

Strategies for nerve regeneration after CNS injury

Xiaodan JIANG^{1*}, Shengbin Kou^{1#}, Zhiqiang Fa^{1#}, Yehai Li^{1#}, Zhenzhou Chen¹,
Shanshan Song², Hongbo GUO¹, Yiquan KE¹, Ruxiang XU¹, Zhicheng XIAO¹

Neurosurgery Institute of Guangdong
Zhujiang Hospital¹ and Nanfang Hospital² of Southern Medical University
258# Gongye Road, Guangzhou 510282, Guangdong Province, P. R. of China.

Who contributed to the research equally

* Corresponding to: jiangxiao_dan@163.com <http://www.zjyy.com.cn>

Abstract: It was traditionally thought that the central nerve system (CNS) defects the regenerated ability, following the injury. However, the peripheral nerve system (PNS) possesses an ability of regeneration after injury. Also it was found that the axon in CNS might extend into the graft, as soon as the peripheral nerve tissue was transplanted into the injured part of CNS. Therefore, it implied that the axons in CNS also possess the regeneration ability, and the regeneration of axon in CNS just depended on the microenvironment around them. The microenvironment of CNS doesn't adapt to the nerve regeneration after damage. The different microenvironment between CNS and PNS mainly results from the different types of glial cells--the oligodendrocytes in CNS play an inhibit role, while the Schwann cells in PNS play an active role in the repairing process following the nerve injury. When CNS damaged, the injured myelin sheath that composed from oligodendrocytes released a lot of inhibitors for axon-regeneration. On the other hand, glial scar inhibited the axon regeneration by space obstruction proteoglycan inhibition (e.g. chondroitin sulfate proteoglycans, CSPGs). Therefore, the repair strategies for nerve regeneration of CNS were just as "Seeds Substitution and Soil Amendment", following injury. For example, Soil Improvement was performed by weakening the inhibitors of obstructing the CNS regeneration, removing the glial scar, supplying the advantageous factors, transplanting the endothelial progenitor cells (EPCs) in order to re-establish the microvascular, and repairing the injured myelin. Seed Substitution was done by transplanting the nerve stem cells (NSCs), and applying the bio-macromolecules as the cellular bridges during the CNS regeneration. Finally, the injured CNS can be repaired.

Key words: Nerve regeneration, Neural stem cells, Central nerve system, Cells transplant, Cellular microenvironment, Oligodendrocyte

1 Overview

The damaged axons of central nerve system (CNS) usually are difficult to regenerate following injury, which will result in the permanent loss of sense, motion and the cognitive in the individuals.

Therefore, it is important to search the new strategies for improving the repair and regeneration of the damaged axons after CNS injury. Then, what are the key factors to effect on the axons regeneration in the injury CNS?

Some interesting investigations ^[1] implied that just the injuring

microenvironment obstructed the axons regeneration in the CNS, because the graft of peripheral nerve tissue permitted the injury axons of the CNS to regenerate in it. As soon as the regenerated axons reached at the edge of the graft and touched with central nerve tissue of the host, however, the axons regeneration was inhibited again. It therefore implied that the axons in CNS also possess the regeneration ability, which just depends on the microenvironment around them. The microenvironment of CNS doesn't adapt to the nerve regeneration after damage. It was well known ^[2] that the main different microenvironment between CNS and peripheral nerve system (PNS) mainly results from the different types of glial cells. The oligodendrocytes in CNS played an inhibit role, while the Schwann cells in PNS played an active role in the repairing process following the nerve injury. When CNS damaged, the injured myelin sheath that composed from oligodendrocytes released a lot of inhibitors for axon-regeneration. Therefore, it implied us that the newest vaccine strategies can be considered to use for decreasing the inhibitors in order to improve the functional recover of injury axons in CNS. On the other hand, the glial scar and the damaged microvascular also inhibit the nerve regeneration following CNS injury. It was found that the CNS injury will result in the formation of lesion scars which include an astrocytic component (glial scar) and a fibroblastic component (connective tissue scar), at the injury site ^[3]. And also the injury of CNS will cause the microvascular damage which effects the nerve regeneration in CNS severely ^[4]. Therefore, the new strategies including effectively minimizing the formation of lesion scars, reestablishing the damaged microvascular, and supplying some advantageous factors such as

neurotrophic factors (NTF) must be concerned, in order to improve the injury axons regeneration in CNS.

Above all, the improvement of microenvironment for nerve regeneration in CNS is just equal to the strategy of "Soil Amendment". Then, which belong to the main "Seeds" in the "Soil"? What is the change of these "Seeds" during the CNS damage and how to make them into the best functional state? For the nerve tissue of CNS, generally, the neurons play an important functional role in the production and transmission of nerve impulse, as the main "Seeds" in the "Soil" which supplies the proper microenvironment for nerve regeneration. As soon as the nerve tissue of CNS was damaged, some of neurons will loss their functions soon. Therefore, the supplementary and substitution of neurons in both structure and function are the necessary. Neural stem cells (NSCs), as a kind of stem cells, possess the potential abilities of proliferation and differentiation, which can differentiate into some of neurons and glials under the suitable conditions and microenvironment. So, the NSCs were usually chosen to repair the injury nerve tissue in CNS by their special properties including the cellular replacement and NTF secretion, which were usually classified as the strategy of "Seeds Substitution".

