NEURAL REGENERATION RESEARCH
Volume 7, Issue 11, April 2012
www.nrronline.org

Cite this article as: Neural Regen Res. 2012;7(11):849-852.

Does repair of spinal cord injury follow the evolutionary theory?☆

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Abstract

Lower vertebrates, such as fish and amphibians, and higher vertebrates in embryonic development can acquire complete regeneration of complex body structures, including the spinal cord, an important part of the central nervous system. However, with species evolution and development, this regenerative capacity gradually weakens and even disappears, but the cellular and molecular mechanisms remain poorly understood. We explored the differences in mechanisms of spinal cord regeneration capability between lower and higher vertebrates, investigated differences in their cellular and molecular mechanisms and between the spinal cord structures of lower vertebrates and mammals, such as rat and monkey, to search for theoretical evidence and therapeutic targets for nerve regeneration in human spinal cord.

Key Words: spinal cord injury; evolutionary theory; lower vertebrates; higher vertebrates; mammals; cell transplantation

Abbreviations: SCI, spinal cord injury; OEG, olfactory ensheathing glia

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Received: 2011-11-29
Accepted: 2012-02-11
(NY20111121002/H)

Zhang ZC, Li F, Sun TS. Does repair of spinal cord injury follow the evolutionary theory? Neural Regen Res. 2012;7(11):849-852.

www.crter.cn
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doi:10.3969/j.issn.1673-5374.2012.11.009

INTRODUCTION

Some clinical and basic problems arising from spinal cord injury (SCI) have not been explained fully. Why can the spinal cord in lower vertebrates completely regenerate after injury, while in higher vertebrates it does not? Why can SCI in the rat get satisfactory functional recovery, including motion, using various integrated intervention strategies, but is not successful in humans? Why is the self-repair capability of neural structures at lower evolutionary level superior to that at the higher evolutionary level following SCI? Does SCI repair follow the principles of evolutionism? Early in the 1970s, Dobzhansky pointed out that "Nothing in biology makes sense except in the light of evolution" [1]. Maybe answers to these questions will lead to a revolution in the repair and treatment of SCI.

EVOLUTIONARY THEORY IN SCI REPAIR

The primary successful application of stem cell transplantation was for Parkinson's disease treatment suggesting that stem cell transplantation could be used to treat other neurological diseases, including SCI[2-3]. This idea seems logical, but it neglects a fundamental and important fact. The pathological basis of Parkinson's disease is the primitive ganglion cell, but that of SCI is the highly developed and advanced Betz's motor neuron. The nervous system has evolved through the following process: no nerve (protozoa) → primitive nervous system (sponges) → reticular nervous system (coelenterates) → ladder nervous system (platyhelminthes) → chain nervous system (annelid and arthropods - ganglion cells) → tubular nervous system (vertebrates - Betz's cells)[4]. There is an interval of millions of years in evolutionary pedigree between mature Betz's cells and ganglion cells. The two kinds of nerve cells are vastly different and not comparable. Lower vertebrates, such as fish and amphibians, and higher vertebrates during embryonic development can acquire complete regeneration of complex body structures, including the spinal cord, an important part of the central nervous system[5]. For example, some kinds of tailed amphibians, newts and salamanders, can regenerate their spinal cord, retina, and even part of the telencephalon. However, tailless amphibians, such as frogs, may regenerate neural structures in larvae but such capability decreases as they develop[6-7]. A high regenerative capacity during development is not unique to anurans, and it has been well reported in higher vertebrates, such as birds and marsupials (a subclass of Mammalia)[8]. Their embryos are easily accessible for manipulation and analysis unlike those whose entire gestation is intrauterine. There are evidences of spinal

cord regeneration in rodent embryos but not in sheep[9]. However, with species evolution and development, this regenerative capacity gradually lessens or even disappears. From the most common animal model, the rat, to the rarer model of macaque[10], many animal models have been established for studies of SCI repair. Clinical trials are limited to assessing nerve regeneration using electrophysiological or functional measures since pathological changes cannot be observed directly in SCI patients. Regeneration of the spinal cord may be detected using histological methods in animal models, but not in humans. Several previous experimental studies on SCI showed that rats can recover more sensory and motor function than humans following various treatments especially after complete SCI. In clinical practices, a little spontaneous recovery of motor function was seen in a longitudinal study of patients with complete SCI[11]. In animals it has been possible to visualize, using special histological methods, axonal regeneration over a collagen nanofiber scaffold after complete transection of the spinal cord[12]. Akhtar *et al* [13] explored the reasons for different responses to multiple neuroprotective agents between the promising animal studies and disappointing clinical trials and concluded that the differences between laboratory-induced SCI and clinical SCI, difficulties in interpreting functional outcome in animals, and inter-species differences in pathophysiology of SCI could be responsible. The differences in neural plasticity between animal models and human SCI have been discussed in relation to the severity of injury, the effect of locomotor training, the localization of neural plasticity, and the implications for interpreting the translatability of animal model data to human study and clinical practice[14]. The evolutionary differences among species may have a direct role on their regenerative capacity and we explored this neglected area of investigation.

