Future perspectives of personalized medicine in traditional Chinese medicine: A systems biology approach

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Summary

Deconstruction of molecular pathways and advances in enabling technology platforms have opened new horizons for disease management, exploring therapeutic solutions to each individual patient beyond the one-size fits all practice. Application of personalized medicine paradigms aims to achieve the right diagnosis and right treatment for the right patient at the right time at the right cost. With the potential to transform medical practice across global communities, personalized medicine is emerging as the flagship of modern medicine. In recent years, the health care paradigm has shifted from a focus on diseases to a major hot of personalized traditional Chinese medicine (TCM) with holistic approach. TCM focuses on health maintenance, emphasizes on enhancing the body's resistance to diseases and especially shows great advantages in early intervention, personalized and combination therapies, etc. Systems biology, a new science of the 21st century, becomes practically available and resembles TCM in many aspects such as study method and design, and is current key component technologies that serves as the major driving force for translation of the personalized medicine revolution of TCM principles into practice, will advance personalized therapy principles into healthcare management tools for individuals and
populations. Such system approach concepts are transforming principles of TCM to modern therapeutic approaches, enable a predictive and preventive medicine and will lead to personalized medicine. To realise the full potential of personalized TCM, we describe the current status of principles and practice of TCM integrated with systems biology platform. Some characteristic examples are presented to highlight the application of this platform to personalized TCM research and development as well as some of the necessary milestones for moving TCM into mainstream health care.

**Keywords:** Personalized medicine, Traditional Chinese medicine, Systems biology, Omics, Biomarkers, Treatment of differential syndrome, Individualized medicine

**Introduction**

One important special feature of biology is its diversity, its variation. That is why personalized medicine is significant. Personalized medicine refers to the right treatment for the right individual at the right time in the health-care world and has the potential to diminish the incidence of drug adverse reactions, eliminate invalid therapy, improve the efficacy of treatments, ultimately, achieve optimal health outcomes. During recent years, most people seem to agree that personalized medicine is the trend of the future. The personalized medicine market is estimated at about $232 billion, and is projected to grow 11% annually, expected to nearly double in size by 2015 to more than $450 billion, according to a recent Price Waterhouse Coopers report. The health-care paradigm has shifted from a focus on diseases to a holistic approach to health care. Owing to the accomplishment of the Human Genome Project (HGP), personalized medicine is looming in the horizon and modern medicine moves towards a new individualized health-care model with biological–psychological–social–environmental–spiritual characteristics that reflect the thinking of patient-centred care. Fortunately, the personalized traditional Chinese medicine (TCM) affords new significance of personalized health care and advances the practice research.

The area of integrating TCM with systems biology approach has become a major hot topic of personalized medicine research. TCM, a key approach to the practice of personalized medicine in the future, has been used in Asian countries for thousands of years, based on the individual's physiology and the holistic characteristics. Recent advances in systems biology technology have enabled the discovery of biomarkers, provided the basis for the development of new targeted drugs, potentially offered ‘the right therapy for the right patient’. Such technologies, for example, genomics, proteomics and metabolomics, have been able to identify biomarkers of a particular disease within the set of genes, proteins and metabolites of a given organism. TCM has developed its own coherent theories with regard to diagnosis and treatment of disease and accrued a myriad of valuable clinical observations, some of which have provided the basis for successful personalized medicines. TCM pays attention to the whole and individual parts of the body, the general and specific character, uses a unique holistic approach to cure human diseases through establishment of equilibrium in the human life, body, mind, intellect and soul, so satisfactory treatment results could be achieved. As one of the most important parts of medicine, TCM has been accepted
by patients as superior value in the treatment of multiple organ system disorders, chronic diseases and metabolic syndromes, and should play a key role in the formation of personalized medicine.\textsuperscript{12}

