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The potential role of Embryonic stem cells in the treatment of spinal cord injuries

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Abstract: . Human embryonic stem (ES) cells capture the imagination because they are immortal and have an almost unlimited developmental potential. After many months of growth in culture dishes, these remarkable cells maintain the ability to form cells ranging from muscle to nerve to blood—potentially any cell type that makes up the body. The proliferative and developmental potential of human ES cells promises an essentially unlimited supply of specific cell types for basic research and for medical therapy such as treating spinal cord injuries

A spinal cord injury is damage done to any part of the spinal cord or nerves at the end of the spinal canal (cauda equina), it often causes permanent changes in strength, sensation and other body functions below the site of the injury.

Effects of this injury might be felt mentally, emotionally and socially.

Many scientists are optimistic that advances in research will someday make the full repair of spinal cord injuries through embryonic stem cells possible. Research studies are ongoing around the world, some are discussed in my report. Current therapeutic strategies for SCI includes surgical decompression and pharmacotherapy, however, there is still no gold standard for the treatment of this devastating condition. Inefficiency and adverse effects of standard therapy indicate that novel therapeutic strategies are required. Because of their neuroregenerative and neuroprotective properties, stem cells are a promising tool for the treatment of SCI. Herein, we summarize and discuss the promising therapeutic potential of human embryonic stem cells (hESC)

Introduction:

The spinal cord is an organized and complex part of the CNS. The spinal cord is a collection of nerves that travel from the bottom of your brain down your back, there are 31 pairs of nerves that leave the spinal cord to your heart, lungs, bowel, bladder. For example signals from the spinal cord are what control our rate of breathing. Other spinal nerves travel from different parts of the body back to the spinal cord. These nerves bring back information to the brain from the different body parts, these include the sense of touch, pain, positioning and temperature. The spinal cord is very sensitive it does not have the ability to repair itself nor does it's cells have the ability to regenerate. We know that the spinal cord is the main relay for signals between the brain and the body, hence injury to the spinal cord would deprive the individual from mobility and sensory input as well as autonomic nervous system control below the level of the lesion (1). There are many factors that cause spinal cord injuries like high-energy trauma, infection etc etc. Spinal cord injuries are classified into complete and incomplete injuries. In complete injuries there is a complete loss of sensation and muscle function to the body below the level of injury. In incomplete injuries there is still some remaining sensation and muscle function in the body below the level of injury. In most cases of spinal cord injuries both sides of the body are affected equally. Currently there is no cure for spinal cord injuries but surgeries have been done to remove any foreign objects, fractured vertebrae, or herniated discs that could further compress the spine also pharmacological agents such as (IV) methylprednisolone has been used as a treatment option for acute spinal cord injury in the past, but recent research has shown that the potential side effects such as blood clots and pneumonia from using this medicine outweighs its

benefits, because of this methylprednisolone is no longer recommended for routine use after a spinal cord injury. Stem cells are thought of as primitive or unspecialized cells that have the ability to differentiate into any type of cells (liver, blood, muscle and others), there are different types of stem cells, embryonic (totipotent), fetal stem cells (pluripotent) and adult stem cells (multipotent). Stem cells are said to be the future of medicine as they have the ability to differentiate into any type of cells and recent studies have shown that stem cells could potentially regenerate spinal cords after SCI (2).

The aim of my study was to point out the future potential of Embryonic stem cells therapy for the treatments of spinal cord injuries.

Methods and materials:

Animals: Experimental animals (Adult female common marmosets) aged only 18 months and older were brought for ESC-NS/PC transplantation (2).

Culture and ESC-NS/PC Differentiation: (2)

Contusive SCI and Transplantation in common Marmosets: Spinal cord injuries were induced on the marmosets at the level of C5 (2).

Behavioral analysis: All of the behavioral tests were done from the time of the initial injury up to 12 weeks after the SCI, the typical open field rating scale was used to evaluate the locomotion of the marmosets, it was done 3 times per week for the first 4 weeks and once a week afterwards (2).

