Neuropsychiatric Disease and Treatment

Dovepress
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REVIEW

Characteristics of Parthenogenetic Stem Cells and Their Potential Treatment Strategy for Central Nervous System Diseases

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Abstract: Stem cells hold significant promise in treating neurological illnesses, such as stroke, spinal cord injury and neurodegenerative diseases. The origins and characteristics of human parthenogenetic stem cells might lead to a new research area in treating nervous system diseases. The current clinical studies in the field of traumatic brain injury and neurodegenerative diseases are reviewed. Some variables that influence common stem cells' survival, proliferation, and therapeutic efficacy will be mentioned in this paper because they may play an important role in studying parthenogenetic stem cells.

Keywords: parthenogenetic stem cells, neural stem cells, traumatic brain injury, spinal cord injury, neurodegenerative diseases, treatment strategy

Introduction

Human parthenogenetic stem cells (hpSCs) belong to one kind of human pluripotent stem cells. They are produced from chemically-activated unfertilized oocytes. These cells can proliferate, replenish themselves, and differentiate into more than one daughter cell, which has great potential for therapeutic purposes.[1,2] At present, many scientists have studied cell therapy, including stem cell therapy is one of them. Cell therapies, considered the key clinical neurorestorative option for central nervous system diseases, have recently been tested for their therapeutic value.[3–6] According to the current experiments in vitro and in vivo, it has been proved that stem cells may have the potential to improve the motor or sensory function of the central nervous system after injury under many pathological conditions, such as traumatic brain injury and Parkinson's disease. However, stem cell treatment has significant drawbacks, as evidenced by previous stem cell experiments. Firstly, embryonic stem cell therapy may cause ethical problems due to the frequent use of embryos or fetuses when obtaining embryonic stem cells.[7] secondly, as we know, most of the embryonic stem cells used in the treatment are allogeneic; immunosuppressive therapy is necessary after transplantation, leading to complications. Thirdly, because of stem cells' strong replication ability, the problem of tumorigenicity after transplantation cannot be ignored.[2,8,9] Since parthenogenetic stem cells are produced from unfertilized oocytes, they bypass the ethical dilemmas associated with embryo or fetal usage.[4,10,11] The ethical issues and debates of stem cells are the products of the possible consequences of the research process and application results of stem cells in conflict with the existing ethical concepts and norms of society. Embryonic stem cells are derived from embryos. Embryos are regarded as a person or a potential life rather than a group of cells for research. Because the process of obtaining embryonic stem cells destroys embryos, it

Received: 24 September 2024
Accepted: 14 January 2025
Published: 3 February 2025

inevitably conflicts with social ethics. Egg cells were simple and unfertilized. Parthenogenetic stem cells derived from egg cells cannot damage the embryo, which can well solve the ethical problems of stem cell research. Moreover, hpSCs are more readily available to homozygous human leukocyte antigen (HLA) types, thereby allowing a more significant number of patients to obtain a potential immune match and avoid rejection after transplantation.[11–14] At the same time, the neural stem cells derived from human parthenogenetic embryonic stem cells express HLA-g and show exceptional resistance to natural killer cells (NK cells) - mediated killing.[15] Additionally, there are safety and potential tumorigenicity problems of undifferentiated human stem cells for the clinical application of general stem cells. Still, for hpSCs, the animals are well tolerated after successful transplantation, and the possibility of tumorigenesis is low.[2,11,16] Based on the above advantages, human parthenogenetic stem cells may be more practical for cell therapy of nervous system diseases than embryonic stem cells (Figure 1).

Stemness of Parthenogenetic Stem Cells

Parthenogenetic stem cells are pluripotent stem cells derived from the chemically activated differentiation of egg cells. Despite lacking a paternal genome, parthenogenetic stem cells can still differentiate into other highly differentiated daughter cells and self-proliferate like embryonic stem cells (Figure 2). For example, a study by Ruhel Ahmad et al shows that parthenogenetic stem cells can differentiate into neural stem cells and other multi-seed cells through chemical induction. These neural stem cells can differentiate into neuron-like cells with physiological functions and maintain the specific expression of imprinted genes' alleles.[17] At the same time, Wei Liu et al, found that parthenogenetic stem cells