Systems biology, a new science of the 21st century, becomes practically available and resembles TCM in many aspects such as study method and design.\textsuperscript{13} Combining the systems biology with in-depth investigations of TCM mechanisms will enable a revolution in our understanding of disease pathology and will advance personalized medicine.\textsuperscript{14} Systems biology studies living systems from whole systems instead of isolated parts, opening up a novel opportunity to reinvestigate TCM.\textsuperscript{15} As an important part of life science, the notions of the ‘whole or system’ of TCM rather than the isolated parts are important concepts, which fit well to the systems biology theory. Adoption of systems biology approach would do much to help explore the scientific connotation of treatment of differential syndrome (TDS, diagnosis and treatment based on over-all symptoms and signs) and revolutionize personalized TCM.\textsuperscript{13, 16, 17, 18} As World Health Organization proposed ‘Health for All’, we should be able to promote the use of traditional medicine. There are new signs that the pursuit of both personalized TCM and systems biology will be a priority for people and pave the way towards personalized health care.\textsuperscript{19, 20} Together with new technologies, such systems approaches are transforming current therapeutic approaches to enable a predictive and preventive medicine that will lead to personalized medicine.\textsuperscript{21, 22, 23, 24} In order to realise the potential role of personalized medicine, our special article describes the increasing importance of principles and practice of TCM integrated with the systems biology platform, and discusses some of the ongoing challenges for integrating personalized medicine into mainstream health care.

\textbf{Basic principles of personalized TCM}

TCM has been used for thousands of years to treat diseases and has many beneficial effects for disease control.\textsuperscript{25, 26} The focus of TCM science is on the patient rather than the disease. The key theories of TCM comprise the yin–yang, the five elements, Qi and Blood, Zang-fu organ and four natures. Consistent with the homeostasis, the holistic adjustment to pursue system balance of the yin and yang is the principle of TCM syndrome. In a mainstream therapeutic manner, system balance has been practiced for centuries in TCM and has attracted worldwide interest. Based on thinking of system medicine, making system balance is the aim for disease treatment; combination therapy is the challenging method for performing the purpose in modern medicine.\textsuperscript{27} TCM views the human body as a dynamic energy system with yin–yang balance, and disease as an unbalanced state. Combination therapy is the main strategy of TCM to adjust a disease state to system balance of a dynamic state. The biological effects of the four natures of TCM, including cold, hot, warm and cool, have an effect on the central nervous system, endocrine system, on the activity of sympathetic nerves, basal metabolic rate, the function of organs and tissues and secretion of cytokines out of the body.\textsuperscript{28} Four natures of TCM will be a multi-factor and target research, connecting Chinese medicine theory. Water, earth, metal, wood and fire are the five elements of the material world. The internal Zang-fu organ systems play an important
role in the yin and yang balance. The clinical diagnosis and treatment in TCM are mainly based on the above theories. Based on the frontier science and key approaches, establishing the direction for personalized medicine with TCM properties was essential for the health of mankind.

**Personalized characteristics of TDS: translating the promise into practice**

Personalized treatment of TCM was first recorded in *The Yellow Emperor's Classic of Internal Medicine*, which is a classical Chinese medicine book. For improving health, TCM applies multiple natural therapeutic methods, such as acupuncture, moxibustion and herbal medicine. All TCM therapeutic approaches come from the effective TDS. Holistic, space–time dynamics and individual variance are three personalized characteristics of TCM syndrome. The external information should appear something of intrinsic disease. From these points of view, syndrome should play an important role in impacting on disease pathogenesis that directly influences the therapeutic effect. Modern medicine aims to explore the specificity of morbidity, while TCM mainly explores the reality of the morbidity by checking the external appearance (that is TDS). Disease treatment based on the syndrome differentiation is to determine the appropriate treatment. TCM treatment of disease does not primarily focus on ‘the similarities and differences of disease’, but rather on the difference of syndrome through TDS and better understanding of the disease. TDS is a typical ‘individualized treatment’ method of TCM diagnosis and treatment process, and focusses on discrimination of the personality characteristics. Individualized treatment highlights personalized features with the specific clinical and appropriate diagnosis treatment. TDS in the treatment process not only pays attention to common features of the human body, but also focusses on the analysis of personality characteristics. Therefore, the individualized treatment is closely related to the TDS process.

