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Review:

Comprehensive therapeutics targeting the corticospinal tract following spinal cord injury*

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Abstract: Spinal cord injury (SCI), which is much in the public eye, is still a refractory disease compromising the well-being of both patients and society. In spite of there being many methods dealing with the lesion, there is still a deficiency in comprehensive strategies covering all facets of this damage. Further, we should also mention the structure called the corticospinal tract (CST) which plays a crucial role in the motor responses of organisms, and it will be the focal point of our attention. In this review, we discuss a variety of strategies targeting different dimensions following SCI and some treatments that are especially efficacious to the CST are emphasized. Over recent decades, researchers have developed many effective tactics involving five approaches: (1) tackle more extensive regions; (2) provide a regenerative microenvironment; (3) provide a glial microenvironment; (4) transplantation; and (5) other auxiliary methods, for instance, rehabilitation training and electrical stimulation. We review the basic knowledge on this disease and correlative treatments. In addition, some well-formulated perspectives and hypotheses have been delineated. We emphasize that such a multifaceted problem needs combinatorial approaches, and we analyze some discrepancies in past studies. Finally, for the future, we present numerous brand-new latent tactics which have great promise for curbing SCI.

Key words: Spinal cord injury (SCI); Comprehensive strategy; Corticospinal tract; Neuroprotective; Development; Glial; Transplantation; Training; Electrical stimulation

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1 Introduction

Spinal cord injury (SCI), which is a severe disease that always results in dysfunction of movement as well as sensation, is hard to recover from especially in mammals. Given the heterogenicity of tracts, concentrating on some specific tracts that play extremely important roles in function will be feasible and impactful. Therefore, the corticospinal tract (CST) whose function is controlling voluntary movement will be the optimal and the primary target to tackle (Fig. 1).

This paper discusses the comprehensive therapeutics used in recent decades, which target the CST following SCI. There are all kinds of useful strategies available to us. Taking a comprehensive approach is often better than implementing a simple mean (Table 1). The variations of tissue over time combined with the multiple regions influenced by the lesion provide us with opportunities to combine numerous methods. After an SCI, it has been observed that different

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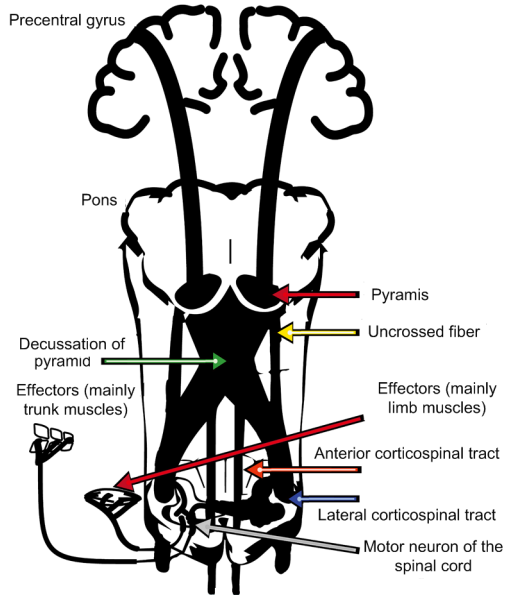

Fig. 1 Corticospinal tract (CST) anatomy in humans
The neurons of precentral gyrus are the upper neurons of CST, which will undergo recombination or even apoptosis following spinal cord injury (SCI). The CST has two components that are respectively called anterior corticospinal tract and lateral corticospinal tract. Further, lateral CST containing most fibers can mainly control limb muscles, whereas anterior CST may just control trunk muscles and plays less important roles in the voluntary movements, and therefore lateral CST can be the focus of strategy

segments of the impaired CST can have different abilities to compensate both in the rat and in the macaque (Bareyre et al., 2004; Darian-Smith et al., 2014). A similar appearance can be observed in zebrafish (Becker et al., 1998). Thus, presumably, the distance between the lesion and the corresponding neuronal soma will greatly influence the prognosis. This influence may be caused by a concentration gradient of some factors referring to the embryonic development of central nervous system (CNS). Then, although the survival of the neuronal soma and upper neuron following SCI is still contentious, enhancing the plasticity of post-impaired CST has been proved to be an effective therapeutic regimen. Some novel agents for neuroprotection are also promising, such as melatonin and some sex steroids (Kim et al., 2006; Samantaray et al., 2008; Song et al., 2016; Yang et al., 2017; Zareen et al., 2017). The administration of an antagonist against the inhibitory factors is also common. Moreover, the advance of transplantation and a brand-new standpoint towards the glia have provided a great deal of new thinking about cures. Finally, spontaneous regeneration after incomplete SCI, electrical stimulation, and physical training are also methods waiting to join comprehensive therapeutics.

