Press Release

Keio University

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Keio University School of Medicine

Research Group Successful in Using Cell Transplantation to Improve Therapeutic Efficacy in Chronic Spinal Cord Injury

Motor Function Recovered Through Combined Rehabilitation Treatment

A research group at the Keio University School of Medicine has successfully transplanted human induced pluripotent stem cell-derived neural stem/progenitor cells (hiPSC-NS/PCs) into mouse models of chronic spinal cord injury combined with rehabilitation using progressive-intensity treadmill training to restore motor function and reveal histological findings. The group was led by Professor Hideyuki Okano of the Department of Physiology, Professor Masaya Nakamura, Assistant Professor Narihito Nagoshi, research assistant Takahiro Shibata of the Department of Orthopaedic Surgery, and part-time lecturer Syoichi Tashiro of the Department of Rehabilitation Medicine.

The research group has previously reported on the efficacy of hiPSC-NS/PC transplantation for subacute spinal cord injury. However, the therapeutic effect of cell transplantation for chronic spinal cord injury with limited treatment sensitivity has been limited, and the need for combination therapy, such as drugs and rehabilitation, has been recognized. To optimize rehabilitation therapy, the group has developed a protocol of treadmill training with increasing intensity for a mouse model of spinal cord injury and has reported that this method improves motor function to some extent, with increased expression of neurotrophic factor and neural activity in the lumbar spinal cord, even in the chronic phase. The results of this study showed that the use of this method was effective in improving motor function to some extent, even in the chronic phase of spinal cord injury.

In this study, the group verified the efficacy of the combined treatment of rehabilitation and transplantation of hiPSC-NS/PCs of sufficient quality for clinical research using the aforementioned training method in a mouse model of chronic spinal cord injury. The combined use of rehabilitation therapy improved the survival rate of transplanted neural stem/progenitor cells and promoted their differentiation into mature neurons. In addition, more neurotrophic factors were expressed in the spinal cord tissues, including the injured area, and increased neuronal activity and serotonergic neuron fibers were observed in the spinal cord. As a result, the combined treatment of cell transplantation and rehabilitation showed better recovery of motor function than cell transplantation alone.

This study is the first report of a combined treatment of hiPSC-NS/PC transplantation and rehabilitation for chronic spinal cord injury, and the researchers believe it is a very significant achievement in establishing a therapeutic foundation for regenerative medicine for chronic spinal cord injury in the clinical setting.

The results of this research were published online in *STEM CELLS Translational Medicine* on January 17, 2023 (EST).

1. Research Background

Spinal cord injury is a condition in which the parenchyma of the spinal cord (the central nervous system) is damaged by trauma, resulting in severe physical disability, such as permanent paralysis, sensory loss, and bladder dysfunction below the injured level. Until now, there has been no basic and effective treatment for functional disorders such as paralysis caused by spinal cord injury. However, with the remarkable progress in basic research in recent years, it has become clear that the injured spinal cord, which was thought to be non-regenerative, can be regenerated if the appropriate environment is provided, and various treatment methods are currently being developed.

Our research group has been investigating cell transplantation therapy using hiPSC-NS/PCs for spinal cord injury and has demonstrated its efficacy in animal models of spinal cord injury, mainly in the subacute phase. Spinal cord injury is more susceptible to different treatments in the acute and subacute phases of injury than in more chronic phases. Since most patients are in the chronic phase of spinal cord injury, treatments in this phase are an important issue. The therapeutic efficacy of hiPSC-NS/PC transplantation for chronic spinal cord injury is limited, and combining the transplanted cells with rehabilitation is essential to integrating them into the host neural circuits functionally. To that end, we had previously developed an intensity-escalating treadmill training protocol that allows for exercise therapy with sufficient load and duration necessary to optimize rehabilitation therapy.

In this study, we focused on the combined treatment of cell transplantation and rehabilitation for chronic spinal cord injury, expecting to improve motor function through synergistic effects. We transplanted hiPSC-NS/PCs into mice models of spinal cord injury and then conducted rehabilitation therapy using treadmill training to verify the efficacy of the therapy.

2. Research Significance and Future Development

Mice with contusive spinal cord injury were transplanted with hiPSC-NS/PCs on day 49 post-injury, which is considered the chronic phase. The results showed that:

(1) Compared to the untrained group that did not receive rehabilitation, the trained group that received rehabilitation showed improved survival of transplanted cells and had more cells differentiate into mature neurons. In addition, the trained group showed increased neural activity in the lumbar spinal cord and an increase in serotonergic neuron fibers, which are important for the recovery of motor function in mice.

(2) The trained group showed increased expression of neurotrophic factor proteins such as BDNF and NT-3 in spinal cord tissue compared to the untrained group.

(3) Hindlimb motor function of mice, which was reduced after spinal cord injury, was significantly improved in the trained group compared to the untrained group.

These results suggest that rehabilitation therapy using treadmill training increased the expression of neurotrophic factors in spinal cord tissues, which were involved in improving survival, promoting the differentiation of transplanted cells, and enhancing neural activity in the lumbar spinal cord. The synergistic effects of hiPSC-NS/PC transplantation and rehabilitation resulted in various plastic changes in the neural circuits of the host spinal cord and recovery of motor function. (See Fig. 1)

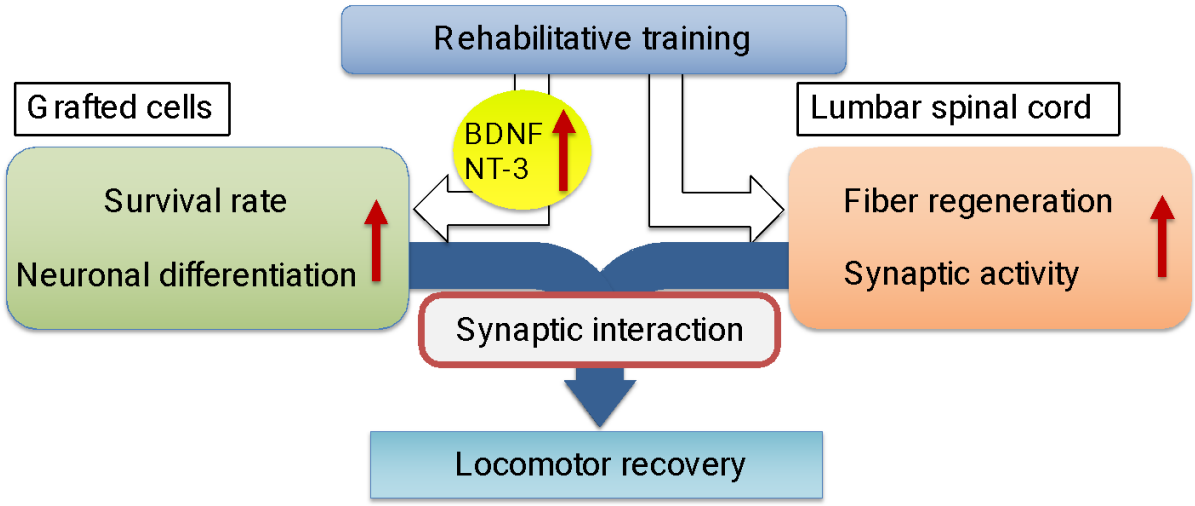

Fig. 1

Rehabilitation was able to enhance the synaptic activity in the lumbar spinal cord and promoted survival rate and neural differentiation of grafted hiPSC-NS/PCs passively through the promotion of neurotrophic factor secretions. Consequently, combination therapy with hiPSC-NS/PC transplantation and rehabilitative training has significantly improved motor functions.

3. Notes

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4. Research Paper

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