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## • Review

# The roles of traditional Chinese medicine in gene therapy

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**ABSTRACT:** The field of gene therapy has been increasingly studied in the last four decades, and its clinical application has become a reality in the last 15 years. Traditional Chinese medicine (TCM), an important component of complementary and alternative medicine, has evolved over thousands of years with its own unique system of theories, diagnostics and therapies. TCM is well-known for its various roles in preventing and treating infectious and chronic diseases, and its usage in other modern clinical practice. However, whether TCM can be applied alongside gene therapy is a topic that has not been systematically examined. Here we provide an overview of TCM theories in relation to gene therapy. We believe that TCM theories are congruent with some principles of gene therapy. TCM-derived drugs may also act as gene therapy vehicles, therapeutic genes, synergistic therapeutic treatments, and as co-administrated drugs to reduce side effects. We also discuss in this review some possible approaches to combine TCM and gene therapy.

**KEYWORDS:** gene therapy; medicine, Chinese traditional; reviews

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## 1 Introduction

Gene therapy is the treatment of diseases via the modification of DNA in appropriate target cells. It has recently become a clinical reality after nearly 30 years of laboratory research. The first gene therapy clinical trial was launched in September 1990 at the National Institute of Health Clinical Center to treat adenosine deaminase deficiency, a genetic

disease that makes patients vulnerable to infections<sup>[1]</sup>. As of June 2012, over 1 800 gene therapy clinical trials have been completed, are ongoing or have been approved worldwide, of which 1 448 trials are in phase I or I/II, 323 are in phase II or II/III and 67 are in phase III<sup>[2]</sup>. A recombinant human adenovirus-p53 injection (trademarked as Gendicine) was approved by the State Food and Drug Administration (SFDA) of China in October 2003 for the treatment of head and neck squamous cell carcinoma,



making it the world's first gene therapy product approved by a governmental agency<sup>[3]</sup>. Currently, Gendicine is being extensively studied in other clinical trials for various cancers<sup>[4,5]</sup>. More recently, in November 2012, the recombinant adeno-associated viral (rAAV) vector Glybera, used to treat lipoprotein lipase deficiency (LPLD), received marketing authorization from the European Commission, becoming the first gene therapy product in the Western world<sup>[6,7]</sup>. All these clinical breakthroughs make gene therapy one of the most innovative areas in current biomedical study.

Traditional Chinese medicine (TCM), an important component of complementary and alternative medicine, has evolved over thousands of years with a standardized system of theories, diagnostics and therapies. In China, TCM practitioners are using a variety of techniques in an effort to promote public health and to treat diseases and recently these techniques have drawn much attention in the Western world<sup>[8,9]</sup>. During the past half century, the role of TCM in preventing and treating infectious diseases such as hepatitis<sup>[10]</sup>, acquired immune deficiency syndrome<sup>[11]</sup>, and chronic diseases such as cancer<sup>[12]</sup>, hypertension<sup>[13]</sup>, diabetes<sup>[14]</sup> and cardiovascular diseases<sup>[15]</sup> has become widely accepted. However, despite the encouraging research, the role that TCM may play in gene therapy, a relatively new biomedical practice, has not yet been systematically discussed. Here we provide an overview of the TCM theories in relation with gene expression and then discuss example approaches to combine TCM and gene therapy.

## 2 Theoretical basis of TCM in relation with gene expression

TCM is based on the guiding principles of viewing the human body as a whole, and syndrome differentiation of the individual case. The *Yellow Emperor's Internal Classics*, or *Huangdi Neijing*, was written over 2 000 years ago and is the oldest complete Chinese medical text. It stated that a person's health is related in part to what he receives while in the womb, which is inherited from the parents, stored in the kidneys, and called kidney essence. Modern TCM theories correlate the kidney essence with genetic material, which is also the basis of human health. The constitution theory of TCM indicates that people all possess his or her unique constitution, which includes different amounts of kidney essence. This can be seen in an individual's unique onset of diseases, clinical manifestations and the subsequent prognoses. Similarly, modern medicine also holds that an individual's susceptibility to pathogenic factors, diversity of clinical manifestations, and responses to drugs are closely related to his or her genetic factors and gene polymorphism. More than 20 years ago, researchers found that human leukocyte antigen, which is closely related with human diseases, has some characteristics such as

polymorphism and the phenomenon of linkage disequilibrium. These characteristics have much in common with the constitution theory of TCM<sup>[16]</sup>.

In the area of treatment, TCM doctors use observation, auscultation and olfaction, interrogation, and palpation for diagnosis and summarization of the patient's individual syndrome, and the treatment is based on this TCM syndrome. This is called syndrome differentiation, a main clinical process in TCM. Under this guide, patients with the same disease may have various TCM syndromes, which is shaped by each patient's condition, such as kidney essence (or genetic background) and living environment. The treatment of illness in TCM clinical practice is primarily guided by the patient's TCM syndrome. Interestingly, modern biomedical research suggests that each TCM syndrome may have a specific gene expression profile. For instance, Weng *et al*<sup>[17]</sup> reported differential gene expression in peripheral blood mononuclear cells isolated from hepatocellular carcinoma (HCC) patients, either with or without liver-kidney yin deficiency syndrome, using a gene chip technique. Analysis of the data showed that both the mRNA and protein expression levels of SEC62, cyclin B1 and baculoviral IAP repeat-containing 3 (BIRC3) are significantly lower in HCC patients with syndrome of liver-kidney yin deficiency. Meanwhile, Wei *et al*<sup>[18,19]</sup> reported that the expression of at least 79 genes was disrupted in patients with syndrome of kidney yin deficiency, compared to normal populations. The difference was even more striking between patients with kidney yin deficiency syndrome versus those with kidney yang deficiency syndrome, with more than 145 differentially expressed genes identified. All these differences may be targets for gene therapy in specific diseases. Thus, we believe that there are some common medical theory bases between the individual therapy guided by the holistic concept of TCM and the experimental research based on gene therapy.

## 3 TCM agents as gene therapy vehicles

To date, a variety of physical, chemical and biomedical methods have been developed to introduce exogenous DNA sequences into eukaryotic cells, including the use of viral and non-viral vectors. Each method has its own pros and cons: viral vectors based on retroviruses and adenoviruses have already been employed in a number of clinical trials but have caused serious side effects<sup>[20-24]</sup>. rAAV vector is not associated with any known disease. However, the inability to transfer large size genes significantly limits its usage<sup>[25]</sup>. Furthermore, all viral vehicles are immunogenic, leading to inflammation, followed by their removal by the host immune system, as well as the inability to readminister the same viral vector. Non-viral vectors, including synthetic liposomes<sup>[26]</sup>, cationic lipids<sup>[27]</sup>, polymer<sup>[28]</sup> and DNA nanoparticles<sup>[29]</sup>,

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