Section 4

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Pharmacology

Network Target: A novel approach to deciphering traditional Chinese medicine

China

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Summary

Having been practiced for thousands of years, traditional Chinese medicine (TCM) has accumulated a wealth of clinical experience and plenty of herbal formulae *(Fang-Ji)* that typically consist of various medicinal herbs to balance the disordered human body. It is challenging to access such clinically-effective but mechanistically-unclear medicine due to the complexity of both the chemical compositions of, and the biological systems targetted by, TCM. To tackle the puzzle, we proposed a new approach of the "network target, multi-component drug" that seeks to update the current "one target, one drug" paradigm. The core idea of the "network target" is to construct a biological network that can be used to capture complex diseases as well as TCM syndromes *(Zheng)* at the system level. Such a network is then used as the therapeutic target to which multi-component remedies such as herbal formulae are applied. Based on the network target concept, we have created a set of methods to infer the network associations between herbs, compounds, biomolecules, phenotypes, diseases and TCM syndromes. By conducting clinical and experimental verifications, we demonstrated the good performance of the methods in constructing the biological networks specific for Cold/Hot Syndrome for the first time, identifying Cold / Hot Syndrome-associated metabolism-immune biomarkers and tongue coating microbiota in a cohort of gastritis patients, connecting Cold/Hot Syndrome and related diseases in the network, and revealing new indications, active compounds, synergistic combinations and network regulation mechanisms for classic herbal formulae including *Liu-Wei-Di-Huang* and *Qing-Luo-Yin*. The results suggest that the network target-based methodology promises to be an innovative way to explore and understand TCM. With the arrival of "big data" and the era of precision medicine, the network target approach ushers in a new research field, TCM network pharmacology, which permits exciting advances in traditional medicine and will contribute to narrowing the gap between Eastern and Western medical practices.

Background and Justification

Holistic thinking has long been central to TCM. TCM has rich clinical experience in using herbal formulae that typically consist of various medicinal herbs to restore imbalances in patients suffering from different TCM syndromes. This holistic medicine meets the philosophy of curing diseases in a systematic and personalized manner. However, is difficult to be understood by current reductionist research strategies that treat both biological entities and herbal ingredients separately. By reason of lacking appropriate methods, the biological basis underlying TCM syndromes and herbal medicine is still

unclear. Meanwhile, the "one gene, one target, one drug" approach currently use widely in Western medicine is being questioned due to its reductionist thinking, trial-and-error methodology and high failure rates.

We are now in the era of big data. To update the current "one target, one drug" approach and find a way to unveil traditional Chinese medicine, we proposed a new approach of "network target, multi-component drug" to shift the research paradigm of TCM (Fig.1). The human body can be viewed as a living system with interconnected networks of molecular entities, and its regulation requires multi-component interventions. The core idea of the "network target" is to use a network to capture the complex biological systems of diseases, and then treat the disease-specific biological network as a therapeutic target. With the rapid growth of various knowledge databases, omics technologies, bioinformatics and systems biology, the network target approach is able to take advantage of big biological data, integrate computational and experimental methods, and develop a holistic way to study TCM.

The novel network target approach with systems thinking and powerful computing capacity can help make sense of traditional practices and explore the modern indications of herbal medicine, showing promise in unveiling how the herbal medicines work and providing valuable insights into current medical study. Network target methods can be widely applied in constructing biological networks for TCM syndromes and related diseases, elucidating mechanisms of actions and combinatorial rules of TCM herbal formulae, and identifying targets and actions of herbal ingredients. This novel approach also leads to a new cutting-edge research field, TCM network pharmacology (TCMNP).

