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Review

Current applications of molecular imaging and luminescence-based techniques in traditional Chinese medicine

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ABSTRACT

Ethnopharmacological relevance: Traditional Chinese medicine (TCM), which is fundamentally different from Western medicine, has been widely investigated using various approaches. Cellular- or molecular-based imaging has been used to investigate and illuminate the various challenges identified and progress made using therapeutic methods in TCM. Insight into the processes of TCM at the cellular and molecular changes and the ability to image these processes will enhance our understanding of various diseases of TCM and will provide new tools to diagnose and treat patients.
Materials and methods: Various TCM therapies including herbs and formulations, acupuncture and moxibustion, massage, Gua Sha, and diet therapy have been analyzed using positron emission tomography, single photon emission computed tomography, functional magnetic resonance imaging and ultrasound and optical imaging. These imaging tools have kept pace with developments in molecular biology, nuclear medicine, and computer technology.
Results: We provide an overview of recent developments in demystifying ancient knowledge – like the power of energy flow and blood flow meridians, and serial naturopathies – which are essential to visually and vividly recognize the body using modern technology.
Conclusions: In TCM, treatment can be individualized in a holistic or systematic view that is consistent with molecular imaging technologies. Future studies might include using molecular imaging in conjunction with TCM to easily diagnose or monitor patients naturally and noninvasively.

Contents

Abbreviations: TCM, traditional Chinese medicine; PET, positron emission tomography; SPECT, single photon emission computed tomography; Fmri, functional magnetic resonance imaging; CMM, Chinese *materia medica*; NIRI, near infrared imaging; OI, optical imaging; NO, nitric oxide; HVECs, human vascular endothelial cells; TMDCDA-BODIPY, 1,3,5,7-tetramethyl-2,6-dicarbethoxy-8-(3′,4′-diaminophenyl)-difluoroboradiaza-*s*-indacence; NCTD, Norcantharidin; MMP-9, matrix metalloproteinase-9; mRNA, messenger ribonucleic acid; NF-κB, nuclear factor-κappa B; C-P, chuanxiongzine-puerarin; ^{18}F-FDG, [^{18}F] fluoro-2-deoxy-D-glucose; BAT, brown adipose tissue; ER, estrogen receptor; PCL, *Psoralea corylifolia* L.; ERRs, estrogen-related receptors; AR, androgen receptor; SGLXD, Shu-Gan-Liang-Xue Decoction; pERE, palindromic estrogen response element; FZS, Fuzhisan; BOLD, blood oxygen level-dependent; ATB, antitumor B; CT, computed tomography; LU, Lung; LI, Large Intestine; ST, Stomach; SP, Spleen; HT, Heart; SI, Small Intestine; BL, Bladder; KI, Kidney; PC, Pericardium; TE, intangible *San Jiao*; GB, Gall Bladder; LR, Liver; NRER, non-repeated event-related; HCs, healthy controls; MCAO, middle cerebral arterial occlusion; rCBF, regional cerebral blood flow; HMPAO, hexamethylpropylene amine oxime; MOR, μ-opioid receptor; fNIR, functional near infrared; HO-1, heme oxygenase 1.

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1. Introduction

Traditional Chinese medicine (TCM) is a unique system to diagnose and cure illness, and TCM has been widely investigated throughout the world, especially in China (Lukman et al., 2007). In TCM, the understanding of the human body is based on the holistic understanding of the universe as described in *I Ching: Book of Changes*, the content of which includes ancient Chinese cosmological beliefs that were later used to treat illness based primarily on the diagnosis. It is important to note that currently TCM practitioners do not directly observe and monitor treatment using modern technology, including molecular imaging (Chen et al., 2009a,b,c).

According to *I Ching*, the universe is harmonious, and people are intimately connected to and affected by their environment. TCM practices including yin and yang, the Five Phases (Fire, Earth, Metal, Water, and Wood), and the meridian/channel system are rooted in meticulous observation of how nature, the cosmos, and the human body interact each other. In TCM, the clinical diagnosis and treatment starts with the analysis of the entire body system, focusing on correcting pathologic changes through readjusting the functions of the Five Organs (Liver, Heart, Spleen, Lung, and Kidney). Therefore, TCM is mainly based on theories mentioned previously constructed based on early Chinese thought.

