Pattern classification in traditional Chinese medicine and precision medicine: a narrative review

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Objective: To supply an overview of Pattern Classification in TCM and the relationship with Precision Medicine.

Background: Precision treatment is the core idea of Western medicine. According to the difference in diseases, physiology, physiques, and genes, doctors will apply different treatment protocols to achieve the best results. Pattern classification is a major methodological means of dialective treatment in Traditional Chinese medicine (TCM) and has a relationship with precision treatment according to the methods applied in the treatment. However, how to explain the material foundation for Traditional Chinese medicine remains scant.

Methods: From the perspective of Traditional Chinese medicine, the treatment method given to patients with even a same disease is different, thereby achieving the best results. This article started from the cold pattern, hot pattern, deficiency pattern, blood stasis pattern, with modern agencies and drug metabolism, to explain the material foundation of pattern classification and treatment of drugs, and the consistency of the precision treatment concept both in traditional Chinese medicine and modern medicine.

Conclusion: The classification of patterns in TCM can provide western medicine with a broader scope and more precise choices in the diagnosis and treatment of diseases, which can greatly help personalized medical treatment for patients and improve the efficacy of treatment.

Keywords: Traditional Chinese medicine; pattern classification; precision treatment

Introduction

Emerging evidence shows that the use of standard treatment methods under a unified standard cannot achieve the best treatment effect in every patient (1,2). This has triggered medical professionals' exploration of treatment approach. The formulation of clinical guidelines was based on the common characteristics of a wide range of people. The advantage of guidelines is that it is applicable to a wide range of people and easy to promote. While the disadvantage is that the statistical calculations in the formulation of clinical guideline for the baseline level ignored individual differences (3). This creates a problem. Under the guideline-based treatment, patients can get an average level of benefit, but they cannot get the maximum benefit if they are far from average (1). This triggered a wave of precision medicine (4). Precision medicine means adjusting the prevention and treatment methods of diseases according to the individual differences of each patient. It is a medical mode that customizes the medical methods according to

the different patients. Different from the original "one size fits all" treatment method, precision medical examinations will penetrate into the smallest molecular and genomic information, and medical personnel will perform diagnosis and treatment methods based on the subtle differences in the patient's information. Based on the guidance of TCM theory, TCM pattern classification is an important way for sustainable development of TCM and innovation of biomedicine. Theoretically, it also displays the advantages of integrated TCM and Western medicine. Pattern classification is of great significance to the individualized clinical diagnosis and treatment in TCM. It boasts broad research and application prospects to combine TCM pattern classification with modern medical disease diagnosis, innovate clinical diagnosis models and promote the development of individualized medicine. The classification of patterns in TCM is also based on the different diagnosis and treatment protocol for each patient, which to some extent coincides with precision medicine. However, the biological basis of pattern classification is still lacking. This article will summarize the cold pattern, hot pattern, deficiency pattern and blood stasis pattern from the perspective of modern agencies and drug metabolism as well as the way of TCM conducting precision treatment in view of biological basis.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/lcm-21-14).

Cold pattern

In TCM, cold pattern is a classification of patients based on comprehensive analysis of systemic symptom information, which can guide the selection of clinical treatment methods (5). The symptoms include aversion to cold, clear and profuse urine as well as loose stool. Through the interpretation of systems biology methods, the theory of cold pattern has been verified from basic experiments (6).

Biological basis of cold pattern

The metabolic phenotypes were different between the cold pattern and the hot pattern in rheumatoid arthritis (RA) patients (7). Metabolomics technology can be used to explore the essence of TCM cold and hot patterns from the level of small molecule metabolites and metabolic pathways for the establishment of precise and quantified 'pattern' standards (8). By way of plasma metabolomics and multi-dimensional data analysis, it can be concluded that there are