Description

The network target approach attempts to map TCM syndromes and herbal formulae to the complex biological systems of the human body in a network manner. To meet this goal, we have created dozens of network analysis tools and integrated into a platform of TCM network pharmacology (Table 1). The platform is capable of predicting genes relating to diseases and target profiles of herbal compounds, and making discoveries from the network connection of disease genes and herb targets. For example, with the idea that "like attracts like", a drugCIPHER algorithm performs well in *de novo* prediction of target profiles for any herbal compounds by inferring the global network association to all available US Federal Drug Authority (FDA)-approved drugs including drug chemical similarity, drug-target interaction, and protein-protein interaction. A sibling method, CIPHER, also shows good performance in gene prediction for diseases or even de novo gene prediction for TCM phenotypes. Other methods have been developed to identify

biomarkers or active herbal ingredients, reveal drug-gene-disease associations, and screen synergistic herbal compounds by evaluating feedback, redundancy and modularity properties from target interactions. These methods make the network target approach an innovative and powerful way to explore the complexity of both TCM syndrome and herbal formulae, to reveal biomarkers, active components, and mechanisms of action of TCM. Overall, two facets of the network target approach are, making full use of current big data to accelerate TCM research; and the outputs can improve the efficiency of biomarker and drug discovery
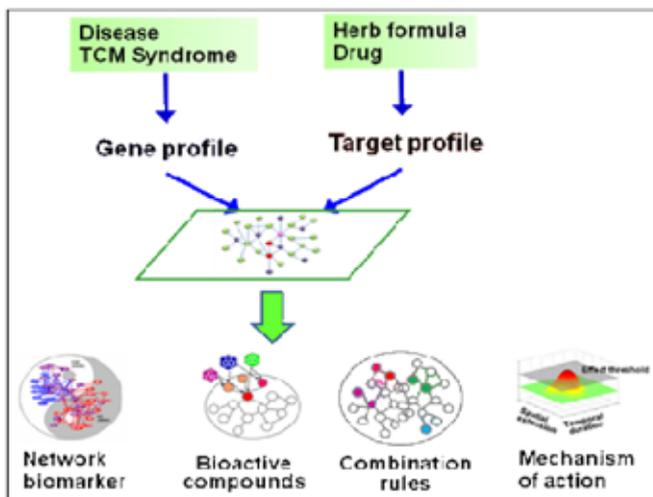

Figure. 1: Schematic diagram of the network target approach and its applications on traditional Chinese medicine.

Concepts and methods	Description	Year	Reference
Network target concepts	Proposed the relationship between TCM Syndrome and biological networks	1999	Li. The First Academic Annual Meeting of the China Association for Science and Technology. 1999
	Proposed the network-based TCM research framework	2007	Li. J Chin Integrat Med 2007, 5: 489-493.
	Proposed the "Network biomarker" concept	2007	Li. JTCM 2009,50:773-776.
	Proposed the "Herb network-Biological network-Phenotype network"	2009	Li. Curr Bioinformat 2009, 4:188-196
	Proposed the "Network target" concept	2011	Li. China J Chin Mater Med 2011, 36:2017-2020; Li et al. BMC Syst Biol 2011, 5(S1): S10
	Proposed the TCM network pharmacology	2011	Li. China J Chin Mater Med 2011, 36:2017-2020; Li & Zhang. CJNM 2013, 11:110-120
	Proposed the "Network target model"	2015	Li. Science 2015;350(6262):S72-S74
LMMA	Disease-specific biological network construction	2006	Li et al. Bioinformatics 2006,22:2143-2150
CIPHER	Network-based prediction for disease genes	2008	Wu et al. Mol Syst Biol 2008,4:189
drugCIPHER	Network-based prediction for drug targets	2010	Zhao & Li. PLoS ONE 2010,5:e11764
DMIM	Herb network construction and co-module analysis	2010	Li et al. BMC Bioinformatics 2010,11(S11): S6
NADA	Network-based assessment for drug action	2010	Li et al. Chin Sci Bull 2010,55: 2974-2980
Drug combination model	A formal model to analyze drug combinations	2010	Yan et al. BMC Syst Biol 2010, 4: 50
CSPN	Disease-specific pathway network construction	2010	Huang & Li. BMC Bioinformatics 2010,11(S1): S32
ClustEx	Disease-specific responsive gene module identification	2010	Gu et al. BMC Syst Biol 2010,4:47
NIMS	Network-based identification of synergistic drug combinations	2011	Li et al. BMC Syst Biol 2011, 5(S1): S10
CIPHER-HIT	Modularity-based disease gene and subtype prediction	2011	Yao et al. BMC Syst Biol 2011, 5:79
comCIPHER	Drug-gene-disease co-module analysis	2012	Zhao & Li. Bioinformatics 2012, 28: 955-961
DGPsubnet	Drug-gene-disease coherent subnetwork analysis	2014	Wang et al. CPT Pharmacometrics Syst Pharmacol 2014;3:e146
GIFT	Global inference of drug substructure-target domain interaction	2015	Zu et al. Bioinformatics 2015;31:2523-9
SidePro	Network-based inferring proteins related to drug side effects	2015	Li et al. Quantitative Biology 2015