TCM theories apply the phenomena and laws of nature to the study of the physiologic activities and pathologic changes of the human body and its interrelationships. A pathologic dysfunction in one of the Five Organs may be reflected on the body's surface through the network of channels and blood vessels inside human body, and at the same time, diseases of body's surface tissues may affect their related organs. The typical TCM therapies include Chinese *materia medica* (CMM), herbal medicine, acupuncture and moxibustion, Gua Sha, diet therapy (Fig. 1). For example, acupuncture stimulates certain areas of the body's surface and Chinese medicine acts on organs internally. In fact, acupuncture and herbal medicine were regularly integrated and sequentially manipulated by ancient Chinese health experts or medical practitioners (Wang et al., 2009a,b).

TCM theory features a holistic, dynamic, natural (painless and noninvasive) view on curing the body, that coincide with ideas of modern science like molecular imaging, which emerged as a discipline that combined molecular biology and in vivo imaging in the early 21st century, enabling the noninvasive visualization of cellular function and tracking of the molecular process in living organisms. The numerous potentialities of molecular imaging are applicable to the diagnosis and could help diagnose diseases such as cancer or neurologic and cardiovascular diseases; molecular imaging contributes to improving the treatment of these disorders by optimizing the preclinical and clinical investigations of new medications or the adjustment and development of therapeutic programs. Molecular imaging has also expected to have a positive economic effect due to earlier and more precise diagnoses, mainly through positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), optical, ultrasound, and near infrared imaging (NIRI) (Chen et al., 2009b; Litschera and Schikora, 2002). Molecular imaging usually detects/visualizes biomarkers interacting chemically with their surroundings, the images change according to the molecular changes occurring within the area of interest depending on the types of contrast tracers, receptor ligands, enzyme substrates, antigen antibodies, and hormone receptors used in the analysis. Many approaches used for optical imaging also depend on fluorescence, bioluminescence, absorption, or reflectance as the source of contrast.

In contrast to optical imaging, molecular imaging has taken on a new direction since the rapid expansion of the both cellular and molecular biology that have been developed to determine potential beneficial effects of stem/progenitor cell-based therapies (Wu et al., 2003; Wu et al., 2006; Zhang et al., 2008). In a sense, these developments could be viewed as an attempt to demystify the ancient knowledge of integrative medicine, such as the power of *Qi* (energy flow and blood flow), the essence of meridians and collaterals, and the concrete effects of serial naturopathies such as Chinese herbal medicine, massage, Gua Sha, diet therapy, which have relatively lagged in clinic and research. It is essential that the effectiveness of these ancient therapies be confirmed by modern technology such as the molecular imaging techniques discussed previously.

In the present review, we briefly summarized the methods of molecular imaging with an emphasis on their potential applications as approaches or assays for elucidating the effects of TCM and partly to unveil the mysteries of TCM.

2. Chinese medicinal materials and compound recipes using molecular imaging

TCM uses various animals, vegetables, and materials to emphasize treating the individual based on the principle of Zheng-syndrome differentiation of disease, aiming to restore the harmony of opposing but complementary forces. CMM, including herbs, is an ancient complete medical system of health care that has undergone continual development over 20 centuries. Prescriptions and remedies assort to 22 types by comprehensive classification (from the book of Complete Essentials of the *Materia Medica*, composed by Wang Ang in 1683 during the Qing Dynasty). Based on classification above, the practitioners of TCM universally prescribe more compound recipe than CMM or single herb as entity to cure the illness and diseases, and believe that it can more rapidly rehabilitate the body than CMM or single herb remedy.

2.1. Main ingredients of CMM authenticated by molecular imaging

Molecular imaging by fluorescent or bioluminescent methods has demonstrated that ingredients of CMM are visible and yet effective on illness or disease in vitro widely. Tanshinone, one of the