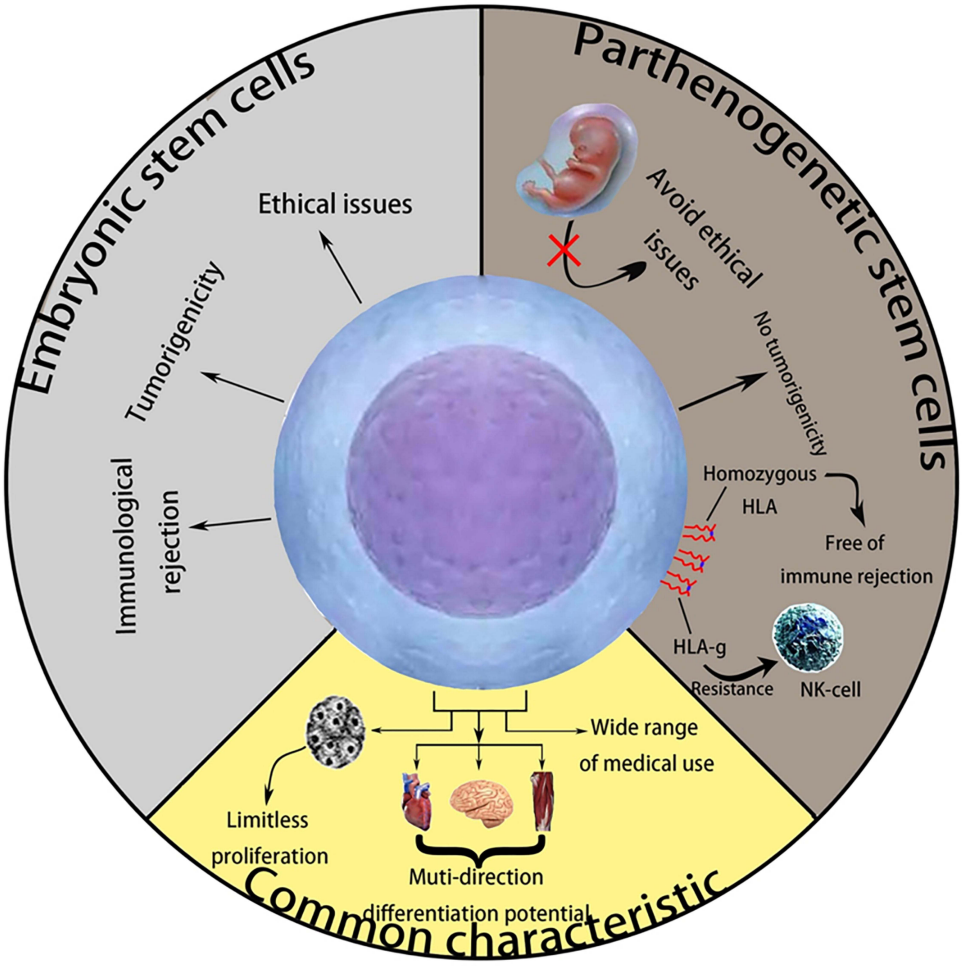

Figure 1 Parthenogenetic stem cells not only have similar characteristics as embryonic stem cells but also have their unique advantages.

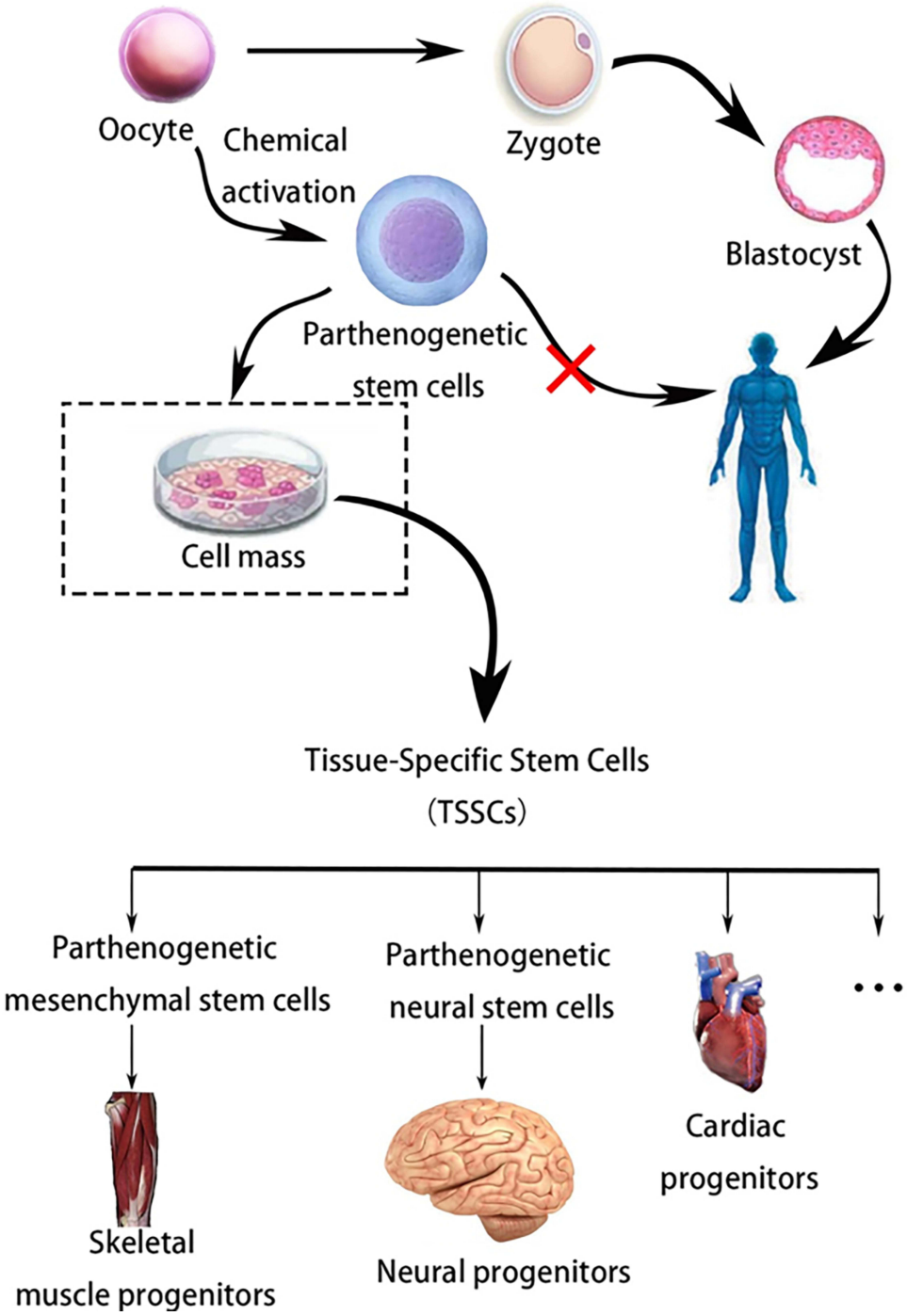

Figure 2 Parthenogenetic stem cells can differentiate into various types of daughter cells.

can spontaneously differentiate into parthenogenetic mesenchymal stem cells, which have the potential for osteogenesis, chondrogenesis, and adipogenesis. Furthermore, mechanical stretching can promote the tendon differentiation of parthenogenetic mesenchymal stem cells and form tendons, providing an effective and practical strategy for regeneration.[18] Yi Sui and others have also proved that the overexpression of insulin-like factor II promotes parthenogenetic stem cells to differentiate into cardiomyocytes and improve cardiac function after acute myocardial infarction in mice.[19] Other related studies have also shown that parthenogenetic stem cells can differentiate into cardiomyocytes.[20] The above results show that parthenogenetic stem cells can differentiate into various cells. Mammalian single-parent embryos cannot develop

https://doi.org/10.2147/NDT.S497758

into mature individuals due to the imbalance of allele-specific expression patterns between imprinted genes and parental origin. However, experiments have shown that stable embryonic stem cells have been isolated from single-parent embryos of several species, including humans.[21–24] For example, rodent single-parent embryonic stem cells can differentiate into multiple cell lines (nerves and transplantable hematopoietic progenitor cells) in vitro.[24–29]