exact biological characteristics of cold pattern at messenger-RNA and metabolite levels (9). Through network topology analysis, it is found that cold pattern is related to hormone level and its related genes mainly mediate energy metabolism pathway (10,11). The differential metabolites indicate that the rates of fat and protein mobilization may be higher in the cold pattern. Some pathways like alanine, aspartate, and tyrosine metabolism were also related to cold pattern (12). The regulation of RA cold pattern on apoptosis is mainly through the pathway of inhibiting nuclear transcription factor E2-related factor (13). Cold pattern can be defined more objectively through qualitative and quantitative analysis of metabolites in biological metabolomics. A study based on hydrogen nuclear magnetic resonance spectroscopy suggested that moxibustion could regulate the production of 8 metabolites and 7 metabolic pathways in the gastric mucosa of rats with stomach cold pattern (13). The main mechanism of moxibustion's effect on gastric mucosa repair of stomach cold pattern involves the central regulation of amino acid metabolism and cell morphology maintenance in vivo. An experimental study of moxibustion found that 11 metabolites in cerebral cortex were closely related to stomach cold pattern and regulated the disorder of 5 metabolites in stomach cold pattern (13). Taking different metabolites as objective indicators is helpful to better understand the pathogenesis of cold pattern and obtain better efficacy in clinical practice. Cold pattern in TCM does not completely conform to the classification of diseases in western medicine. In genomics, the clinical symptom sets of the hot and cold pattern can be presented through construction of gene networks. The genes significantly related to the hot and cold pattern were identified by correlations analysis in the following study. Miao Jiang suggested that the hot and cold pattern is related to different pathways in RA, which might also be used for identification of the pattern classification in other diseases (12). The comparison of CD4+ positive cells on gene expression proved that cold pattern in TCM had its own genomic basis (14,15). Some genes were expressed significantly more in cold pattern. The genes significantly related to cold pattern can be identified through correlations analysis. In the biological network of these genes, EIF4A2, CCNT1 and IL7R are important genetic markers of RA cold pattern (13). Particularly, the cold pattern was related to Toll-like receptor signaling pathway (16). The difference of gene expression indicates that cold pattern in TCM possesses gene expression profile. In proteomics, by constructing and analyzing the molecular network and drug target network

in corresponding with cold pattern, the common biological pathway of cold pattern and the target of medicine can be found. This is also one of the molecular biological mechanisms of "drug-pattern correspondence" of TCM in the treatment of diseases. A study identified the network-based gene expression biomarkers for cold pattern of RA (17) and may be applicable to further stratification of diseases for the decision on interventions or clinical trials. In another study, RA patients with a TCM cold pattern responded better to biomedical combination therapy than those with a TCM hot pattern (18).

Therapeutic effect based on cold pattern

In the view of Western medicine, cold pattern mostly belongs to non-specific clinical manifestations of diseases. Finding the occurrence regularity of symptoms can guide clinical treatment for the purpose of precision medicine. Through factor analysis of rheumatoid arthritis (RA) symptoms, Cha *et al.* obtained four common factors with high contribution rate, one of which reflected the clinical manifestations of cold pattern in TCM. A meta-analysis on the clinical characteristics of RA pattern showed that activity-related indicators such as erythrocyte sedimentation rate and C-reactive protein in cold pattern was significantly Lower than those in other patterns, and that patients with cold pattern were in a weak activity state (19,20). On basis of this, some researchers used the American College of Rheumatology (ACR) response to evaluate the efficacy and concluded that after a certain treatment period, western medicine curative effect on cold pattern is better than that on non-cold pattern (19-21). RA patients with cold pattern will respond better to biomedical therapy (22). By analyzing the differences of cytokines and clinical indicators between cold and hot pattern, Zhao LH found that the CRP of cold pattern was lower than that of hot pattern in early RA patients (23). On the other hand, observation of the tongue is an important basis in TCM syndrome differentiation. Generally speaking, white tongue coating represents cold pattern and yellow tongue coating represents hot pattern. A study on RA patients with white tongue coating showed higher effective rate than those with yellow tongue coating in drug intervention (24). Through the above analysis, the optimal treatment plan for cold pattern can be obtained. Through modern symptom classification, personalized treatment is adopted to patients with cold pattern, which is in line with precision medicine (25).

