ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2023 January 16; 11(2): 255-486

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

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The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

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The *WJCC* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Current Contents®/Clinical Medicine, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJCC* as 1.534; IF without journal self cites: 1.491; 5-year IF: 1.599; Journal Citation Indicator: 0.28; Ranking: 135 among 172 journals in medicine, general and internal; and Quartile category: Q4. The *WJCC*'s CiteScore for 2021 is 1.2 and Scopus CiteScore rank 2021: General Medicine is 443/826.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Hua-Ge Yu*; **Production Department Director:** *Xu Guo*; **Editorial Office Director:** *Jin-Lei Wang*.

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

PUBLICATION DATE
January 16, 2023

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 January 16; 11(2): 322-331

DOI: 10.12998/wjcc.v11.i2.322

ISSN 2307-8960 (online)

MINIREVIEWS

Prospects for the use of olfactory mucosa cells in bioprinting for the treatment of spinal cord injuries

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Specialty type: Neurosciences

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Oliva J, United States; Sun Z, China

Received: September 19, 2022
Peer-review started: September 19, 2022
First decision: November 14, 2022
Revised: November 28, 2022
Accepted: January 5, 2023
Article in press: January 5, 2023
Published online: January 16, 2023

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Abstract

The review focuses on the most important areas of cell therapy for spinal cord injuries. Olfactory mucosa cells are promising for transplantation. Obtaining these cells is safe for patients. The use of olfactory mucosa cells is effective in restoring motor function due to the remyelination and regeneration of axons after spinal cord injuries. These cells express neurotrophic factors that play an important role in the functional recovery of nerve tissue after spinal cord injuries. In addition, it is possible to increase the content of neurotrophic factors, at the site of injury, exogenously by the direct injection of neurotrophic factors or their delivery using gene therapy. The advantages of olfactory mucosa cells, in combination with neurotrophic factors, open up wide possibilities for their application in three-dimensional and four-dimensional bioprinting technology treating spinal cord injuries.

Key Words: Olfactory mucosa cells; Neurotrophic factors; Cell therapy; Injury of spinal cord; Three-dimensional bioprinting; Four-dimensional bioprinting

Core Tip: The development of an optimal strategy for the treatment of spinal cord injuries is a relevant and topical issue in modern medicine. Olfactory mucosa cells and neurotrophic factors showed their effectiveness in transplantation into the area of the injured spinal cord. In this review, the authors discuss the possibility of their application in four-dimensional bioprinting to create transplants that would have a complex impact on the transplant-mediated repair of the damaged area of the spinal cord.

Citation: Stepanova OV, Fursa GA, Andretsova SS, Shishkina VS, Voronova AD, Chadin AV, Karsuntseva EK, Reshetov IV, Chekhonin VP. Prospects for the use of olfactory mucosa cells in bioprinting for the treatment of spinal cord injuries. *World J Clin Cases* 2023; 11(2): 322-331
URL: https://www.wjgnet.com/2307-8960/full/v11/i2/322.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i2.322

INTRODUCTION

Therapy for spinal cord injury is a relevant issue in modern neurobiology and medicine because the mechanical injury of the spinal cord can lead to irreversible changes in the neural tissue. Spinal cord injuries often lead to disabilities and sometimes can have a lethal outcome[1].

One of the current strategies for the treatment of spinal cord injury is cell therapy. The most optimal source of cells for transplantation may be olfactory mucosa cells. Obtaining olfactory cells is an atraumatic procedure for a patient, which makes the application of this tissue in therapy a promising field of study in personalised medicine. For cell transplantation of the olfactory mucosa cells, neural stem/progenitor cells (NSPCs), olfactory ensheathing cells (OECs), and mesenchymal stem cells (MSCs) are obtained. It was shown that the transplantation of these cells contributed to the reparation of the injured tissue of the spinal cord[2]. Besides, spinal cord therapy involves the application of various neurotrophic factors. Neurotrophins exert an antiapoptotic effect and contribute to the survival of mature neural cells, which is especially important at the site of injury[3]. The application of neurotrophins in combination with olfactory mucosa cells can enhance the therapeutic effect of these cells. This combination promotes cell survival, axonal regeneration, structural repair and function recovery after injury Table 1.

