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Academic Exploration

Shen-Jing as a Chinese Medicine Concept Might Be a Counterpart of Stem Cells in Regenerative Medicine*

REN Yan-bo, HUANG Jian-hua, CAI Wai-jiao, and SHEN Zi-yin

ABSTRACT As the epitome of the modern regenerative medicine, stem cells were proposed in the basic sense no more than 200 years ago. However, the concept of "stem cells" existed long before the modern medical description. The hypothesis that all things, including our sentient body, were generated from a small origin was shared between Western and Chinese people. The ancient Chinese philosophers considered Jing (also known as essence) as the origin of life. In Chinese medicine (CM), Jing is mainly stored in Kidney (Shen) and the so-called Shen-Jing (Kidney essence). Here, we propose that Shen-Jing is the CM term used to express the meaning of "origin and regeneration". This theoretical discovery has at least two applications. First, the actions underlying causing Shen-Jing deficiency, such as excess sexual intercourse, chronic diseases, and aging, might damage the function of stem cells. Second, a large number of Chinese herbs with Shen-Jing-nourishing efficacy had been proven to affect stem cell proliferation and differentiation. Therefore, if Shen-Jing in CM is equivalent with stem cells in regenerative medicine, higher effective modulators for regulating stem-cell behaviors from Kidney-tonifying herbs would be expected.

KEYWORDS Shen-Jing, Kidney essence, Kidney tonifying herbs, regenerative medicine, stem cells

Some newly formed ideas initially lack substantial evidence but usually play an essential role in incubating real scientific findings and the development of theories. The discovery of stem cells was born from the idea that every organ of our adult body originated from a very small constituent. This hypothesis was metaphorically compared to biological atomism.[1] The term "stem cell" can be traced back to the late 19th century. In 1868, Ernst Haeckel, a famous German professor of zoology, used Stammzellen (stem cells) to describe unicellular organisms or protozoa, which he believed to be the phylogenetic ancestors of multicellular organisms.[2] In 1892, Valentin Haecker[2] referred to Stammzelle (stem cells) as the common precursor cells describing the embryonic development of the crustacean Cycolops. The same year, Theodor Boveri[3] described those cells derived from a fertilized egg cell as Stammzellen (stem cells). By this time, the connotation of stem cells was something similar to what would be considered modern embryonic stem cells (mESCs). A wide variety of cell populations with similar biological characteristics and functionality in nearly all tissues in adult body were discovered in subsequent years. The development of regenerative medicine where stem cell biology is a core part of the revolution in medical philosophy, medical science, and therapeutics. Regenerative medicine holds great promise to treat a wide range of complex diseases. Indeed, some therapies based on regenerative medicine have already entered clinical trials.

If the concept that all things, including our bodies, were generated from a pure and small origin was a commonality between ancient Western and Chinese societies, it is reasonable that we can identify terminologies that express similar ideas. Chinese medicine (CM) is characterized by a number of unique theories or concepts; Shen-Jing, also known as the Kidney (Shen) essence, is one of them. Just like every process of scientific discovery, the term Shen-Jing in CM might express the notion that our body was developed from a small origin and that our adult body possesses the potential to regenerate. Two thousands years ago, a handful of ideas regarding the origin of all things of world had already been developed in China. A collection of essays of

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Institute of Integrated Chinese and Western Medicine, Huashan Hospital, Fudan University, Shanghai (200040), China
Correspondence to: Prof. SHEN Zi-yin, Tel/Fax: 86-21-62490934, E-mail: ziyinshen@126.com
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ancient philosophy written by Guan Zi said that Jing is essential for all things. It can generate everything on the earth and stars in the sky.[4] Discussion on *Shang Shu·Hong Fan*, expressed the same viewpoint when describing that water is generated from one and is an origin of any other thing.[5] This concept that Jing is the origin of things was gradually merged into CM theory. *Huangdi's Internal Classic* (Huang Di Nei Jing), who authored one of the most ancient and important representative books about CM, expressed the concept of Jing as follows, "At the beginning of human development, Jing initially formed, then bone, pulse, tendon, muscle, skin, and hair were developed".[6] Ancient physicians noted that "Jing is stored in Kidney (Shen) and is called Shen-Jing".[7] Such theories of CM guide the clinical use of Chinese herbs. According to CM theory, Shen-Jing plays a key role in maintaining healthy bodily function. If Shen-Jing is decreased or depleted, a specific combination of symptoms should appear. This Shen-Jing deficiency pattern in CM is associated with several pathological changes: weakened reproductive function, premature senility, tinnitus, loosing of teeth, hair loss, and forgetfulness.