Magnetic Resonance Imaging: Since in a preclinical trial only noninvasive devices can be used, MRI was used to detect any cavity formations, edema's and hemorrhages. (2)

Results:

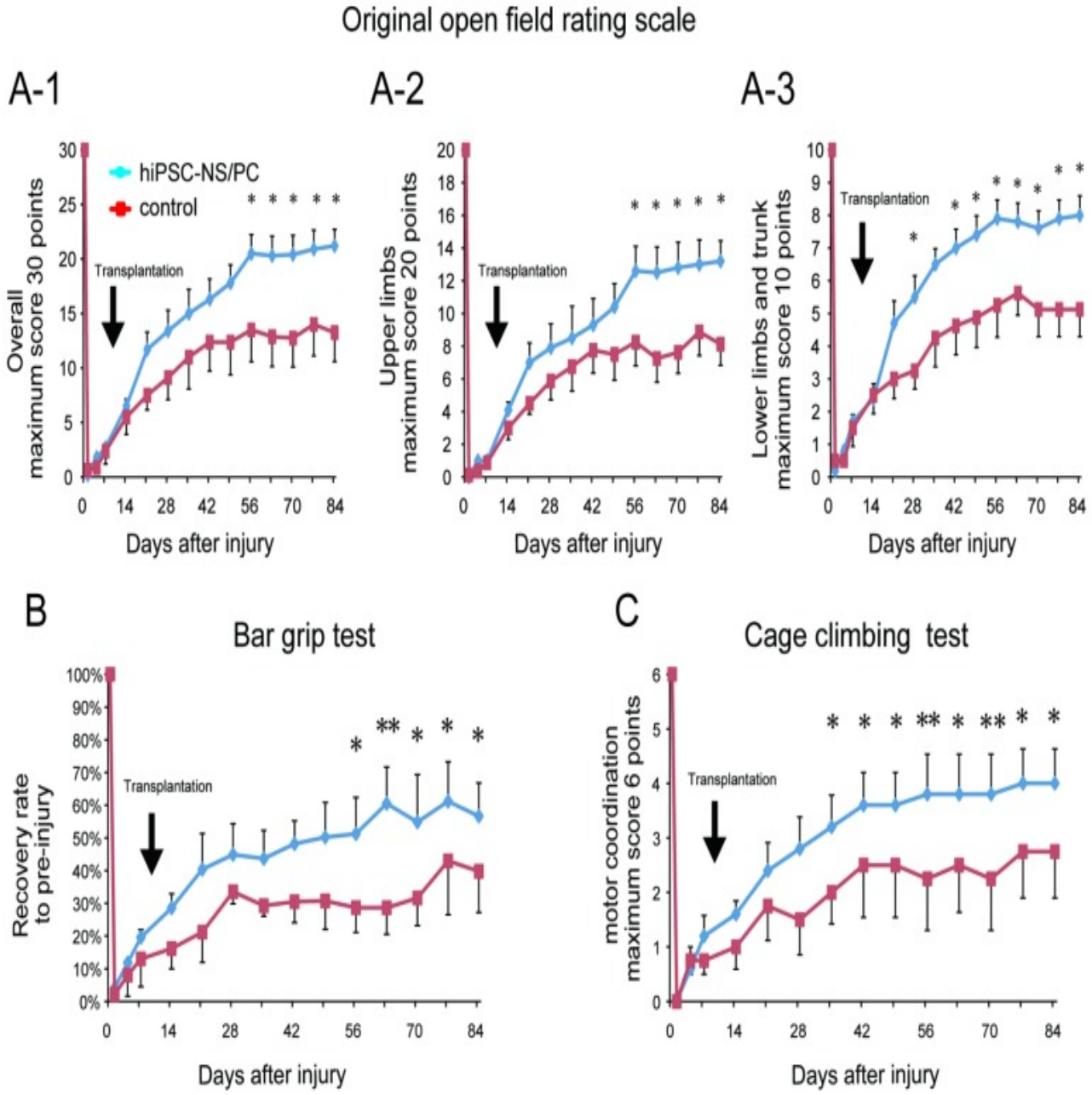
Differentiation of Transplanted ESC-NS/PCs Into Three Neural Lineages in the Injured Spinal Cord: Anti-GFP immunohistochemistry, which detected venus-positive cells, was performed to investigate the survival of grafted cells. Immuno-histological analysis showed

that allogeneic grafted ESC-NS/PCs survived well in the injured spinal cord, indicating that immune-rejection was prevented, even in the presence of a low dose of tacrolimus. (2)