Hot pattern

Based on TCM classical pattern classification, symptoms of hot pattern usually include restlessness caused by heat in the body, thirst, vexation, short urine, red tongue and yellow tongue coating, turbid yellow urine and fever. These symptoms can guide the choice of treatment methods.

Biological basis of hot pattern

At present, metabolomics (26), genomics, proteomics and other methods are used in the biological exploration of hot pattern. For example, in the current research reports, Rheumatoid Arthritis is divided into cold pattern and hot pattern. In the research of RA, the blood samples of typical RA patients with hot pattern were collected by researchers and tested with genomics technology. Then the detected data is analyzed with bioinformatics technology (27). The biological basis of hot pattern was explored in some researches, and the result is that PRKAA1, HSPA8, and LSM6 are related to fatty acid metabolism and I-κB kinase/NF-κB. They are the important biomarkers in hot pattern of RA. And the calcium signaling pathway, cell adhesion molecules, peroxisome proliferation activated receptor signaling pathway as well as fatty acid metabolism pathway are related to the hot pattern of RA (12,21,28). Another study on the correlation between cold and hot pattern of traditional Chinese medicine and gene expression profiles in RA showed that histidine metabolism and lysine degradation were related to hot pattern. In a systematic biology study on RA, the researchers divided RA patients into cold pattern group and hot pattern group according to TCM theory, and collected the blood samples of 33 rheumatoid arthritis (RA) patients and 16 healthy volunteers to analyze the total gene expression. The result showed that caspase 8 activated apoptosis seems to be stimulated in the RA ho pattern group, and molecular differences in apoptotic activity between the cold pattern and hot pattern groups were found. Through collecting fasting venous blood of normal people, the researchers found that the gene expression profile between the active and stable stages of RA is difference and it provides a reference for the hot pattern of RA.

Based on the curative effect of hot pattern treatment

The individual differences of patients are noticed in precision medicine (PM) to adjust the prevention and

treatment of diseases, and PM is also a medical mode which is customized for different medical methods to treat patients (29). Under this medical mode, according to the subtle differences in the patients' disease information, appropriate adjustments and changes to the diagnosis and treatment methods will be made by medical personnel. This is consistent with the strategy of TCM doctors to treat diseases through differentiation of symptoms and signs (30). For instance, in the research report on the TCM pattern type of RA, a combined evaluation study on the TCM symptoms of RA and its efficacy showed that the symptom combination includes hot sensation in the joint, turbid urine with yellow color, fever, which are related to the hot pattern in TCM. And in this study, the 18 TCM symptoms in RA could be classified into 4 factors (symptom combinations). The classification of symptom combinations is similar to the patterns differentiated with TCM theory in RA patients with 3 basic patterns including cold, hot, and deficient ones. A number of disease-modifying drugs are available for RA, but are limited by severe toxicity requiring adjunct therapy, or of variable efficacy. The combined therapy seems to be effective (18,31,32). Then, a study on RA tongue diagnosis for the first time demonstrates the association between tongue appearances and the ACR20 (ACR20 response based on American College of Rheumatology) response in RA patients treated with Chinese medicine and western medicine interventions TCM was less effective on the patients with pale tongue body, and WM was less effective on the patients with purple or red tongue body, or white tongue coating. These results suggest that the color of tongue coating and body may serve as a factor in deciding on treatment methods and improving the efficacy of RA (30). On the other hand, the hot pattern classification can also be applied to diabetes mellitus, chronic gastritis, chronic diarrhea and other diseases. In the pattern classification of diabetes, the lung and stomach are often related to diabetic hot pattern. In a certain stage of diabetes, symptoms of a hot pattern such as weight loss, dry mouth, polydipsia, and hunger will often appear. In terms of treatment, Wumei pills [Syzygium cumini (L.) Skeels, Asarum nipponicum var. nankaiense (F.Maek.) T.Sugaw., Zingiber officinale Roscoe, Coptis chinensis Franch., Angelica sinensis (Oliv.) Diels, Aconitum carmichaeli Debeaux, Zanthoxylum bungeanum Maxim., Neolitsea cassia (L.) Kosterm., Panax ginseng C.A.Mey., Phellodendron amurense Rupr.] are often used clinically to treat diabetes. In the research on Wumei pills, it has also been found that Wumei pills may stimulate the secretion of insulin by promoting the regeneration of pancreatic islet B cells and functional recovery and repair, and increase the use of glucose by peripheral tissues and other ways to play a hypoglycemic effect (33). In the pattern classification of chronic gastritis, patients with chronic gastritis were divided into cold pattern and hot pattern and were treated with traditional Chinese medicine in clinical research. Chronic gastritis patients with hot pattern will show symptoms such as gastric distension and upper abdominal pain. After treatment with traditional Chinese medicine, the clinical effect was remarkable in reducing adverse reactions and the recurrence rate (34).

