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Biological basis of "depression with liver-*qi* stagnation and spleen deficiency syndrome": A digital gene expression profiling study

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Abstract *Objective:* To investigate the biological basis of "depression with liver-*qi* stagnation and spleen deficiency syndrome".
Methods: A digital gene expression profiling method was conducted to explore global changes in the mRNA transcriptome in a rat model of depression with liver-*qi* stagnation and spleen deficiency syndrome. Real-time quantitative polymerase chain reaction (q-PCR) was performed to verify the five genes most interest based on the Kyoto Encyclopedia of Genes and Genome (KEGG) analysis. *Sini San*, which disperses stagnated liver qi and strengthens the spleen, was administered to the model rats to observe whether it could reverse these genetic changes in the liver.
Results: Forty-six differentially expressed genes were identified. Three of the five genes of most interest—*Hnf4*α, *Hnf4*γ and *Cyp1a1*—based on KEGG analysis, were confirmed by real-time q-PCR. *Sini San* reduced the gene expression changes of *Hnf4*α, *Hnf4*γ and *Cyp1a1* in the rat model.
Conclusions: Hnf4α, *Hnf4*γ and *Cyp1a1* are involved in "depression with liver-*qi* stagnation and spleen deficiency syndrome". These findings indicate that depressed rats with liver-*qi* stagnation and spleen deficiency syndrome are at risk of liver diseases. Furthermore, our results will inform exploration of the etiology of depression and help in the development of effective therapeutic strategies.

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Introduction

Depression is a complex psychiatric disorder characterized by anhedonia and feelings of sadness.[1] According to the World Health Organization (WHO), depression is expected to be the second leading cause of disability after heart disease by 2020.[2] Although depression has been intensively studied, its etiology and effective therapeutic strategies are still elusive. In China, traditional Chinese medicine (TCM) has been widely used in the treatment of depression and often provides good therapeutic effect. According to TCM theory, dysfunction of the liver *zàng* is the cause of depression and the most common syndrome in depression is "liver-*qi* stagnation and spleen deficiency".[3] *Sini San*, which disperses stagnated liver *qi* and strengthens the spleen, is a prescription that has proven beneficial for curing depression.[4,5] Hence, study of the biological basis of "depression with liver-*qi* stagnation and spleen deficiency" syndrome is necessary to understand the etiology of the condition and to develop effective therapeutic strategies.

TCM posits that the response of the body to stress is associated with the function of liver *zàng*.[6] Hence, chronic unpredictable mild stress (CUMS), which mimics daily stress levels in humans, has been commonly used in researching liver *zàng* dysfunction. Exposed to stress, different tissues and organs have to interact extensively to adapt to environmental challenges. Among these organs, the liver, as defined by its anatomy, is of particular interest given its vital roles in maintaining homeostasis and health as well as regulating nutrient utilization and overall metabolism.[7] Besides, in TCM theory, the function of the liver, as defined by modern anatomy, is an important component of liver *zàng*.[8] Hence, we speculate that changes in the liver must be an important part of the biological basis of "depression with liver-*qi* stagnation and spleen deficiency syndrome".

Based on the above speculation, we first established a reliable rat model of depression with liver-*qi* stagnation and spleen deficiency syndrome, according to the method established in our previous studies.[9] Second, digital gene expression profiling (DGE), which can analyze global changes in the mRNA transcriptome, was conducted to analyze genetic changes in the liver. Finally, the classic prescription, *Sini San*, composed of Chinese thorowax root (*Bupleurum chinense* DC), immature orange fruit (*Citrus aurantium* L), red peony root (*Paeonia lactiflora* Pall) and licorice (*Glycyrrhiza uralensis Fisch*), was administered to the model rats to observe whether it could reverse the genetic changes in the liver.

Materials and methods

Animals

One hundred and ten male Sprague—Dawley rats (weighing approximately 200 ± 20 g) (Animal license No: SCXK Beijing 2012-0001) were purchased from Beijing Vitalriver Laboratory Animal Research Center, China. All rats were raised in a common animal room with a temperature of 18—24°C and humidity of 40—60%. The rats were given free access to conventional feed and water. The experimental protocols were approved by the Beijing University of Chinese Medicine Institutional Animal Care and Use Committee (Ethics number: 2013BZHYLL1001B). All efforts were made to minimize animal suffering.

Grouping

After adaptive feeding for 2 weeks, the rats were randomly divided into two groups according to body weight: CUMS group (n = 89) and control group (n = 21). Rats in the CUMS group were housed in isolation, while the other rats were housed in groups of four to five. After 6 weeks, the CUMS rats were considered the depression model with liver-*qi* stagnation and spleen deficiency syndrome and were randomly divided into three groups according to behavioral tests: (1) model group (M group)—21 rats receiving distilled water and subjected to the CUMS procedure; (2) *Sini San* + CUMS group (S group)—14 rats receiving *Sini San* dissolved in distilled water and then subjected to the CUMS procedure; (3) fluoxetine + CUMS group (F group)—18 rats receiving fluoxetine in distilled water and then subjected to the CUMS procedure. Rats in the control group (C group) remained the same.

Sini San and fluoxetine administration

Sini San is composed of Chinese thorowax root (*Bupleurum chinense* DC.), immature orange fruit (*C. aurantium* L), red peony root (*P. lactiflora* Pall) and licorice (*G. uralensis* Fisch) in a ratio of 1:1:1:1. The herbs were purchased from Beijing Tong Ren Tang Group (Beijing, China), and identified according to the Pharmacopoeia of the People's Republic of China (2010 edition), by the China—Japan Friendship Hospital Pharmacy in Beijing. *Sini San* granules were prepared by Beijing Kang Ren Tang Pharmaceutical (Beijing, China). The granules were dissolved in distilled water to make a *Sini San* suspension, containing raw materials at a concentration of 0.25 g/mL. *Sini San* dosage for human adults is 24 g/day (assuming a body weight of 60 kg for an adult human). This dosage is 2.5 g/kg/day, calculated using a human to rat dose conversion coefficient.[10] Fluoxetine was purchased as 20 mg capsules from Lilai Suzhou Pharmaceutical (Jiangsu, China) and was dissolved in distilled water at a concentration of 0.2 mg/mL. Prior to daily CUMS exposure, rats in the S group were gavaged with *Sini San* suspension (1 mL/100 g), rats in the F group were gavaged with fluoxetine suspension (1 mL/100 g) and rats in the M and C groups were gavaged with distilled water (1 mL/100 g).

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