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Transplantation of adult spinal cord tissue: Transection spinal cord repair and potential clinical translation

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Spinal cord injury (SCI), often resulting from car accidents, falls and violence, represents a complicated trauma affecting multiple tissues, such as the vertebrate, disks of the spinal column, or the spinal cord itself. Direct injury to the spinal cord, which is the focus of this insight, may disrupt the neuronal connections between the brain and the periphery, leading to the loss of motor function and paralysis. Consequently, SCI patients suffer neurologic deficits and disability, and are subjected to high healthcare costs for a lifetime. Unfortunately, there are no currently available medications or surgical technologies that are able to fully restore the structure and function of an injured spinal cord. In recent years, it has been recognized that early intervention, through the administration of methylprednisolone sodium succinate or surgical decompression, may result in better neurological recovery (Evaniew et al., 2015). However, the variable efficacy and a very short treatment window limits their utility, particularly in situations of chronic SCI. In recent years, different neuroprotective and regenerative strategies, including pharmaceuticals or biologics, have been tested in animal models, some of which have come under active investigation in clinical trials. However, the application of these methods in a clinical setting still requires further investigation. The unmet clinical need for the treatment of SCI thus necessitates the new concepts and strategies.

The recent publication by Shen et al. has explored a novel method, utilizing adult allogeneic spinal cord segments, for SCI repair (Shen et al., 2019). In this study, the T8–T9 spinal cord tissue grafts (aSCGs) were collected from adult rats expressing green fluorescent protein (GFP), and then transplanted to other athymic nude rats, whose T8–T9 spinal cords had been surgically removed. The aim of this study was to examine if the allograft can survive in the condition of SCI, and if spinal cord transplantation can improve functional recovery of recipients after complete SCI. In addition, three growth factors were applied into the transplants to provide a favorable microenvironment for repair, including the brain-derived neurotrophic factor, neurotrophin-3 and vascular endothelial growth factor (VEGF). The results showed that a variety of donor cells (e.g. neurons and oligodendrocytes) survived after transplantation, and the aSCGs transplantation improved functional recovery, especially with the combination of growth factors, which was indicated in electrophysiological and behavioral assessments. To the best of my knowledge, this is the first comprehensive study utilizing allogeneic spinal cord tissue from adult donors for SCI transplantation. Although more mechanistic studies are necessary, the strategy developed in this study, which combines the allograft transplantation and cocktail of growth factors, opened up a new avenue for SCI repair. These results provide a fundamental description of reparative outcome and explore the potential mechanism,

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laying the ground work for future study in large animals, particularly those with normal immune systems.

In the past years, researchers from this same group have combined the functional collagen scaffolds with mesenchymal stem cells or neural stem cells to improve the neural regeneration effect and eliminate the inhibitory effect of glial scarring, after acute or chronic SCI (Pajarinen et al., 2019; Wang et al., 2018; Xu et al., 2017). Although transplanting cells and scaffolds to repair SCI have exhibited the enhancement of functional outcomes, whole pieces of engineered or allogeneic spinal cord constructs would be greatly needed for SCI treatment, in order to replace the loss of the complex microenvironment and cell types after complete SCI. However, only a few studies have previously reported that transplanting allogeneic E14 embryonic neural tissue pieces into the lesion area of newborn or adult rats could partially replace the lost tissue and repair SCI (Horvat, 1991; Iwashita et al., 1994; Jakeman and Reier, 1991; Reier et al., 1986). After transplantation surgery, the embryonic central neural tissue pieces survived, displayed axonal growth and re-growth, newly formed some neural connections between the donor and host, and consequently improved the motor function recovery of the recipients. Embryonic central neural tissues contain a large number of neural stem/progenitor cells, and functional restoration is also achieved by the survival and differentiation of the neural stem cells in these fetal neural tissues. Hence, fetal spinal cord graft transplantation could be almost considered as neural stem/progenitor cell transplantation. In order to examine the long-term viability and functionality of transplanted embryonic spinal cords, Gulino et al. implanted the fetal spinal cord tissue into the lumbar spinal cord of adult rats up to 10 months (Gulino et al., 2010). Interestingly, they found that E12 transplants survived and gave rise to mature neural cells, while the E17 fetal spinal cord segments, which were assumed in the stage of motoneuron development terminates, were unable to survive.