Table 1: Network target concepts and method established in author's laboratory.

Results

As summarized in Table 2, the network target approach can make sense of TCM syndromes and explore the modern indications of herbal medicine. For example, the traditional use of herbal formulae is to treat TCM syndromes, e.g. the Cold/Hot Syndrome, a pair of Yin-Yang imbalance conditions. Correspondingly, most medicinal herbs can be categorized into Cold, Cool, Warm and Hot properties for tailored treatment of individual syndromes. Taking Cold and Hot as examples, as illustrated in Fig. 2, a biological network for Cold/Hot Syndrome is first constructed. With this network in hand and subsequently conducting measurements including microarray and deep sequencing, we identified the Cold/Hot related metabolism-immune imbalance patterns, candidate network biomarkers, as well as two groups of tongue-coating microbes in a cohort of chronic gastritis patients. We further found that hub genes in Hot network may get involved in the process from inflammation to cancer. A case from one of our cooperative works is, IL1β/IRAK1 signaling can promote gankyrin expression in inflammation-enhanced hepatocarcinogenesis (Su et al., 2015). These results indicate that the TCM Cold/Hot concept may have an imbalanced network as its molecular basis, providing a new way to subtype complex diseases.

For the treatment, we found that some herbs with Cold or Hot properties can differentially restore the Hot or Cold network imbalance. For instance, a Hot-Cooling formula, *Qing-Luo-Yin*, can synergistically suppress the cytokine and VEGF pathways to clear away Hot in the treatment of inflammation and angiogenic disorders. A Yin-nourishing formula, *Liu-Wei-Di-Huang*, can restore the metabolism-immune pathways by groups of bioactive ingredients. We also predicted modern indications of this formula by its target network. Several anti-angiogenesis, anti-cancer, anti-tumorigenesis compounds or synergistic combinations were subsequently identified. The results suggest that the network target approach could help reveal the "component–target/biomarker–indication" relations of herb formulae and accelerate TCM-based precision medicine.