**Combinatorial formulae for personalized therapy**

As a unique medical system, TCM advocates combinatory therapeutic strategies by prescriptions called ‘formulae’. Typically, formulae are comprised of several types of crude herbs or minerals, in which one represents the key component, and others serve as adjuvant ones to assist the effects or facilitate the delivery of the key component. It is believed that formulae can hit multiple targets and produce a synergistic therapeutic effect. The pharmaceutical industry has shifted from the search of disease treatments with the ‘one disease-one target-one drug’ and the ‘one-drug-fits-all’ concepts to the pursuit of combination therapy that comprise more than one active ingredient. Combination medicine with multi-effect-pathway targets have better efficacy than a single drug alone, and can change the current predicament state in the therapy. Modern medicine has acknowledged that combination application of TCM can achieve a synergistic interaction capable of yielding a sufficient effect at low doses that has increased significantly in recent years. On the basis of characteristics of patients and guided by the TDS, formulae contain a combination of different herbal or mineral medicine to improve efficacy. TDS is the basis for Chinese medicine, and formulae compatibility is the core of prescriptions; they both are complementary and
mutually dependent. Formulae compatibility is the goal to achieve overall balance and regulation of the holistic features. Modern pharmacology from the multi-target effects mainly refers to a drug molecule that can occur on multiple metabolic aspects of the key role of efficacy, but it ignores the overall balance adjustment. Fortunately, the systems biology approach may contribute to explain individual differences in response to treatment, as well as adverse drug response differences.

**TDS corresponding formulae**

TDS corresponding formulae (TCF), a unique dialectical model, refers to the collection, analysis, comparison and identification of clinical data, to find out the relationship between the syndrome and corresponding prescription and understand the effect and mechanism of the prescription. Syndromes and prescriptions are two important parts of TCM. Syndrome is a certain stage of a comprehensive response of patients with body condition, whereas prescription is the primary means of TCM treatment. Seizing the corresponding relationship between the syndrome and prescription and clarifying the mechanism of prescription has great clinical value for the patient. As one of the key principles of TCM prescription, each prescription has its specific syndrome and treatment. As an important part of TDS, TCF is the embodiment of the principles of TDS diagnosis and treatment. The combination of syndrome and formulae will set up a bridge to explore the intrinsic link between clinical and efficacy.

**Physique characteristics**

Physique characteristics are often the best embodiment of TDS, and play an important role in certain diseases. Human physique is considered as a special state of an individual with relative stability in function, structure and metabolism, formed during growth, development and ageing, undering effects of the environment and on the basis of individual heredity. Physique theory of TCM is based on various human physical characteristics, physical type of physiological and pathological characteristics, and thus the response and development of disease status, to guide disease prevention, treatment and health rehabilitation. It emphasizes regulating the overall function of the human body based on the physical characteristics and more attention is given to differences between individuals, and at the same time, due to individual differences of physique in the dose response and tolerability, which should be based on physical differences, are adopting different methods and principle of treatment and dosage. The physical characteristics are the innate and relatively stable endowments and form the basis of morphological, physiological and psychological status comprehensively, with the natural and social environment suited to human personality characteristics. Some think that attention in the 21st century will develop in both macroscopic and microscopic directions. The former is about how humans go into the universe and rule the universe and the latter includes how humans know themselves and reshape themselves. It could be seen that humans will gradually focus on themselves in the future. This trend is getting ever clear from developments in biology, genetics and immunology; certainly, it will be the favourite of the times.
A systems biology technology platform for practice of personalized medicine

Systems biology has developed from a technology-driven enterprise to a new strategic tool in life sciences, particularly for innovative TCM development. A systems biology approach has been explored to find subtypes of rheumatoid arthritis patients enabling a development towards more personalized medicine. The identified biomarkers have the potential to bring increased accuracy in disease diagnosis and monitoring. Combining systems biology with in-depth investigations of personalized TCM will enable a revolution in our understanding of disease and will advance personalized medicine. A prerequisite for deriving the benefits of such a systems approach is a well-validated bioanalytical platform, especially a genomics, proteomics and metabolomics platform.

Genomics platform

Genomics, which is the use of information from genomes and their derivatives to guide medical decision making, is a key component of personalized medicine, which uses genetic information to tailor strategies for each patient. Researchers believe that genomics has the potential to revolutionize the practice of personalized medicine, and improve the diagnosis, prevention and treatment of disease, and reduce adverse drug reactions. With the completion of the HGP in May 2006, genetic testing for every person is rapidly becoming a reality. Personalized medicine can take advantage of the genetic framework to provide the health-care system with useful tools that can optimize the effectiveness of treatment. The combined genome-wide expression analysis with methods of systems biology can identify the functional gene networks for the sets of clinical symptoms that comprise the major information for pattern classification related to hot and cold patterns in TCM. Wang et al. studied the patients with cold syndrome using gene chip method and found that gene expression spectrum of the patients with cold syndrome was significantly different from that of normal controls. Among the 59 differently expressed genes, most of them were related with metabolism such as energy metabolism or protein metabolism, etc., indicating that the metabolic network may be the major component in differentiation of cold syndrome. The new discoveries of genomics provide meaningful insights that will increase doctors’ ability to personalize treatment in a not-too-distant future.