In the last few years, experimental medicine research included the application of various variants of stable polymers that can deliver cells and neurotrophic factors as a three-dimensional (3D) scaffold[4]. This method has shown its safety in various clinical studies[5,6]. The 3D scaffold provides support for the transplanted cells in more native conditions, which contributes to their survival in the area of injury [7,8]. However, such 3D scaffolds have low adaptivity to the changes in the area of injury and limited changes in shape. The solution to this problem is the development of conceptually novel "smart" materials. The application of such materials will allow specialists to create four-dimensional (4D) scaffolds that will not only combine the advantages of 3D scaffolds, but can also adapt to changes in the area of injury, and respond to external signals[9].

Thus, the creation of structures that have all the advantages of 4D bioprinting and can deliver olfactory mucosa cells and neurotrophic factors will be a breakthrough in the treatment of spinal cord injuries.

OLFACTORY MUCOSA CELLS IN THE TREATMENT OF SPINAL CORD INJURIES

The olfactory mucosa of the nose contains several cell types that can be successfully used in cell therapy for spinal cord injuries: NSPCs, ECs, and MSCs.

Despite the fact that cell-therapy based on olfactory mucosa cells is one of the most promising treatments for spinal cord injuries there are some limitations to this approach. Transplantation of OECs from olfactory mucosa significantly improves motor function recovery and reduces the size of cysts[10, 11]. However, there is a problem with OEC culture heterogeneity because it is currently difficult to purify these cells to a 100% pure culture, so there might be some side effects[12-14]. Mesenchymal stromal cells can also be obtained from olfactory mucosa. As it was mentioned in the manuscript, studies show that mesenchymal stromal cells transplantation has side effects such as neuropathic pain

Table 1 Effects of using olfactory mucosa cells with neurotrophins in spinal cord injuries

	BDNF	NT-3	NGF
NSPCs	Improved hindlimb function[75]	Promoted differentiation into neurons [76]; promoted axon regeneration and functional recovery[77]	Reduced oligodendrocyte loss, improved functional recovery, preservation of motor neurons, attenuation of astrocytosis[78]
OECs	Improved cell survival[79]; promotes cell migration[80]	Improved cell survival[79]; improved limb mobility and; improvement of growth promoting properties[81]	Improved cell; survival[79]
MSCs	Enhanced recovery of motor function, reduced damage of spinal neurons[82] Improved hindlimb function[83]	Improvement of motor function[84], structural and functional recovery of SCI[85,86] and axonal regeneration[86]	Improvement of proliferation, differentiation, immunomodulatory[87]; promoted the growth of blood vessels[88]; increase of expression of genes related to neural differentiated cells[89]

NSPCs: Neural stem/progenitor cells; OECs: Olfactory ensheathing cells; MSCs: Mesenchymal stem cells; BDNF: Brain-derived neurotrophic factor; NT-3: Neurotrophin-3; NGF: Nerve growth factor; SCI: Spinal cord injury.

[15]. The use of neurospheres containing NSPCs from olfactory mucosa is associated with difficulties in calculating the number of cells and the percentage of NSPCs in suspension.

Safety of cell-based treatments is a fundamental concern for regenerative medicine. Efficacy is usually the main focus, however, the safety of each treatment is also tested during the trials[16]. Clinical observations show that OEC transplantation is safe for patients and there were no serious adverse reactions in all cases[17]. Clinical trials of NSPCs and MSCs from the olfactory mucosa have not been performed to date.

NSPCs

NSPCs were discovered in the spinal cord and brain (in the subventricular area and the hippocampus), as well as the olfactory mucosa layer. These cells can differentiate into glial cells and mature neurons and encode neurotrophic factors for successful neuroregeneration[18-20].