Table 1 Outline of comprehensive strategies targeting the corticospinal tract following spinal cord injury

Method	Strategy
1. For the neurons of corticospinal tract (CST) and the soma of propriospinal tracts	Enhance the plasticity of the cortex
	Tackle more extensive regions
	Apply some novel neuroprotective agents
	Heighten the innate growth capacity
	Find or create cerebral regions which promote the re-growth of axons in the human
2. Provide regenerative microenvironment	Add a positive substance
	Antagonize a negative substance
	Sort out local ischemia
3. Provide glial microenvironment	
Radial glial cells	Induce the migration, generate new neurons
Astrocytes	Dual functions and have led to an interesting hypothesis
Microglial cells	Phagocytic function and recruitment
Lemmocyte and oligodendrocyte	Characteristic making the axons grow inside
Olfactory ensheathing cells	The structure of axon tracts during the development
4. Other significant remedial methods	
Transplantation	Restoration following spinal cord injury (SCI) may be a variant way of embryonic development
The plasticity of the residual CST	Still a controllable means for improving the prognosis of SCI
Training and electrical stimulation	May achieve accurate information flow via cut-off mechanism

2 Neurons of the CST

2.1 Plasticity of the cortex

Fouad et al. (2001) demonstrated that the cortex of corticospinal motor system has huge potential for compensation, which is helpful to functional recovery. In detail, researchers found that the cortical synaptic structures will undergo recombination, and the quantity of cerebral fiber tract will increase in contrast to control animals (Kim et al., 2006; Ramu et al., 2008).

To harness this phenomenon, scientists have exploited many valid tactics, such as modifying the environment, transplantation of embryonic tissue of spinal cord, application of neurotrophin and epidural electrical stimulation (Kim et al., 2008; Song et al., 2016). These trials show huge potential for human SCI in the near future.

2.2 Neuronal soma of the CST

It is debatable whether cortical motor neurons can survive robustly following SCI even in animals. In the early research, Hains et al. (2003) suggested that motor neurons will undergo apoptosis after SCI. Their work used indirect evidence from a tracer and dyes. However, later, Nielson et al. (2010) used a novel method involving counting the number of axons in the medullary pyramid as well as assessing Wallerian degeneration, via which they came to contrary conclusion that following SCI the neuronal soma of the CST will remain robust. As another example, adult zebrafish can achieve functional restoration within 6–8 weeks after complete spinal cord transection relying on regenerative processes in addition to having surviving upper motor neurons (Becker et al., 1997; Briona et al., 2015). It is reasonable to suppose that the brain and the spinal cord interact after either one is damaged. The surprise is that even an isolated SCI can trigger cognitive alternations along with neurodegeneration in the brain (Faden et al., 2016).

No matter the outcome, the phenomenon appears only to occur in the rat. Furthermore, even if the neurons of the CST can survive, they may confront atrophy (Purves, 1975) (Fig. 2). Since atrophy of the injured neurons will lead to a decrease of input, the upper neuron needs to be treated and simultaneously the output of atrophic neurons needs to be enhanced. Furthermore, the structure of the human spinal cord is quite different from the spinal cord of animals such as the lizard whose spinal cord is uninterrupted from brainstem to the terminal of the tail (Gilbert and Vickaryous, 2018). Therefore, during the SCI in mammal, the soma of propriospinal tracts will be damaged and this may crucially impede functional restoration. That may be one of the possible reasons explaining the effectiveness of neuroprotective agents. It may be that more extensive regions need to be handled, not just the site of lesion as well as the adjacent area. Also, nutritional help may be required to tackle the nutrition problem caused by the possible atrophy.