It remains poorly understood why this regeneration potential is lost with evolution and development and becomes very limited in adult mammals. Regenerative capacity changes are most likely due to a combination of several factors, such as cellular and molecular changes during evolution, environmental difference between embryonic and adult spinal cord, and the decrease in number of neural progenitors[15], or the capacity to recruit them *in vivo* in the adult spinal cord of higher vertebrates[16]. We should study the mechanism of spinal cord regeneration and the difference in the capability between lower vertebrates and higher vertebrates. We could also explore differences in their intercellular, cellular and molecular mechanisms and the spinal cord structures in animals from different evolutionary levels, *e.g.* fish, chick, rats and monkeys, to search for a theoretical basis, the guiding principles and therapeutic targets.

INVESTIGATION AND VERIFICATION OF THE EVOLUTIONARY THEORY IN SCI REPAIR

First, the mechanisms of spinal cord self-regeneration and self-repair capabilities in various species from different evolutionary levels can be explored[17]. In the high evolutionary mammals, SCI has been considered unable to regenerate and repair. However, research on various integrated intervention strategies following rat spinal cord contusion injury has resulted in satisfactory functional recovery including motor function[18]. Cell transplantations may bridge disrupted axons, support axonal regeneration, secrete various growth factors to promote nerve regeneration, and may replace damaged neurons. Each of these procedures may involve an aspect of SCI repair. The basis of stem cell application in SCI repair is the plasticity of stem cells to differentiate into the mature cell type. The lesser the maturity of stem cells, the stronger capability they have to repair the injury, however, there is a greater risk of malignant transformation. A large number of studies have reported that different stem cells, including embryonic and adult stem cells, have been transplanted into animal models of SCI *via* different administration paths. Fortunately, in many cases, stem cells transplantations have resulted in modest sensory and motor recovery[19]. However, it is important to confirm that the stem cell transplantation could maintain a long lifespan and to determine whether or not tumors will eventually form. In addition, it is necessary to confirm whether oriented differentiation and long-term survival of stem cells are required for functional recovery, and which type of progenitor cells and quantity are optimal[20].

If the spinal cord progenitor or stem cells are not available, then the cells of more primitive evolutionary structures in human central nervous system evolution, olfactory system, limbic system or reticular formation[21], could be used to repair SCI. Recent studies have shown that the olfactory system has a better repair capability than the limbic system or the reticular formation. Cells from the olfactory system can be obtained readily from the nasal mucosa epithelial tissue of the olfactory bulb and the lateral ventricles system. Indeed, the olfactory system has a wide range of cells, far more than the olfactory ensheathing glia (OEG). When the OEG were transplanted into rat corticospinal tract of SCI, fairly satisfactory functional recovery including motor function was observed[22]. On the other hand, patients who received OEG transplantation treatment using the same target corticospinal tract injection only gained slight functional improvement[23].

Clinical studies of cell transplantation include a study of more than 400 SCI patients who have been treated with OEG transplantation[24]. Some functional recovery of lower evolutionary level spinal cord structures, such as skin temperature and color recovery, bladder and bowel function improvement (autonomic nerve function), muscle tonus decrease (spinocerebellar tract), was detected in the majority of these patients. However, these functions were not easily measured in most clinics or were often ignored. Some patients also had significant sensory function improvement (touch and pain) and the

sensory level dropped 3 to 10 spinal segments and the American Spinal Injury Association sensory scores increased significantly. Several patients experienced motor function recoveries of the injured spinal cord level with increased strength of an injured level key muscle. However, no motor recovery was found below the injured level that resulted in any obvious motor score increase. Our clinical study of 11 SCI patients treated with OEG transplantation obtained similar results[23]. On the contrary, SCI animals that received OEG transplantation obtained fairly satisfactory functional recovery, including motor function[22]. Hierarchical order of the extent of functional recovery and the possibility of recovery from high to low was skin nutrition, spasms, bladder and bowel function, superficial sensation (up to 10 levels), and motor function. Coincidentally, this is entirely consistent with the theory of evolution. The lower evolutionary level structures have higher repair capability and these low-level functions were restored first[25]. Although OEG transplantation can result in some repair of SCI, it is far from complete. Due to the complexity of spinal cord and SCI, any single therapeutic intervention cannot be expected to solve all the problems. Transplanted cells play some roles in SCI repair, providing means of bridging, supporting, secreting growth factors and replacing damaged cells, evidence has shown that several intervention strategies need to be integrated to optimize recovery[18].