The treatment of modelled spinal cord injuries includes suspension cell cultures in the form of neurospheres containing NSPCs. Studies have shown the effectiveness of neurospheres, from the olfactory mucosa, in the treatment of spinal cord injuries. Their transplantation in the acute phase of rat spinal cord injury contributes to the restoration of motor activity of the hind limbs and regeneration of axons of the rubrospinal tract[21,22].

Chronic injury of the spinal cord can be associated with pathological processes that lead to the formation of a posttraumatic cyst. The cyst can enlarge and compress the spinal cord, which complicates the processes of regeneration and mediation of nervous impulses to the limbs[23]. However, the application of these neurospheres in the chronic phase of spinal cord injury remains understudied. In the authors' laboratory, the first transplantation of neurospheres from the olfactory mucosa was performed in rats with modelled posttraumatic cysts. It was shown that transplantation contributed to the improvement of motor activity of the hind limbs and the reduction of the cyst size[24]. The proven effectiveness of neurospheres, obtained from olfactory mucosa in the experimental studies, can provide grounds for preclinical studies and further application in the treatment of spinal cord injuries in patients.

Ensheathing cells

OECs obtained from the olfactory mucosa are a unique type of glial cell found in the peripheral nervous system. In an adult organism, these cells manage the growth of new axons in the olfactory epithelium and protect a growing axon from growth-inhibiting factors, which allows an axon to grow to the size of an olfactory bulb and form a synapsis[25]. Besides, *in vitro* and *in vivo* studies have shown that OECs of an adult organism secreted molecules associated with myelinization: Protein zero (P0) and myelin basic protein[26]. It is suggested that this type of cells can maintain the growth and integrity of axons throughout an organism's life and contribute to the formation of the myelin sheath around demyelinated axons[27,28]. OECs can also express neurotrophic factors that promote neuroregeneration [29].

It has been shown that transplantation of OECs in the acute phase of spinal cord injury contributed to the regeneration of the nervous tissue and remyelination of axons, which leads to the restoration of limb motor activity. Furthermore, introducing these cells in the acute phase contributes to a reduction of posttraumatic astrogliosis[30]. Transplantation of OECs in the chronic phase promotes the recovery and growth of the damaged axons and improves limb motor activity[31]. In the authors' laboratory, for the first time, the therapeutic effect of OECs was shown in the treatment of posttraumatic spinal cord cysts. The transplantation of OECs contributed to a decrease in the volume of cysts and restoration of limb motor activity[32,33].

Preclinical studies have demonstrated the safety and efficacy of the use of olfactory mucosa cells in the treatment of acute and subacute stages of spinal cord injury[34-36]. The conducted clinical studies also demonstrated the safe use of autologous OECs in the treatment of patients with spinal cord injuries [37-39]. Thus, OECs from the olfactory mucosa can be considered the optimal cell material for personalised cell therapy in such patients.

MSCs

Experimental studies have shown that the transplantation of MSCs, derived from olfactory mucosa, contributed to the growth of axons in the injured rat nerves. A positive effect of these cells on the myelinization of axons was also evident *in vitro*[40]. However, MSCs derived from olfactory mucosa remain understudied in *in vivo* conditions.

MSCs obtained from bone marrow were also used in the treatment of spinal cord injuries. Even though the transplantation of these cells showed positive results in experimental models, clinical studies did not prove their effectiveness[41]. Besides, some studies describe the side effects of MSC transplantation, including neuropathic pain[15]. The application of MSCs obtained from olfactory mucosa can have the same consequences, which makes the other two types of olfactory mucosa cells (OECs and NSPCs) the most promising for cell therapy.