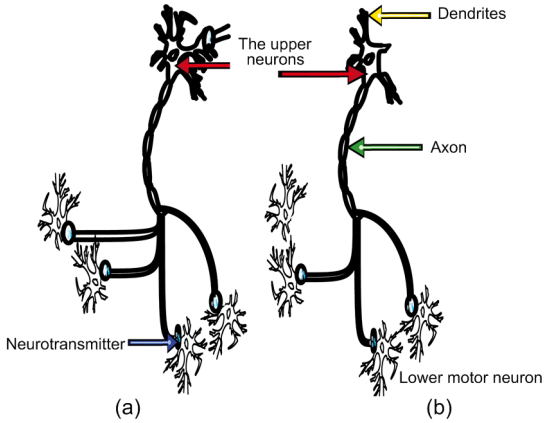

Fig. 2 Normal (a) and atrophic (b) upper neurons and lower motor neurons (Purves, 1975)
The atrophy occurring on the upper neurons will decrease both the quantity of dendrites and their branches of axon, which will greatly reduce the input and output of the neurons, doing harm to the function movement. Therefore, the situation of the upper neurons following SCI should be taken seriously and more extensive regions need to be cared

Some treatments for the neurons of the CST have already proven effective, such as transplantations, electrical stimulation, and the use of neuroprotective agents (Sasaki et al., 2006; Zareen et al., 2017). The novel neuroprotective agents mainly operate in six respects: reducing excitotoxicity, mitigating apoptosis, scavenging free radicals and refraining oxidative stress, reducing neuroinflammation, adjusting autophagy, and ameliorating demyelination (Yawno et al., 2017; Golabchi et al., 2018). It should be emphasized that cell necrosis, apoptosis, and autophagy are not independent phenomena and there are crossover paths. Mitochondrion is an important organelle, and its dysfunction (such as hypoxia) will decrease the necessary energy resulting in cell necrosis, but mitochondrial cytochrome c will penetrate the cytoplasm

stimulating the process of apoptosis. Any rise in the intracellular free calcium ion also has multiple effects, which will not only activate various enzymes leading to degradation of substance and cell necrosis but also start apoptosis via calpain or specific endogenous nuclease. Similarly, there are countless ties between autophagy and necrosis. A lot of research has already established that inducing autophagy is beneficial resulting in the inhibition of apoptosis (Tang et al., 2014).

During the last few years, melatonin and sex steroids via their many-sided effects have become star molecules in the firmament of neuroprotective agents. For instance, melatonin, a kind of intense antioxidant, can not only cover the aforementioned six areas, but also restrain amyloid-β peptide fibril formation, a formation which will lead to dysfunction of the brain (Carloni et al., 2017; Aridas et al., 2018; Golabchi et al., 2018; Hornedo-Ortega et al., 2018). As with other neuroprotective agents, whose function may not be so potent or have other limitations, it can be put into operation by means of novel techniques such as making a co-ultramicronized compound, using a novel delivery system, utilizing nanotechnology or employing hydrogels (Wu et al., 2014; Weiner et al., 2015; Siracusa et al., 2016; Zhao et al., 2016; Wang ZC et al., 2017). Sex steroids such as androgen may be a promising neuroprotective agent from work on features of the CNS of the canary. Neurogenesis observed in the canary high vocal center can be induced by testosterone and the newborn neurons will form the correct synapses and then make the junctions to the appropriate targets (Dittrich et al., 2014; Shevchouk et al., 2017). Sex steroids which have proven neuroprotective are: 17β-estradiol, progesterone, dehydroepiandrosterone, and tamoxifen that is a kind of analog of estrogen (Elkabes and Nicot, 2014; Arbo et al., 2016; Colon et al., 2016). In addition, riluzole, magnesium, and minocycline, although their functions are limited, are still commonly used and efficacious.

2.3 Innate growth capacity of cortical neurons

The intrinsic growth capacity of mature CNS neurons in the mammal will decrease over time (Geoffroy et al., 2016; Assinck et al., 2017). In comparison to the mammal, even in the adult brain, zebrafish exhibit extensive neurogenesis where the new neuron integrates into the existing circuits to give effects (Grandel and Brand, 2013). In the mammal, parts of the subventricular zone and the subgranular zone retain the ability of spontaneous neurogenesis (Lipp and Bonfanti, 2016). CST following SCI is regarded as the structure which will not regenerate but degenerate (Facchiano et al., 2002).