2 Application of therapeutic vaccine to decrease the inhibit factors in damaged CNS

The neurite growth inhibitors associated with oligodendrocytes and myelin usually include as below: oligodendrocyte myelin glycoprotein (OMgp), myelin-associated glycoprotein (MAG), Nogo A and tenascin-R (TN-R). Generally, there is a physiological autoimmune response at the injury site

accordance with the myelin antigens following CNS injury. Therefore, the artificial co-adjuvant that was actively/passively treated by adequate myelin antigen may activate the protective autoimmune T lymphocytic reaction, then decrease the secondary nerve damage and improve the nerve function, following its administration in vivo. DNA vaccine modified with the neurite growth inhibitors associating with oligodendrocytes and myelin, as a kind of therapeutic vaccine, can effectively neutralize those homologous inhibitors by releasing the antigens to product the accordant antibodies in the individual after using in vivo, which may belong to either the cellular or the humoral immunity. These characteristics of DNA vaccine are propitious for the nerve regeneration in the injured CNS. Some of researches have shown that DNA vaccine may obviously improve the axons regeneration in model of spinal cord injury (SCI) [5]. It provides us a new way for promoting the recovery of nerve function after CNS damage.

3 Strategy to minimize the formation of lesion scars in damaged CNS

As soon as the CNS was injury, the glial scar will appear as the one of secondary lesion at certain time point, which may inhibit the axon regeneration by both Space obstruction and proteoglycan inhibition especially the chondroitin sulfate proteoglycans (CSPGs) . However, it was found recently that chondroitinase ABC (chABC) might effectively promote the axon regeneration, and improve the motor/sensory functions in rat SCI model because the chABC might breakdown the CSPGs in the glial scar [6]. The

X-irradiation also was used as a new way for removing (or reducing) the lesion scar formation and the levels of CSPGs because it might reduce the astrocytic number sufficiently to attenuate glial scar formation but maintain the sufficient numbers of astrocytes for structural integrity and neurotrophic support[3].

4 To supply the advantageous factors, and to transplant the endothelial progenitor cells (EPCs) for promoting the nerve regeneration

The nutrition factors (NTF) produce their marked effects by the special receptors generally. The transmission ways of NTF mainly include injecting locally, releasing slowly by biogel/nanoparticles, and secreting persistently by transgene cells besides the endogenous secretion. It is worth to paying attention to the axons reactance of the different NTF just depends on the axons types [7]. On the other hands, it has been shown that the EPCs indeed can play an effect role in reestablishing the damaged microvascular[8].

5 About functional recover of damaged CNS by NSCs transplantation

It was well known that the NSCs possess the main merits including the potentials of differentiation into nerve tissue cells and self-renew, the carrier with purposed genes, and the ability to migrate directly to the injured region without oncogenicity within certain check time-point^[9-10]. The main resources of NSCs include Embryo, Adult (bone marrow or adipose, etc) , Clone, and iPS. In all of them, the NSCs from Adult were considered

as the most suitable seed-cells for therapeutic application because they possess some of advantages: □ Abundant source and harvesting easily, □ Without either ethic problems nor immuno-repulsion when autotransplantation for therapeutic

application. In order to trace the transplanted NSCs in structure and function *in vivo*, it is necessary to label the NSCs with effective marker before graft. Magnetic resonance imaging (MRI) can be considered as the important tool for tracing *in vivo*.

6 Others

If there is a large cavity in the damaged CNS, the bio-macromolecule also can be used, in order to guide the growth axons into normal nerve tissue, across the obstacles such as glial scar vesicles, etc., and supply the sustentaculum for filling the big cavity following severe damage, and attaching the graft cells. There're some of common biomacromolecules such as polyacrylonitrile, vinyl chloride, polycarbonate, poly- α -hydrox acids, polyethylene glycol, etc. All of them generally have the absorbable and degradational characteristics.

7 In summary

The repair strategies for nerve regeneration of CNS were just as "Seeds Substitution and Soil Amendment" following injury, in which the "Soil Improvement" might be performed by receding the inhibitors of obstructing the CNS regeneration, removing the glial scar, supplying the advantageous factors, transplanting the endothelial progenitor cells (EPCs) in order to re-establish the

microvascular, and repairing the injured myelin. "Seed Substitution" was done by transplanting the nerve stem cells (NSCs), and applying the bio-macromolecules as the cellular bridges during the CNS regeneration.

8 Acknowledgments

The research was supported by grants from the Natural Science Foundation of China (No. U0632008), Funds for Key Sci-Tech Research Projects of Guangdong (No. 2008A030201019, 2007-05/06-7005206) and Guangzhou (No. 09B52120112, 2008A1-E4011-6).

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