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Nervous system disorders

Cracking the black box – and putting it back together again: Animal models of spinal cord injury

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The last two decades have seen an increased interest in and improved understanding of the molecular mechanisms that underlie regenerative failure after central nervous system (CNS) lesions, such as spinal cord injury (SCI). This has spurred the development of a range of experimental approaches in laboratory animals to (i) model the complex pathophysiology of CNS lesions, (ii) design therapeutic interventions and (iii) assess various outcome measurements. The challenges in this endeavor have been to limit inter-animal and inter-laboratory variability and to ensure relevance to human SCI. Here, we review current animal model techniques that aim at providing a framework for the development of rational therapies for human SCI.

Introduction

Spinal cord injury (SCI) occurs at an incidence of 11.5–53.4 per million in Western countries [1]. The leading primary causes in developed nations are traffic accidents (ca. 50%), followed by work accidents, falls, sports-related accidents and violence. SCI most frequently occurs in young adults (with an average age at injury of 33.4 years, <http://www.campaignforcure.org>), and patients that survive the acute and sub-acute stages (see Box 1)

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have life expectancies that approach those of the normal population. The only very limited spontaneous functional improvement leads to prolonged morbidity (prevalence of 721–906 per million [1]) with many patients requiring repeated and prolonged hospitalization to treat complicating conditions. In 2005, 2.5 Mio people worldwide are estimated to live with SCI (<http://www.campaignforcure.org>) resulting in enormous human and monetary costs. In 1990, approximately \$4 billion are spent annually for the management of SCI in the US [2]. The low incidence, yet high cost has led the FDA to grant orphan product designation to first experimental SCI therapies (<http://www.fda.gov/orphan/designat/list.htm>).

In vivo models

The most widely used model organisms in mammalian SCI research are adult rodents, although some work has been done in cats and dogs, and increasingly non-human primates are used as translational models. Genetically engineered mouse mutants, such as mice lacking myelin-associated inhibitors of neurite growth allow for assessing regenerative fiber growth in an environment that has been turned more permissive. These experiments have shown that the genetic background of the mutant mice has a strong influence on the intrinsic regenerative capabilities of the lesioned neurons

Box 1. Clinical features of SCI

The clinical features of SCI vary greatly depending on the type, level and severity of the lesion. They range from slight and possibly transient motor impairments of the lower extremities in the case of partial damage to the lumbar or sacral cord to total loss of all motor and sensory function below the site of injury, which, in the case of high cervical lesions, results in a permanent state of tetraplegia with concomitant loss of spontaneous breathing. In addition, bladder and bowel control and autonomic functions such as blood pressure and sexual functions can be affected. The progression of SCI is often classified in three phases: the acute phase (up to a few days) is characterized by flaccid paralysis of the extremities, hyporeflexia, bradycardia and hypotonia (spinal shock). Primarily, the focus is on the general stabilization of the patient and decompression surgery of the spine may be required. A high dose regimen of methylprednisolone started within the first 8 h after injury may have a beneficial effect under certain conditions [38]. In the sub-acute phase (days to months after injury), returning reflexes may overshoot, due to a lack of supraspinal inhibition. If the damage to the spinal cord was incomplete, recovery of residual function may be observed. This recovery often plateaus within the first year after injury. During the sub-acute phase the patient is typically transferred to a rehabilitation unit or facility, trained to adapt and adjust to his disability, and then released to his home or a long-term care facility. In the chronic phase (more than a year), in addition to muscle loss, long-term complications such as spasticity and neurogenic pain may occur. Patients also may be re-admitted for treatment of urinary tract infections or pressure sores. Syringomyelia, a degeneration slowly spreading from the original site of injury may also lead to a loss of regained functions years after the accident.

[3,4]. Recently, non-human primates have been used increasingly to test pro-regenerative therapies for safety and efficacy before moving to clinical studies and trials. Although more closely related to humans, locomotion in these monkeys still differs significantly from the complex autonomic functions in bipeds in terms of anatomy, posture, physiology, and kinematics and results from behavioral experiments in animals can therefore not directly be extrapolated to the human situation (see Box 2).