It is a challenge to procure extensive neurogenesis in the mammalian brains. In addition, in zebrafish, there are indications that the nuclei of the medial longitudinal fascicle and the intermediate reticular formation promote the re-growth of axons following SCI (Noorimotlagh et al., 2017). It could be important to find analogous cerebral regions in the human and give appropriate stimulations to realize cortical support.

There are many ways to increase the innate growth capacity of mature CNS neurons: (1) transplanting stem cells and other immature cells; (2) using some neurotrophins and other positive proteins such as transcription factors; (3) exerting all kinds of ways against the inhibitory element such as vaccinum of the recombinant Nogo-66 receptor (NgR), short hairpin RNA which targets phosphatase and tension homolog (PTEN), and the inhibition of protein kinase C (PKC) (Yu et al., 2008; Zukor et al., 2013; Wang et al., 2014).

3 Positive or negative substances

The deficiency of the necessary permissive trophic factors and local ischemia with hypoxia along with the presence of external inhibitory factors will greatly hinder restoration after SCI (Anderson et al., 2016; Assinck et al., 2017).

As early as the last century, researchers discovered that neurotrophin-3 promotes sprouting of CST following SCI (Schnell et al., 1994). With development in techniques, increasingly positive factors are revealed and there are now more ways to administer the stimulation. Brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), p53, sonic hedgehog (Shh), and some transcription factors have also proven impactful to the post-impaired CST (Facchiano et al., 2002; Sasaki et al., 2009; Floriddia et al., 2012; Lowry et al., 2012; Wang ZM et al., 2017). There are also some burgeoning factors like neuronal calcium sensor-1 (NCS1), C3

peptide, insulin-like growth factor 1 (IGF1), and even the culture medium of neural stem cell which are beneficial to CST (Boato et al., 2010; Yip et al., 2010; Liang et al., 2014; Liu et al., 2017).

As for the technique of administration, different from the original local injection, there are mainly four means. (1) Special kits are implemented like hydrogel depots to make continuous local delivery of positive factors and the nutrition factors can be made into liquid hydrogel which can gradually release the active ingredients (Piantino et al., 2006; Anderson et al., 2016). (2) Some viral vectors can be used to transfer the neurons making them intensely and continuously express positive factors or fusion proteins (Blackmore et al., 2012; Lang et al., 2013; Weishaupt et al., 2014). In this way, surprisingly, muscle injection of the relative substance can make sense as well (Fortun et al., 2009). (3) Special modified transplanted cells which can overexpress trophic factors are also feasible (Weidner et al., 1999; Sasaki et al., 2009). (4) Combination of ordered scaffolds and binding neurotrophin will also provide benefits to CST (Fan et al., 2010). From the viewpoint of safety and multifunction, the last two methods are more promising and available.

The inhibitory factors with the approaches to application are also progressing. The target of the strategy has altered from Rho kinase or Nogo-A to PTEN and PKC (Fournier et al., 2003; Simonen et al., 2003; Liu et al., 2010; Wang et al., 2014). In a recent discovery, researchers have found that a competitive relationship exists between proprioceptive afferents and CST, which makes curbing proprioceptive afferents to be another beneficial way to protect CST (Jiang et al., 2016). For administration of the antagonist against inhibitory factors, vaccinum of recombinant NgR and short hairpin RNA which targets PTEN may be distinctive (Yu et al., 2008; Zukor et al., 2013).

It should be noted that sometimes the effect of trophic factors will cover the influences of negative factors and some factors may have dual functions along with the variation in circumstances (Hagg et al., 2005).

Finally, ischemia as well as hypoxia and other complications may inhibit the repair after SCI. There are currently numerous solutions especially neuroprotective agents to address this. As hypoxia will of course lead to a deficiency of energy material like ATP, it would be a common-sense thought to find the succedaneum. Fortunately, acetyl-L-carnitine can be the substitute and ketone metabolism will have positive effects (Prins and Matsumoto, 2014; Ewan and Hagg, 2016). Moreover, restoration of mitochondria dysfunction may be another reasonable choice (Scholpa and Schnellmann, 2017). The method involves numerous mechanisms: maintaining mitochondrial homeostasis like melatonin, protecting neurons against excitotoxic attack to decrease consumption like riluzole, reducing oxidative stress and scavenging free radicals like melatonin and docosahexaenoic acid (Paterniti et al., 2014; Ahuja et al., 2017; Golabchi et al., 2018). It is worth mentioning that the positive influences of docosahexaenoic acid can be observed in the CST (Liu et al., 2015). This makes this substance more promising.