Recently, we searched an electronic database of Chinese-language medical and scientific literature, the China National Knowledge Infrastructure (CNKI), and found that in 1996 some authors claimed that Shen-Jing is the source of information, similar to DNA.[8] In 2002, Sun, et al[9] reported that Jing expressed the meaning of "origin and regeneration" in CM. Until 2004, just one paper had proposed that Shen-Jing has similarity to stem cells.[10] Our group realized that there are a large number of Chinese herbs or formulae with the effect of nourishing Shen-Jing. If Shen-Jing corresponds to stem cells, effective modulators for regulating stem cell behaviors could be found among these Chinese herbs, and it might be possible to find evidence supporting the claim that activation of endogenous stem cells is one of mechanisms by which CM therapies exert their effects.[11]

Chinese Herbs Affect Stem Cells

We searched the major electronic database of Chinese-language medical and scientific literature in CNKI for publications from January 1, 2000 to October 31, 2012 with two sets of search key words, "Gan Xi Bao" (stem cells) or "Zai Sheng Yi Xue" (regenerative medicine) and "Zhong Yi" (Chinese medicine) or "Zhong Yao" (Chinese herbs). A total of 782 papers were initially identified. Non-original articles including reviews, comments, and news were excluded from further analysis. We ultimately obtained 205 original articles that focused on the pharmacological effects of Chinese herbs, including formulae (*n*=106), single herbs (*n*=50), components from formulae or single herbs (*n*=20), and pure compounds (*n*=29), on various types of stem cells.

The annual distribution of publications among the total of 782 papers dramatically increased by about 3-fold from the year 2000 (*n*=27) to the year 2013 (*n*=77). In 2012 , there were 80 papers. This indicates that the topic of regenerative medicine in CM is an increasingly attractive field. The distribution frequency of articles by year is represented as a histogram in Figure 1A. Next, we analyzed the distribution of the type of stem cells used in these articles; 52.2% articles reported bone mesenchymal stem cells (bMSCs), 9.1% described neural stem cells (NSCs), and 6.6% were hematopoietic stem cells (HSCs). Other types of stem cells accounted for about 32.1% (Figure 1B). According to the therapeutic principles of CM, all drugs in publications can be grossly classified into Kidney-nourishing, qi-nourishing, and blood circulation-promoting drugs. The frequency distribution of therapeutic principles is presented in Figure 1C. Kidney-nourishing drugs accounted for 21.5%, blood circulation-promoting drugs for 15.7%, and qi-nourishing drugs were 12.8%. A total of 46.4% described mixed therapeutic principles (Figure 1D). bMSCs were the most heavily studied stem cells (52.2%).

Among drugs used in these studies, some were reported to stimulate the proliferation of bMSCs, but many more drugs induced differentiation toward a wide spectrum of cell lineages. We performed a detailed analysis of the effects of pure compounds, and the results are listed in Table 1. Among them, icariin (ICA), isopsoralen, osthol, and naringin could stimulate bMSC differentiation toward osteoblasts,[12-15] while astragaloside Ⅳ promoted MSC proliferation.[16] Baicalin, ligustrazine, and salidroside induced bMSC differentiation to neurons.[17-19] Salvianolic acid B induced bMSC differentiation into cardiomyocytes,[20] while Panax notoginsenoside Rg1 did so in combination with 5-azacytidine.[21] Baicalin also could induce differentiation of human umbilical cord blood-derived mesenchymal stem cells into neuron-like cells.[22] While these findings