EXOGENOUS NEUROTROPHIN THERAPY

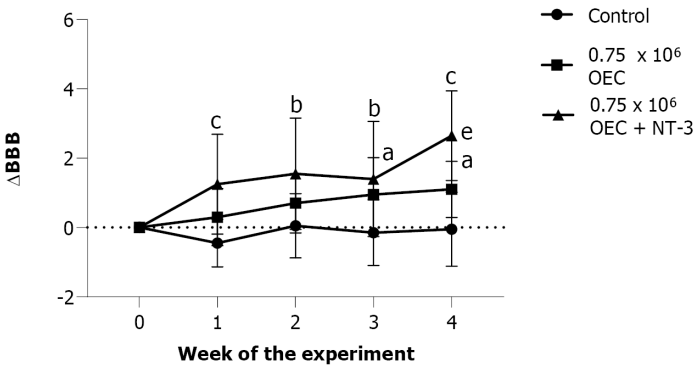
Another promising method for the treatment of spinal cord injuries is exogenous neurotrophin therapy since the endogenous neurotrophic factor count is insufficient for the regeneration of the injured tissue [42]. Neurotrophic factors, including nerve growth factor (NGF), neurotrophin-3 (NT-3), NT-4, and brain-derived neurotrophic factor (BDNF), play an important role in the processes of neuroregeneration and axon growth after injury[43].

One of the methods for delivering exogenous neurotrophins to the area of injury is injection. Studies conducted at the end of the last century have shown that the delivery of NGF for two weeks after resection of the spinal cord fragment in rats promoted the regeneration of the nervous tissue of the spinal cord[44]. Later, it was shown that the delivery of BDNF in the acute and chronic phases of rat spinal cord injury also contributed to nervous tissue regeneration[45,46]. Further *in vitro* studies showed that BDNF expressed by the OECs contributed to the transplant-mediated axon growth[47]. For the first time, the authors of this paper have demonstrated that the combined introduction of OECs and exogenous NT-3 to the modelled cysts in the rat spinal cord improved the motor activity of the hind limbs and reduced the cyst size[32]. The use of NT-3 improves the effects obtained from cell therapy and the data are presented in Figure 1[48].

However, after neurotrophins are directly administered to the area of injury, they degrade quickly. Currently, the most promising method of neurotrophin delivery to the area of injury is the use of adenoviral vectors[49]. There are direct and indirect deliveries of adenoviral vectors. Direct delivery involves the injection of the vector to the area of injury or nearby, resulting in the transduction of neurons, astrocytes, oligodendrocytes, macrophages, lymphocytes, and microglia. With indirect delivery, an adenoviral vector is injected intramuscular or into the peripheral nervous system.

Gene therapy *ex vivo* is a variant of indirect gene delivery. This therapy includes obtaining cells, genetic modification of these cells *in vitro*, and transplantation of a gene-cell construct into the patient [50]. Experimental studies investigated gene-cell constructs based on Schwann cells[51], MSCs[52,53], NSPCs[54,55], and OECs obtained from olfactory bulb[56]. In the authors' laboratory, an OEC-based gene-cell construct from the olfactory mucosa was studied. It was shown that transplantation of OECs obtained from olfactory mucosa, transduced by an adenoviral vector encoding a mature form of BDNF, into a post-traumatic cyst could have a therapeutic effect. This is observed not only due to increased secretion of neurotrophin but also due to the regenerative potential of the cells themselves[32]. Other authors showed the effectiveness of OECs obtained from olfactory mucosa transduced with adenoviral vector transcoding NT-3. This construct intensely encoded NT-3, which contributed to the growth of injured axons[57].

Thus, gene-cell constructs are being actively studied, however, it is necessary to continue the investigation of various combinations of cells and adenoviral vectors to create an optimal drug for gene-cell therapy. Special attention should be paid to the safety of this technology. Adenoviral vectors are the most studied in this respect. They are successfully used in the creation of vaccines and treatment of oncological diseases. At present, they are being actively studied for use in regenerative medicine. Although great success has been achieved in this field, it is necessary to improve the immune system response, the life span of the virus, and the packing ability of the vectors. However, the evolution of the adenoviral vector as a tool for the transfer of genetic material has revolutionized how doctors and scientists can approach the treatment of even the most debilitating diseases[58].