Lesion paradigms

The most commonly used lesion techniques in experimental spinal cord injury consist of either transection or transient compression of the cord. Transection, usually carried out by the use of fine surgical scissors (iridectomy scissors) allows the targeted interruption of particular nerve fiber systems such as motor tracts (corticospinal tract, rubrospinal tract) or sensory tracts (dorsal columns), or even complete interruption of the spinal cord. Although these types of injury are rare in human SCI, they allow the investigator to test hypotheses that concern regeneration, degeneration or plasticity on an axonal level. These types of lesions are most usefully combined with neuroanatomical tract tracing and electrophysiological studies. Much closer to most clinical cases are injury techniques that compress the exposed spinal cord for a short time (contusion). Several devices exist to produce these contusions in rodents in a controlled way to limit the variation between

animals and allow the comparison between results obtained in different laboratories. The most widely used such apparatus is the MASCIS impactor (<http://keck.rutgers.edu/MASCIS/mascis.html>), sometimes also referred to as NYU impactor, that employs the drop of a weight from various heights to induce injuries of various grades. Simultaneous recording of kinematic parameters of the impounder probe allows the validation of the injury process. The ESCID device developed at the Ohio State University [5] electromagnetically drives an impounder tip onto the cord until a desired displacement of the cord surface is reached. After a defined time, the tip is retracted and the pressure released. In a similar way operates the only commercially available device, the Infinite Horizon Impactor (IH, Precision Systems and Instrumentation, Lexington, KY) [6]. A stepping motor applies a defined force to the cord. Once the force is reached, the impactor retracts. Although the MASCIS impactor is somewhat easier to use, the ESCID and IH devices allow more control over the injury process and appear to produce lesions more reliably and with less variability.

Interventions

Application of bioactive compounds

Although some potential therapeutic compounds are easily penetrating the blood–brain barrier and can be administered systemically, many others are not and therefore require direct application to the injured spinal cord or to the corticospinal fluid such as for example to the brain ventricles, from where they get distributed throughout the central nervous system (CNS). Several avenues of delivery have been developed. The simplest ones consist of direct, sometimes stereotaxically

Box 2. Pathophysiology of human SCI

Human SCI are clinically heterogeneous and usually classified into four groups based on gross findings: contusion, laceration, compression or maceration and solid cord injuries. Complete transection of the spinal cord is rarely observed, rather various amounts of residual tissue crossing the cord remain. The initial mechanical disruption of tissue directly leads to death of cells, including neurons, oligodendrocytes, astrocytes and precursor cells as well as hemorrhage mostly in gray matter following contusion injury due to ruptured blood vessels. Secondary injury mechanisms, including inflammation and release of deleterious factors, such as Ca^{2+} , glutamate and free radicals, cause ongoing cellular damage and progressive axonal loss over time laterally and longitudinally to areas undamaged by the initial trauma. The inflammatory responses that follow early after CNS injury are initiated by peripherally derived immune cells (macrophages, neutrophils and T-cells) and activated glial cells (astrocytes and microglial) that proliferate or migrate into the lesion site [22]. Macrophages and microglia contribute to the secondary pathological and inflammatory response in part through the release of cytokines such as tumor necrosis factor, interleukins and interferon. The chronic phase is characterized by Wallerian degeneration, astroglial and mesenchymal scar formation, development of cysts and syrinx, and schwannosis, an aberrant intra- and extramedullary proliferation of Schwann cells.

guided injections into the injury site or its vicinity. For prolonged infusion of small molecules, growth factors, enzymes, neutralizing antibodies or receptor-blocking fusion proteins, osmotic minipumps, with their catheters placed into the lateral ventricle or intrathecally to the cord, have been used [7–9]. Treatment durations of 1 day to 4 weeks can be reached with a single pump and pumps can be replaced to extend this period. For some bioactive compounds, stability over such periods can be a problem and continuous local synthesis at the lesion site may be preferable. To this goal, viral vectors to deliver transgenes locally have been designed and tested in SCI paradigms. Although early adenovirus-derived constructs elicited strong immune responses and suffered from downregulation of transgene expression after a short time [10], more recent adeno-associated virus (AAV) and lentivirus-derived (LV) vectors seem to have overcome these problems [11]. The future challenge will be to design viral vectors that allow the regulated expression of transgenes. In addition to soluble factors, various natural and synthetic polymers have been introduced to spinal lesions to reduce scarring, fill cavities and provide a substrate for re-growing axons and/or cells transplanted to the site of injury [12].