Different results were obtained in clinical and animal experimental studies using the same transplantation strategy. This fact may reflect the evolutionary differences between the nervous systems of the human (mammals, primates, human subjects) and the rat (mammals, rodents, murine). First, we could analyze the anatomical differences to ascertain any differences in response to the same treatment strategy. Second, the mechanism of differences among self-repair and self-regeneration capability of neural structures with different evolutionary level should be explored. The modern human central nervous system is the most complex and develops biological system. Archeological studies have identified the oldest structures of the modern central nervous system are the olfactory system, limbic system and reticular formation[21]. These systems exist in early vertebrate fossils, but other systems exist only in later evolutionary species and their fossils.

The repair possibility of different neural structures seems to follow the order of evolution. That is, the more ancient structure, the larger possibility of repair and regeneration. Newer structures have less capacity[26]. The order of the development of nervous system, relevant to the spinal cord, from the ancient to today is the reticular formation, cerebellum system, sensory thalamic system and forebrain systems, followed by the motor system[3] (Figure 1). The spinal cord has structures connecting to the brain and peripheral nervous system, so it covers a broad range of neural structures from the earliest evolutionary structure (reticular formation) to the most developed neurons (Betz's cells) and their axons (pyramidal tract).

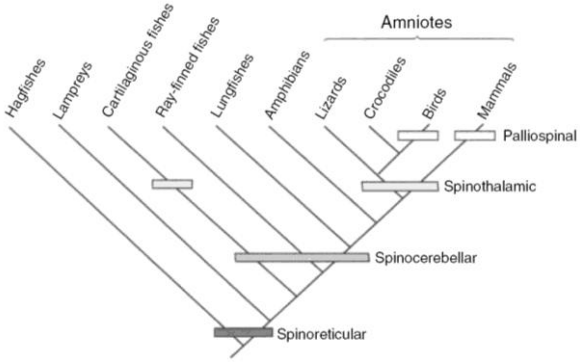

Figure 1 Phylogenetic order of development of the central nervous system[3].

Current basic research results showed that the sequence of spinal cord structure repair capacity is reticular formation, cerebellum tract, rubrospinal tract, spinothalamic tract, and corticospinal tract[25]. Furthermore, the reticular formation is also involved in the repair of injured spinal cord. These results were entirely consistent with the theory of evolution which has important significance in the law of nerve tissue repair. However, not only regeneration capacity and plasticity difference but also the role in repair of the spinal cord among neural structures of different evolutionary levels remains poorly understood. In clinical practice, the neurological function recovery sequence may also follow the evolutionary principles. Current assessment systems of functional recovery have some deficiencies in that most attention has been paid to the recovery of motor function. The functions at the low evolutionary level, including skin nutrition, bladder function, gastrointestinal function and sensory functions, are also significant. These should be included in a broader assessment system for future clinical studies.

PROSPECTS

The differences in capability and mechanisms to repair SCI among different evolutionary species and neural structures should be explored at the genetic, molecular, cellular, organ and systems' levels in the body with possible approaches of developmental biology, comparative biology, pathology, and cellular biology and molecular biology. The potential molecular mechanisms may include the change and evolution of polymers, *e.g*. DNA, large proteins (receptors), small proteins (growth factors) or small molecules, *e.g*. ligands or changes in the systems at the molecular level, *e.g*. signaling. It will provide an evolutionary theory basis for transition from basic research to clinical applications. According to the

differences of evolution in genes, molecules, cells, and organs, several interventions should be performed to find new therapeutic targets to improve the regeneration of human SCI.

Acknowledgments: We thank Dajue Wang from the National Spinal Injuries Centre, Stoke Mandeville Hospital UK for giving us inspiration, some useful ideas and information.
Funding: This work was supported by the National Natural Science Foundation of China, No. 30872604.
Author contributions: Zhicheng Zhang reviewed the references, extracted the data, and wrote the manuscript. Fang Li contributed to the paper revision and study instruction. Tiansheng Sun designed this study.
Conflicts of interest: None declared.

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(Edited by Liang GB, Guo SW/Su LL/Song LP)