of network pharmacology [5], network-based approaches are promptly used to interpret the mechanism of TCM at molecular network level [6–9]. Some research linked the component targets to disease targets in protein interaction network (PIN) to understand therapeutic action of TCM on patterns. For examples, Jiang et al. linked TCM targets with disease targets of cold and hot patterns based on PIN [10]. Li S proposed a map of "Phenotype network–biological network–herb network" with an attempt to uncover the network systems underlying TCM syndrome and Herb formula [11]. Their works demonstrated that the interventions in treating some diseases with TCM pattern-specific formulae could be more effective than treatments without TCM pattern classification from the perspective of network pharmacology.

Protein–protein interaction network (PIN) is typically deduced directly from systematic two-hybrid [12,13] and affinity purification–mass spectrometry data [14]. So the interaction between

Abbreviations: TCM, traditional Chinese medicine; CHD, coronary heart disease; EGS, entity grammar systems; QSB, Qi-stagnation induced blood-stasis syndrome; QDB, Qi-deficiency induced blood-stasis syndrome; DS, Dan-Shen decoction for QSB; BYHW, Bu-Yang-Huan-Wu decoction for QDB; PIN, protein–protein interaction network

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proteins in PIN means binding, which is an edge with no directions. As PIN is an undirected and unsigned network (lacking positive or negative labels) [15], it cannot be used to depict the biological delivery effect of drugs through signal transduction of network. In other words, even if we know the proteins affected by TCM components, it would still be limited to illuminate the related therapeutic effects for specific disease.

So in this paper we used the signalling transduction network from pathway interaction database (PID) as background, which is signed and directed. We not only focused on the targets hit by chemical components in a formula directly, but also disease proteins influenced by these targets through network delivery. To fulfil this task, entity grammar systems (EGS) as a system modelling theory was used, which has already been successfully used in biological network construction [16]. And based on EGS a new concept, TCM grammar system (TGS) [17] was proposed, which is a universal method applied to uncover the molecular mechanism of TCM. So by EGS we inferred the relationship between component targets and disease proteins, and then built the pharmacologic networks of DS and BYHW to uncover the mechanism of QSB and QDB, respectively. Then we compared the two networks of DS and BYHW to obtain the intersection and difference networks. By Gene Ontology (GO) enrichment analysis, we discovered the common and different pharmacological effects of two pattern-specific formulae.

2. Method

2.1. Data sources

As two empirical prescriptions in clinic, Dan-Shen decoction (DS) and Bu-Yang-Huan-Wu decoction (BYHW) have been used to treat CHD with Qi-stagnation induced blood-stasis syndrome and Qi-deficiency induced blood-stasis syndrome, respectively, for thousands of years.

DS consists of three herbs, including *Radix et Rhizoma Salviae Miltiorrhizae*, *Lignum Santali Albi*, *Fructus Amomi*. BYHW consists of six herbs, including *Flos Carthami*, *Radix Angelicae Sinensis*, *Rhizoma Chuanxiong*, *Radix Paeoniae Rubra*, *Radix Astragali*, Pheretima.

The components of nine herbs are from Traditional Chinese Medicines Database (TCMD) [18] Traditional Chinese Medicine Basic Information Database of State Administration of Traditional Chinese Medicine of People's Republic of China (http://dbshare.cintcm.com/ZhongYaoJiChu/) and A Handbook on Analysis of the Active Composition in Traditional Chinese Medicine [19]. Totally, 118 components of DS and 226 components of BYHW were collected from the database and literature (Additional file 3).

The component targeting proteins were derived from the database of STITCH1.0 (http://stitch1.embl.de/cgi/show_input_page.pl?UserId=8xW_ofqsp9Hs&sessionId=1J1OYwhxclvB). STITCH [20] is a search tool for interactions of chemicals, integrating information about interactions from metabolic pathways, crystal structures, binding experiments and drug–target relationships. When inputting the chemical name into STITCH, "Homo sapiens" species should be select from the organism drop-down box. In order to obtain the more overall results, the parameter of required confidence score was set higher than 0 and the interacting entity number was set with 500. More information about the chemicals involved in this paper, such as chemical structure information, could be obtained from STITCH or PubChem (http://www.ncbi.nlm.nih.gov/pccompound). In DS, totally 46 components with 765 targets were collected from STITCH1.0, and 132 components with 3691 targets for BYHW (Additional file 4).

