

## Reviews

### Yin-yang Balance Therapy on Regulating Cancer Stem Cells

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**Abstracts:** Researches have shown that cancer stem cells, regulated by the niche where they reside, are the roots of oncogenesis, relapse and metastasis. To date, very few treatments have targeted on cancer stem cells. The authors study that the regulated factors in the niche share the characteristics of yin-yang in the theory of traditional Chinese medicine, which has confirmed its therapeutic effects in the prevention and treatment of cancer. So the authors presume that the mechanisms of traditional Chinese medicine on the prevention and treatment of cancer may be related to the *yin-yang* balance of the niche of cancer stem cells.

**Keywords:** *yin and yang; traditional Chinese medicine; cancer stem cells; niche*

Traditional Chinese medicine (TCM) holds the theory that diseases are induced by the imbalance of yin and yang. Cancers are no exception. Yin-yang balance therapy is the main principle of TCM in the prevention and treatment of cancer. Based on this principle, TCM has confirmed its therapeutic effects in the prevention and treatment of cancer, but the mechanisms are still obscure.

Researches have shown that cancer stem cells (CSC), regulated by the niche where they reside, may be the roots of oncogenesis. To date, very few treatments have targeted on cancer stem cells. Moreover, we study that the factors in the niche, controlling CSC, resemble the characteristics of yin-yang. Therefore, the authors presume that the anti-cancer mechanisms of TCM may be related to the yin-yang balance therapy of CSC, which would make it possible to interpret the effects of TCM.

#### Yin-yang Balance Therapy is throughout the Whole Cause of Cancer Treatment

The theory of TCM holds that the pathogenesis of all diseases is caused by the imbalance of yin and yang of the body. It is recorded in *Su Wen* (素问 Plain Questions) that "If yin and yang are in a relative equilibrium, life activities will be normally maintained; if yin and yang are separated, exhaustion of vital essence will happen." The balance of yin and yang correlates with the harmony of the joint functions of each system, the Zang organs in particular. If the human body is balanced, people remain healthy. Otherwise, diseases or even death will occur.

Just as the origins of all the diseases, the cause of cancer is also induced by the imbalance of yin and yang, which is manifested as the stagnation of *qi*, coagulation of phlegm, stagnation of blood, and accumulation of toxic heat. If the imbalance of yin and yang continues, "yin may separate from yang", and "vital essence" be exhausted, leading to an ultimate stage of cancer. The imbalance of yin-yang is throughout the whole cause of cancer. So treatment principle is to restore the balance of

yin-yang. As was proposed by two famous Chinese oncologists YU Ren-cun (郁仁存) and LIU Jia-xiang (刘嘉湘), the cancer treatment should follow the principle of regulating yin and yang to stabilize the internal environment and reestablish the internal balance. Then tumor can be controlled, and the antipathogenic *qi* be protected, symptoms relieved, quality of life improved, and the survival time prolonged.<sup>1,2</sup>

TCM with the principle of balancing yin-yang exerted antitumor effects through multiple actions aiming at multiple targets. Experimental studies have shown that TCM have many effects, including inducing tumor cell apoptosis and differentiation, regulating cellular transduction pathway, suppressing tumor angiogenesis, inhibiting telomerase activities, regulating immune function, and reversing multiple drug resistance, etc.<sup>3</sup> But all of these molecular mechanisms can not interpret the essence of TCM therapy overall.

#### Cancer Stem Cells are the Roots of Oncogenesis, Relapse and Metastasis

Accumulating evidence has been reported that cancers are organized in a hierarchy of heterogeneous cell populations with different biological properties and that the capability to sustain tumor formation and growth exclusively resides in a small proportion of tumor cells, termed CSC or tumor initiating cells. CSC have been identified in leukemia,<sup>4</sup> breast cancer,<sup>5</sup> brain cancer,<sup>6</sup> prostate cancer,<sup>7</sup> gastrointestinal cancer,<sup>8</sup> etc. These studies have shown that CSC are responsible for tumor growth and metastasis.<sup>9</sup>

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Although the origins of CSC may vary, they share several properties with normal stem cells especially the extensive capability of self-renewal.<sup>10</sup> CSC can self-renew to generate additional CSC and also differentiate to generate phenotypically diverse cancer cells with limited proliferative potential. The existence of CSC might explain why there are so many recurrence, even tumor disappeared completely by radiotherapy or chemotherapy since CSC have the properties of quiescent or slowly proliferating nature,<sup>11</sup> the high expression level of ATP-binding cassette transporter,<sup>12</sup> the intrinsic high levels of anti-apoptotic molecules, and their efficiency of DNA repair.<sup>13</sup>

