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MODELS OF CNS INJURY IN THE NONHUMAN PRIMATE: A NEW ERA FOR TREATMENT STRATEGIES

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Abstract

Central nervous system (CNS) injuries affect all levels of society indiscriminately, resulting in functional and behavioral deficits with devastating impacts on life expectancies, physical and emotional wellbeing. Considerable literature exists describing the pathophysiology of CNS injuries as well as the cellular and molecular factors that inhibit regrowth and regeneration of damaged connections. Based on these data, numerous therapeutic strategies targeting the various factors of repair inhibition have been proposed and on-going assessment has demonstrated some promising results in the laboratory environ. However, several of these treatment strategies have subsequently been taken into clinical trials but demonstrated little to no improvement in patient outcomes. As a result, options for clinical interventions following CNS injuries remain limited and effective restorative treatment strategies do not as yet exist. This review discusses some of the current animal models, with focus on nonhuman primates, which are currently being modeled in the laboratory for the study of CNS injuries. Last, we review the current understanding of the mechanisms underlying repair/regrowth inhibition and the current trends in experimental treatment strategies that are being assessed for potential translation to clinical applications.

Keywords

• Nonhuman primate • Central nervous system • Traumatic brain injury • Stroke • Perinatal hypoxic-ischemia • Animal models • Clinical interventions

Introduction

Central nervous system (CNS) injuries such as traumatic brain injuries (TBI) [1], strokes [2], spinal cord injuries (SCI) [3] and perinatal hypoxic-ischemia (pHI) [4] can result from either exogenous factors such as physical or mechanical force trauma (TBI, SCI), or endogenous causes (ischemia and hemorrhage). CNS injuries affect all levels of society indiscriminately, impacting on physical and emotional wellbeing and life expectancies and inflicting considerable socioeconomic burdens on victims and their families.

In the United States, the incidence of CNS injuries per year are estimated to be (average numbers; Figure 1): TBI, 1.7million [5]; SCI, 12,000 [6]; pHI, 4,800 [7] and strokes, 750,000 [8]. Even so, there are no effective restorative or pharmacological strategies developed for the treatment of CNS injuries in humans as yet and current options for clinical interventions remain limited.

Although several treatment strategies have been previously brought to clinical trials based on optimistic experimental results, these trials fail to demonstrate improvements in functional outcomes [9]. Failure of these trials may be due in part to lack of understanding of the numerous sources of inhibition of repair present in the injured CNS. Though recent studies have made great strides to better understand the complex cellular and molecular mechanisms underlying the pathophysiology of injury, many questions still remain unanswered. Furthermore, comprehensive pre-clinical testing of any novel therapeutic strategies for the treatment of CNS injuries is necessary using appropriate animal models before they can be brought to human clinical trials.

In this review, we discuss current animal models, with focus on the nonhuman primate (NHP), being employed in the study of CNS injuries. We also evaluate current understanding of the cellular and molecular factors that impede axonal regrowth and regeneration, inhibiting functional recovery following CNS injuries. Finally, we discuss the recent trends in therapeutic strategies being developed and assessed in the laboratory, which may translate into a suitable intervention for the treatment of CNS injury in the human.

Current models of CNS injury research: The importance of the nonhuman primate

To investigate the cellular and molecular events surrounding regeneration, various animal models have been developed to mimic the different types of CNS injuries. These models are important to examine the pathophysiology of injurious conditions affecting the CNS. Furthermore, they are essential for testing novel therapeutic strategies aimed at counteracting the various aspects of CNS injury in a reliable and reproducible manner.

Since the 1990s, rodent models of CNS injuries have dominated the field (reviewed by [1]), being the most widely used species in TBI and SCI research. However, other species such as dogs [10], pigs [11], sheep [12], cats [13,14], zebrafish [15] and nonhuman primates (NHP) have been used to develop animal models of CNS injuries [16,17].