	Subject investigated	Network target contents	Year	Reference
TCM Syndrome	Cold Syndrome / Hot Syndrome	Network construction, topological temperature measure	2007	Li et al. IET Syst Biol 2007, 1: 51-60.
	Gastritis patients with Cold / Hot Syndrome	Imbalance of metabolism-immune, network biomarker	2013	Li et al. Sci Rep 2013;3:1543
	Tongue coating of Cold / Hot Syndrome patients	Cold / Hot microbe network	2012	Jiang et al. Sci Rep 2012;2:936
Herb medicine	Qing-Luo-Yin (Hot-Cooling formula) Wen-Luo-Yin (Cold-Warming formula)	Network relationship between Herbal formula and Cold / Hot Syndrome	2007	Li et al. IET Syst Biol 2007, 1: 51-60.
	3865 herbal formulae including Liu-Wei-Di-Huang	Herb network construction and herb-target-diseases co-module	2010	Li et al. BMC Bioinformatics 2010,11(S11): S6
	61 herbs or compounds including Qing-Luo-Yin ingredients	Synergistic combination screening	2011	Li et al. BMC Syst Biol 2011, 5(S1): S10
	Qing-Luo-Yin	Jun-Chen-Zuo-Shi network regulation	2013	Zhang et al. ECAM 2013:456747
	Man-Jing-Zi (*Vitex rotundifolia*), a Qing-Luo-Yin compatible herb	New activity of anti-tumor angiogenesis and target network	2013	Zhang et al. ECAM 2013: 278405
	Liu-Wei-Di-Huang formula	Network regulation mechanism, active compounds, modern indications	2014	Liang et al. Mol BioSyst 2014,10:1014-22
	Ge-Gen-Qin-Lian decoction	Network effects on type 2 diabetes	2014	Li et al. ECAM 2014:495840
	Tetramethylpyrazine from *Ligusticum wallichii Franchat* (Chuan-Xiong)	Activity of ameliorating methotrexate-induced oxidative organ injury	2015	Zhang et al. J Ethnopharmacol 2015
	Wu-Tou decoction	Network effects on rheumatoid arthritis	2015	Zhang et al. Sci Rep 2015; 5: 9463
	871 TCM doctor's clinical prescriptions including Qing-Luo-Yin	Network effects on rheumatoid arthritis	2015	Li et al. ECAM 2015:451319

Table 2: Applications of the network target approach from the author's laboratory.
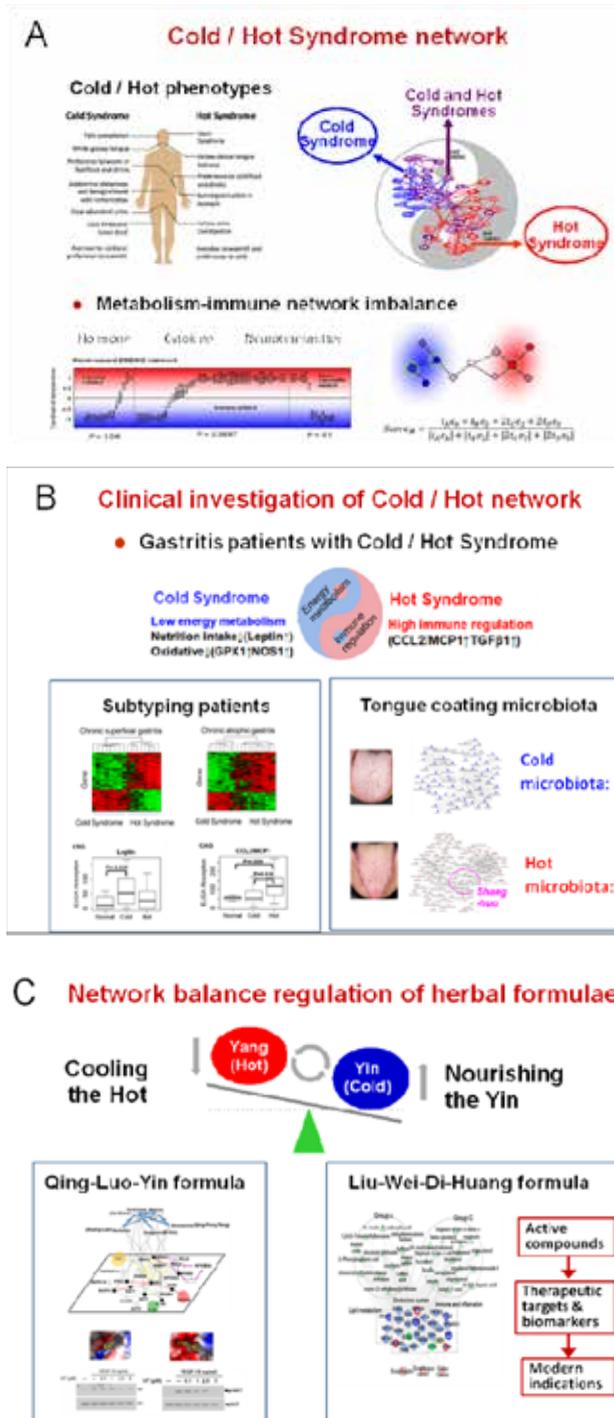
Figure 2: Network-based case studies on TCM Syndromes and herbal formulae.