ESC-NS/PC-Derived Oligodendrocytes Contributed to Remyelination After SCI: To demonstrate the capacity of grafted cells to prevent demyelination or to promote remyelination after SCI, LFB staining was performed at 14 weeks after injury. The LFB-positive areas were measured at sites that were 4 mm rostral and 4 mm caudal to the lesion. The LFB-positive areas within the lesion epicenter were significantly larger in the NS/PC group than in the control group. Furthermore, noninvasive MRI of myelin (myelin map) was conducted at 10 weeks after transplantation to assess myelination by noninvasive imaging. The myelin map showed that the myelin-positive areas were significantly larger at the lesion epicenter and at the site 1.5 mm rostral to the lesion epicenter in the grafted group than in the control group, similar to the histological findings of LFB-positive myelinated areas after SCI. Although some discrepancy between the myelin map and LFB-based histological findings was observed, this could be explained by the technical differences, including problems with voxel sizes and resolutions. (2)

ESC-NS/PC Transplantation Prevented Atrophy of the Injured Spinal Cord and Promoted Angiogenesis: H&E staining was performed to investigate the effect of transplanted NS/PCs on the atrophy and cystic cavities of the injured spinal cord. The H&E-positive areas were quantified, not only at the lesion epicenter, but also at sites that were 2 and 4 mm rostral and caudal to the lesion epicenter, respectively. In the transplantation group, the H&E-positive areas in the region of the lesion epicenter, but not at the rostral and caudal sites, were significantly larger than those in the control group. In addition, the cystic cavities in the transplantation group were significantly smaller than those in the control group. NS/PC transplantation prevented spinal atrophy and cavity formation after contusive injury. Furthermore, the ESC-NS/PCs did not result in any microscopic tumors at 12 weeks after transplantation. To evaluate the effect of ESC-NS/PC transplantation on angiogenesis after SCI, immunohistochemical analyses for PECAM-1 were performed on day 84 after transplantation. Quantitative analysis revealed that the areas of PECAM-1-positive vessels were also significantly larger at the lesion epicenter in the grafted group than in the control group. (2)

ESC-NS/PC Transplantation Promoted Functional Recovery After SCI: Motor function was evaluated using the original open field rating scale score for general motor function and the bar grip test for grip strength. The score in the original open field rating scale decreased to near zero shortly after contusive SCI. The ESC-NS/PC transplantation group showed rapid functional recovery in the open field rating scale score compared with the control group. The difference was statistically significant at 4 weeks after transplantation. In contrast, the control animals showed a gradual increase in the open field rating scale score after SCI, with a plateau at approximately 8 points. The bar grip test also yielded similar results to the open field rating scale scores. Contusive SCI sharply decreased the grip strength in the bar grip test to approximately 0%, which then gradually recovered. A significant difference was found in the bar grip strength between the transplantation and control groups at 9 weeks after transplantation. (2)



Discussion:

The advantage of using common marmosets instead of rodents is their common similarities between them and humans in neurological anatomy and immune responses. For example, most CST fibers in humans and marmosets cross to the contralateral side through pyramidal decussation and descend the lateral funicles, and CST fibers descend the dorsal funicles in rodent spinal cord._Immunological responses to allografts in primates also differ from those in rodents. Regulatory T cells (Treg) play an important role in allogeneic immunity, and the Treg functions and features in humans are similar to those in nonhuman primates but quite different from those in rodents. Moreover, CD40/CD40 ligand interactions and major histocompatibility (MHC) complexity differ between primates, including common marmosets and rodents.Many reports have referred to the benefit of using nonhuman primate models in translational research of spinal cord injury or allogeneic transplantation. Thus, it is critical to determine whether allogeneic transplantation of NS/PCs can promote functional recovery in nonhuman primates as a part of the translational research required for clinical trials. (2)(3)