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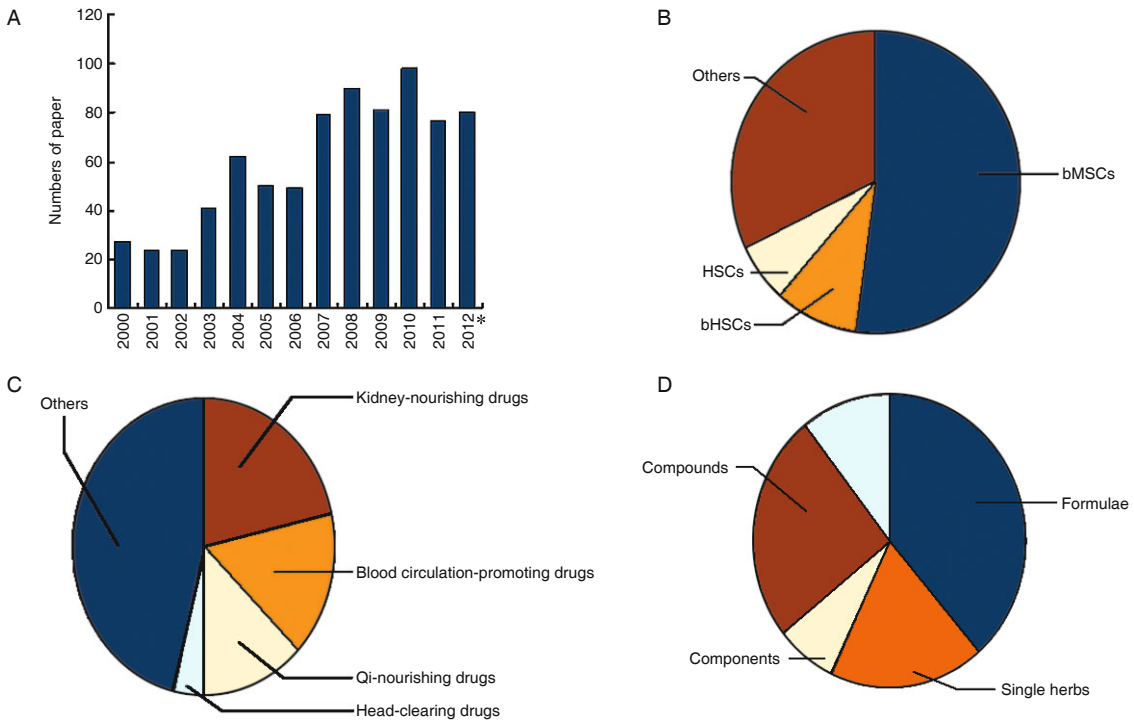

Figure 1. Chinese Herbs Affect Stem Cells

Notes: A total of 782 papers were obtained by searching the keywords "Shen-Jing" or "regenerative medicine" and "traditional Chinese medicine" or "Chinese herbs" in their Chinese form inCNKI. (A) The annual number of total publications (n=782) from January 1, 2000 to October 31, 2012 are indicated in histogram. *To October 31, 2012. (B) The frequency distribution of stem cell types used in the original research articles (n=205) is presented in the pie chart. (C) The Chinese herbs or compounds extracted from herbs in publications (*n*=274) were grossly divided into Kidney-nourishing, qi-nourishing, blood circulation-promoting and heat-clearing drugs, and their distributions are presented in the pie chart. (D) The drugs used in publications (*n*=205) can be classified into formula, single herb, component of formula or single herb, and pure compound. The frequency distribution of these entities was calculated and is presented in the pie chart.

were very interesting, not all of the studies investigated the underlying mechanisms by which they exerted their effects. We noted that the most of Chinese herbs used in publications had Shen Jing-nourishing effects, such as *Carapax Trionycis*, *Cortex Eucommiae*, *Herba Cistanches*, *Herba Epimedii*, Guilu Erxian Glue (龟鹿二仙胶), Yougui Pill (右归丸), Zuogui Pill (左归丸), and Dihuang Yinzi (地黄饮子).[23] There are 25 papers describing the action of Chinese herbs on NSCs. Several pure compounds, such as salidroside,[24] Antler polypeptides,[25] baicalin,[26] and geniposide,[26] were reported to promote differentiation of NSCs into neurons. However, these studies were affected by the same problem in that they reported the general effects of Chinese herbs but did not perform experiments to elucidate the underlying mechanisms. The signaling pathways and molecular targets of these drugs remain elusive. This may be an important research focus in the future.

Next we searched the Web of Knowledge database with the keywords "herbal medicine" and "stem cells" and obtained a total of 43 papers that we manually filtered. The effects of reported pure compounds are listed in Table 1. *Radix Ginseng*, which belongs to the genus Panax of the family Araliaceae, has been known to possess diverse effects. To discover the potential effect of ginseng on ESCs, Sasaki, et al[27] demonstrated that bioactive compounds screened from *Panax ginseng* could promote mESC differentiation into beating cells. Kim, et al[28] found that *Radix Ginseng Rubra* extract accelerated the proliferation of undifferentiated hESCs and promoted the differentiation of embryonic bodies into a mesendoderm lineage. *Herba Epimedii* is widely used as a tonic, aphrodisiac, and antirheumatic in China. Flavonoids of epimedium regulate osteogenesis of human mesenchymal stem cells through bone morphogenetic protein (BMP) and the Wnt/beta-catenin signaling pathway.[29] ICA, icaritin (ICT), and desmethylicaritin (DICT) are constituents of *Herba Epimedii* , and all of them exert inducible effects on the directional differentiation of mESCs into cardiomyocytes. *In vitro*, ICA stimulated the generation of reactive oxygen species (ROS)