Since parthenogenetic stem cells are chemically induced and differentiated from unfertilized oocytes, compared with other stem cells, these stem cells only have maternal genes and lack paternal genes. Moreover, the parentally imprinted genes in the genome are related to regulating the differentiation of nerve cell types. Ruhel Ahmad et al, demonstrated that parthenogenetic stem cells could differentiate into functional nerve cells in vitro without changing the imprinted state. This experiment confirmed that hpSCs are more likely to differentiate into neurons and less likely to differentiate into glial cells. The electrophysiological characteristics of neurons cultured and differentiated in vitro are similar to those of human nerve cells induced in vitro.[17] Annie Varrault showed that although parthenogenetic stem cells only had maternal genes, they did not maintain the imprinted gene pattern in cells with two maternal genes. In contrast, the expression levels of most imprinted genes were similar to those in biparental embryonic stem cells (BP-ESCs).[30] Therefore, parthenogenetic stem cell derivatives may have potential in future cell therapy.

Genes of Parthenogenetic Stem Cells

Pluripotent stem cells are derived from parthenogenetic stem cells. Parthenogenetic stem cells have only maternal genes and lack patrilineal genes. This is very different from that observed in normal embryonic stem cells. When comparing parthenogenetic epiblast stem cells (pEpiSCs) and epiblast stem cells (EpiSCs), there were differences in imprinted gene expression and DNA methylation status between pEpiSCs and EpiSCs. Still, there was no significant difference in morphology, multipotential gene expression, and differentiation potential.[31] This suggests that there may be similar gene expression in parthenogenetic stem cells and other embryonic stem cells. This study provides a research basis for the utilization and safety of parthenogenetic stem cells.

In addition to imprinted genes, miRNAs and lncRNAs in non-coding RNA are also worth studying in parthenogenetic stem cell research. Many studies have shown that miRNA plays a vital role in embryonic stem cells' self-renewal, differentiation, and reprogramming. For example, miR-29a suppresses a set of genes that regulate the breakdown of the basement membrane of adult muscle stem cells and control skeletal muscle regeneration during injury.[32] In another report, miR-29a has been shown to induce mouse ESC to differentiate into vascular smooth muscle cells, which is mediated by inhibiting the yin-yang (YY1) gene and may have some significance in treating cardiovascular disease diseases.

LncRNAs are rich in quantity and regulation and are now involved in almost all cellular processes because they regulate gene expression in an all-around way. Genome-wide screening shows that multiple lncRNAs can activate key pluripotent markers, such as Oct4, Nanog, and Hoxa, and play a potential role in the potential and differentiation of mammalian embryonic and adult stem cells.[33,34]

To date, similar studies on parthenogenetic stem cells are rare, in contrast to the large-scale genetic analysis of embryonic stem cells. Such a global analysis could help clarify many unknown aspects of the basic biology of hpSCs and determine whether further research on using hpSCs for safer and better clinical applications can be completed. In addition, integrating hpSCs data into the general ESC framework will improve our understanding of pluripotent stem cell biology.

Treatment of Parthenogenetic Stem Cell-Derived Neural Stem Cells in Specific Nervous System Injury: Traumatic Brain Injury (TBI)

Traumatic brain injury is a widespread injury during both peacetime and wartime. It has a high incidence of disease globally. However, only a small number of patients experience severe craniocerebral injuries. These severe craniocerebral injuries will leave severe sequelae, such as disturbance of consciousness, disability, etc. These outcomes significantly impact patients' quality of life and cause significant distress to family members, along with enormous treatment and care costs. TBI always exists, and the incidence is not low, highlighting the importance of post-TBI treatment. In addition, it

has aroused researchers' interest in studying the potential role of stem cells in restoring sensation and movement after TBI.

As mentioned above, using parthenogenetic stem cells to treat TBI may be a better choice because of the inconvenience and shortcomings of using embryonic stem cells. Annie Varrault et al, demonstrated that parthenogenetic stem cells could differentiate into cortical progenitor cells and electro-physiologically active glutamatergic neurons. The derivatives derived from parthenogenetic stem cells integrate into the damaged adult cortex and emit axons with a typical cortical neuron projection pattern in the host brain. Therefore, parthenogenetic stem cell-derived cells are suggested to treat traumatic brain injury (it could be more than just TBI).[22] In an animal experiment, Jea-Young Lee et al, demonstrated that parthenogenetic stem cells were transplanted into rodents' brains after TBI and evaluated the efficacy of parthenogenetic neural stem cells in treating behavioral and histological defects in the animal model of traumatic brain injury. They demonstrated the safety of parthenogenetic stem cells and suggested improvements based on the evaluation of animal behavior. Simultaneously, cell experiments proved that parthenogenetic neural stem cells could differentiate into neuron-like cells and then develop into neurons at all stages. This experiment's results confirmed a particular relationship between the injection dose and the improved effect after TBI.[35] Still, this experiment did not find the optimal injection dose or best method for parthenogenetic neural stem cells.

Spinal Cord Injury

Spinal cord injury (SCI), similar to TBI, is a devastating neurological disease with minimal functional recovery and a significant impact on the quality of life of patients and their families. However, the treatment for SCI is currently limited. The pathological changes after SCI include the primary and secondary stages. The preliminary phase involves developing the initial damage caused by the impact, followed by a rapid and gradual cascade of secondary injuries. At this stage of SCI, a series of processes, such as edema, neuroinflammation, and excitatory toxicity, lead to the death of glial and nerve cells. Therefore, stem cell transplantation is one of the most promising strategies for SCI therapy. Many studies have shown that stem cells and their derivatives can modify the lesion environment and promote the regeneration of injured neurons, remyelination of axons, trophic support, or a combination thereof.[36–39] Among various stem cell studies, neural stem cell transplantation has been shown to benefit recovery after spinal cord injury – a benefit associated with an increase in oligodendrocytes capable of regenerating semi-myelinated axons. Preclinical and clinical studies have confirmed the use of bone marrow mesenchymal stem cells (B-MSCs), umbilical cord blood (MSCs), adipose (MSCs), neural stem cell (NSCs), induced pluripotent stem cell (IPSCs), embryonic-derived oligodendrocyte precursor cells (OPC) and Schwann cells for effective stem cell therapy.[40–42]