DOI: 10.12998/wjcc.v11.i2.322

Figure 1 Dynamics of recovery of hind limb motor activity in rats after transplantation of human olfactory ensheathing cell alone and in combination with neurotrophin-3 into SC cysts. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$ in comparison with the control; $^{e}P < 0.01$ in comparison with transplantation of olfactory ensheathing cell alone. Control = DMEM:F12 (1:1) without cells. Each group includes 10 animals. Neurotrophin-3 significantly improves the efficiency of olfactory ensheathing cells. OEC: Olfactory ensheathing cells; NT-3: Neurotrophin-3.

THREE-DIMENSIONAL BIOPRINTING IN THE TREATMENT OF SPINAL CORD INJURIES

Another promising method for delivering cells and neurotrophins to the area of injury is 3D bioprinting. The development of tissue-specific scaffolds that imitate the natural architecture of the studied tissue is the most important task of modern medicine. To create such structures, the field of 3D bioprinting is being actively explored. Scaffolds are printed layer-by-layer, using 3D printers, and each of the layers can be filled with cells and neurotrophic factors[9]. This technology has been actively studied for some years and has already been applied in the treatment of a wide range of pathologies, including spinal cord injuries[59].

The effect of 3D polymers on the restoration of nervous tissue is currently being studied in experimental models. For example, the transplantation of a printed 3D scaffold from biodegradable polyurethane, which contains mature neural stem cells (NSCs) of a mouse, positively affected the regeneration of the central nervous system of Danio-rerio embryos. Transplantation of this construct to adults with brain injury increased their survival rate and had a positive effect on the restoration of motor activity [60]. In addition, there are studies available on the application of printed agarose tubes in combination with mouse bone marrow stem cells after sciatic nerve injury in rats. It was shown that the application of this transplant was more effective in the restoration of motor and sensory activity than an injection of collagen or transplantation of nervous tissue into the area of injury. These studies showed that a solid scaffold increased cell survival rates and positively affected the regeneration of the damaged areas of nervous tissue[61]. The study of the application of a 3D printed polyethylene glycol gelatin methacrylate scaffold with rat neural progenitor cells (NPCs) also showed that transplantation of a scaffold with cells led to a better recovery of hind limbs motor activity in injured rats compared to groups that received cells without a scaffold or a scaffold without cells[62]. To improve the performance of 3D matrices, a combination of germanium phosphide and hyaluronic acid was developed. This construct significantly improved the recovery of motor activity of the hind limbs in rats with modelled spinal cord injury and also increased the migration of rat NPCs in the spinal cord to the area of injection [63].

A promising direction is the study of 3D printing based on OECs obtained from olfactory mucosa, since, as noted earlier, the production and application of these cells do not pose any danger to the patient. 3D microbeads were obtained from OECs and Matrigel. OECs survived the printing process and retained their phenotype. It is assumed that such a 3D construct can have a therapeutic effect when transplanted into the spinal cord of animals and promote the growth of axons along the scaffold[64].

Furthermore, there was a study made on the printed multichannel poly (propylene- fumarate)-collagen scaffold containing neurotrophin NT-3. Implantation of this construct into the spinal cord of an injured rat had a significant neurotrophic effect and contributed to the growth and regeneration of the damaged axons. The porous structure of the scaffold facilitated the migration of endogenous NSCs in rats and promoted neuronal regeneration[65].

However, materials used for 3D printing can rarely respond to the changes in the injured area or adapt to the changing shape, which is a limitation of such therapies. To remove these limitations, 4D bioprinting is being explored.

FOUR-DIMENSIONAL BIOPRINTING IN THE TREATMENT OF SPINAL CORD INJURIES

The development of more complex and "smart" materials will allow researchers to create novel polymers that have distinctive features: they change shape, can self-assemble, are capable of autonomous activation, and can capture a wide range of signals[66]. This type of polymer is used in 4D printing. Currently, these technologies are widely used in bone and skin grafting[67-70]. However, further research into the possibilities of 4D bioprinting will allow the use of four-dimensional polymers in the treatment of spinal cord injuries as well.

