

EDITORIAL

Molecular nuclear medicinal imaging in the translation of traditional Chinese medicine

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Nuclear technology is a vital component of contemporary science. It is one of the most advanced technologies currently available and has greatly promoted the rapid development of natural science and medicine. Over the past 20 years, Molecular Nuclear Medicinal Imaging (MNMI) has made great progress in the dynamic and quantitative visualization of biochemical processes and target positioning modes that are not visible at the anatomical level. Further, it provides the advantage of not interfering with the observed cells, environments, or important pathophysiological processes. This technology has provided numerous possibilities for uncovering the mystery of traditional Chinese medicine (TCM) and promoting the development and integration of MNMI use within TCM practices. Herein, we are delighted to add this editorial on the application of nuclear medicine to the American Journal of Translational Medicine. We will introduce: (1) the general theoretical basis of MNMI and TCM; (2) applications of MNMI in the interpretation of the theory and mechanisms of TCM; (3) cooperation in the development of "diagnosis and treatment integration" between TCM and MNMI; and

(4) development and translations of MNMI under the guidance of TCM theory. A collective overview of these aspects will add insight into medical imaging-guided diagnosis, treatment, and clinical translations under the theoretical framework of TCM.

THE GENERAL THEORETICAL BASIS OF MNMI AND TCM

TCM embodies Chinese philosophies in which the "overall concept" and "syndrome differentiation and treatment" are important principles. The "overall concept" regards the human body as a unified whole, constituting the structure between the parts of the human body that are unmediated, coordinated in function, and influenced by each other pathologically. "Treatment based on syndrome differentiation" is a comprehensive analysis of the available clinical

information to identify the cause, nature, and location of the disease, and the relationship between “Zhengqi (正 气)” and “Xieqi (邪气)”. Molecular imaging is a technology that utilizes principles of TCM to evaluate physiology and pathology non-invasively in live subjects. The “whole” is reflected in the observation of the whole body after the injection of the molecular probes and “syndrome differentiation” is reflected in differential imaging of the area where the labeled ligand is concentrated. For example, the current positron emission tomography (PET) clinical application of tumor diagnosis, [¹⁸F]-FDG, follows the whole body, evaluates the whole body, and compares the differential imaging diagnosis of tumor sites, which is a real-life portrayal of the “whole” and “syndrome differentiation” principle of TCM.

MNMI USE IN THE INTERPRETATION OF TCM THEORY AND MECHANISMS

“Yin (阴)” and “Yang (阳)” constitute the basis of TCM theory. Hu et al. (2005; 2010) explored the material basis of the theory of TCM with the help of radioligand binding analysis and autoradiography. The authors explained the diagnosis model of “Yin Deficiency (阴 虚)” and “Yang Deficiency (阳 虚)” in TCM and the treatment method of “Nourishing Yin (滋 阴)” and “Tonifying Yang (补 阳)”, guiding the application of MNMI to explore the material basis of TCM theory. He et al. (2019) systematically analyzed the current methodological problems with PET/PET-CT in acupuncture research and provided useful references for the study of acupuncture efficiency and TCM. Clinically, Yin et al. (2019) evaluated the mechanism of acupuncture in treating functional constipation with PET. Zeng et al. (2015) used PET technology to evaluate the brain reaction of acupuncture at different points to treat postprandial functional dyspepsia. “Exterior interior correlation (表里络属)” is a classical

TCM theory regarding the meridians (Zhang et al., 2020). The tissue distribution of ¹⁸F-labeled andrographolide was observed through PET in animal models, which provided a biological basis for a classical theory of TCM that “lung and intestine are related to the exterior and interior of meridians.” Han et al. (2022) used PET technology to evaluate the anti-asthma effect of paeoniflorin, an extract from Chinese herbal medicine. Similarly, Wu et al. (2020) explored the anti-prostate-cancer effect of icariin; another extract. Regarding compound-based Chinese medicines, such as Ma Ren Chengqi Decoction, a classic TCM prescription for constipation, Chen et al. (2021) used ⁶⁸Ga-NOTA PET to evaluate its effect on delayed gastric emptying caused by constipation. Lu et al. (2020) used PET to evaluate if Qiliqiangxin, a TCM compound, could trigger the transformation of metabolism from glycolysis to oxidation, and directly reverse the right ventricular remodeling secondary to pulmonary hypertension.