Based on these observations, it can be speculated that the adult spinal cord tissues composed of various types of mature cells, such as neurons, astrocytes, oligodendrocytes, and endothelial cells, would hardly survive after transplantation. To deal with this dilemma, Shen et al. applied a growth factor "cocktail" to the lesion site after transplantation (Shen et al.). Although the survival levels of the grafts and cells were decreased with the increase of transplantation time, the supplement of the growth factor 'cocktail' rescued the dying cells and grafts, resulting in enhancement of the potential of aSCGs for SCI repair. Therefore, these results once again emphasize the importance of growth factors in repairing SCI. In the previous studies carried out by the same group, it has been revealed that utilization of collagen scaffolds, immobilized with multiple neurotrophic factors or neutralizing proteins, promoted neural reconnection of injured neuronal circuits and facilitated spinal cord regeneration (Han et al., 2014; Klionsky et al., 2016; Li and Dai, 2018; Li et al., 2017; Shi et al., 2014; Xiao et al., 2016). More importantly, VEGF was used in this study, which has been shown to augment the repair outcome through functioning by itself (Wang et al., 2015), or synergically with other factors (Lutton et al., 2012). The potential mechanisms from VEGF treatment include direct neurotrophic effect, modulation of inflammation and increase of vascularization of newly formed tissues. Although further mechanistic study is needed in the future, this novel "cocktail" has shown its great potential for SCI repair.

It has been recognized that a complete SCI repair may need the formation of neuronal relays between injured long tract axons and denervated neurons (Bonner and Steward, 2015; Li et al., 2017). Although the underlying mechanism of functional restoration by aSCGs transplantation was not the focus of this study, it could be assumed that the aSCGs might (1) bridge the lesion and provide physical support for host neurons to grow; (2) provide new neurons at the lesion site to restore the neural connections and neuronal cross-talk between the adult donor and recipients; (3) supplement neurotrophic factors, which were further enhanced by an exogenous growth factor cocktail. The first two mechanisms have been more or less addressed in the current study. In the future, special attention should be paid to the secretome from grafts.

Although this original work has established the effect of aSCGs on functional improvement and provided additional evidence of transplanting allogeneic neural tissue for SCI treatment, there are still some challenges that need to be resolved in future studies. The tissue pieces and cells in aSCGs survived; however, less than 10% of the donor neurons remained in the host spinal cords 12 weeks post-surgery, which extremely hindered the formation of neural connections/relays and influenced the functional restoration. Therefore, to further improve the significance and potential clinical translation, the survival level of the neurons from adult donor tissue pieces should be enhanced. With more viable donor neurons present in the lesion area, neural relay formation would increase, and could be further enhanced by specific training procedures (Bonner and Steward, 2015). Also, as discussed by the authors, neuro-vascularization will be an important step in aSCGs transplantation. Without the support of blood vessels, the survival of grafts and cells would be poor, thus compromising their therapeutic efficacy. Hence, the promotion of new blood vessel formation might support SCI repair. Finally, in the future clinical application, the receipts will have an intact immune system, and the long-term usage of immunosuppressive drugs would be needed. Whether these conditions affect repair outcome needs to be carefully investigated in the large animals, such as monkeys.

In summary, the current study explores a new strategy for motor function improvement by using complete spinal cord

segments from adult tissue combination with the recombination growth factors to replace the loss of the tissue and construct an appropriate microenvironment for SCI repair. This work not only addresses applying spinal cord tissue to repair server SCI, but also inspires the *in vitro* construction of spinal cords by tissue engineering and translation to a new clinical approach for SCI treatment.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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