4 Glial cells available

4.1 Radial glial cells

Radial glial cells, which are highly conspicuous, can not only induce the migration of associated neurons during the development, but also generate new neurons during the development and restoration (Hansen et al., 2010; Nulty et al., 2015).

In gecko and zebrafish, it is radial glial cells' proliferation that patches the lesion leading to functional restoration (Kroehne et al., 2011; Gilbert and Vickaryous, 2018). By contrast, radial glial cells will almost differentiate to astrocytes especially in the spinal cord in the mammal (Chanas-Sacre et al., 2000; Jacquet et al., 2009). However, via reprogramming, astrocytes can realize a conversion to the neurons (Su et al., 2014).

The radial glial cells will only work to the specific neurons of specific regions and the same characteristic can be seen in the astrocytes (Tsai et al., 2012). Therefore, if transplantation is the route taken, according to the region of lesion, region-specific transplanted cells should be used.

4.2 Astrocytes

It is very controversial what the function of astrocytes is. Although some researchers claim that scar formation aids CNS axon regeneration, it is also

reasonable to consider that astrocytes have dual influences (Karimi-Abdolrezaee and Billakanti, 2012; Anderson et al., 2016).

On the one hand, firstly, the scar is essential to restrain secondary wound enlargement and further axonal loss (Sabelström et al., 2013). The migration of the astrocytes is beneficial for allaying inflammation (Renault-Mihara et al., 2011). Secondly, there are all kinds of interaction among astrocytes and other cells. For instance, following SCI, necroptosis will occur in reactive astrocytes induced by M1 microglia possibly resulting in tough recovery (Fan et al., 2016). In lampreys, which have the ability to regenerate after SCI, the aminoacidergic neurotransmitters can be observed as released by neurons and accepted by astrocytes. This may reveal that astrocytes play crucial roles in the communication on regeneration (Fernández-López et al., 2014). In addition, the existence of astrocytes which are readily able to interfere with specific transplanted cells makes the specific transplanted cells more effective (O'Neill et al., 2017).

On the other hand, inhibiting astrocyte growth is claimed to be valid and remyelination will be hindered by astrocytes following SCI (Wang et al., 2011; Ren et al., 2014). According to an early study, demyelination impairs conduction and interrupts an important metabolic shuttle between oligodendrocytes and axons causing the disruption of functional connections following SCI (Fünfschilling et al., 2012).

The positive or negative effects of astrocytes are too numerous to mention. However, it is worth noting that the situation can be reversed in certain circumstances, indicating that astrocytes following SCI can be just dysfunctional rather than harmful. Following SCI, the administration of transforming growth factor-α (TGF-α) makes the astrocytes growth-supportive and some sex steroids can realize neuroprotection via influencing astrocytes (White et al., 2011; Arbo et al., 2016).

There is another hypothesis. Since the development of the nervous system is highly conserved phylogenetically, the discovery of adult zebrafish related to SCI could provide valuable insight for human study. The glial scar is undetectable in adult zebrafish following SCI (Kroehne et al., 2011). However, acute inflammatory response and gliosis still exist, indicating the need of a blocking agent for acute reactions to sustained responses. In addition, an interesting work has indicated that the scar-forming astrocytes always derive from endogenous progenitors after SCI, unlike the reactive astrocytes in the undamaged vicinity of the lesion (Anderson et al., 2016). From the above trials, the hypothesis is that the scar may be the outcome of the failing regeneration rather than the impediment of restoration, and the activation of astrocytes itself is not harmful but subsequent occurrences may be responsible (Rolls et al., 2009).

4.3 Microglial cells and immunoregulation

Microglial cells, which play important roles in regeneration, will react rapidly and then retreat soon in zebrafish and they will produce laminin promoting the regrowth of axons in leech (Chen et al., 2000; Baumgart et al., 2012). Both animals can make a successful recovery after SCI.