Table 1. Effects on Stem Cells and Associated Mechanisms of Compounds Derived from Chinese Herbs

Compound	Type of stem cells	Main outcome and mechanisms	Reference
Icariin	bMSCs	Enhanced differentiation → osteoblasts, associated with increased TGF β 1 and BMP2	[12]
	mESCs	Enhanced differentiation → cardiomyocytes; ROS, p38signalling was involved	[30,31]
Desmethylicaritin	mESCs	Enhanced differentiation → cardiomyocytes	[30]
Baicalin	bMSCs	Enhanced differentiation → neurons	[17]
	ucMSCs	Enhanced differentiation → neurons	[22]
	NSCs	Enhanced differentiation → neurons	[26]
Salvianolic acid B	bMSCs	Enhanced differentiation → cardiomyocytes	[20]
	mESCs	Enhanced differentiation → cardiomyocytes when combined with vitamin C	[34]
Rg1	bMSCs	Enhanced differentiation → cardiomyocytes when in synergy with 5-azacytidine	[21]
Isobavachin	mESCs	Enhanced differentiation → neurons or astrocytes, increased ERK, decreased p38, JNK were involved	[32]
Isopsoralen	bMSCs	Proliferation ↓, enhanced differentiation → osteoblasts	[13]
Osthole	bMSCs	Proliferation ↓, enhanced differentiation → osteoblasts	[14]
Astragaloside	bMSCs	Proliferation ↑, stem cell factor was increased	[16]
Ligustrazine	bMSCs	Enhanced differentiation → neurons	[18]
Geniposide	NSCs	Enhanced differentiation → neurons	[26]
Salidroside	bMSCs	Enhanced differentiation → neurons	[19]
	NSCs	Enhanced differentiation → neurons	[24]
Naringin	bMSCs	Enhanced differentiation → osteoblasts; MAPK signaling was involved	[15]
Ginkgolide B	mESCs	Increased apoptosis, increased JNK activation, ROS formation was involved	[33]
Antler polypeptides	NSCs	Enhanced differentiation → neurons	[25]

Notes: mESC: mouse embryonic stem cells; bMSCs: bone mesenchymal stem cells; NSCs: neural stem cells; ucMSCs: umbilical cord blood mesenchymal stem cells; TGF: transformation growth factor; BMP: bone morphogenetic protein; ROS: reactive oxygen species; PI3K: phosphoinositide 3-kinase; Akt: also known as protein kinase B; ERK: extracellular signaling-regulated kinase; JNK: c-Jun N-terminal kinase; MAPK: mitogen-activated protein kinase

and then initiated the ICA-inducible differentiation cascade, including activation of the p38 mitogen-activated protein kinase (MAPK) pathway.[30,31] Isobavachin, a major component of *Malaytea Scurfpea*, was shown to induce differentiation of mouse ESCs into neurons and astrocytes under different conditions that involved decreased phosphorylation of p38 and JNK and increased ERK phosphorylation.[32] Ginkgolide B, a chemical component extracted from *Ginkgo Biloba* leaves, was reported to induce mouse ESC apoptosis *via* ROS generation, c-Jun N-terminal kinase (JNK) activation, loss of mitochondrial membrane potential (MMP), and caspase-3 activation.[33] Salvianolic acid B, an active constituent of *Salvia miltiorrhiza* Bunge, was tested for potential effects on ESCs. The results showed that the effect of salvianolic acid B alone was minimal, but with vitamin C it could effectively induce ESC differentiation into cardiomyocytes.[34]

From the published literature, we know that there are a large number of Chinese herbs and ingredients extracted from them that can affect stem cell behavior. In the present study, most of these drugs were found to belong to the Shen Jing-nourishing entity, which supports the hypothesis that the concept of Shen-Jing in CM is associated with stem cells in regenerative medicine. However, additional evidence from physiological and pathological studies regarding the association between Shen-Jing and stem cells is needed.