Neural stem cells derived from parthenogenetic stem cells are similar to those derived from embryonic stem cells. Therefore, it is reasonable to believe that parthenogenetic stem cells may be able to repair spinal cord injury. Parthenogenetic stem cells can be studied in SCI through research on other types of stem cells. Through in vivo calcium imaging experiments, Steven Ceto et al found that graft neurons respond to sensory stimuli delivered to the host, including light touch, pinch, and limb movement. This finding indicates that the transplanted neural stem cells form a major active network in repairing spinal cord injury, functionally combined with the host spinal cord and supraspinous neuron population, similar to the physiological pattern of cortical spinal cord projection in the normal spinal cord.[43] Hye-LanLee et al used 3D culture technology to cultivate peripheral nerve-derived stem cells. They found that these cells positively affect functional recovery after spinal cord injury and reduce mechanical allodynia and inflammation after spinal cord injury.[44] DongZhong et al found that exosomes derived from neural stem cells significantly accelerated microvascular regeneration, reduced syringomyelia, increased the score of Basso mice, and promoted functional recovery after SCI in spinal cord-injured mice.[45]

Neurodegenerative diseases

Parkinson's Disease

In pathophysiology, it is known that neurodegenerative diseases are caused by the loss of neurons or myelin sheath, so it is reasonable to use neural stem cells to differentiate into corresponding neurons to improve or reverse the symptoms of the pathological process of neurodegenerative diseases. For this reason, Parkinson's has become one of the first choices for

scientists to study stem cells in treating neurodegenerative diseases. At the same time, Parkinson's disease has the second-highest incidence of neurodegenerative diseases (after Alzheimer's disease),[46,47] mainly caused by the death of dopaminergic neurons in the ventral midbrain. Parthenogenetic stem cells may also have the potential to treat this disease.

Some studies have shown that parthenogenetic stem cells may improve Parkinson's symptoms and slow disease progression in cells, rodents, and non-human primates. Rodolfo Gonzalez et al injected parthenogenetic stem cells into the Parkinson's model of non-human primates and compared the experimental results of the control group to those of the low-dose and high-dose groups. Regarding function and histopathology, the improvement of the low-dose group was significantly better than the control group. In contrast, the high-dose group's improvement effect was better than that of the control group, but the high-dose group's improvement effect was not as good as that of the low-dose group. However, the specific optimal value is not mentioned in this experiment. Simultaneously, the team evaluated the safety and functional activity of human parthenogenetic neural stem cell-derived neural stem cells in rodent and non-human primate Parkinson's disease models. In this experiment, they observed that compared with the control group, the transplantation group had higher dopamine levels without adverse events, indicating that human parthenogenetic neural stem cells were safe and well-tolerated.[11,16] In other experiments, clinical-grade parthenogenetic stem cell-derived dopaminergic neurons were used to treat the Parkinson's monkey model, proving that when the motor deficit of Parkinson's monkeys was improved, the cells were tumor-free and had minor damaged brain and almost no inflammatory response. Further support for parthenogenetic stem cells can be a promising method for Parkinson's treatment.[48]

Current research shows that the use of pluripotent stem cells in treating Parkinson's disease has entered the clinical stage. However, given stem cells' previously mentioned shortcomings, the exploration of parthenogenetic stem cells in Parkinson's may also be worth studying.

Dementia

Dementia is a fatal clinical disease characterized by amnesia, progressive cognitive impairment, disorientation, behavioral disorders, and loss of daily function. Alzheimer's disease (AD) is the most commonly associated pathology. However, treatment of dementia has little effect. Age is a significant risk factor for dementia, and the number of people with dementia increases with life expectancy. With the continuous development of society, the population structure of many countries is aging to varying degrees, which makes us pay attention to this disease.

Stem cell-based cell therapy may be a promising method for treating dementia. The paracrine effect of neural stem cells has been proven to have significant therapeutic potential. Transplantation of neural stem cells secreting growth factors can increase neurogenesis and cognitive function of rodent AD model[49] and aging primate brain.[50] In contrast, transplantation of human neural stem cells with high choline acetyltransferase expression into cholinergic neurotoxic rodent models can reverse spatial memory and learning impairments. In elderly rodent models, transplanted MSCs have been shown to differentiate into nerve cell types, increase local concentrations of acetylcholine neurotransmitters, brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), and improve motor and cognitive function.[51] In a review, Fabinhan et al described the potential of embryonic pluripotent stem cells for Alzheimer's disease.[52]

Ischemic Stroke

Stroke, which often occurs in middle-aged and elderly individuals, is a leading cause of death and disability worldwide. The primary methods for treating stroke mainly include using recombinant tissue plasminogen activator within 4–6 hours. However, due to the limitation of the time window, many patients do not receive good treatment at the initial stage of stroke. Moreover, the disability caused by stroke (many of them are permanent) brings a considerable burden to patients, families, and society. However, for patients with severe disabilities, it is challenging to obtain noticeable results with traditional drug treatment and rehabilitation therapy.

As we all know, the nervous system does not have the same good repair tissue as other tissues, so finding a suitable method to treat stroke is urgent. Using neural stem cells in treating stroke has always been considered an ideal treatment. To this end, many researchers have done much research on this. Xue Gang Yuan et al showed that the treatment of human mesenchymal stem cell aggregation might have the ability to improve the survival rate of stroke and the efficacy of cell therapy.[53] Matthew et al also demonstrated that bone marrow mesenchymal cells activated by interferon-γ promote

recovery after stroke by regulating inflammation and oligodendrocytes.[54] At the same time, short-lived human umbilical cord blood-derived neural stem cells also positively treat stroke. Anna Jablonska and others have proved that these cells can regulate the increase in endogenous secretory bodies and neural progenitor cells.[55] Jiang found that neural stem cells transfected with reactive oxygen species significantly improve the survival rate of ischemic stroke mice.[56] In addition, in ischemic cells and animal models, the experimental results show that the therapeutic effect of the combination of neural stem cells and microglia or astrocytes is better than that of neural stem cells alone.[57] At present, the research on parthenogenetic stem cells in treating stroke is still scarce. According to the previous comparison, the properties of neural stem cells derived from parthenogenetic stem cells are similar to other stem cells. Therefore, it is reasonable to believe that we can refer to different stem cell research ideas for further research on parthenogenetic stem cells to promote cell therapy in patients with stroke.