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Although we acknowledge that animal models in other species other than NHPs are important to elucidate the physiological and mechanistic responses to injury, these models offer poor translation of experimental treatment strategies to clinical applications. For example, rodent models of CNS injuries are advantageous for their versatility, low cost, and wide availability, however, they offer little in regards to translational clinical interventions for human therapies due to vast species differences encompassing physiological and behavioral factors which they do not mimic [18]. Therefore, more representative models such as the NHP models of CNS injury have been gaining in popularity for their ability to provide better anatomical and pathophysiological representation of human injuries. The use of NHP models for the study of neocortical injuries are ideal due to the relative complexity of their sensory systems (compared to rodents [19,20]), the organization and cytoarchitecture of which is more similar to that of human's. Specifically, injuries induced in the NHPs visual cortex results in functional visual deficits that are akin to those experienced by human patients with equivalent injuries [21]. Furthermore, NHP models provide opportunities for the development and testing of therapeutic strategies with better translation to clinical applications. Here, we review current models of CNS injuries that have been developed in the NHP.

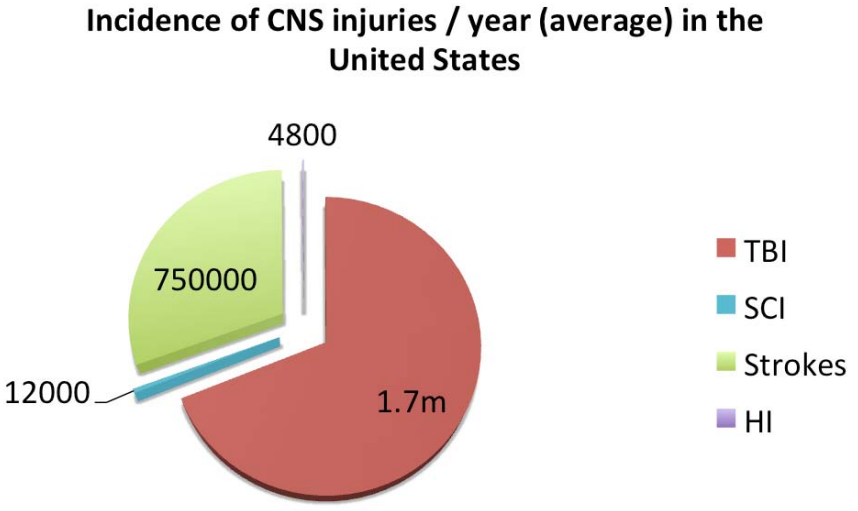

Figure 1. Estimated incidence of CNS injuries per year in the United States. Figures do not reflect mortality rates. TBI, traumatic brain injuries; SCI, spinal cord injuries; pHI, perinatal hypoxic-ischemia.

Ischemic Stroke

The prevalence of ischemic stroke (≈90% of strokes) has prompted the development of animal models in various species to aid in the investigation of ischemic and reperfusion injuries. Among them, NHP models of reversible and permanent ischemic stroke offer distinct advantages over non-primate models due to similarities in cerebral vascular anatomy and circulatory patterns [22-24]. NHP stroke models also allow for better assessment of functional deficits using behavioural and neurological tests, such as assessment of limb reflex, and coordination [23], as well as tests to assess sensory acuity with greater parallels to functional deficits observed in human patients. Occlusion of the middle cerebral artery (MCA) and resultant downstream ischemia remains the most commonly employed method in stroke studies. Surgical techniques for inducing middle cerebral artery occlusions (MCAO) in NHPs involves one of the following methods: 1. temporary application of surgical clips [25]; 2. ligatures [26]; 3. endovascular techniques using inflatable cuff-type catheters [27] or detachable coils [24]; 4. autologous clot embolism [28]; and, 5. vasoconstrictor administration [23]. In most MCAO studies, a reproducibly large zone of infarct is usually observed in the cortical and subcortical MCA perfusion territories. More focal models of ischemic stroke have also been developed through occlusion of smaller arteries (usually the distal M1 portion of the MCA), resulting in relatively smaller and more focal zone of infarcts affecting the M1 territory (for a review, see [18]). The consequence of MCAO on functional outcomes depends greatly on the type (reversible vs. permanent occlusion) severity and extent (proximal vs. distal branch occlusion) of infarct and may range from loss of sensorimotor capacity to death. Some progress has also been made in developing a NHP stroke model in the anterior cerebral artery territory [24]. However to the best of our knowledge, no previous attempts have been made to develop a model for focal ischemic stroke in the NHP posterior cerebral artery (PCA) territory, specifically targeting the visual cortex. The development of such a model is important because a focal injury specifically affecting the visual cortex would allow for qualitative and quantitative assessments of functional visual deficits following PCA strokes and investigation into the mechanisms and consequence of anterograde degeneration of axons in thalamic visual nuclei.