### CSC are Regulated by the Niche

CSC lives in a certain circumstance, named niche. The biological behavior of CSC is strictly regulated by the signal from niche in the physiological condition.<sup>14</sup> On the one hand niche sustains both self-renewal and characteristics of CSC; on the other hand it also controls the quantity and proliferation of CSC, which may be the mechanism of cancer prevention in human body.<sup>15</sup> As to CSC, niche can control the quantity and proliferation of CSC by regulating the biological behavior of CSC. It was confirmed by the evidence that a tumor had been quiescent for 10 years.<sup>16</sup> However, if the abnormality occurs in the niche, the quantity and proliferation of CSC will be out of control, and then cancer relapse and metastasis will occur, e.g., abnormal factors, secreted by cells nearby niche and extracellular matrix, delivered the signal of proliferation may promote cancer progression, relapse and metastasis;<sup>15</sup> the related signals of self-mutation of CSC may lead to the establishment of their own niche,<sup>17</sup> and finally the proliferation of niche would cause the cancer relapse or metastasis. So CSC is strictly regulated by the niche.

### Therapy Discovery for CSC

The authors have mentioned above that cancer might relapse ten years later. Why were cancer cells being quiescent for so many years? This can be explained by the theories of TCM and CSC. Under normal conditions, regulated factors in the niche controlling oncogenes and suppressor genes, proliferation, differentiation and apoptosis, activation and inactivation of signal transduction pathways are maintained in a balanced condition in order to regulate the normal quantity of stem cells. These factors are similar to the yin and yang of TCM theory, e.g., for the function of CSC, the authors may think that oncogenes are yang, and suppressor genes are yin. Once destroyed, the balance of oncogenes (yang) and suppressor genes (yin) will not exist, and the proliferation of CSC would be out of control. Then cancer will occur, and relapse and metastasis will develop. If we want to control the proliferation of CSC, oncogenes (yang) should be suppressed, or suppressor genes (yin) should be activated. Therefore, based on the principle of yin-yang, the treatment on the regulation of the niche of CSC is quite important.

Since the regulation of CSC is quite complicated, single target seems unlikely to change the biological behavior of CSC. To date, very few treatments have targeted on CSC. However, clinical studies of TCM have confirmed its advantages in the treatment and prevention of malignant tumor.<sup>18,19</sup> Experimental studies also have shown that TCM regulates the self-renewal of adult stem cells,<sup>20-22</sup> e.g., Saponins of Huang Qi (Radix Astragali seu Hedysari) specifically promoted neural stem cells to differentiate into neurons;<sup>23</sup> Yin Yang Huo (Herba Epimedii) flavonoids could promote the proliferation and migration of adrenocortical stem cells in rats with kidney-yang deficiency;<sup>24</sup> as early as 1999 GAO Rui-lan, et al.<sup>25</sup> studied that total saponins of panax ginseng had an effect on progenitor cells of leukemia which was different from the effect on normal progenitor cells, and different concentrations of total saponins of panax ginseng showed bilateral effects of proliferation and suppression. Although the direct objects of these studies were not CSC, it provided certain supporting details for the hypothesis of TCM on regulating CSC.

In brief, the mechanisms of the regulation of CSC and the balance of yin-yang share many similarities that are to regulate the environment from the imbalanced state to balanced state. Thus, we propose that the mechanism of cancer treatment by TCM may be related to CSC.<sup>26</sup> Based on the principle of yin-yang balance, TCM may regulate the balance of human internal environment, indirectly balance the niche of CSC, and control the tumor.

### Summary

The detection of CSC shed light on the treatment of cancer. However, the regulation of CSC is quite complicated, single target seems unlikely to change the biological behaviors of CSC. TCM has a history of more than two thousand years, the principle of which is to regulate the disharmonized yin and yang. Just as is mentioned in *Su Wen* (素问 Plain Questions) "check the disharmony of yin-yang, then regulate it until balanced conditions". Therefore, the authors believe that further study on the mechanisms of TCM on regulating CSC may explore the molecular mechanisms of therapeutic effects and provide a potential strategy for eradicating cancers.

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