Theoretical Approach

The Change-Over of *Yin-yang* and Gene Regulation in Kidney Deficiency Syndromes

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The present paper studies gene regulation in kidney deficiency syndromes from the simple Nephrotic Syndrome and with the principle of positive-negative regulation to control the change-over of *yin-yang*, the modern molecular biological techniques can be used, such as gene chip, representational difference analysis (RDA) and gene sequence analysis, so as to investigate the inner relationship between the genes and kidney deficiency syndromes and prove the effect given by these genes on the pathophysiological status of change-over of *yin-yang* in kidney deficiency syndromes. This philosophical approach and method can also be adopted for studies of the related genes in other TCM syndromes.

**Key words:** nephritic syndrome; kidney-deficiency syndrome; change-over of *yin* and *yang*; gene regulation

In recent years, great progress has been made in studies on the nature of kidney deficiency syndromes. But many problems have not been solved yet. For example, in the study on the specific indexes for the kidney-*yang* deficiency syndrome, the same results of urine 24h 17-hydroxyl-steroid can also be found in the syndromes of deficiency of spleen-*yang*, deficiency of lung-*qi*, and deficiency of stomach-*yang*. So, the study of the pathological features from genomics for *yin-yang* change-over of nephritic syndrome may also shed light on the study of kidney deficiency syndromes because the change-over of *yin-yang* in nephritic syndrome is typical, especially in the first stage of treatment with a large dose of glucocorticosteroid. Under the effect of glucocorticosteroid, the pathological condition of the patient with edema due to *yang* deficiency may change into *yin* deficiency with deficient fire presenting the symptoms of exogenous adrenocortical hyperfunction like Cushing's syndrome, such as malar flush, dry throat, hot sensation in the palms and soles, acne, polytrichosis, red tongue with less moisture, wiry and rapid pulse. But with a decreased dose of glucocorticosteroid in the maintenance period, the patient may present different degrees of corticosteroids withdrawing syndrome with the pathological changes for *yin* deficiency to *yang* deficiency marked by listlessness, tiredness, pale complexion, soreness in lumbus and knees, shortness of breath, unwillingness to talk, light red tongue, deep and thready pulse. Therefore, it is necessary to integrate the present studies on *yin-yang* change-over in kidney deficiency syndrome with the nature of gene regulation.

The Study of Gene Regulation for *Yin-Yang* Change-Over in Kidney Deficiency Syndrome is a Feasible Measure for the Study on the Nature of Kidney Function

In the studies of integrated traditional and Western medicine in 1950s, the doctors discovered that the 24h 17-hydroxy-steroid tended to decrease in kidney-*yang* deficiency syndrome, which may be taken as one of diagnostic indexes. Later, they found that kidney-*yang* deficiency syndrome was closely related to the pathological changes of the neural system, endocrine system and immunologic system, and it was a functional disorder of hypophysis – hypothalamus – gonad, thyroid and adrenal gland, in which the main problem was in the hypothalamus.
Further study proved that Chinese medicines for warming and reinforcing kidney-yang could directly increase the transcription and expression of the hypothalamus CRF hormone gene to improve the restrained state of Hypothalamus-Pituitary-Adrenal-Thymus (HPAT) axis, indicating that kidney-yang deficiency syndrome should be regulated from the hypothalamus and neuroendocrine-immune system. TCM scholars also proved that the kidney-yang deficiency syndrome possessed the foundation of modern pathophysiology. These experimental data and clinical applications were strong evidence, but not adequate, for the study of the nature of kidney deficiency syndrome. Therefore, regarding the congenital essence in TCM as the hereditary substance (genome) is of great significance for the study of gene regulation in the process of yin-yang change-over in kidney deficiency syndrome.