Further developments of NHP models of ischemic stroke are essential for the ongoing investigation of cellular and molecular mechanisms as well as functional (and behavioural) consequences of injury following ischemic strokes. Furthermore, the similarities between vascular anatomical and circulatory physiological between the NHP and the human CNS would allow for more reliable testing of novel therapeutic strategies with considerable potential for translational clinical outcomes for the treatment of ischemic stroke in humans.

Traumatic Brain injury (TBI)

TBI can be broadly categorized into focal or diffuse injuries. Focal TBI (fTBI) is a result of external force vectors that are focused on a narrow and limited region of the brain, such as contusions and penetrating brain injuries [29]. Diffuse-type TBI (dTBI) usually presents as concussion or diffuse axonal injuries, where linear and angular acceleration / deceleration forces causes stretching and twisting of axons, predominantly in the cortical white matter and corpus callosum [30]. dTBI is commonly seen in

victims of motor vehicle accidents from coup-contrecoup or concussion injuries.

Numerous injury-specific models of TBI have been developed in the various non-primate species, either induced through the skull or directly to cortical surface. These models have been developed for the study of the pathophysiology of direct brain deformations, penetrating wound, impact acceleration, closed head, repetitive and impact brain injuries in many species including rodents, cats, pigs, rabbits dogs and sheep. However, limited literature exists describing NHP models of TBI. Here, we discuss several models of TBI developed in the NHP. (For comprehensive reviews on non-primate models of TBI, see [1,31,32])

A marmoset monkey (*Callithrix jacchus)* model of fTBI was developed to study the mechanisms of astrogliosis following an ablative injury through unilateral partial ablation of the marmoset primary visual cortex (V1; [33]). Although ablative injury is primarily observed following penetrating, ballistic or battlefield neurotrauma [34], this model bears more relevance to neurological deficits resulting as from the surgical resection of damaged cortical tissue, due to traumatic injury, tumours or masses [35] and surgical interventions for the treatment of epilepsy [36]. Surgically induced lesions of the orbital frontal cortex (OFC; Walker's area 11 and 13) and amygdala have also been preformed on the rhesus monkey (*Macaca mulatta)* using either aspiration or intracortical injections of neurotoxic compounds (ibotenic acid [37-39]) to induce excitotoxic lesions. These models were developed primarily for the investigation of the relationship between stimuli/reinforcement and learning as well as reward-guided and object reversal-learning behaviors in primates and not for the study of the consequences of injury. However, the successful implementation of the aspiration / neurotoxic lesion procedure would potentially be beneficial for the development of other TBI models with previously demonstrated capacity for behavioral assessments as a consequence of injuries. An example of dTBI developed in the primate involved acceleration of the head without impact in either coronal, parasagittal or oblique planes [40]. The study reported that the extent of axonal damage was directly related to acceleration in the coronal plane, whilst sagittal motion produced the largest incidence of coma (<15 minutes) and consequences of lateral plane injuries were the most consistent with those seen in human with severe dTBI.