Overall, parthenogenetic stem cells, like embryonic stem cells, are pluripotent. This implies that they can differentiate into neural stem cells and further into various nerve cells, such as neurons, glial cells and so on. Such pluripotency offers the possibility of treating a variety of neurological disorders. For example, they can repair the damaged dopaminergic neurons in Parkinson's disease. Moreover, the transplanted parthenogenetic embryonic stem cells can provide a cell source for nerve regeneration. They can secrete multiple neurotrophic factors, which can promote the survival, growth, and differentiation of nerve cells. They can also improve the local microenvironment, facilitating the repair and regeneration of damaged nerve tissues. Therefore, parthenogenetic stem cells possess great potential for treating neurological diseases. However, in the treatment of neurological diseases, it is required that parthenogenetic embryonic stem cells precisely differentiate into specific types of nerve cells, such as neural stem cells. However, with the current technology, it is difficult to ensure that they only differentiate into the desired nerve cells in vivo, and the differentiation of non-target cells may occur, thus affecting the treatment outcome. Secondly, the research on the safety of parthenogenetic embryonic stem cells after long-term survival and functioning in the nervous system is currently insufficient. These uncertainties may limit their wide application in clinical treatment, and further research is needed to verify the feasibility of applying parthenogenetic stem cells in clinical treatment.

Different Routes of Administration Affect the Outcome of Stem Cell Therapy (FIGURE 3)

The injection method significantly affects stem cell therapy's efficacy and side effects, that is, the safety and effectiveness of stem cell transplantation. Stem cell transplantation can be divided into stereotactic and intravascular injections. Stereotactic injection is more commonly used in stem cells to treat nervous system diseases.[58] However, the stereotactic infusion has a more significant potential of damaging the subjects, affecting subsequent experiments. In contrast, intravascular injection of stem cells causes minor damage. It has less impact on the experimental results; therefore, the intravascular injection of stem cells can be used to treat nervous system diseases. The intravascular injection can be classified into intravenous injection and intra-arterial injection. Related studies have shown that most stem cells are intercepted in the lungs after intravenous infusion of stem cells for nervous system diseases. Only a minimal number of stem cells can enter the brain.[59]

Studies have shown that intra-arterial injections would more efficiently deliver stem cells to the central nervous system.[60–63] Namestnikova et al, demonstrated that mesenchymal stem cells labeled with superparamagnetic iron oxide could be detected in the basal ganglia and cerebral cortex after arterial injection.[64] Besides, ischemic brain injury leads to the release of CXCL-1, which leads to the loss of nerve cells in the damaged tissue.[65] Dabrowska et al, found an increase of CXCL-1 in rat brain tissue 48 hours after focal brain injury. Experiments showed that stem cells and their exocrine function strongly inhibited the production of CXCL-1 after arterial injection, which improved the prognosis of ischemic brain injury to some extent.[66] In the experiment of rats, Lanfen Chen et al concluded that in the cerebral ischemia model, melatonin injection through different ways has a specific protective effect on neurons, and the therapeutic effect of caudal vein injection is better than that of intraperitoneal injection.[67] This also shows that the injection method particularly influences the therapeutic effect. Maybe we can use this idea to improve the cell survival rate of stem cell transplantation.

