Press Release

Keio University

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Keio University School of Medicine

Successful Development of Combined Therapy Using Human iPS Cell Transplantation for Chronic Complete Spinal Cord Injury

New combination therapy brings together human iPS cell transplantation and scaffolds containing hepatocyte growth factor

A research group at the Keio University School of Medicine has developed a new treatment for chronic complete spinal cord injury for which there was no effective treatment. The group conducted animal experiments resulting in the world's first successful restoration of motor function and urinary function and was led by Professor Hideyuki Okano of the Department of Physiology, Professor Masaya Nakamura of the Department of Orthopedic Surgery, Assistant Professor Shogo Hashimoto, and Lecturer Narihito Nagoshi of the Department of Orthopedic Surgery.
Previously, this research group transplanted human iPS cell-derived neural stem/progenitor cells[1] into animals with subacute[2] incomplete[3] spinal cord injury and reported their efficacy in improving motor function. Here, the efficacy of the same transplantation therapy was investigated in rats with chronic[4] complete[5] spinal cord injury. Previous studies have reported that the functional improvement of rats with chronic complete spinal cord injury is limited by various neuroregeneration inhibitory factors[6] and that transplantation of human iPS cell-derived neural stem/progenitor cells alone does not improve the function of animal models. As such, the group first pre-administered a collagen scaffold[7] containing hepatocyte growth factor[8] to the injured area to improve the microenvironment of the spinal cord. The group then performed standby transplantation of human iPS cell-derived neural stem/progenitor cells and succeeded in achieving functional recovery by increasing the engraftment rate of the transplanted cells. The results of this study demonstrated that the efficacy of cell transplantation therapy for chronic spinal cord injury can be enhanced by modifying the spinal cord microenvironment prior to transplantation. Based on these findings, the group expects to establish a clinical treatment method for complete spinal cord injury in the chronic stage, a condition that has been thought to be difficult to recover from.

The research results were published online in *Biomaterials* on January 26, 2023 (GMT).

1. Research Background

Spinal cord injury occurs when the parenchyma of the spinal cord is damaged in a motor vehicle accident or other traumatic events. The condition causes paralysis of the sensory and autonomic nervous systems, and approximately 5,000 new patients are diagnosed each year. While no fundamental treatment has been established, the cumulative number of patients in Japan continues to increase. It is estimated that there are currently 100,000 to 200,000 patients. Both the treatment of patients in the subacute stage and those in the accumulating chronic stage are considered major challenges.

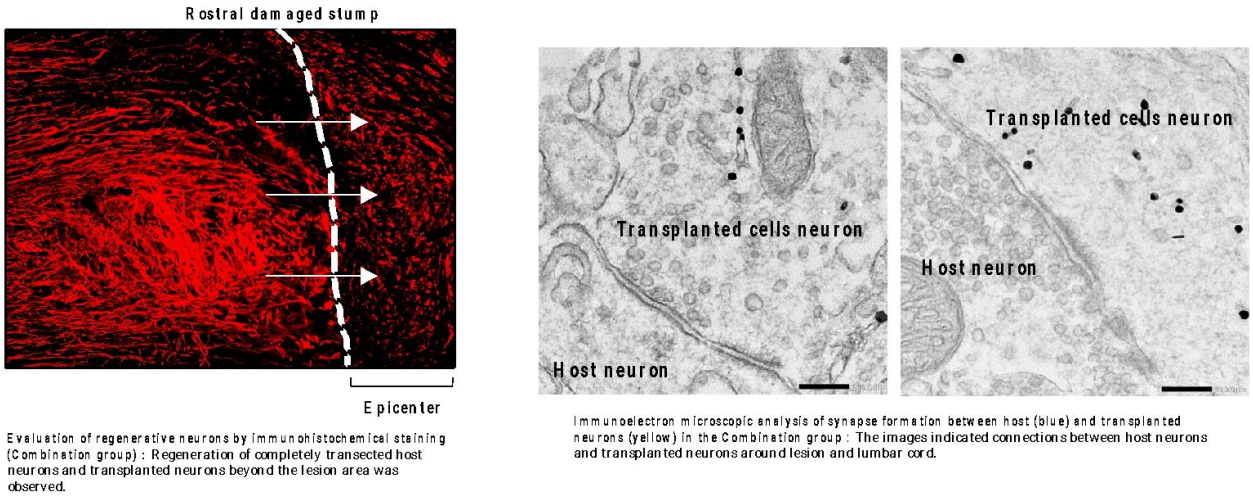
This research group aims to regenerate the damaged spinal cord and is the first in the world to develop a human iPS cell-derived neuronal cell line. We have successfully transplanted neural stem/progenitor cells into animal models of spinal cord injury in rodents and primates to restore motor function. Since then, we have continued our research toward the realization of spinal cord regenerative medicine and clinical research.
Clinical research on "Regenerative medicine using iPS cell-derived neural progenitor cells for subacute spinal cord injury" (Study ID: UMIN000035074, Regenerative Medicine Provision Plan Number:

jRCTa031190228) has been initiated.
Since there is no effective treatment for chronic, complete spinal cord injury (SCI), which accounts for the majority of SCI patients, even in animal studies, our research group has sought to develop a combination therapy with other therapies, not only human iPS cell-derived neural stem/progenitor cell transplantation alone. As part of this effort, this study focused on the modification of the spinal cord microenvironment prior to cell transplantation. In the chronic stage of complete injury, human iPS cell-derived neural stem/progenitor cell transplantation alone is known to result in poor cell engraftment and functional improvement.

Therefore, hepatocyte growth factor is currently used in clinical trials for acute spinal cord injury (Study ID: UMIN000041030), and collagen is clinically used as artificial dermis for trauma and burns. Improving the spinal cord microenvironment is key to the efficacy of human iPS cell-derived neural stem/progenitor cell transplantation therapy.

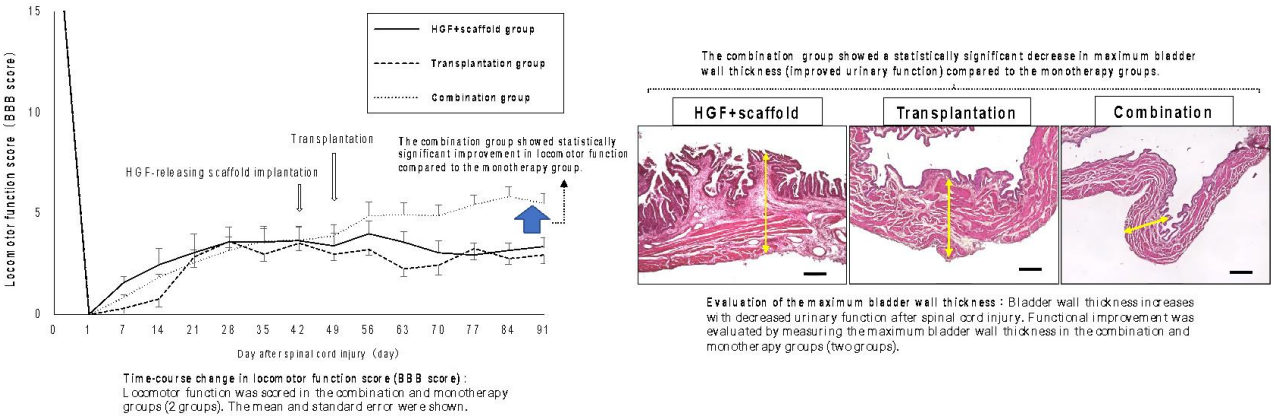
2. Research Significance and Future Development

We found that administration of a collagen scaffold containing hepatocyte growth factor to the injured area restores the spinal cord microenvironment by promoting angiogenesis, improving inflammatory response, and reducing scar tissue and syringomyelia. Transplantation of human iPS cell-derived neural stem/progenitor cells into a spinal cord with an improved environment.
The increased engraftment rate of the transplanted cells enhances the effect of building new neural circuits, resulting in improved motor function. (See Fig. 1)
We have been able to achieve improved urinary function and will continue to offer services for chronic complete spinal cord injuries. Based on the results of this study, further complex therapies using cell transplantation are expected to be developed and applied clinically.