Although we do not argue against the value of non-primate models in the study of TBI, we do assert that the use of NHP models of TBI is more appropriate in studies that carry greater clinical relevance. For example, the larger relative brain size and corresponding degree of neocortical myelin/white matter composition in relation to grey matter (compared to rodents) present in the NHP brains [41-44]. It is important to note that the majority of TBI commonly affects the neocortex and underlying white matter. Therefore, the relative degree of myelin/white matter damage that result as direct or indirect consequences of TBI becomes more profound in species with higher degree of neocortical myelin/white matter composition. The implication of this in the development of clinical therapeutic strategies is in the more significant contribution by factors involved in myelin-associated inhibition (MAI) that negatively influences the process of repair and regeneration following TBI in human. We believe that this paradigm remains inadequately reflected in most non-primate models. It is our opinion that NHP models are better suited for more clinically relevant investigations of the mechanisms underlying TBI-associated injury and repair.

Perinatal Hypoxic-Ischemia

Hypoxic-Ischemic (HI) brain injury is a major cause of perinatal morbidity. Surviving infants are usually afflicted with chronic seizures, epilepsy, cerebral palsy, long-term neurological and behavioural deficits as well as delayed mental development and/or mental retardation [4]. A common sequelae of pHI is periventricular leukomalacia (PVL) which results in white matter lesions surrounding the periventricular region [45]. In some cases, intracerebral and intraventricular hemorrhages can occur as a result of by pHI [46]. The neurogenic zones (subventricular zone; SVZ and dentate gyrus; DG in the hippocampus) are particularly susceptible to HI insults. Studies have demonstrated significant declines in SVZ cell survival [47] and increased apoptotic response in the DG [48] following HI injury compared to age-matched controls. The pathological impacts on the neurogenic zones may account for the developmental deficits that result from HI insults during early life. It is well established that the major pathological processes underlying HI injury is the deprivation of glucose and oxygen supplies, ultimately leading to necrotic cell death [49]. The subsequent reperfusion injury also exacerbates neurological damage by increasing oxidative stress and excitotoxicity [4]. Selective degeneration of interneurons in the NHP motor cortex has been demonstrated following perinatal HI insults [50]. NHP models of pHI insults have been used successfully to investigate HI injuries, revealing similarities to the neuropathological responses observed in human infants. Using various methods of induction, these models have been successful in mimicking asphyxia insults to human infants: total asphyxia, partial asphyxia with acidosis, partial asphyxia without acidosis and partial asphyxia in association with total asphyxia [51-56].

More recently research into pHI has involved larger species (such as NHP and sheep) that posses an overall larger brain size and with considerably greater myelin/white matter composition. This is due in part to the prevalence of periventricular white matter damage (PVL) observed in human pHI cases. And while studies in small-animal models (rabbit, rodents) have been instrumental in addressing the genetic and biochemical events associated with pHI [57,58], the temporal and pathophysiological sequelae of the injury does not detail the same mechanisms that might be occurring in the primate brain. To that end, the further development of NHP models of pHI is important for the purpose of investigating the consequences of pHI in a system that is more reflective of the human condition and allow better corollary for future therapeutic developments.

Spinal Cord injuries (SCI)

The consequence of SCI commonly leads to paraplegia or quadriplegia, severely impeding locomotor and skilled limb functions as well

as manual dexterity. Animal models of SCI, especially in rodents [59-62], are the most commonly used models in the field of CNS injury and repair. However, the availability of literature on primate models of SCI remains somewhat limited. Examples of NHP models of SCI include studies performed by Darian-Smith and Brown [63] using a macaque model of dorsal root lesions to demonstrate periphery-mediated reorganization of sensory afferents in the somatosensory cortex. Studies have also been conducted by Babu *et al*., [64] using NHP models of unilateral spinal hemisections and weight-drop contusions [65] at the T12-L1 level of the Bonnet macaque (*Macaca radiata*) spinal cord. Follow-up studies conducted in the spinal hemisection model investigated deficits in locomotor capacity through behavioural assessments [66,67] and mechanisms underlying functional recovery following injury [68], implicating a role for synaptic plasticity and collateral sprouting in the strengthening of undamaged fibers. More recently, a model of SCI was developed by C7 lateral hemisection in the rhesus monkey [69] for the purpose of functional assessment of candidate therapies in restoration of manual dexterity after SCI. This study reported spontaneous recovery of forelimb function of ≈50% from baseline performance using a series of behavioral tests to assess skilled forelimb functions.