Cell based approaches

Cellular therapies for SCI may offer several advantages: in addition to presenting an avenue for continuous factor delivery, transplanted cells may bridge the lesion and cystic cavities to provide a substratum for axonal re-growth or take part in the endogenous repair processes. They also may replace lost glial and neuronal cells and re-establish new functional local circuits. The cells can either naturally secrete compounds (e.g. monoclonal antibodies from hybridoma cells) or can be genetically engineered *ex vivo* to block growth inhibitory cues, secrete attractive cues or enhance the intrinsic regenerative capacity of CNS neurons. The time and location of cell placement is dependent on the function and survivability of the cells, their repair task and the type of lesion. To this end a variety of cell types have been used, such as fibroblasts that have been modified to secrete the various neurotrophins that can promote sprouting and re-growth of lesioned axons [13]. Among the cells acutely implanted into the lesion site, macrophages activated by peripheral nerve have led to functional improvement while Schwann cells and olfactory ensheathing glia (OEG) limited central cavitation [14]. Cells have also been implanted at longer times post-injury to fill the cysts and provide a growth-permissive terrain (reviewed in [13]). Although many different cell types used in transplantation so far have shown promising effects in animals and genetic modification significantly enhanced their efficacy, several obstacles, such as availability of sufficient cells for transplantation, potential for tumorigenesis and gene delivery system, still have to be addressed.

Rehabilitative therapy

Locomotor physical therapy in form of body-weight-supported treadmill training, robotic or manually assisted training and/or functional electrical stimulation, has been used in clinical trials resulting in significantly improved independent walking ability in patients with incomplete SCI [15]. However, to design more effective and safe therapy regimens, a better understanding of the mechanisms of recovery induced by rehabilitative training is needed. Work in rats demonstrated the beneficiary impact of swimming on hindlimb function after contusion of the spinal cord [16]. It also leads to a transient improvement of sensory function after contusion while treadmill training resolved allodynia after several weeks concomitant with normalization of brain-derived neurotrophic factor (BDNF) levels in the spinal cord and peripheral muscle [17]. The development of a robotic device to impose programmed force on the hindlimbs of rats during stepping allows to implement treadmill training and simultaneously measure stepping parameters in an efficient way in partially paralyzed animals [18,19].

Outcome assessment

Analysis of the site of injury

Standard histological analysis of the lesion site (hematoxylin and eosin- (HE), Nissl-, Luxol fast blue-staining) can yield valuable information on the extent of the primary injury, preservation of particular fiber tracts, cellular infiltration and secondary degeneration. At later stages it can be used to assess demyelination, the formation of scar tissue and cysts, both of which are believed to be impediments to re-growth of lesioned axons. Magnetic resonance imaging (MRI) has been successfully applied to rodent SCI models in several studies [20]. Similar to standard histological analysis it allows the differentiation between white and gray matter, an estimation of the lesion size and the formation of scars and cavities. Because it can be applied to living animals, it allows the monitoring of individual injuries over time. Its spatial resolution does, however, not yet match that of histology. In addition to traditional histological stainings a wide range of specific antibodies and/or mRNA *in situ* hybridization probes allow the analysis of many injury-relevant cell types, structures and processes. Glial markers are used to monitor astroglial and microglial activation and proliferation [10] as well as de- and re-myelination by oligodendrocytes and Schwann cells. Enzyme- (TUNEL) and antibody-based (activated caspase 3) methods allow to visualize apoptotic cells [21,22]. A wealth of markers is also available to detect the various blood-derived immune cells and monitor the expression of cytokines, tumor necrosis factor, interleukins and activation of interleukin receptors [22]. Recently, microarray technology has been employed to study genome-wide gene expression changes at and around spinal cord lesion sites with the aim of better understanding the molecular events

occurring after SCI and identifying key signaling factors that may serve as therapeutic targets to beneficially influence outcome after SCI [23].