In the study of patterns of chronic diarrhea, clinicians found that patients with chronic diarrhea often had mixed patterns of cold and hot. After treatment with Wumei pills, they found that the long-term curative effect was significantly better than that of Smecta, and there were no obvious adverse reactions (35). In short, the curative effect of the treatment plan for hot pattern is related to the patient's symptom combination in TCM, and the organic combination of symptoms is the main content of TCM classical pattern classification. For the disease, the efficacy of treatment may be improved if the suitable pattern for Chinese medicine treatment is identified. This is consistent with the treatment approach of adjusting and implementing medical strategies by identifying individual differences of patients in precision medicine.

Deficiency pattern

Deficiency pattern is a common pattern in TCM. Deficiency pattern is a generalization of various clinical manifestations of human weakness. There are many reasons for the formation of deficiency pattern, such as congenital deficiency, acquired deficiency and disease depletion. The clinical manifestations of deficiency pattern are quite complicated, but there are also some common and regular manifestations, such as fatigue, shortness of breath, pale face, lassitude etc., but it is difficult to identify a deficiency pattern according to WM (36).

Biological basis of deficiency pattern

We are currently exploring its mechanism through the combination of TCM theory and modern biological research. Some studies use omics methods to carry out mechanism research to further clarify the meaning of deficiency pattern. At present, proteomics technology is applied to the research of Qi deficiency pattern, blood

deficiency pattern, Yin deficiency pattern, and Yang deficiency pattern in TCM. By analyzing the different expression of various pattern proteins, the corresponding biomarkers can be explored for the diagnosis of TCM patterns (37). Proteomics technology has identified 14 different proteins in lung tissues of lung-qi deficiency rats and normal rat. It is believed that eukaryotic translation initiation factors and transfer proteins may be related to the molecular biological mechanism of lung-qi deficiency pattern (38). Using proteomics related technology to study the liver mitochondria of the blood deficiency pattern model rat, Gong *et al.* found that there were 14 protein spots in the blood deficiency pattern compared with the normal group, of which 6 were the αβ subunits of ATP synthase and 2 were pyruvate. A subunit of the E1 component of dehydrogenase, the changes in these differential proteins are all related to energy metabolism (39). Proteomics study was conducted on the ileum tissue of the yin deficiency pattern model rats. Compared with the control group, 6 differentially expressed protein spots were found. It is believed that the down-regulation of heat shock protein 90 expression is closely related to the occurrence of spleen-yin deficiency pattern (40). Twelve differentially expressed proteins were found in the cortical bone of the femur in the kidney-yang deficiency model rat. Among them, the up-regulated proteins are apolipoprotein AI, α-enolase and heat shock protein 60, and the expression of the remaining 9 proteins is down-regulated. These proteins may participate in the mechanism of kidney-yang deficiency pattern (41). As a part of modern systems biology, metabolomics studies the overall effects of biological metabolic changes, which coincides with the overall concept and pattern classification of TCM. Metabolomics can reflect the biological nature and pathogenesis of deficiency pattern by studying the small changes of small molecular metabolites with relative molecular weights less than 1,000 in blood, urine and other metabolites and finding its specific molecular markers (42). By analyzing the metabolic profile of free fatty acids in the plasma of diabetic patients, Xu *et al.* found that arachidonic acid and oleic acid can be used as potential markers of Qi-deficiency diabetes (43). Metabolomics studies were conducted on the endogenous metabolites of blood deficiency pattern model mice caused by radiation damage, and the results showed that lysophospholipids, glucuronides, monoacylglycerides, and trihydroxybutyrate were found in the serum of mice with blood deficiency pattern. The content of acid, ceramide, aspartate phosphate, glycerophospholipid and other metabolites changed significantly (44). Through