COOPERATIVE DEVELOPMENT OF THERANOSTICS BETWEEN TCM AND MNMI

The “theranostics” between TCM and MNMI is promising. One such important application is in cancer research. However, there are various side effects in the clinical application of radiotherapy. The rich medicinal resources, therapies, and individualized differential treatment systems can reduce the side effects of radiation while regulating the overall state of patients and helping the development of “theranostics” of MNMI. For example, Huang et al. (2022) conducted a systematic review and found that TCM could alleviate xerostomia and other related complications caused by head and neck cancer radiotherapy. In addition, a systematic review by Ni et al. (2020) showed that

acupuncture effectively improved dry mouth symptoms of radiotherapy patients, suggesting that TCM can complement radiotherapy. However, more high-quality evidence and systematic research are needed to explore the underlying mechanisms.

DEVELOPMENT AND TRANSLATION OF MNMI DIAGNOSIS AND TREATMENT UNDER THE GUIDANCE OF TCM

Diagnosis Translation

Based on the theory of TCM, “syndrome differentiation and treatment (辨证论治)” is a feature that distinguishes TCM from other diagnosis and treatment systems. Even if there is no clear diagnosis of the disease name, it can provide a therapeutic strategy. However, factors such as the clinician's experience and the differences in diseases make it difficult to be objective and standardized. Furthermore, the transformation of syndrome types in the whole cycle of the disease can undoubtedly hinder accurate diagnosis and treatment. Developing a special probe for the syndrome type diagnosis of TCM would promote the objective and rapid visual determination of the syndrome type, as well as guide disease diagnosis, treatment, efficacy, and prognosis judgment. Thus, TCM can guide MNMI to develop a more accurate personalized diagnosis and treatment model. For example, He et al. (2004) explored the difference between patients with and without blood stasis of non-small cell lung cancer, using PET technology. In addition, Tan et al. (2015) explored the association between different types of TCM syndromes and coronary heart disease. The research on objective standardization syndrome types by MNMI is growing rapidly, a difficult endeavor to undertake

comprehensively, and one that necessitates further exploration and research.

TCM also lays the material foundation of MNMI research. For example, Yang et al. (2022) used radioactive iodine labeled hypericin, a Chinese herbal forsythia (连翘) extract, as a tracer for detecting acute myocardial infarction. In addition, Fingolimod, an immunosuppressant derived from the traditional Chinese herb Cordyceps Sinensis (冬虫夏草) extract, can exert long-term functional antagonism by first strongly activating and then ultimately down-regulating sphingosine-1-phosphate (S1P) receptor 1 (S1PR1), which acts as a target for neuroinflammatory and neurodegenerative diseases. TCM is also valuable in cancer medicine, immunity, cardiovascular medicine and other fields of research (Lucaciu et al., 2020). The probe targeting the S1PR1 ligand was used to evaluate the status of diseases in various physiological states (Jin et al 2017; Liu et al., 2018) and the effects of different therapeutic interventions (Liu et al., 2016; 2017).

Treatment Translation

TCM includes the theory of “meridian belonging (经络归属)”. That is the special bias of targeted meridians. For example, the Chinese herbs “Platycodon grandiflorum (桔梗)” and “Forsythia suspense (连翘)” are commonly used to treat pulmonary diseases. Shen et al. (2019) synthesized a [¹⁸F]-phillygenin probe, which is used as a tracer for PET scan to explore the effects of Platycodon saponins, suggesting that the platycodon saponins is an important ingredient to help drug delivery to the lung tissue and improve the treatment of respiratory disease. Research indicated that the active ingredients in some Chinese herbs have anti-tumor properties. Yang et al. (2017) developed a radiosynthesis method of using [¹⁸F]fluoroethyl bufalin (the main ingredient of Chinese herb venenum bufonis) to non-invasively evaluate the tissue biodistribution and pharmacokinetics in hepatocellular carcinoma-bearing mice. This experiment demonstrated the bioactivity of bufalin. Developing TCM ligands to carry radiopharmaceuticals, orally or by injection, takes advantage of TCM's dual target characteristics of targeting sites and pathology. Developing TCM ligands

would enable more accurate delivery of radionuclides, giving play to the biological effect of local ionizing radiation, inhibiting the destruction of diseased tissues, and enabling the therapeutic effect of precise delivery.

In summary, the fusion of TCM with MNMI is necessary. The rich theory and material resources of TCM could provide a lamp-oriented direction for future molecular diagnosis, treatment, and personalized medical system construction. This fusion would also promote NMMI and TCM interaction and convergence.

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