However, in the mammal, it is microglia that recruit peripheral neutrophils whose by-products are primarily considered harmful and cytotoxic (Orr and Gensel, 2018). The leakage of cellular debris as well as intracellular substances can be observed following SCI, and this can trigger the activation of astrocytes and microglia (Donnelly and Popovich, 2008). In the reaction of microglia, not only its morphology but also the state of secretion will alter to recruit such as neutrophils into the lesion (Gensel and Zhang, 2015). Since neutrophils and their products will open a cascade of inflammation, optimal measures should be implemented during or before this period.

4.4 Lemmocytes and oligodendrocytes

Although lemmocytes and oligodendrocytes have ability to secrete factors promoting the growth of axons, Nogo-A in their membranes is an intense inhibitor for axon growth (Paganetti et al., 1988; Yu et al., 2007). This characteristic makes the axons grow inside the space besieged by these glial cells but cannot contact the cells let alone surpass the cellular barrier. Therefore, simply transplanting these cells to the lesion cannot get the supreme curative effect and we may as well transplant these cells arranged in a specific shape linking the CST via the lesion (Fig. 3).

4.5 Olfactory ensheathing cells

During development, neurons expressing gonadotropin-releasing hormone (GnRH) will migrate to

CNS from placode along with the former axon tracts (Larco et al., 2018). The available schedule is building the structure of axon tracts first and then letting the axons elongate along them following the SCI. Therefore, olfactory ensheathing cells become a focus.

However, the regrowth response of CST is feeble to the olfactory ensheathing cells and thus the extra plasma membrane and L1-neural cell adhesion molecule (L1-NCAM) may need to be used (Witheford et al., 2013).

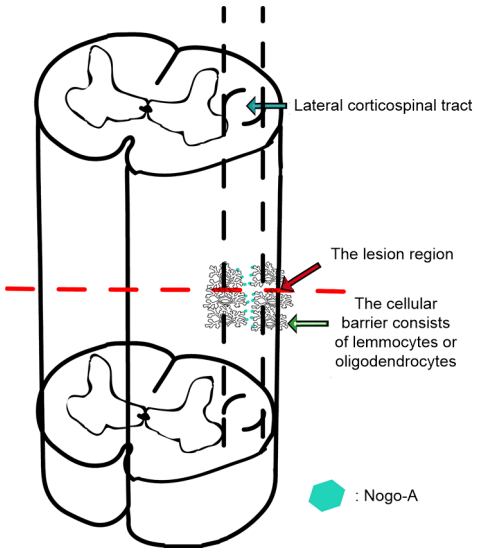

Fig. 3 Transplanting lemmocytes or oligodendrocytes arranged in a specific shape linking the CST via the lesion

Nogo-A in these cell membranes is an intense inhibitor for axon growth. This characteristic makes the axons grow inside the space besieged by these glial cells but cannot contact the cells let alone surpass cellular barrier presumably

5 Transplantation

According to a recent trial report on the gecko, during spinal cord regeneration, the gecko first expresses the onset of vimentin that in mammals is characteristic of the embryonic precursors of radial glia and neuroepithelial cells, and then expresses glial fibrillary acidic protein (Gilbert and Vickaryous, 2018). This phenomenon supports a presumption that successful restoration following SCI is a variant way of embryonic development. In fact, embryonic development and the recovery process have all kinds of connections. Transplanting stem cells and then imitating embryonic development plus other comprehensive strategies may be currently the best choice for SCI.

The forms and media of transplantation are numerous. The grafts can be ordered in scaffold loaded with positive factors or they can be ordered in hydrogel bridges including growth factors and immature cells (Fan et al., 2010; Li et al., 2016). There are also some conventional transplantations, for example, using the neurons and glia cells, using the cells genetically modified to over generate positive factors or using homologous neural stem cells (Kuhlengel et al., 1990; Sasaki et al., 2009; Kadoya et al., 2016). As for promoting the CST, Lewandowski and Steward (2014) discovered a comprehensive strategy that synthesizes the intracortical injection of inhibitor against PTEN and the injection of salmon fibrin.