It should be noted that there are remarkable correlations between evidence gathered from clinical observations in humans [70-73] and experimental data in rat SCI models [74-76] of functional improvement through physical rehabilitative training following SCI. However, it remains unclear whether molecular and cell-based therapeutic strategies developed from rodent experiments can be extrapolated to primates including humans. This is due to marked species difference in the relative size and cortico- versus rubrospinal tract anatomy and function between rodents and primates [77-79]. Furthermore, NHP models provide more reliable translational data with regards to behavioral studies involving hand and arm dexterity as well as posture and bipedal gait [78]. While we agree that rodent studies do provide important insights into the underlying molecular and cellular mechanisms surrounding SCI, NHP models provide better clinical significance for the testing of novel therapeutic strategies for the treatment of SCI in human.

Molecular and cellular consequences of CNS injury: implications for regeneration

In the acute stage (within minutes) following a CNS injury (Figure 2A), the first wave of cell death (necrosis) affecting both neuronal and glial cell types usually occurs as a direct consequence of the injury, this zone is known as the lesion / necrotic core [80]. The lesion penumbra (Figure 2B), an area of tissue surrounding the lesion core, that is less severely affected by the lesion, remains metabolically active [81] depending on the severity and type of lesion. The first wave of necrosis, occurring in the lesion core, is characterized by cell swelling and mitochondria / endoplasmic reticulum breakdown followed by rupturing of the plasma, organelle and nuclear membranes [82]. Disruption of the blood brain barrier (BBB) may be caused by the injury or the resulting intracerebral hemorrhage [29,83], which may also initiate a localized neuroinflammatory response from chemotactic recruitment of immune cells [84]. Subsequently, rapid recruitment of microglia (resident macrophages) and astrocytes to the affected area occurs to limit the extent of damage and remove debris from necrotic cells.

In the subacute period after injury (hours-days; Figure 2B), a second wave for cell death (necrosis and apoptosis), known as the secondary injury can occur in the lesion penumbra. This can be caused by a variety of factors. For example, prolonged hypoxia or ischemia, excitotoxic and oxidative stress caused by reperfusion (after transient cerebral ischemia [85]) injuries and free radicals [86] or debris from necrotic cells, homeostatic and osmotic stress from cerebral edema [83] and anterograde degeneration of neuronal processes [87] from axonal shearing or loss of terminal fields. Anterograde degeneration of long projecting axons from areas distal to the lesion site (such as thalamocortical projecting axons) may also result in distal neuronal cell death that is secondary to the injury. The result of the secondary wave of cell death leads to a compounded effect on astrocyte and microglial recruitment to the lesion core and penumbra. Furthermore, oxidative stress [88] and axonal degeneration can result in death of oligodendrocyte populations that myelinate the affected axons [89]. The myelin debris left behind by apoptotic oligodendrocytes in addition to that resulting from the initial trauma further exaggerates the unfavorable environment at the lesion site and penumbra.

As a result of these molecular and chemical inhibition, capacity for neuronal regeneration in the penumbra is significantly reduced [90]. To address this issue, a large proportion of experimental studies regarding the mechanisms of injury are focused on understanding the molecular and cellular consequences of injury in the penumbra. The bulk of therapeutic strategies being investigated are also aimed at promoting survival and limiting degeneration/cell death in the penumbra in hopes of enhancing regrowth, rerouting and regeneration of damaged connections (Figure 2C). This review will discuss some of the major factors in the molecular and cellular inhibition of neurite regrowth and axonal regeneration as well as current research trends in therapeutic strategies being developed for the treatment of CNS injury in animals models and human.