Proteomics platform

Proteomics have provided a means for molecular profiling that allows personalized therapy. It is the information of a whole proteome, which refers to the entire complement of proteins including the modulation made to a particular set of proteins within an organism or system. The ability to detect expressed proteins has enormous potential for early diagnostics and intervention at curable stages of disease. The analysis of this extended range of biomarkers will prove critical for the development and implementation of personalized medicine. In addition, the components of Chinese herbal medicine, that is, either a single herb or formulae, are complex chemical
systems, and each component binds to its own target receptor. Individual variance is the foundation of TCM syndrome science. All these characteristics of TCM syndromes might be related to various proteins with differences in contents, functions and structures. With the help of functional proteomics, functions, structures and interactions of proteins expressed by a cell, a tissue or body fluid in different syndromes, and the changes of proteins before and after treatment with single herb or a formulae could be analysed. Therefore, the characteristic of proteomics is analysing numerous proteins; simultaneously, proteomics could provide a platform for research of the essence of TCM syndromes.

**Metabolomics platform**

Metabolomics is a novel area that promises to contribute to the identification of personal metabolic features that can predict response to therapies. It incorporates the most advanced approaches to provide the ideal technology platform for the discovery of biomarker patterns associated with healthy and diseased states, for use in individualized health-monitoring designs. From a clinical standpoint, the metabolomics has two major potential applications. The first is the early diagnosis and characterisation of disease phenotypes. The second application concerns the identification of individual characteristics able to predict drug effectiveness or toxicity. Metabolomics, based on the systematic complement of metabolites in a biological sample, is the best to fit the holistic concept of multi-target systems of TCM. Many claims have been attached to the ‘promise’ of personalized medicine. One example of this approach is that Chen et al. found that the metabolic network of animal model with kidney-yang deficiency was significantly different from that of normal controls using the metabolomics analyses. Moreover, Chinese herbs with the property of warming kidney-yang could normalize the metabolic chart of the animals with kidney-yang deficiency, showing that changes of metabolic network could be repaired with proper herbal treatment. The future goals for metabolomics are the validation of existing biomarkers, in terms of mechanism and translation to man, together with a focus on characterising the individual health care. Metabolomics will pave the way for a better understanding of the mechanisms of disease, ultimately advance the personalized TCM and lay the groundwork for the application of personalized medicine in the 21st century. The rapid advances in systems biology are making these dreams come true.

**Conclusion and future perspective**

With the recent understanding of systems biology, the era of ‘one size fits all’ therapy concepts has passed and a new era of personalized medicine has started. Several ‘omics’ technologies are being increasingly used for this purpose and personalized medicine efforts are in progress in major therapeutic areas. The individualisation of medicine and health care appears to be following a general societal trend. Hence, the main rationale of personalized medicine could focus on treating disease by relying on relevant structure and state of patient's whole molecular network, thus implying right therapy for the patient at the right dose and time. The
future of personalized TCM should therefore rely on the methods of systems biology to develop the efficient and effective diagnostic, prognostic and predictive biomarkers. Personalized medicine introduces the promise to use biomarkers that signal the risk of disease or its presence before clinical signs and symptoms appear. This information underlies a new health-care strategy focussed on prevention and early intervention, rather than reaction to advanced stages of disease. Systems biology approaches identifying molecular drivers and biomarkers will facilitate the practice of personalized TCM. It is conceivable that the application of technologies developed in proteomic, genomic and metabolomic platforms will eventually lead to the reconciliation and integration of TCM with contemporary medicine. TCM is fundamentally a highly personalized medicine; perhaps it is time to embrace the arrival of TCM-OMICS era. We are at the dawn of a new era of personalized medicine.

Competing financial interests

The authors declare no competing financial interests.

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