Neuroanatomical tract tracing

An important objective of regeneration research is to correlate motor or sensory deficits and their recovery to the underlying neuronal circuitry. A wide range of tools is currently available to visualize neurons and their axonal projections in experimental animals. Anterograde tracers are applied to the vicinity of the neuronal cell bodies, either by pressure injection or electrophoretically, taken up by the neurons and transported along the axon until they completely fill it, thus displaying efferent fibers. The tracers can be visualized either by a fluorophore or an enzyme driving a color reaction, or indirectly via a hapten (e.g. biotin) coupled to them. Efficient anterograde tracers are fluorescently or biotin-labeled dextrans, wheat germ agglutinin-horseradish peroxidase, or cholera toxin subunit B. Frequently anterogradely studied fiber tracts include the corticospinal and rubrospinal tracts and the ascending sensory pathways of the dorsal column bundles. Retrograde tracers are used to detect neuronal cell bodies that project to the site of tracer injection (afferent fibers). An injection into the spinal cord below the site of injury will for example yield information on neurons in the brain that send axons across or around the lesion. Many anterograde tracers can also be used for retrograde visualization of neuronal circuitry. In addition, several inherently fluorescent compounds such as Fluorogold, Fastblue and Diaminidino yellow [24] can also be employed for this purpose. Some neurotropic viruses such as pseudo-rabies virus are retrogradely transported even across synapses and can be used to trace higher-order neurons by injection of the virus into the peripheral muscle [25]. Because retrograde tracers generally do not label the axons well, they are of only limited use for studies aimed at determining the exact pathways of axons. Recently, transgenic mice have become available that express fluorescent proteins (FP) in subsets of neuronal populations [26]. The FPs fill the whole cell and thus label also long projecting axons. These mice have been successfully used to visualize axons in SCI paradigms and will be increasingly important in studies of (other) CNS diseases. In combination with advanced imaging techniques such as 2-photon laser scanning microscopy, genetically traced nerve fibers can be observed and their reaction to injury studied in living animals [27].

Behavioral testing

The ultimate goal of spinal cord regeneration research is the restoration of motor and sensory functions lost through the injury. However, to further our insight into the mechanisms that underlie these functions, behavioral assessment of animal models after SCI should also allow for a correlation of the

observed functional deficits and recovery to lesion severity as judged from anatomy and regenerative treatments. Ideally, the analysis of behavior yields data that can be directly relayed to the anatomical or physiological analysis of neuronal circuitry that may mediate the recovery [28].

In rodents, observation of spontaneous locomotion in the open field as scored, for example, by the Basso-Beattie-Bresnahan (BBB) rat locomotor score or the Basso Mouse Score (BMS) that rate individual movement components in clearly defined steps, is one of the oldest and conceptually simplest ways to evaluate locomotor performance [4,29]. However, the detection of small changes resulting from treatment interventions or the identification of the neural substrates of motor recovery often requires more specific and sensitive behavioral tests. The grid walk and narrow-beam tests both measure different aspects of precise motor control: the former assesses forelimb-hindlimb coordination by requiring the ability to precisely control and place the hindlimbs on a horizontal, irregular ladder-like grid. When an animal misses a grid bar, a withdrawal movement occurs, which is known to be modulated by supraspinal input. The latter can quantify even very small deficits in foot placement and body balance including tail movements. Foot print analysis records gait coordination, body balance and placement of the feet [30]. The most sensitive behavioral evaluation tool used in spinal cord research to date is video recording-based kinematic analysis. It allows quantitative assessment of individual components of step cycles thus enabling the researcher to discriminate significant changes in the execution of movements that are undetectable by visual observation alone. Translational studies in monkeys require adaptation of behavioral tests to the specific locomotor modes in these animals. Iwanami *et al.* [31] developed a system where spontaneous motor activity is recorded by infrared sensors and compared to pre-injury activity. The animal's ability to generate force with the fingers or grasp an object placed before the animal can be assessed using the reach and grasp drawer [32] or the bar grip test [31]. Neurogenic pain or hypersensitivity to otherwise non-noxious stimuli (allodynia) are conditions that frequently accompany SCI in humans. Standard pain tests such as hot/cold plate, tail flick or von Frey hairs have therefore also been applied in SCI animal research [33,34].