the blood metabolomics study of the diabetic Yin deficiency pattern model rats caused by thyroxine and streptozotocin, it was found that compared with the normal group, the blood of the model group contained glycine, lactic acid, urea, D-glucose, glucose. The lactose content was significantly increased (45). A metabolomics study was carried out on the urine of patients with kidney-yang deficiency pattern by gas chromatography-mass spectrometry and pattern classification methods. Compared with the normal group, alanine and 3-methylglutaenedioic acid increased (46). As for rheumatoid arthritis, it was further discovered that deficiency pattern is potentially related to Toll-like receptor activation of NF-κB which regulates gene transcription and apoptosis pathways, and also related to immune response. The TCM deficiency pattern-related genes network comprises 7 significantly, highly connected regions which are mainly involved in protein transcription processes, protein ubiquitination, toll-like receptor activated NF-kB which regulates gene transcription and apoptosis, RNA clipping, NF-kB signal, nucleotide metabolism-related apoptosis, and immune response processes. Toll-like receptor activated NF-kB which regulates gene transcription and apoptosis pathways are potential specific pathways related to TCM deficiency pattern in RA patients. TCM deficiency pattern is probably related to immune response (32). One study carried out data mining to explore the biological basis of deficiency pattern in rheumatoid arthritis. Through analysis of these networks, Zheng *et al.* concluded that the deficiency pattern in rheumatoid arthritis might be directly or indirectly by the chronic inflammation (47).

Based on the above-mentioned research content, we can conclude that in proteomics research, by analyzing the differential expression of proteins, we can distinguish Qi deficiency pattern, blood deficiency pattern, Yin deficiency pattern, and Yang deficiency pattern. For example, the mechanism of Qi deficiency pattern is related to the transport protein, the mechanism of blood deficiency pattern to the energy metabolism of protein, the occurrence of Yin deficiency pattern is closely related to the downregulation of heat shock protein, and the Yang deficiency pattern is related to both the up-regulation of protein and the down-regulation of protein. In metabolomics research, the mechanism of deficiency pattern can be further clarified through analysis of small molecular metabolites in blood and urine. For example, arachidonic acid and oleic acid in patients' plasma can be used as potential markers of Qi-deficiency diabetes. Network pharmacology also shows that the occurrence

of deficiency pattern may be related to immune response and inflammatory response. The combination of modern biomedical technology and TCM has shown synergistic effects. Researchers use theoretical methods such as omics and network pharmacology to promote the development of precision medicine through continuous exploration of patterns in TCM.