Inhibition of CNS regeneration after injury

The swollen dystrophic ends of damaged axons first described by Cajal [91] were originally thought to be incapable of regeneration, eventually succumbing to anterograde degeneration (Wallerian degeneration [92]) resulting in neuronal death [87,93]. However, more recent investigations of spinal cord [94,95] and cortical neurons [96] have demonstrated the development of regenerative growth cones after axonal damage but which are inhibited in the non-permissive environment at the lesion site. *In vitro* studies using neocortical neurons have established that these regenerative growth cones retain some intrinsic capacity for pathfinding [97] in permissive environments. Therefore, the need to identify the molecular

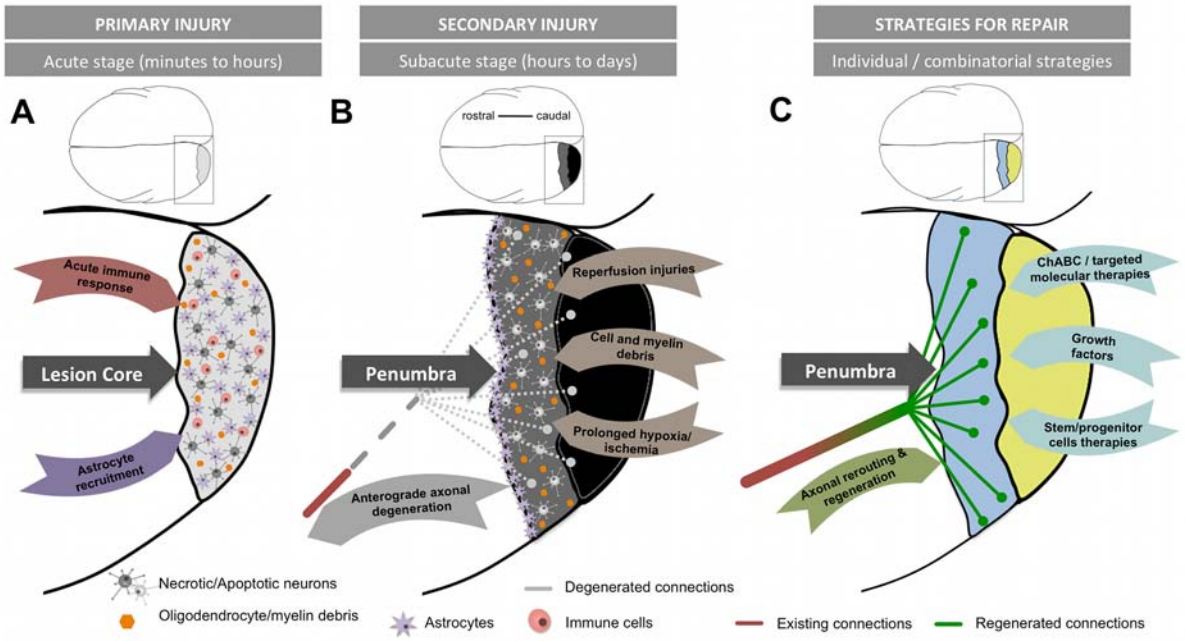

Figure 2. Cartoon illustrating the cellular and molecular events occurring during primary (A) and secondary (B) injuries in the lesion core and penumbra respectively. In the acute stages after injury (A), the first wave of necrotic cell death occurs as a direct consequence of the trauma. Disruption of the blood brain barrier (BBB) from intracerebral hemorrhages may also result in ischemia, hemodynamic stress and localized inflammatory response from chemotactic recruitment of immune cells. Local cellular responses include recruitment of astrocytes and microglia to the lesion core occures to limit the extent of damage and to remove debris from necrosed cells. In the subacute stages of the injury (B), a second wave of cell death can occur in the metabolically active region surrounding the lesion core (penumbra). This secondary injury is usually a result of excitotoxic, oxidative and osmotic stress caused by repurfusion injuries and/or chemical, molecular and cellular debris from the lesion core. Anterograde degeneration of axons from the lesion core also results in distal cell death in upstream areas and increased presence of oligodendrocyte/myelin debris. The result of primary and secondary injuries is a CNS environment that is severely inhibitory to regrowth, rerouting and reconnection of damaged axons. To this end, novel therapeutic strategies (C) aims to promote regeneration of damage connections following adult CNS injuries by: 1. Counteracting the inhibitory environment at the injury site through targeted molecular strategies and introducing localized plasticity using chondroitinase ABC (chABC), 2. Promoting survival of injured neurons and axons through delivery of growth and neuroprotective factors and 3. Through integration of endogenous and exogenous stem/progenitor cell therapies. The administration of individual or combinatorial therapeutic strategies would potentially counteract the growth-inhibitory environment in the damaged CNS to promote survivability as well as the rerouting and regeneration of damaged axons to repair damaged neural circuitry.

and cellular factors responsible for the inhibition of neuronal regeneration at the lesion site, development of appropriate models for their investigation as well as strategies to counteract them will be crucial for the potential development of effective therapeutic approaches to promote rewiring and reestablishment of connections following injury.