As we mentioned above, we may as well transplant these cells arranged in a specific shape linking the CST via the lesion. First, it is rational to use the techniques of magnetic resonance imaging and retrograde trace or the common sense of statistics to confirm the morphology and diameter of the CST we need. Then using the material that will directionally adhere oligodendrocytes to form the myelinated tract linking the CST is highly reasonable. Also, perhaps some permeation holes should be used to implement some factors.

6 Other auxiliary methods

6.1 Spontaneous repair

In the incomplete SCI, spare tracts will generate intraspinal circuits boosting the post-damaged function, which is led by CST sprouting into the propriospinal neurons (Bareyre et al., 2004). Moreover, the CST following SCI will manifest a huge capacity of plasticity that makes corticospinal reorganization, which will enhance functional restoration (Oudega and Perez, 2012).

The compensational effects by the spare CST are quite limited. Yet, it is still a controllable means to improve the prognosis of SCI.

6.2 Rehabilitation training

Numerous regenerating neurons are observed to express SRY-box containing gene 11 (*SOX11*), which

can increase the intrinsic regenerative capacity to CNS neurons, whereas overexpression of this factor can be the impediment of functional recovery (Wang et al., 2015). We may as well compare this discovery with the development of the vertebrate nervous system to find potential mechanisms underlying this phenomenon. In the early period of neural development, there is, by some way, a larger quantity of synapses as well as projections than there is in the adult. It is the lack of a cut-off mechanism that triggers consistent behavioral impairments caused by the overexpression of *SOX11*. Excision of the synapses and neurons has many probable mechanisms to explain it. It certainly can be used for restoration combined with promoting axons' regrowth after SCI. These mechanisms including nutrition- and exercise-dependent mechanisms finally achieve accurate information flows (Fig. 4).

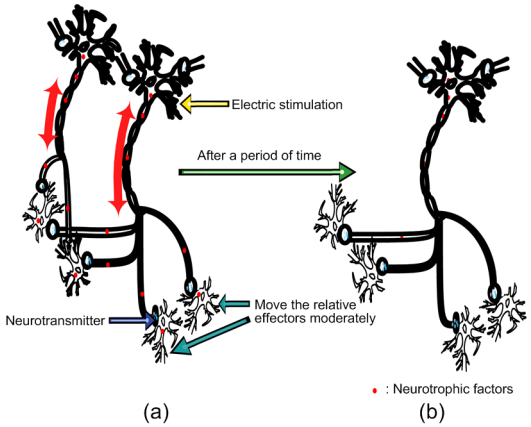

Fig. 4 Hypothetical cut-off mechanism

(a) The early period of neural development or overexpression of positive factors following SCI; (b) After a period of time when selective electric stimulation or the movement of the relative effector started. The neurotrophic factor can be transported both retrogradely and anterogradely; however, these substances are the more the better. When both or ever one fountainhead is available, the neurons involved will gain the competitive edge comparatively. It can be also said that neurons as well as synapses are surplus. Nevertheless, the neurotrophic factors are relatively limited

6.3 Effect of exercise

The motor neurons from rats with complete spinal cord transection displayed marked atrophy, with loss of dendritic membrane and elimination of branching. By contrast, this finding is not observed in motor neurons if hindlimbs are exercised (Gazula et al., 2004). From the outcome of the trial, we may conclude: (1) exercise can avoid atrophy in the soma as well as retaining branches, which may let these neurons embrace a sort of superiority making them removed from the procedure of cut-off; (2) via stimulating exercise, such as electrical stimulation, pharmacologic agents, and physical therapy, training programs may also be valid; (3) the essence of this exercise-dependent mechanism may be a nutrition-dependent mechanism, or the relationship between them may be quite close.

The impact made by the training is exhibited in multiple ways. The plasticity of the CST will be enhanced by the training but the functional recovery is relative to the type of the training—only trained movements will be easier to accomplish while a new task may get tougher (Kanagal and Muir, 2009; Krajacic et al., 2010). This phenomenon can be elucidated by the cut-off mechanism we mentioned above.

6.4 Electric stimulation

By means of electric stimulation, the quantity of neurotrophic factors such as BDNF and glial cell line-derived neurotrophic factor (GDNF) will be highly enhanced (Baumbauer et al., 2009; Willand et al., 2016). The inhibitor molecules will be simultaneously decreased (Ding et al., 2011). In the early period of neural development or during the regeneration of axons, neurons as well as synapses are surplus. Nevertheless, the neurotrophic factors are relatively limited. Therefore, either electric stimulation or direct provision of neurotrophic factors will have approximately similar effects, which offers a benefit for competition to retention. That is another form of the cut-off mechanism we mentioned above.