Therapeutic effect based on deficiency pattern

In terms of therapeutic effects, the combination of TCM theory and modern biotechnology is conducive to the integration of Chinese and Western perspectives, helps medical professionals to acknowledge more deeply the mechanism of disease occurrence and development, and builds a theoretical basis for disease treatment and research (48). From the perspective of network pharmacology, Shengmai San [Ophiopogon japonicus (Thunb.) Ker Gawl., Panax ginseng C.A.Mey., Schisandra sphenanthera Rehder & E.H.Wilson] may exert its multiple active ingredients, multiple targets, and multiple pathways to treat tachyarrhythmia by regulating calcium ion transport, potassium ion transport, endothelial function, and oxidative stress (49). The active ingredients of Jiajian Xiangsha Liujunzi Decoction [Panax ginseng C.A.Mey., Atractylodes macrocephala Koidz, Smilax glabra Roxb., Glycyrrhiza glabra L.,Citrus × aurantium L., Pinellia ternata (Thunb.) Makino, Wurfbainia villosa (Lour.) Skornick. & A.D.Poulsen, Aucklandia costus Falc.] can combine with 3CL hydrolase, ACE2, PTGS2, and regulate IL-17, TNF, T cell receptor, MAPK, VEGF and other signaling pathways to inhibit inflammation, regulate the body's immunity, and expel pathogens in the lung. Injury can promote cell growth and differentiation and pulmonary angiogenesis, thereby improving patient symptoms, promoting recovery of patients improving immunity, and reducing the risk of disease recurrence or re-infection (50). Tongxie Yaofang [Citrus × aurantium L., Atractylodes macrocephala Koidz., Paeonia lactiflora Pall, Saposhnikovia divaricata (Turcz. ex Ledeb.) Schischk.] in the treatment of irritable bowel syndrome with liver Qi stagnation and spleen deficiency pattern is related to reducing the content of serum and colon Vemer-Morrison syndrome. It is most likely caused by a negative feedback mechanism after the gastrointestinal motility is enhanced (51). In future work, we can use omics and network pharmacology methods to conduct more in-depth research on TCM deficiency pattern, and at the same time, further clarify the significance of patterns.

Blood stasis pattern

Biological basis of Blood stasis pattern

Blood stasis pattern is a type of pattern in TCM, which represents a condition of poor blood circulation resulting from the increase of blood viscosity and concentration (52). It involves the pathological progress in severe diseases, such as coronary heart disease (CHD) (53), type 2 diabetes (54), IgA Nephropathy (55), rheumatoid arthritis (RA) (56), etc. In Western medicine, the concept of BSS mainly refers to unsmooth blood circulation, decreased blood flow to the body, or impurities in the blood (57). However, it is difficult to identify BSS in clinical diagnosis correctly. Recently, some studies have found some biomarkers about BSS by using metabolomics, proteomics, and genomics (58). In metabolomics, after preparing the animal model of BSS successfully, an experimental study showed that 21 metabolites were identified during the development of BSS, which are involved in the metabolic pathways of tryptophan metabolism, phenylalanine metabolism, and so on. 22 different metabolites were identified in BSS rats, and these metabolites mainly involve seven metabolism pathways in different impact values (59). A study found that the occurrence of BSS in rats was closely related to the disorder of 4 potential target metabolism pathways in plasma and 4 potential target metabolism pathways in urine, respectively. The former includes Arachidonic acid metabolism and proline metabolism, and the latter includes Phenylalanine and Linoleic acid metabolism (60). A study focused biomarkers of coronary heart disease (CHD) patients with BBS (61). In proteomics, after establishing the model of BSS of chronic myocardial ischemia successfully, researchers studied the differences of proteomics between the sham-operation group and BSS group, and found that the differential proteins were mainly oxidative stress proteins and relevant myocardial structural proteins including heat shock 27 kDa protein (HSP27), cardiac troponin T (cTnT) and so on (62). A study found that BBS may be identified through detection of the serum protein fingerprints in IgA nephropathy. It suggested that by using proteomics, we can explore some biomarkers to identify BBS. In genomics, studies have pointed out that CHD-BBS is closely related to inflammatory response-related genes, angiotensin-converting enzyme gene (ACE), vascular Willebrand factor (vWF) gene, IL gene (63,64). They suggested that the genes are associated with different pathways in some diseases. Hence, by using metabolomics, proteomics, and genomics, we can explore the potential biomarkers for objective and precise clinical diagnosis.