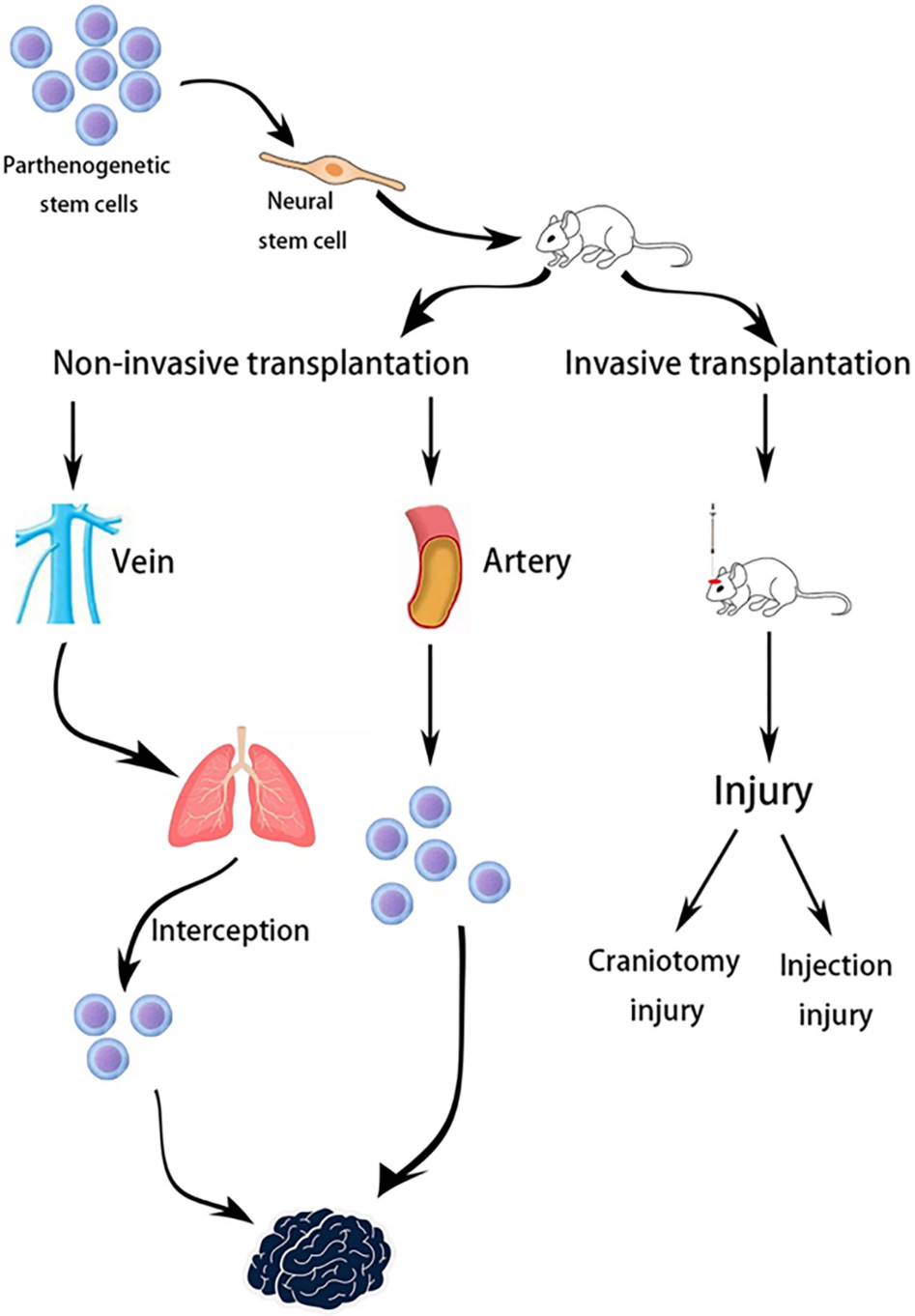

Figure 3 Different injection methods affect the outcomes of stem cell therapy to some extent.

Combination Therapy

Many therapeutic strategies have been proposed, including rehabilitative and pharmaceutical procedures and biotechnological and bioengineered approaches to managing brain and spinal cord diseases. None of them can cure the disease alone; however, they provide a starting point for discovering promising treatments.

Currently, stem cell-based cell therapy has a bright future. Due to the low regeneration ability of injured nervous system neurons, stem cells in treating nervous system diseases have aroused many scientists' interest. Although many studies have proven that stem cells have a positive effect on the treatment of nervous system diseases, the current

research results show that the functional recovery level of stem cells in the treatment of nervous system diseases is limited. Previously, some scientists have tried to ablate the endogenous neurons in the damaged area in advance, then treated them with neural stem cells, and found that after endogenous neuronal ablation, neural stem cells cannot induce functional recovery after injury.[68] As a result, the scientists concluded that endogenous neurons' partial survival at the injured site might be necessary for effective stem cell treatment. It has also been suggested that neuroprotective substances can be used to increase the survival of endogenous neurons in nervous system injury.

Utilizing stem cells to treat nervous system diseases requires using other substances to cooperate with stem cell therapy. For example, the high mobility group box-1 (HMGB1) triggers an inflammatory response after injury.[67,69–71] In the mouse experiment, Yu Okuma et al, used anti-high mobility kit-1 (Anti-HMGB1) to treat traumatic brain injury before using stem cells to treat traumatic brain injury and then transplanted stem cells into mice's brains. They found that Anti-HMGB1 significantly improved brain damage by protecting the blood-brain barrier (BBB) from damage caused by ischemia.[72] Naohiro Uezono et al also used Anti-HMGB1 to treat mice with spinal cord injury, transplanted stem cells into mice and obtained surprising results. At the same time, they also found that the recovery effect of HMGB1 alone was similar to that of stem cell transplantation alone (Figure 4).[68]

Studies on the effects of lithium on neurogenesis have shown that lithium can promote progenitor cells' proliferation in the hippocampal dentate gyrus and enhance Schwann cells' mitotic activity.[73–75] Thus, it might be related to lithium's neuroprotective and neurotrophic effects, which is reflected in the improvement of synaptic plasticity, the promotion of cell survival, and the inhibition of apoptosis. In clinical studies, lithium treatment increased the brain's grey matter, mainly in the frontal lobe, hippocampus, and amygdala.[76] Recent findings suggest that lithium can reduce the risk of dementia and play a beneficial role in neurodegenerative diseases. Shaun W Carlson et al, found that lithium can improve dopamine transmission in the striatum and increase the abundance of dopaminergic protein and hippocampal SNARE protein after traumatic brain injury.[77,78] Atiyeh Mohammad Shirazi et al, conducted further research on lithium-ion. Rats with spinal cord injury were treated with lithium ions and stem cells. The results showed that the functional scores of the lithium-ion and lithium-ion + stem cell groups were significantly higher than those of the stem cell groups at 6–7 weeks. Similarly, in the motor-evoked potential test, the amplitude, latency, signal, and signal duration of motor-evoked potentials recorded in the lithium-ion and lithium-ion + stem cell groups were better than those in the control group.[79]

For stem cells in treating nervous system diseases, their therapeutic effect does not achieve ideal results. After an injury to the nervous system, the internal environment may not be suitable for cell survival, as the stem cell survival rate after transplantation is low. Therefore, stem cells and other substances are essential for treating nervous system diseases.

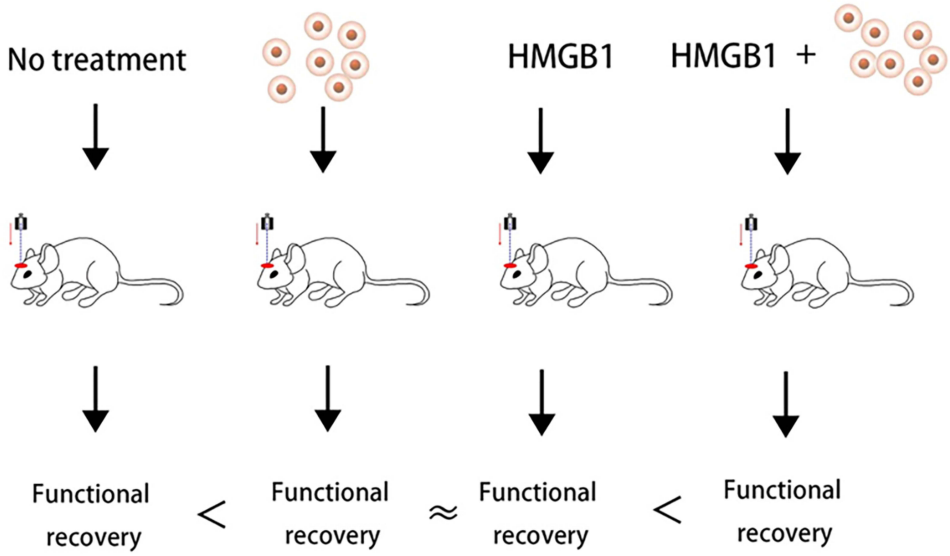

Figure 4 The therapeutic effect of HMGB1 alone was similar to that of stem cell transplantation alone, but the therapeutic effect was greatly increased after the combination of HMGB1 and stem cells.

https://doi.org/10.2147/NDT.S497758

Combination therapy to improve the internal environment after nervous system injury increases the survival number of cells in the injured area and provides a suitable living environment for subsequent stem cell transplantation. Therefore, combining stem cells with other drugs to treat nervous system diseases may be a promising treatment strategy.