Electrophysiology

Functional recovery of walking patterns in rats after SCI may be difficult to interpret with respect to the role the treatment plays. In addition to actual regenerative fiber growth, compensatory adaptive plasticity of undamaged motor systems has to be taken into account. Apart from neuroanatomical tract tracing, electrophysiological approaches provide the possibility to investigate neuronal circuitry in the context of spinal cord lesions. Both, motor evoked potentials (MEPs) and sensory evoked potentials (SSEPs) have been successfully

Table 1. Experimental approaches to spinal cord injury

	Pros	Cons	Best use of model	Refs
SCI lesion paradigms				
Spinal cord transection	High confidence of nerve fiber interruption, can be targeted to various fiber systems (motor and sensory)	Uncommon in human SCI	Studies of fiber re-growth	[7]
Spinal cord contusion	Best model of most human SCI situations	Difficult to distinguish spared vs. re-grown fibers	Studies of secondary injury processes, validation of transection studies, development of translational therapies	[6]
Interventions				
Transgenic animals	Allow testing of molecular hypotheses such as the involvement of growth inhibitors in regenerative failure or cytokines in inflammatory processes	Does not reflect human SCI situation	Studies on specific basic science questions	[39]
Substance infusion to the spinal cord	Controlled delivery of bioactive compounds	Placement of catheter may exacerbate initial injury	Testing of bioactive compounds	[7]
Direct gene therapy	Using viral vectors, endogenous cells produce factors at physiological levels; novel non-toxic AAV or LV vectors allow long-term expression of therapeutic gene in neurons and glia; minimally invasive (single injection)	Long-term expression of neurotrophins may cause side-effects: regulated transgene expression needed	Studies on neural protection and promotion of fiber re-growth	[11]
Cell based approaches	Transplanted cells can replace lost cells, provide a scaffold for nerve fibers to grow on, deliver bioactive proteins (e.g. growth factors, enzymes) from transgenes	Require space and transplantation may exacerbate initial injury, poor control over substance delivery		[13]
Implantation of 'bridges'	Provides substrate for fiber growth in complete and partial injuries	Often requires resection of intact tissue	Provides insight on basic substrate requirements of regenerating fibers	[12,40]
Rehabilitative training	Easily applicable to human SCI	Laborious		[16–19]
Outcome assessment				
Standard histology (HE, Nissl)	Good general indicator for tissue preservation and degeneration	Less useful for assessment of preservation of specific spinal tracts	Useful for all lesion paradigms and interventions	
Specific histology (immunohistochemistry, in situ hybridization)	Yields highly valuable information on important processes (gene regulation, inflammation, glial activation, apoptosis . . .), as well as structures (cell types, glial scars, fiber tracts, myelination)	Laborious	Studies on specific basic science questions, but also development of experimental therapies	
Neuroanatomical tract tracing	Detailed visualization of specific neuronal connections	Amenable to only certain spinal tracts, laborious	Studies of regeneration and plasticity after defined fiber lesions (transection), complementation of functional and physiological studies	[24,26]
Behavioral testing of motor and sensory functions	Ultimately the most relevant outcome measure for translational therapies	Very laborious, often very variable between animals, investigators, laboratories Does not yield much mechanistic insight	Useful for all lesion paradigms and interventions	[30,33,34]
Electrophysiology	Yields highly valuable information on the functional preservation or re-establishment of neuronal connections	Laborious	Complementation (validation) of tract tracing studies	[35–37]

employed to investigate the functional state of spinal circuitry after experimental SCI [35]. Electrical stimulation can be achieved from needle electrodes with high spatial precision. For less invasive procedures and longitudinal studies, transcranial magnetic stimulation can be applied from a coil placed on top of the head [36]. Amplitude and latency of recorded responses have been shown to correlate with the number of intact connections, the number of synapses and the myelination state of the pathways investigated. One of the most sophisticated approaches to assess functional locomotor performance consists in the combination of video kinematics with recordings of spontaneous electromyographic activity (EMG) in rodents moving on a runway. This presents a way to compare pre- and post-lesion walking sequences and identify underlying alternative patterns of muscle activity that the animals developed following SCI [37].