Therapeutic effect based on Blood stasis pattern

Metabolomics, proteomics, and genomics can be used to diagnose and detect clinical efficacy. An experimental study identified 69 metabolites that showed different expression in the plasma of CHD-BSS patients before and after treatment with Xue-Fu-Zhu-Yu decoction [Juglans regia L., Carthamus tinctorius L., Angelica sinensis (Oliv.) Diels, Rehmannia glutinosa (Gaertn.) DC., Achyranthes bidentata Blume, Conioselinum anthriscoides 'Chuanxiong', Platycodon grandiflorus (Jacq.) A.DC., Paeonia lactiflora Pall., Citrus × aurantium L., Glycyrrhiza glabra L., Bupleurum falcatum L.]. Moreover, lipid metabolism, which plays an important role in the dysfunction of CHD are involved (65). Through the analysis of TCM network diagram in the treatment of diabetes and RA, a study found that by treating BBS, the condition of diabetes and RA can be alleviated (66). By observing the differences in urinary protein, serum creatinine and blood urea nitrogen before and after the treatment, Yang RY found that Ginseng injection combined with high ground was an effective method in the treatment of diabetes nephropathy IV (67). By observing the differences in blood routine, urine routine before and after the treatment, a clinical research found that Ziyin Huoxue decoction [Anemarrhena asphodeloides Bunge, Phellodendron amurense Rupr., Rehmannia glutinosa (Gaertn.) DC., Ligustrum lucidum W.T.Aiton, Lycium barbarum L., Cornus officinalis Siebold & Zucc., tortoise plastron, turtle shell, Paeonia lactiflora Pall., Salvia miltiorrhiza Bunge] can treat convalescence of ischemic stroke patients more safely (68). By observing the differences in IL-6, IL-10, TNF-α in prostatic fluid and PSEP in urine before and after the treatment, Yang *et al.* found that Jingtian Siwu Decoction has a good therapeutic effect on type III prostatitis (69). Besides, metabolomics, proteomics, and genomics can be used to explore the mechanism of toxicity reduction. Metabolomics may be an available way to explain the scientific connotation of controlling toxic reaction while toxic herbs are used for the disease (70). A study points out that metabolomics, proteomics, and genomics are effective tools to explore the key molecules and pathways for toxicity reduction (71). As mentioned above, integrating TCM theory with modern technology such as metabolomics, proteomics, and genomic is beneficial to clinical diagnosis through classification into cold pattern, hot pattern, deficient pattern and BBS to achieve precision medicine. In the next step, based on the indicators of metabolomics, proteomics, and genomics

for personalized treatment, it is beneficial to detect clinical efficacy by observing the differences before and after the treatment. Other functions were found in metabolomics, proteomics, and genomic to explore the mechanism of diseases. Therefore, the combination of TCM theory and modern technology is conducive to implementing precision medicine.

Drugs with different natures in TCM

In TCM, doctors need to classify the patterns of patients during the diagnosis process. When treating diseases and using drugs, they still need to choose the appropriate drugs according to the patient's pattern. In the theory of Chinese medicine, medicine also has corresponding hot or cold nature. The nature of drugs can be classified into hot and cold nature. It is important to identify the nature of drugs since the TCM clinical treatment can be summarized as "treating cold pattern with hot drugs, treating hot pattern with cold drugs". Recently, some studies have explored the differences between drugs with hot nature and drugs with cold nature. First of all, a study has transformed the medicinal natures of TCM into a new model of "network targets" and then distinguished between cold and hot natures of herbs (72). By using network pharmacology, a study constructed a model in accordance with drug biological effects. It is a new strategy for the classification model about herbs with cold or hot nature (73). The research used a pharmacological network to explore the herbs with the cold or hot nature in terms of biological effects. It explored the identification pathways of drugs with cold or hot nature (74). A study explored the mechanism of heat-clearing in TCM and found the different components and related targets in herbs with cold or hot nature (75). The research found that Chinese herbs with hot nature were more associated with inflammation and immunomodulation (76). Moreover, network pharmacology consequences suggested that we can probe some material basis related to constitutions with hot and cold natures. Microcalorimetry can measure the hot or cold nature of drugs in TCM, too. Researchers investigated the energy transfer and thermal change in the metabolism progress of organism and the intervention effects of different Chinese medicines in this progress (77). Drugs with hot nature have strong anti-bacterial ability, while drugs with cold nature have mild anti-bacterial ability (78). In another study, researchers found that drugs with hot nature tend to promote heat energy in bacteria, while drugs with cold nature increase