Partnerships

We collaborated with hospitals to validate the network biomarkers of TCM syndromes as candidates in subtyping diseases such as inflammation disorders and cancer abd with drug companies by patent transformation to discover TCM-derived natural products and elucidate their mechanisms of action.

Impact

The author, Shao Li won the National Outstanding Young Scientist Award, China, in 2012 for his contributions to the field of "new technology and new methodology in traditional Chinese medicine". His works have been positively evaluated by over 2000 papers by Chinese and international researchers, including publications in journals such as Nature, Cell and Science Translational Medicine.

He has also been considered as a pioneer in TCM systems biology and network pharmacology by some publications (e.g. Indian Journal of Traditional Knowledge).

He is Chairman of the Specialty Committee of network pharmacology, World Federation of Chinese Medicine Societies (2015), vice chair of the Specialty Committee of network pharmacology, Chinese Pharmacological Society (2014), leading guest editor of the first special issue on "Network Pharmacology in Traditional Chinese Medicine" in Evidence-Based Complementary and Alternative Medicine (2012-2013), and the leading scientist of the first book entitled "Network Pharmacology: A New Way to the Modernization of Traditional Chinese Medicine" published by China Science and Technology Press (2014).

He has delivered keynote speeches and invited talks at more than 20 international conferences. His works made the headlines in The Wall Street Journal with the title of "New data on ancient remedies" on 4 November 2014. This news was selected as one of "The World top 10 news of traditional Chinese Medicine 2014" by the World Federation of Chinese Medicine Societies.

Replicability

The author and his colleagues have had seven patents awarded, while another five patent applications are currently under review. In addition, copyright has been granted on four pieces of computer software developed by the group.

Lessons Learned

The main obstacle faced is the complexity both in TCM diagnosis (syndrome) and treatment (herbal medicine). TCM syndrome focuses on the observation of the human body at the macro-level. Herbal medicine always consists of many herbs with a large number of ingredients. Currently, the understanding of the biological basis of TCM diagnosis and treatment is far from complete. To tackle this complexity, the network target approach uses the biological network, a representation of the complex biological systems of patients, as a common basis that enables information exchange between traditional and modern medicines. Then, the network association analysis can be created to make full use of current big data to reveal the biological basis underlying TCM syndromes and herbal formulae, which can also narrow the gap between traditional and modern knowledge and practices.

The network target-based TCM network pharmacology is essentially an interdisciplinary frontier in both TCM and modern medical research fields. The development of this innovation is dependent upon a cooperative and multidisciplinary team. Now the approach is being accepted by a growing number of people from different disciplines, especially TCM practitioners, pharmacologists, clinical doctors, and researchers from related fields.

Future Plans

For the network target methods, we will continue to improve the prediction accuracy of computational algorithms by integrating multilayer omics data, more comprehensive databases, and network-level experiments to make the discovery of TCM more efficient.

For the application, we will conduct more clinical investigations to find new biomarkers that combine TCM phenotypes and Cold / Hot network molecules to subtype patients, and make the pattern of "component–target/biomarker–indication" much clearer to improve the modern use of herbal formulae.

For the collaboration of the novel approach, we will work closely together with TCM and Western medicine doctors, as well as biomedical, pharmacological and computational scientists to make the discovery of TCM more productive and more prosperous.

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