Model comparison

The diverse aspects of human SCIs and their clinical pathophysiology can clearly not be reproduced by a single animal model. Instead, every experimental hypothesis calls for a suitable lesion paradigm and appropriate evaluation tools to assess the outcome of the study (see Table 1). To illustrate this point, let us consider a study that aims at testing a treatment that is believed to improve locomotor behavior by reducing scarring at the lesion site, thus allowing interrupted descending motor tracts to re-grow. It cannot be enough to induce a contusion lesion and assess motor behavior by determining open-field locomotor performance. Rather a transection lesion should be chosen to ensure that the nerve fibers were cut in the first place. Then, it should be investigated whether the applied treatment in fact does reduce scarring. To this end careful histological analysis of the lesion site, maybe even by electron microscopy, is required. As a next step, the re-growth of fibers needs to be demonstrated by neuroanatomical tracing. Ideally, electrophysiological analysis will be applied to link a possible behavioral recovery to re-established functional circuitry. In a second step, it can then be tested whether the treatment in question is equally efficient in a contusion paradigm, which is more reflective of human SCI, but not suited well for the analysis of the initial hypothesis. In this light, it becomes clear that there cannot be a 'gold standard' SCI model that is in all aspects superior to other approaches. Rather, experimental treatments should be evaluated in various lesion and assessment paradigms to understand the underlying mechanisms and also realize their potential as a treatment for human SCI. The observation that most experimental therapies offer only limited benefits has spurred the design of combined interventions, with the aim at maximizing the therapeutic effect. In these combination treatments care should be taken to compare their outcome to the outcome of each individual

intervention alone, to ensure that the overall efficacy can be attributed to the individual components of the treatments and possible interactions of different treatments can be identified.

Model translation to humans

Many aspects of human SCI are reproduced reasonably well in the current animal models. However, not all results gained in animal experiments can directly be extrapolated to the situation in humans. For reasons of feasibility and animal welfare, in the majority of studies, injuries are induced at mid-thoracic levels and have concentrated on the restoration of functions provided by the long spinal pathways. This does not closely reflect the human situation in which most injuries occur in cervical segments and the loss of neuronal substrates at the segment where the injury occurs contributes often significantly to the clinical impairments (<http://keck.rutgers.edu/MASCIS/mascis.html>). Future studies will have to address whether and how local spinal circuitry can be saved from secondary degeneration or re-established, for example, by transplantation of neuronal precursor cells. Therapies that aim at stimulating the growth of nerve fibers may, in addition to the intended regenerative effect, also cause aberrant growth and novel neuronal circuitry that may cause problems such as chronic pain. Only very few regeneration studies have included pain tests in their evaluation protocols. Clearly, a more comprehensive assessment of sensory functions after experimental treatments is warranted. A problem of testing locomotor performance in experimental animals and its application to humans is the inherent difference in the mode of locomotion. Although translational therapies are increasingly taken from rodents to non-human primates, even these closer relatives of humans do not display the bipedal walking which is characteristic to humans. Therefore, the direct extrapolation of behavioral data obtained in animal experiments to outcome after human SCI remains problematic.

Conclusions

In the last few years, great progress has been made at developing animal models that closely reproduce the various aspects of human SCI. A wide range of methods has been designed to assess outcome of experimental SCI on the anatomical, physiological and behavioral level and many promising therapeutical interventions have been tested. The first of these experimental therapies have entered clinical trials and it is to be expected that others will follow. Meanwhile, it also has become clear that the task of curing SCI is a formidable one and will likely not be achieved by a single treatment alone. Research into SCI and other traumatic CNS injuries will therefore remain an important branch of basic and translational neuroscience research and the tools to model, treat and assess spinal cord injuries will become further refined.

Links

- Spinal Cord Injury Information Network: <http://www.spinalcord.uab.edu>
Offers a wealth of statistical, medical, psychosocial and other information relevant to SCI patients, their families, and others.
- International Campaign for Cures of Spinal Cord Injury Paralysis (ICCP): <http://www.campaignforcure.org>
Umbrella organization of ten non-profit foundations that support research into spinal cord injury therapies. Includes links to the individual charities.
- MedlinePlus Spinal Cord Injuries: <http://www.nlm.nih.gov/medlineplus/spinalcordinjuries.html>
Site of the U.S. National Library of Medicine on all aspects of SCI.
- Journal of Neurotrauma Special Issue on Spinal Cord Injury Repair: <http://www.liebertonline.com/toc/neu/23/3-4>
A recent collection of review articles of various aspects of spinal cord injury research.

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