temperature in bacteria slightly (79). It suggests that the differences in the temperature are associated with drugs' nature. Moreover, there are some differences in the ingredient index of drugs with hot or cold nature. A study found that the contents of minerals in drugs with hot nature were significantly higher than those with cold nature (80). By comparing the protein contents between drugs with hot and cold nature, researchers found that the protein contents in drugs with hot nature are more concentrated (81,82). Another study has found that drugs with hot nature had significantly higher 390 sugar content than those with cold nature (83). It suggests that minerals, protein, and sugar content may be related to drugs hot and cold nature. Some studies are suggesting that some drugs also have hot or cold nature. Researchers have found that Reserpine displayed cold nature (84), and another study found that cold nature is the feature of some antibiotics (85). Morphological observation found that cells treated with cold drugs showed lower cell density (86). Besides, TCM clinical practitioners have pointed out that using drugs with hot or cold nature depending on patients' cold or hot pattern can achieve better outcome (87). Therefore, integrating the natures of drugs with the pattern of patients can help clinical practitioners to treat patients more effectively (88).

Discussion and conclusions

In general, according to TCM theory, symptoms of a cold pattern include aversion to cold and pain relieved by warmth. Symptoms of a hot pattern include aversion to heat, sometimes pain which can be relieved by cold. The deficiency syndrome includes a feeling of weakness, mental weakness, and muscle atrophy. Blood stasis refers to slowed blood flow, accompanied by pain, sometimes accompanied by petechiae. The precision of medical treatment conforms to the general trend of society. Therefore, the main principle of precision medicine is to rely on the patient's entire molecular network or the related structure and state of the gene network for diagnosis and treatment. At the same time, the corresponding drugs should be used at the correct time and with the correct measurement to treat the patient precisely, so that patients get the best benefit. The classification of patterns in TCM is such a precision medicine model. The pattern classification of TCM is for the patients even with a same disease. It is a supplement based on guideline medicine for the diagnosis, treatment, and drug selection of patients. The use of modern omics technology to study the biological basis of TCM pattern classification, and the use of systems biology methods

to determine molecular driving factors and biomarkers will promote the practice of personalized TCM. The development of proteomics, genomics, and metabolomics platform technologies will eventually lead to the coordination and integration of TCM and contemporary medicine, because TCM is fundamentally a highly personalized and precise medicine. At present, most animal experiments and clinical specimen detection are limited to the study of a single pattern. But when the human body is sick, several patterns are often mixed together. Patterns can be classified into pairs or more since it is difficult to separate them. Therefore, we hope that that future research can conduct research on mixed pattern to get closer to the diseases of the human body, so as to obtain more effective treatment. At the same time, we hope that researchers will conduct comparative studies on pattern, such as comparison between cold pattern and hot pattern and comparison between blood stasis pattern and blood deficiency pattern, and further clarify the difference in pathogenesis through comparison. We are able to classify into cold or hot pattern according to TCM theory and use modern histological techniques to uncover the nature of the cold and hot pattern in TCM. We can use, for example, genomics and metabolomics to distinguish between cold and hot pattern. Further, we can use these targets to combine TCM and Western medicine, or avoid combining certain TCM and Western medicine to achieve better efficacy for the ultimate benefit of patients. The classification of patterns in TCM can provide western medicine with a broader scope and more precise choices in the diagnosis and treatment of diseases, which can greatly help personalized medical treatment for patients and improve the efficacy of treatment. It is worthy of in-depth study in the future.

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Footnote

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