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Review

Application of proteomics to determine the mechanism of action of traditional Chinese medicine remedies

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ABSTRACT

Ethnopharmacological relevance: The rationale for using traditional Chinese medicine (TCM) is based on the experience that has been gained from its wide use over thousands of years. However, the mechanisms of action of many TCM are still unclear. Proteomics, which mainly characterizes protein functions, protein–protein interactions, and protein modification in tissues or animals, can be used to investigate signaling pathway perturbations in cells or the whole body. Proteomics has improved the discovery process of effective TCM compounds, and has helped to elucidate their possible mechanisms of action. Therefore, a systematic review of the application of proteomics on TCM research is of great importance and necessity. This review strives to describe the literature on the application of proteomics to elucidate the mechanism of action of TCM on various diseases, and provide the essential discussion on the further utilization of proteomics data to accelerate TCM research.

Materials and methods: Literature survey was performed via electronic search on Pubmed with keywords 'Proteomics' and 'Traditional Chinese Medicine'. The papers written in English were acquired and analyzed in this review.

Results: This review mainly summarizes the application of proteomics to investigate TCM remedies for neuronal disease, cancer, cardiovascular disease, diabetes, and immunology-related disease.

Conclusions: Researchers have applied proteomics to study the mechanism of action of TCM and made substantial progresses. Further studies are required to determine the protein targets of the active compounds, analyze the mechanism of actions in patients, compare the clinical effects with western medicine.

Contents

Abbreviations: TCM, traditional Chinese medicine; 2DE, 2-dimensional electrophoresis; LC–MS/MS, liquid chromatography coupled with tandem mass spectrometry; SILAC, stable isotope labeling by amino acids in cell culture

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1. Introduction

Traditional Chinese medicine (TCM) has been used and developed for more than several thousand years in China, but its clinical application is limited because the pharmacology of most remedies is unclear. Conventional medicine does not accept the rationale of TCM because it is based on original prescription, which is incompatible with modern pharmacology (Bauer and Chan, 2010). For TCM to be modernized, it is critical to use modern technology to determine the mechanism of action of TCM remedies. One way to develop TCM is to separate, extract, and identify the effective compounds. A description from a 1900 year-old book led researchers to identify artemisinin as the effective constituent of the malaria treatment with the acrial part of *Artemisia annua* L. (青蒿). (Tu, 2011). Chen's group studied a formula that contained multiple constituents, which was used to treat leukemia. They discovered that the effective component of the TCM decoction was arsenic trioxide (As_2O_3). Their later study determined that the mechanisms of action of As_2O_3 mainly involved the induction of the apoptotic pathway. Consequently, As_2O_3 is now widely used to treat acute promyelocyte leukemia (Zhu et al., 2002; Wang et al., 2008). Translational medicine is the conventional strategy that is used to overcome the difficulty of investigating the efficacy of TCM remedies, which are based on the decoction of multiple herbs. PHY906 consists of 4 herbs and is derived from the formulation of Huang Qin Tang that was initially described in Chinese canonical medicine approximately 1800 years ago. Lam et al. (2010) using a gastrointestinal cancer model to study its efficacy to reduce chemotherapeutic toxicity, found that, in mice, PHY906 restored normal intestinal structure, increased proliferating progenitor cells, blocked inflammatory cell migration to the gut, and inhibited inflammatory factors (Lam et al., 2010). The only 2 herbal drugs that are approved by the Food and Drug Administration are Veregen, a polyphenon from tea extract that is used for genital warts, and Fulyzaq, which contains extracts from the resin of *Croton lechleri* Muell. Arg. (秘鲁巴豆) that are used for diarrhea. The main obstacle preventing more TCM remedies from meeting the stringent requirements of conventional medicine is efficacy and economic utilization of modern pharmacological tools to investigate their mechanism of action.