Previous studies show that a severe inflammation occurs at the site of the SCI due to the presence of high levels of inflammatory cytokines with neurotoxic effect such as (IL-1, IL-6 and TNF) which decrease 24 hours afterwards. This indicates that the microenvironment is not suitable for the differentiation or survival of the grafted cells. We also demonstrated that the chronic phase is not suitable due to the formation of many cysts and glial scarring which may inhibit axonal regeneration, based on the present study we demonstrated that the sub-acute phase is the optimal time for the transplant to take place

Undeveloped cell based treatments for SCI could speculatively influence histological as well as practical results through various gainful systems, including axonal recovery, neighborhood hardware reproduction, neurotrophic impacts, angiogenesis and immunomodulation, all of which have been accounted for to recover the harmed spinal string in past examinations utilizing rat ESCs/iPSCs. Contrasted and rodents, non-human primates, for example, normal marmosets have unmistakable contrasts as far as life structures, utilitarian neural pathways in the spinal string, and insusceptible reactions. In spite of the fact that it is hard to assess the practical recuperation of the forelimbs in the rodents, this is conceivable in the SCI model of the non-human primates. Besides, to approve and anticipate the restorative impacts of intercessions utilized as human medications, contusive injury is viewed as the most applicable to human SCI. In this manner, the present examination utilizing normal marmosets could be significant for the pre-clinical assessment of human iPSC treatment for human SCI.

Transplanted NS/PCs advance substitution as well as apply immunomodulatory and neuroprotective impacts to forestall tissue harm. Moreover, undifferentiated NS/PCs enduring in the harmed spinal line can discharge trophic variables equipped for shielding endogenous neural cells from cell demise, forestalling glial scar arrangement, and expanding endogenous re-myelination alongside immunomodulatory particles. We performed Iba1 recoloring to evaluate microglial initiation and GFAP recoloring to evaluate glial scar arrangement. Be that as it may, the size of the Iba1-positive region was not essentially extraordinary among control and transplantation gatherings, and there was no proof of immunomodulation by hiPSC-NS/PCs (12 weeks after transplantation).

hiPSC-NS/PCs added to the conservation of myelin sheaths as opposed to re-myelination after SCI. It is conceivable that adult oligodendrocytes show up sometime in the not too distant future point, as oligodendrocyte forebear cells were available in the united cells.

All in all, NS/PCs got from the pre-assessed safe human iPSC clone 201B7 endure and separated into three neural ancestry cells inside the harmed spinal rope of grown-up normal marmosets, with no proof of tumor arrangement. The hiPSC-NS/PCs additionally added to critical utilitarian recuperation right now primate model of SCI. In spite of the fact that hiPSCs hold incredible guarantee as a cell hotspot for the investigation and treatment of human sicknesses and

disarranges, it is basic to deliberately evaluate security worries before their utilization in the center. Specifically, hiPSCs produced utilizing retroviruses show mix of the infection DNA into have chromosomes, which may prompt unusual hereditary brokenness. Hence, further investigation utilizing combination free hiPSC-determined NS/PCs is required to approve the security of such cells for immature microorganism intercessions following SCI.. (3)

Conclusion:

In this study I demonstrated that allogenic transplantation of ESC-NS/PC in a nonhuman primate improved functional recovery without any tumorgenicity, specifically the ESC-NS/PC which differentiated into oligodendrocytes after the transplantation contributed to remyelination of the demyelinated host axons. In addition, a large number of allogeneic grafted ESC-NS/PCs survived in the presence of a low dose of tacrolimus, since the nonhuman ESC-NS/PC can suppress immune rejection. Our findings support the use of allogeneic multipotent stem cell derived-NS/PCs for the treatment of SCI, not only in nonhuman primates but also in patients.

Future work:

In the future I hope for the use of stem cells as the treatment of many neurodegenerative diseases including SCI which would really help a lot of individuals as it has been shown possible in recent studies.

Reference

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