Human signalling pathways are connected with each other in cells. In other words, if one node was perturbed by a drug, many other nodes in the network will be influenced as well. TCM formulae treat disease not only by acting on disease targets directly but also affecting the related proteins which can regulate the disease targets by the network signalling delivery. In this paper, we are aimed to find how chemical constitutes influence CHD proteins by network delivery in a background bionetwork.

For constructing a comprehensive network of human cells, we integrated 136 human signalling pathways retrieved from PID (pathway interaction database, http://pid.nci.nih.gov/index.shtml). Fifty-seven disease targets of CHD were collected from Sciclips (http://www.sciclips.com/).

In the network, the interactions between nodes were represented with positive direction and negative direction only. In order to deduce the effect of chemical constitutes to CHD, the end nodes of the network were marked with disease targets of CHD. The networks were visualized with Cytoscape [21].

2.2. Network model construction by entity grammar systems

Entity grammar systems is a formal grammar system that aims at complex biological system modelling [16]. Because of the scalability features of EGS, it has already been used to establish the regulating flow graph of chemical processes [22]and illustrate the mechanism of TCM [17].

An entity grammar system G is a quintuple, $G=(V_N, V_T, F, P, S)$, where, $V_N \bigcup V_T = V$. V_N is finite set of non-terminal symbols, V_T is the finite set of terminal symbols, and $V_N \bigcap V_T = \Phi$. F is the finite set of operations. The entities in the system were expressed as $E(V, F)$. P is a set of inference rules for deducing relationships between entities, S is the start entities. The details for establishing a definite entity grammar system were described in Ref. [16].

Identification of the TCM effective component combinations need the explicit relationship between components and disease. The model was established using EGS for predicting signal transduction effect and extracting sub-network. In this model, set V contains different types of nodes, set F contains the distinctive types of relationships between the adjacent nodes prepared before deduction, and set P contains the rules used for inferring the new relations of nodes. The concrete content was described as follows:

(1) $V=V_1 \bigcup V_2 \bigcup V_3 \bigcup V_4$
V_1 is the set of proteins on which the TCM chemical components act. V_2 is the set of the disease targets of CHD. V_3 and V_4 represent the sets of proteins and non-proteins in the pathway interaction network, respectively.

(2) F={link(X,Y,Z,W),left(X,Y,Z,W),right(X,Y,Z,W),road(X,Y,Z,W), tnet(X,Y,Z,W), minnet(X,Y,Z,W),in(X),out(Y).}
Link(X,Y,Z,W) represents biomolecular interactions. In link(X,Y, Z,W), $X,Y \in V_3 \cup V_4$, $Z \in$ {pos,neg},$W \in Z^*$. The value of W means the number of interactions through which X transforms into Y. In left(X,Y,Z,W), $X \in V_1, Y \notin V_2, Z \in$ {pos,neg},$W \in Z^*$. In road(X,Y, Z,W), $X \notin V_1, Y \notin V_2, Z \in$ {pos,neg},$W \in Z^*$. In right(X,Y,Z,W), $X \notin V_1, Y \in V_2, Z \in$ {pos,neg},$W \in Z^*$. In tnet(X,Y,Z,W) and minnet(X,Y,Z,W), $X \in V_1, Y \in V_2, Z \in$ {pos,neg},$W \in Z^*$. In in(X), $X \in V_1 \cap V_3$, in out(Y), $Y \in V_2 \cap V_3$.

(3) $P=P_1 \bigcup P_2 \bigcup P_3 \bigcup P_4 \bigcup P_5 \bigcup P_6 \bigcup P_7 \bigcup P_8 \bigcup P_9 \bigcup P_{10} \bigcup P_{11} \bigcup P_{12} \bigcup P_{13}$
P_1={link(A,B,C,1),not in(A),not out(B) ⇒ road(A,B,C,1)},
P_2={link(A,B,C,1),in(A),not out(B) ⇒ left(A,B,C,1)},
P_3={link(A,B,C,1),not in(A),out(B) ⇒ right(A,B,C,1)},
P_4={left(A,B,pos,D),road(B,C,pos,E),$F=E+D, F<=14$ ⇒ left(A,C,pos,F)},
P_5={left(A,B,pos,D),road(B,C,neg,E),$F=E+D, F<=14$ ⇒ left(A,C,neg,F)},
P_6={left(A,B,neg,D),road(B,C,neg,E),$F=E+D, F<=14$ ⇒ left(A,C,pos,F)},
P_7={left(A,B,neg,D),road(B,C,pos,E),$F=E+D, F<=14$ ⇒ left(A,C,neg,F)},

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