Electro acupuncture may allow the CST to dominate with an advantageous position against other tracts like primary sensory afferents whose function is relatively less important than CST following SCI (Jiang et al., 2016).

7 Discussion

During the past decades, the techniques and the perspectives have been changing constantly. As soon as an SCI is confirmed, comprehensive therapeutics targeting CST should be exerted as follows: interfering

with more regions especially the neurons of the CST, increasing the positive substance as well as restraining the negative factors, harnessing the glial cells available, applying transplantation, promoting spontaneous repair, and utilizing rehabilitation training and electrical stimulation.

Among these investigations, there are still two important divergences: the discrepancy of the astrocytic functions and the survival situation of the neuronal soma of CST. As for the survival situation of the neuronal soma, no matter what the outcome it is, in case of atrophy, we propose that more extensive regions need to be handled. As for the astrocytes, presumably, they have dual characteristics, which make conversions towards astrocytes to be a rational measure against SCI.

In the future, there are many promising tactics to be developed. As successful restoration following SCI may be a variant way of embryonic development, except for the transplantation of immature cells, guide factors and specific concentration gradient of the specific molecules should be used to construct the appropriate environment for regeneration. Given that the leakage of cellular debris and intracellular substances can trigger the activation of astrocytes and microglia, some biogel should be used to conceal the lesion of membranes as soon as SCI occurs (Donnelly and Popovich, 2008). From the macroscopic aspect, the blood–spinal cord barrier following SCI will be demolished, leaking the substances to trigger secondary damage. To prevent this, some novel neuroprotective reagents, such as retinoic acid and apolipoprotein E, have already proven valid in animals (Zhou et al., 2016; Cheng et al., 2018). Moreover, finding or even creating analogous cerebral regions as with the zebrafish as mentioned above in humans and giving stimulation will also promote the regrowth of axons. In addition, we may as well transplant region-specific immature cells originating from the specific phase during the embryonic development arranged in a specific shape linking the CST via the lesion for the sake of characteristics of radial glial cells, lemmocytes, and oligodendrocytes mentioned above (Fig. 3). Special material or cells recognizing and combining the naked axons can be a rational choice for the treatment of demyelination. Furthermore, redundant neurons and synapses should be pruned as follows: doing exercise of the limbs, carrying out electrical stimulation, and distributing nutrition. Shallowly pursuing the regeneration like overexpressing *SOX11* has been shown to be damaging to the function (Wang et al., 2015).

It is not hard to imagine that comprehensive therapeutics will be increasingly concise and effective so that the prognosis of acute SCI is going to be more and more positive.

Contributors

An-kai XU set up the theme and the frame of this review, wrote and edited the manuscript. Zhe GONG and Yu-zhe HE performed the reference collection and selection. Kai-shun XIA was responsible for editing the grammar and vocabulary of the manuscript. Hui-min TAO examined the manuscript and guided the modification process.

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Compliance with ethics guidelines

An-kai XU, Zhe GONG, Yu-zhe HE, Kai-shun XIA, and Hui-min TAO declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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中文概要

题　目：脊髓损伤后针对皮质脊髓束的综合治疗策略

概　要：本文根据脊髓不同传导束之间存在竞争以及其再生需要的条件存在异质性，得出优先关注皮质脊髓束的结论。同时，旨在通过归纳目前治疗脊髓损伤（特别是对皮质脊髓束）有效的各种策略，寻找治疗脊髓损伤的最佳策略组合。脊髓损伤的恢复涉及众多方面的问题，单一策略的失效（如本文提及的 *SOX11* 的过度表达反而对功能有害）往往提示治疗方案需要综合其它方面的问题。因此，有必要总结一下脊髓损伤治疗的几个关键方面，并梳理一套可能的治疗路线规划。本文另一目的在于对过去一些关键理论、假说、矛盾进行总结，并在此基础上进行新的综合和思考。

关键词：脊髓损伤；综合策略；皮质脊髓束；神经保护；发育学；神经胶质细胞；移植；康复训练；电刺激