Systems biology, which consists of genomics, epigenomics, proteomics, and metabolomics, seeks to describe the complex interactions between biological system components and to predict biological system behavior (Oberg et al., 2011). Genomics is a discipline in genetics that applies recombinant DNA, DNA sequencing, and bioinformatics to sequence, assemble, and analyze the function and structure of genomes (Freyhult et al., 2008). Epigenetic regulation involves heritable alteration of gene expression by modifying chromatin structure without changing primary DNA sequences (Boonsanay et al., 2012). Metabolomics is one of the key approaches of systems biology that consists of studying biochemical networks having a set of metabolites, enzymes, reactions and their interactions (Tagore et al., 2014). Proteomics has emerged as a powerful tool to investigate physiological conditions, mutations, changes in response to external factors, and adaptation. Due to rapid developments in proteomic analytical tools such as 1-dimensional polyacrylamide gel electrophoresis and 2-dimensional electrophoresis (2-DE) coupled with tandem mass spectrometry-based isobaric tags (one of the most effective methods for analyzing the complete proteome of cells, organs, and tissues), proteomics now allows the systematic quantitative and qualitative mapping of the whole proteome during disease (Hussain and Huygens, 2012). Proteomics can identify altered proteins as potential drug targets, and the global analysis of protein alterations can help understand a drug's mechanism of action. Proteomics can also identify post-translational protein modifications such as phosphorylation, glycosylation, acetylation, and proteolysis, and sequence variants such as mutants, alternatively spliced isoforms, and amino acid polymorphisms (Mann and Jensen, 2003; Zhang and Ge, 2011). Post-translational modification, which can occur after disease progression or drug treatment, substantially affects protein function and protein-protein interactions *in vitro* and *in vivo*. By analyzing these protein changes in tissue and cultured cells before and after TCM treatment, proteomics is a powerful tool to study the mechanism of action of TCM remedies (Cho, 2007). Published papers related to the topic of the present review were searched in Pubmed using the key words 'proteomics' and 'traditional Chinese medicine'. A total of 148 papers, including 28 reviews, were found (up to 10 February 2014). 53 papers written in Chinese character were not involved in this review. Among 120 original research papers, some were focused on studying syndromes of TCM and clinical application of TCM, and some were focused on application of Chinese medicine resources. Those papers which described the pharmacological effects, mechanism of action, and targeted proteins in specific diseases were selected to be discussed here.

This review summarizes the recent application of proteomics in TCM research and development, focusing on how proteomics can determine the mechanism of action of TCM remedies for various diseases including neurological disease, cancer, diabetes and the immunological response (Tables 1 and 2). Our own findings on the application of proteomics to determine the anticancer mechanisms of natural compounds are also discussed. Finally, the review

Table 1
Summary of the application of proteomics to determine the mechanism of action of TCM remedies for various diseases.

Disease name	TCM or compound	Targets or signaling pathways	References
Alzheimer's disease	Hupreazine A	p53	Tao et al. (2013)
Alzheimer's disease	*Gastrodia elata* Bl. (天麻)	Nxn, Dbnl, Mobkl3, Mki67 and Bax; HSP 70/90 and FKBP3/4	Manavalan et al. (2012)
Epileptic seizures	*Uncaria rhynchophylla* (Miq.) Jacks. (钩藤)	MIF and cyclophilinA	Lo et al. (2010)
Cerebral artery occlusion	Baicalin	Energy metabolism	Zhang et al. (2009)
Neurodegenerative diseases	*Ginkgo biloba* L. (银杏) extracts	PPAP subunit B and CRMP2	Koh (2011)
Cardivouscular disease	Salvianolic acid B	HSP27 and mitofilin	Feng et al. (2011)
Arrhythmias	Dingxin recipe	Prohibitin	Jia et al. (2012)
Ischemic myocardial injury	Buyang Huanwu decoction	Atrial natriuretic factor, HSP β-6 and peroxiredoxin-6	Zhou et al. (2012)
Type 2 diabetes mellitus	Tian-Qi-Jiang-Tang Capsule	Haptoglobin, transthyretin and prothrombin	Zhang et al. (2010)
Type 2 diabetes mellitus	Zi-Bu-Pi-Yin recipe	DRP-2 and PDHE1α,	Shi et al. (2011)
Allergic airway inflammation	Xiao-Qing-Long-Tang	Spectrinα2	Nagai et al. (2011)
Immunological liver injury	*Salvia miltiorrhiza* Bge. (丹参) polydacchride	PRDX6	Sun et al. (2011)
Liver fibrosis	Fuzheng Huayu	Vimentin, S-adenosylhomocysteine hydrolase isoform and HSP90	Xie et al. (2013)
Liver injury	Yin-Chen-Hao-Tang	Zinc finger protein 407, haptoglobin, macroglobuin, α-1-antitrypsin, transthyretin, vitamin D-binging protein and prothrombin	Zhang et al. (2011)

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