Formation of the glial scar: Astrocyte mediated inhibition.

One of the most potent inhibitors to regeneration is the formation of the glial scar The presence of a glial scar creates a structural and molecular barrier that severely limits axonal regeneration and rewiring. The glial scar consists predominantly of reactive astrocytes and extracellular matrix (ECM) molecules, especially chondroitin sulfate proteoglycans (CSPG's), which are extremely inhibitory to axonal regrowth [59,98,99].

Reactive astrocytes

In the normal CNS, astrocytes perform important roles including support of normal neurotransmission and synaptic networks [100,101]. However in response to injury, astrocytes (especially those proximal to the lesion site) can become reactive, triggering a proliferative and migratory response, resulting in the accumulation of reactive astrocytes at the lesion core and penumbra, and subsequently forming the glial scar.

Although the exact mechanisms by which astrocytes become reactive after injury remains unclear, several studies have reported that EphA4 (receptor tyrosine kinase) signaling plays a role in modulating astrocyte reactivity. For example, significant decrease in reactive astrogliosis and glial scarring were detected after SCI in EphA4$^{-/-}$ compared to wild-type mice [102]. Furthermore, *in vitro* studies on NHP astrocyte cultures revealed that EphA4 activation was involved in triggering proliferative and migratory responses in a scratch wound assay, suggesting a role in modulating primate astrocyte reactivity in response to injury [33], most likely through the Rho-GTPases [103] and ERK/MAPK [104] signalling pathways.

Inhibition of axonal regeneration from glial scarring may only partly due to the structural barrier caused by the accumulation of reactive astrocytes at the lesion site. The subsequent upregulated production and release of ECM molecules, especially CSPGs, caused by the

cascade of inhibitory molecules present at the lesion site contributes significantly to the inhibition of neurite and axonal outgrowth after injury [98,105-107].

Chondroitin sulfate proteoglycans

CSPGs are a family of macromolecules (aggrecan, brevican, neurocan, NG2, phosphacan and versican) consisting of sulphated glycosaminoglycan (GAG) chains covalently linked to a protein core [3,108,109]. CSPG are present in high concentration on the lattice-like perineuronal nets (PNN [110-112]), expressed on neuronal cell bodies, proximal dendrites and perisynaptic areas but absent from axons and the synaptic cleft [113,114]. It has been postulated that the developmentally-linked expression of CSPG [115] in the adult CNS is partly responsible for the decline in developmental plasticity. This is thought be achieved through the stabilization of established connections and prevention of aberrant neurite sprouting after the critical period of development [116]. For this reason, CSPG expression is frequently used as a developmental marker for the immunohistochemical parcellation of the neocortex [117-119].

After a lesion, CSPG production is upregulated significantly by reactive astrocytes proximal to the lesion site resulting in a graded barrier to neurite outgrowth and regenerative sprouting. The growth-inhibitory properties of CSPG have been suggested to involve the GAG chains linked to the core protein. Evidence of the inhibitory action of the GAG sugar chains arise from studies using the enzymatic cleaving of the GAG chains from their core protein, demonstrating a decline in growth inhibition [90,120]. Rho/ROCK signaling has also been implicated in the inhibitory activity of CSPGs on neurite regrowth [121] to cause collapse of growth cone upon contact with CSPG. More recent studies have demonstrated that the growth inhibiting effects of CSPG may function through association with the nogo receptors (NgR [122]), a class of reticulon receptors which has until recently, been thought to only be involved in oligodendrocyte/myelin-associated inhibition (OMAI) of regeneration (discussed below). The possibility that NgR may function as a shared receptor to CSPGs and OMAI suggests a degree of functional redundancy [122] in the mechanisms of growth inhibition. This bears great significance in the field of neurorepair/regeneration with considerable potential for the development of therapeutic strategies.