Relationship between Shen-Jing and Stem Cells

Understanding the association between Shen-Jing in CM and stem cells in regenerative medicine is significant in many ways. Previous studies support some points of this hypothesis. According to CM theory, Shen-Jing deficiency is usually caused by several reasons, including dysplasia induced by multiple damages before birth, prolonged excessive sexual activity, chronic stress or disease, and aging. According to this hypothesis, we could deduce that stem cells might residing within tissues is damaged by these processes. This idea perhaps enhances

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our understanding of the role of stem cells in the pathogenesis of abnormal emotions, development, stressors, behaviors, and aging. Neurogenesis in adult male Sprague Dawley rats has been extensively analyzed in the forebrain and hippocampal formation, and different stress paradigms (emotional, systemic, psychological, or physical) have been reported to decrease progenitor cell proliferation and the production of immature neurons in the hippocampal dentate gyrus in many mammalian species. The extent of this decrease varies in general from 30% to 76%.[35,36] Just like stress, aging might also influence stem cell function. In CM, the major symptoms of aging are considered to be caused by Shen-Jing deficiency, including tinnitus, tooth and hair loss, and forgetfulness. It is said that a living organism is as old as its stem cells, but surprisingly little is known about the impact of time and age on these basic units of life, that is tissue-specific or adult stem cells. An understanding of the molecules and processes that enable stem cells to initiate self renewal and to divide, proliferate, and differentiate might be the key to regenerative medicine and an eventual cure for many diseases. Finding ways to reactivate stem cells and control their target destination might create unforeseen opportunities for treating or even curing degenerative diseases.[37]

Regarding the relationship between stem cells and diseases, scientists often focus on how abnormal stem cells relate to diseases and the therapeutic effects of stem cell-based therapies. From the unique perspective of CM, a chronic disease will inevitably damage Shen-Jing, so maybe there is a common pathological change that causes stem cell dysfunction in the late stage of various diseases. So far, this has not been investigated. According to CM, in cases in which Shen-Jing is injured, whether stem cell dysfunction occurs remains to be investigated. However, the results of existing studies have already indicated that understanding the concept of Shen-Jing and the association between Shen-Jing and stem cells may be helpful to advance modern stem cell biology.

Discussion

In the present study, we proposed that the ancient hypothesis that our adult body has a pure and small origin that exists throughout adult life and provides a replacement source for tissues has played an important role in the discovery of stem cells. The meaning of "origin and regeneration" in CM is expressed by term Shen-Jing. This theoretical discovery about Shen-Jing at least has two applications.

Firstly, those processes that result in a Shen-Jing deficiency pattern, such as dysplasia, excessive sexual activity, prolonged stress, chronic disease, and aging, would damage stem cell function. Some aspects in stem cell biology that had not been paid much attention to could become important issues again. Moreover, we might reasonably deduce that stem cells residing within affected tissues are damaged by these processes. This idea perhaps enhances our understanding of the role of stem cells in the pathogenesis of abnormal emotion, development, stressors, behavior, and aging.

Secondly, screening systematic studies have revealed a low hit rate of effective modulators on stem cells. Wu, et al[38] used the mouse embryonic carcinoma cell line P19 and mouse ESCs for high throughput screening and found that just 35 of 100,000 compounds induced myosin heavy chain (MHC) expression; the most potent compound was Cardiogenol C, which is a hit rate of only 0.035%. In addition to screening molecules directing ESC differentiation, a cell-based screen of chemical libraries was carried out to identify small molecules that control self-renewal of the transgenic OG2 (Oct4-GFP)-mESC line.[39] Just 17 of 50,000 (0.034%) screened compounds were identified to maintain mESC self renewal. Sabrina, at al[40] screened a library of 2,880 small molecules from a library that contained a broad set of biologically active and structurally diverse compounds, including a set of 748 currently marketed drugs. Only 89 of 2,880 (3.1%) compounds increased Oct4 (a pluripotent marker) intensity, which is suggestive of elevated self-renewal ability. To screen large numbers ($>10^5$) of discrete compounds for those molecules that selectively induce neuronal differentiation, Ding, et al[41] constructed a luciferase reporter by inserting 1.1 kb of the regulatory region of neuronal Tα1 tubulin, a specific neuronal marker, upstream of the luciferase gene. A single stable P19 clone transfected with the pTα1-Luc reporter afforded a significant increase in luciferase signal by a number of molecules in the selected library; however, the hit rate was not reported.

Chinese herbs have been clinically used for thousands of years, and there is a large body of literature reporting the efficacy and response of body to these herbs. There are many Chinese herbs with Shen-Jing-nourishing activity, and if Shen-Jing is the counterpart in CM to stem cells, we speculate that there would be a higher hit rate of effective agents with the ability to regulate stem cell behaviors among Shen-Jing-nourishing herbs and/or formulas.

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