Design of Study and Matters Needing Attention

Although there is a lot of research on stem cells and significant progress has been made in understanding the characteristics of stem cells and the use of stem cells in the treatment of nervous system diseases, if stem cells are used in the clinic or by patients, the current research and knowledge is far from sufficient. The shortcomings of embryonic stem cells, such as ethical issues, immune rejection, and tumorigenicity, limit the research and use of embryonic stem cells. Parthenogenetic stem cells have no ethical problems, immune rejection, tumorigenicity, or other problems and can become a sharp weapon for treating nervous system diseases. However, current research on parthenogenetic stem cells is insufficient. The test of parthenogenetic stem cells mainly aims to study their safety.[80] However, many related variables that affect the therapeutic effect have not been reviewed, such as the dose of stem cell transplantation, transplantation mode, transplantation time, etc. For arterial injection, which is more effective for stem cell transplantation, it is also helpful for parthenogenetic stem cell transplantation.

Similarly, as mentioned above, Anti-HMGB1 and lithium-ion effectively promote stem cells in treating nervous system diseases. Whether these or other substances can also promote parthenogenetic stem cells in treating nervous system diseases is worthy of careful consideration and study. Few tasks have been done on this variable, which requires more research, but these studies are difficult to carry out due to the high costs. Therefore, researchers must weigh the pros and cons and find the best solution.

Many studies have shown that stem cells are helpful in the treatment of diseases of the nervous system. However, with the continuous in-depth research on stem cells, researchers have found that the low biological efficacy of stem cells and the low implantation rate in harsh environments are also worthy of attention, hindering the clinical application of stem cells. To overcome some of these problems, three-dimensional (3D) culturing has been developed. This cultivation method enhanced stem cells' biological efficacy, cell survival, and engraftment compared with traditional cultivation methods.[81] This has helped improve the effectiveness of stem cell therapies, but the improvements have not been as good as expected.

Many researchers believe that the most positive results in the treatment of neurological diseases with stem cells may be attributable to exosomes derived from stem cells. Compared with stem cells, exosomes have the following advantages: First, exosomes can better control the amount needed, reducing the biological efficacy and cell survival considerations required for stem cell transplantation. Second, target specificity; exosomes can target specific cell types or tissue functions after engineering. Third, Personalized exosomes can be modified with specific active ingredients for better treatment of various diseases. Fourth, exocrine therapy is an acellular therapy that avoids all kinds of problems existing in cell therapy. Above all, perhaps the overall efficacy of acellular therapy using stem cell-derived exosomes is greater than the advantages of using stem cells. And parthenogenetic stem cells can also solve the problem of the source of exosomes. The source of parthenogenetic stem cells is relatively easy for other stem cells, thus avoiding many types of stem cell-related problems. However, the characteristics of exosomes derived from parthenogenetic stem cells are poorly understood. Research on treating nervous system diseases using parthenogenetic stem cells for exosomes is scarce. Due to the problem of parthenogenetic stem cells, it is unclear whether the exosomes produced by them are defective. However, as mentioned earlier, parthenogenetic stem cells can differentiate into neural stem cells. The expression levels of most imprinted genes were similar to those of parental embryonic stem cells. These exosomes deserve further in-depth study.

In a review, Michelle Werdann et al described how changes in circadian rhythms leading to changes in the composition of the internal environment may be associated with neurodegenerative diseases.[82] The change of circadian rhythm may be divided into the change of sleep rhythm, the change of hormone release, and the change of core body temperature. Dementias are neurodegenerative diseases caused by the accumulation of amyloid-beta (A-β) peptides in the brain. The biological clock affects plaque formation and Aβ activity. Kress et al knocked out related genes in mice. The results show that the suprachiasmatic nucleus (central pacemaker of the circadian rhythm system) plays an essential role in regulating amyloid β aggregates in the brain.[83] Frontotemporal dementia (FTD) is a type of dementia, and the researchers found that patients with the disease had less active time during the day and

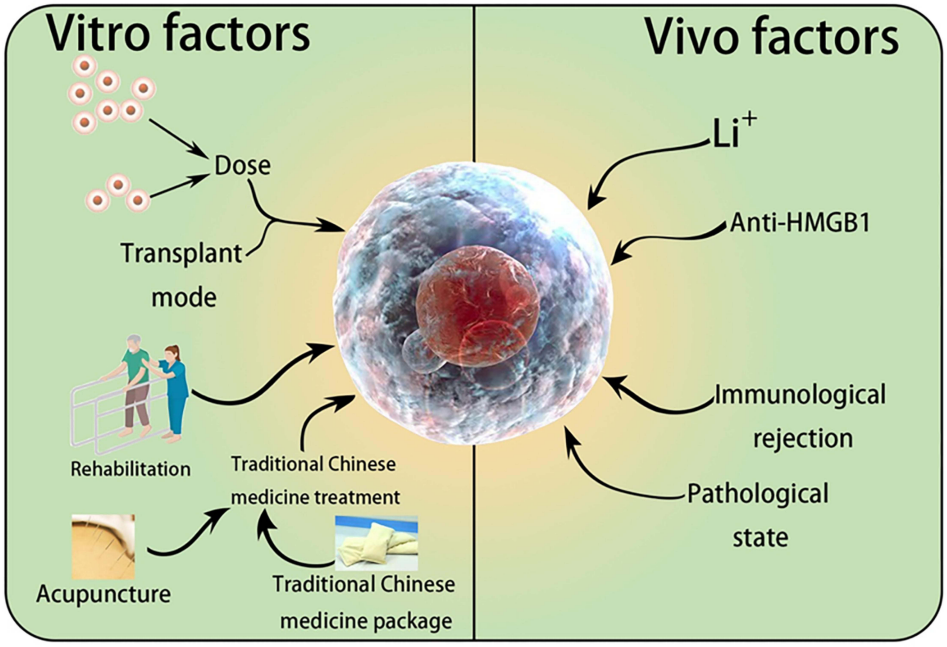

Figure 5 Different factors affect therapeutic outcomes after stem cell transplantation, including in vitro and in vivo.

less sleep at night.[84] A study has found that FTD patients have regular body temperature changes but rhythmic changes, which insufficient orexin levels in the cerebrospinal fluid may cause.[85] Therefore, it is reasonable to hypothesize that the changes in the internal environment caused by circadian rhythm may have a particular influence on the transplantation, survival, and therapeutic effect of stem cells. Alternatively, whether the use of stem cells affects circadian rhythms may affect patients.