At the moment, a matrix has been developed that combines the developments of 3D printing with the advantages of novel technologies. Hybrid gelatin methacrylate-microcapsule hydrogel, in combination with polylactide-clicolide capsules with NT-3, can secrete growth factors at a certain level for 20 d. This, in turn, contributed to the recovery of the spinal cord after injury, differentiation of NSCs located in the spinal cord, and improvement in motor activity of the hind limbs in rats with spinal cord injury[71].

In parallel, a polymer based on epoxydated acrylate of soybean oil in combination with graphene and human MSCs was developed based on laser stereolithography technology[72]. In the present study, cells in the 4D polymer were placed in the medium for neural differentiation. Two weeks later, MSCs on the polymer showed a significantly higher level of neurogenic genes in comparison with the same cells cultivated on a regular 3D polymer. In addition, such material could reversibly change the structure and shape of memory[72]. These results allowed the authors to study MSCs on NSCs *in vitro*. A later study, by the same authors, focused on the design of polymer microwells with a memory function[73]. This was achieved by combining laser stereolithography, a polydimethylsiloxane mould, and organic glass for the formation of wells 400-800 μm in diameter. This approach allowed the authors to create a micro surrounding of a cell that could change its shape and achieve more favourable conditions for cell cultivation. NSCs in polymer showed a significant increase in the expression of markers of neural and glial differentiation compared to cultures cultivated on plastic and glass surfaces[73]. Another research group used technology based on polymer melt modelling and obtained an effect that was similar to that described above, from the cultivation of NSCs in combination with a polymer from polyurethane, nanoparticles, and gelatin. The resulting polymer also had a memory effect, was capable of maintaining its shape, and was suitable for cryo conservation[74].

PROSPECTS FOR THE APPLICATION OF OLFACTORY MUCOSA CELLS AND NEUROTROPHINS IN 4D BIOPRINTING

As already discussed in this review, olfactory mucosa cells have great potential in the treatment of spinal cord injuries and are optimal for personalised cell therapy. Four-dimensional bioprinting is a novel, actively developing direction in regenerative medicine. The application of olfactory mucosa cells and neurotrophins in the creation of 4D constructs will allow researchers to design unique transplants that will have a complex effect on damaged tissue. It is necessary to study 4D constructs based on both cells with the addition of a neutrophilic factor and transduced cells, which will intensively secrete various neurotrophic factors in the area of injury. Particular attention should be paid to constructs capable of adapting to changes in shape and size, which is especially important in the treatment of post-traumatic cysts.

CONCLUSION

The most promising vector for the development of spinal cord injury therapy is the development of smart 4D constructs. Such constructs can contain both neurotrophins and cells. The most optimal source of cells for 4D printing is olfactory mucosa due to its atraumatic production and proven therapeutic efficacy of the cells obtained from it. The study of 4D bioprinting based on olfactory mucosa cells and neurotrophic factors is necessary for developing an optimal strategy for the treatment of spinal cord injury.

FOOTNOTES

Author contributions: Stepanova OV designed the manuscript and drafted the abstract and introduction; Fursa GA drafted the chapters "4D bioprinting in the treatment for spinal cord injuries"and "Conclusions"; Andretsova SS drafted the chapter "Exogenous neurotrophin therapy"; Shishkina VS drafted the chapter "3D bioprinting in the therapy for spinal cords injury"; Voronova AD drafted the chapter "Neural stem cells/progenitor cells"; Chadin AV drafted the chapter "Ensheathing cells"; Karsuntseva EK drafted the chapter "Mesenchymal stem cells"; Reshetov IV contributed to the improvement and revision of the manuscript; Chekhonin VP provided the final approval of the version to be published.

Conflict-of-interest statement: There is no conflict of interest associated with any of the senior authors or other co-authors who contributed their efforts to this manuscript.

Country/Territory of origin: Russia

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S-Editor: Chen YL
L-Editor: A
P-Editor: Chen YL

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