Evaluation of regenerative neurons by immunohistochemical staining (Combination group) : Regeneration of completely transected host neurons and transplanted neurons beyond the lesion area was observed.

Immunoelectron microscopic analysis of synapse formation between host (blue) and transplanted neurons (yellow) in the Combination group : The images indicated connections between host neurons and transplanted neurons around lesion and lumbar cord.



Time-course change in locomotor function score (BBB score) : Locomotor function was scored in the combination and monotherapy groups (2 groups). The mean and standard error were shown.

Evaluation of the maximum bladder wall thickness : Bladder wall thickness increases with decreased urinary function after spinal cord injury. Functional improvement was evaluated by measuring the maximum bladder wall thickness in the combination and monotherapy groups (two groups).

(Fig. 1) Spinal cord microenvironmental improvement combined with human iPS cell-derived neural stem/progenitor cell transplantation promotes functional recovery after chronic complete spinal cord injury.

3. Notes

This research was conducted at the Center for Disease- and Tissue-Specific Practical Application of iPS Cell-Derived Neural Progenitor Cells, the Regenerative Medicine Network Program of the Japan Agency for Medical Research and Development (AMED), and the Center for Tissue-Specific Practical Application of Neural Progenitor Cells. This research was also supported by a Keio University School of Medicine Research Grant, Keio Medical Association Medical Research Grant, Keio Orthopedic Surgery Hosoya-Umezawa Research Grant, and JST Postdoctoral Student Support Project Grant. This research was also performed using recombinant hepatocyte growth factor provided by Kringle Pharma, Inc. (Osaka, Japan), and a collagen scaffold (Pelnac G plus) provided by Gunze, Inc. (Kyoto, Japan).

4. Research Paper

Title: *Microenvironmental modulation in tandem with human stem cell transplantation enhances functional recovery after chronic complete spinal cord injury*

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5. Glossary

1 The ability to self-renew, which allows proliferation while maintaining an undifferentiated state, and the ability to maintain the central nervous system, which are human cells that have both multilineage differentiation potential and the ability to differentiate into three cell lineages (neurons, astrocytes, and oligodendrocytes). The transplantation of these cells is currently undergoing clinical trials as a treatment for subacute spinal cord injury and expectations are high for this new treatment for spinal cord injury.

2 In humans, this is approximately 14 to 28 days after spinal cord injury.

3 A mild to moderate injury in which the nerve fibers of the spinal cord have not been completely severed.

4 In humans, this is approximately 28 days after spinal cord injury.

5 This is the most severe injury in which the nerve fibers of the spinal cord are completely severed.

6 Factors that inhibit nerve regeneration, such as scar tissue, syringomyelia, and axon elongation inhibitors.

7 Artificial scaffold material is composed mainly of collagen. Used in various fields of regenerative medicine. It not only functions as a scaffold for regeneration but also promotes angiogenesis, anti-inflammation, and sustained release of the drug.

8 Discovered in Japan as an in vivo protein that promotes the proliferation of mature hepatocytes. Subsequent studies have shown that, in addition to cell proliferation, HGF promotes cell motility, inhibits cell death, and induces apoptosis. It has a variety of physiological activities, such as morphogenesis induction, anti-fibrosis, and angiogenesis, and has been used not only in the liver but also in the regeneration and protection of various tissues and organs, including the nervous system, lungs, kidneys, heart, skin, etc. It has also been shown to have neuroprotective and axon-lengthening effects in spinal cord injury. It is currently in Phase III clinical trials for acute spinal cord injury.

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