**Possible Mechanism for Gene Regulation in The Occurrence of Kidney Deficiency Syndromes**

The positive and negative controlling genes, the enhancers and attenuators, and the dominant genes and recessive genes of the human body all reveal yin-yang features in pairs. They are possibly the genes for regulating yin-yang change-over in kidney deficiency syndrome. In addition, some genes may possess bidirectional or adverse feature of yin-yang, that is, yang may have its root in yin or yin may have its root in yang. Patients with nephritic syndrome, after being treated with steroids, will present with the pattern transforming from yang asthenia to yin asthenia and then to yang asthenia, which is the result of gene regulation. If we design a scientific study to examine the positive controlling genes and negative controlling genes, the enhancers and attenuators or the dominant genes and recessive genes, we can bring to light the nature of the symptom-complex with gene regulation. Pathogenesis of kidney yin-yang deficiency syndromes, such as promoting apoptosis genes and antiapoptosis genes, degradation and synthesis of protein, inflammation and anti-inflammatory, can also be explained by the theory of gene regulation. In addition, the over-expression or ectopic expression of genes in chronic renal disease and the gene regulation or gene knock-out in correlated experiments can be explained by gene regulation in kidney yin-yang deficiency syndrome if these factors would destroy the system balance or block the signal conduction.

In yin-yang theory, yin represents epithelial cells and yang represents renal interstitium, interacting with each other to induce renal interstitium differentiation and form nephrons to maintain normal kidney function. Mono-cell is yin while cell function is yang at the cellular level. From the corpuscular substructure, we may think that stem cells are yang and others are yin. As to the kidney of an adult, when injured, an epithelial cell will transform from epithelium to interstitium (yin-yang transformation inside the kidney). An inflammatory reaction (from the outside of the kidney, or an invasion of yang) leads to kidney fibrosis. If we want to repair the function of an epithelial cell, yin should be increased, with interstitium transforming to epithelium, that is, a process of decreasing yang so as to recreate the balance of yin-yang. Stem cells are activated because of exogenous temporary yang stimulation in renal injuries. Stem cells transform to epithelial cells because of yin transforming to yang, thus establishing the yin-yang balance. If the effort to restore balance fails, it may lead to kidney-yang deficiency or kidney-yin deficiency.

**The Genes Possibly Affecting Yin-Yang Change-Over in Kidney Deficiency Syndromes**

Kidneys are the congenital foundation of human existence and govern sperm storage, relating to the basic living activities of cells, such as cell proliferation, cell differentiation and aging and death. There are two aspects affecting yin-yang change-over in kidney deficiency syndrome at the molecular level, one of which is the change of telomere genes. Telomere is a region of high-level duplicate nucleotide sequence in the terminal end of a chromosome, with the function of maintaining structural integrity of chromosomes in its reproduction process. Normal cells gradually lose
approximately 100bp terminal sequence of telomeres in a cell cycle split. When telomeres shorten too much to retain the structural integrity of duplicated chromosomes, cells will enter into the state of yang asthenia or yin asthenia.\textsuperscript{4} Multi-potent stem cells or tumor cells possess the ability of rapid proliferation and prolonged life compared to normal mature cells because telomerase activation can compensate for telomere loss in the process of proliferation, but telomerase in the normal mature differentiated cells is generally inactivate. The study of another mechanism of yin-yang change-over in kidney deficiency syndrome derives from the study of the cell cycle, which finds that yin-yang change-over in kidney deficiency syndrome is regulated by the CDK inhibiting genes (including P53, P16\textsuperscript{INK4a}, P21\textsuperscript{waf1}, etc.), as the limiting factor in the cell cycle. These genes can induce yin-yang change-over in kidney deficiency syndrome in the process of importation or expression activation. But the study is short of data to prove whether there does exist a relationship and a signal path. Therefore, with a scientific idea, we will promote the progress of the study of the nature of kidneys by carrying out animal model studies from signal transduction path and gene regulation.\textsuperscript{5}

Propects

Yin-yang change-over in kidney deficiency syndrome is the result of gene expression and regulation. Although it is affected by interactive genes, environment, nutrition and the background of medications, phaenotype is mainly regulated by regulating factors, topoismerase, reading frames, methylation degree of gene and glycosylation. The experimental study for kidney-yang deficiency syndrome done by WANG Mi-qu et al. confirmed the complexity of gene array to a certain extent.\textsuperscript{6} With the theory of gene regulation, yin-yang and functional system and with a concept of deficiency cold syndrome as a kind of multiple phaenotype, the cause for deficiency cold syndrome in elderly people is a great quantity of gene methylation. We think the change of gene groups is an important direction for the scientific research on the nature of this syndrome. And the study of the nature of the TCM syndromes will be greatly promoted by the substantial study of the yin-yang change-over model in nephritic syndrome.

References