Most current studies combine certain chemicals with stem cells, evaluate the subjects' body structure and function, and conduct statistical analysis to determine whether this change is statistically significant. In most of these studies, researchers pay attention to the effect of the internal environment on stem cells while ignoring the impact of the external environment on stem cells. In future research, researchers should pay attention to these statistically significant and clinically meaningful changes. Most cited studies ignored crucial variables that cannot be overlooked in improving nervous system diseases, such as rehabilitation treatment, integrated traditional Chinese and Western medicine treatment, etc. Related studies, such as those on the effect of stem cell transplantation in animal models with or without external environmental influences, support this view. The impact of stem cells on recovery increases with the stimulation of the external environment.[86] Aravamudhan et al, have also endorsed interactions based on cell therapy, rehabilitation, and other interventions to maximize stem cell therapy.[87] Concerning rehabilitation treatment and integrated traditional Chinese and Western medicine treatment, we think some non-invasive techniques, such as transcranial magnetic stimulation and transcranial electrical stimulation, can be used, enhancing the therapeutic effect of stem cells on the brain or the use of acupuncture in traditional Chinese medicine, traditional Chinese medicine packets, and so on, together with stem cells to promote the recovery of nervous system function. Robotics, polymer materials, and other newer therapeutic devices and strategies may be more effective than stem cells combined with traditional treatments (Figure 5).

Summary

Increasing evidence shows that stem cells play a beneficial role in reducing nervous system injury and improving patient prognosis. Different types of stem cells have been used to treat various neurological diseases. However, many stem cell therapy problems exist, such as moral and ethical problems, immune rejection, tumorigenicity, and scarcity. The parthenogenetic stem cells formed by the chemical induction of egg cells can avoid the above issues, indicating that parthenogenetic stem cells can become a sharp weapon for stem cells to treat nervous system diseases. The research on

https://doi.org/10.2147/NDT.S497758

parthenogenetic stem cells in the treatment of nervous system diseases is still very rare. However, parthenogenetic stem cells have a good effect in treating Parkinson's disease and brain injury. It has been revealed that parthenogenetic stem cells may potentially treat nervous system diseases. According to the above, the characteristics of parthenogenetic stem cells are similar to those of ordinary stem cells. This paper compares the studies of other types of stem cells in nervous system diseases to provide research ideas for researchers to facilitate further research on parthenogenetic stem cells. However, because the research on parthenogenetic stem cells is still insufficient, many variables that affect the therapeutic effect have not been studied, such as dose, injection mode, timing, combined substance, and other questions have not been answered, which will require different experiments to help determine the best treatment strategy. In addition, parthenogenetic stem cells may also have some limitations in practical applications. For example, the costs of acquisition and culture are high, and the difficulty of cell culture is relatively high. The culture process of parthenogenetic stem cells usually requires specific culture media and growth factors. Moreover, to maintain the undifferentiated state of the cells and their good growth characteristics, it is often necessary to use specially treated culture vessels and complex culture environment control systems, such as hypoxic incubators, which greatly increase the culture costs and limit the feasibility of large-scale culture. Furthermore, when parthenogenetic stem cells are cultured on a large scale, uneven cell differentiation may occur. As the number of culture passages increases, it becomes difficult to maintain the stemness of the cells, and they are prone to spontaneous differentiation, resulting in a decrease in the proportion of pluripotent stem cells and affecting the scalability. The research on the long-term safety and stability of parthenogenetic stem cells after treatment is still insufficient. It is very difficult to determine whether these cells can still function stably and whether they will cause other delayed adverse reactions many years after transplantation. For parthenogenetic stem cells to be widely used in clinical treatment, sufficient long-term experimental data and clinical trials are needed. In addition to understanding the most favorable microenvironment for stem cells, the influence of the external environment on the therapeutic effect of stem cells, such as rehabilitation therapy and integrated traditional Chinese and Western medicine treatment, cannot be ignored. At present, these methods have been applied to the treatment of nervous system diseases and play an important role in the recovery of patients.[88,89,90] Combining stem cells with these treatments may improve the effectiveness of stem cells in treating nervous system diseases and improve the prognosis of patients. Although the above research is challenging, the results of related studies on parthenogenetic stem cells show that it is worth our efforts because it may become a stem cell therapy strategy for patients with acquired or degenerative neurological diseases.

Abbreviations

AD, Alzheimer's disease; Anti-HMGB1, anti-high mobility kit-1; BP-ESCs, biparental embryonic stem cells; BBB, blood-brain barrier; B-MSCs, bone marrow mesenchymal stem cells; BDNF, brain-derived neurotropic factor; EpiSCs, epiblast stem cells; FTD, frontotemporal dementia; HMGB1, high mobility group box-1; HLA, human leukocyte antigen; HpSCs, human parthenogenetic stem cells; IPSCs, induced pluripotent stem cells; NK cells, natural killer cells; NGF, nerve growth factor; NSCs, neural stem cells; OPC, oligodendrocyte precursor cells; pEpiSCs, parthenogenetic epiblast stem cells; SCI, Spinal cord injury; TBI, Traumatic brain injury.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was sponsored by the Self-funded research projects by Guangxi Zhuang Autonomous Region Health Commission [Z202111633], the National Key Research and Development Program of China [2022YFA1104900 and 2022YFA1104904], the Innovation Team Project of General Universities in Guangdong Province [2023KCXTD007], and the Special Project in Key Fields of General Universities in Guangdong Province [2021ZDZX2011].

Disclosure

The authors declare no conflicts of interest.

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