Oligodendrocyte / myelin-associated inhibition.

In addition to the glial scar, another major source of axonal outgrowth inhibition following CNS injury is debris from damaged oligodendrocyte and CNS myelin. Unlike the components of the glial scar that are activated or upregulated after injury, components of OMAI are present as myelin debris or are continuously expressed by oligodendrocytes after injury [123]. As an acute consequence of brain injury, demyelination of axons at the lesion site and penumbra occurs as a result of necrosis or apoptosis of oligodendrocytes [124]. Disruption of myelin in the CNS following injury leads to the release of myelin debris (soluble proteolytic fragments and myelin-associated inhibitory factors) that has been shown to cause neurite growth inhibition *in vitro* [125,126]. These factors include the Nogo ligands [127], myelin-associated and oligodendrocyte myelin glycoproteins (MAG, OMgp). Furthermore, the expression of transmembrane Semaphorin4D [128] and ephrinB3 [129] by oligodendrocytes after injury are also responsible for myelin-based inhibition of axonal sprouting and outgrowth.

The molecular mechanisms underlying OMAI are largely mediated by NgR and the paired immunoglobulin (Ig)-like receptor B (PirB [130]). The high affinity interactions of PirB [130-134] and of the GPI-linked NgR with Nogo66 [130,135], MAG [136-138] and OMgp [138,139] are the major source of MAI-associated neurite and axonal regrowth inhibition following injury. Although the downstream signaling targets of NgR/PIR-B induced OMAI remains unclear, NgR-specific inhibition is dependent on co-signaling through the co-receptor p75 [133,138], TROY [140-142] and LINGO-1 [143-145]. The activation of the NgR/p75/LINGO-1 or NgR/TROY/LINGO-1 signaling complexes are thought to mediate inhibition of neurite outgrowth through activation of downstream RhoA to cause cytoskeletal depolymerization leading to neurite collapse and retraction.

Strategies for neural repair: current trends in research

Using animal models of injury, great strides have been made in the development and testing of treatment strategies to address the sources of growth inhibition after injury. It has been hypothesized that by reintroducing localized plasticity at the site of injury, especially in adults, higher degrees of functional recovery could be achieved. Based on this hypothesis, several studies were designed targeting CSPGs, myelin associated inhibitors or astrogliosis (Figure 2C). These studies were able to demonstrate, with varying degrees of success, that greater functional recovery could be achieved using targeted treatment strategies compared to untreated controls following injury. However, it remains uncertain whether these methods will be able to promote similar responses in the more complex environment of the injured brain. Here, we discuss the current trends of treatment strategies in the study of functional recovery after injury.

Chondroitinase ABC

Administration of the bacterial enzyme chondroitinase ABC (chABC) is a potential treatment strategy currently in animal trials demonstrating promising results in functional recovery, primarily following SCI. ChABC cleaves the CS-GAG chains that are covalently linked via their core proteins [146,147], effectively preventing interactions between CSPG and matrix glycoproteins. This ultimately renders them functionally inactive to axonal/neurite growth inhibition. By eliminating the growth-inhibitory environment in the CNS following injury, transient localized plasticity can be achieved to provide a window of opportunity for damaged connections to be re-established or rerouted (for a comprehensive review, see [116]). Early *in vitro* studies [106] and subsequent examination of postfixed [148] and live rat cerebral tissues (*in vivo* [149]) demonstrated the capacity of chABC to eliminate *wisteria floribunda* agglutinin (WFA)-labeled perineuronal nets. *In vitro* studies using

chABC treatment revealed promotion of growth permissiveness, offsetting the inhibitory effects of CSPG resulting in overall increase in neurite outgrowth and length compared to controls [106,150].

Initial experiments performed on the effects of chABC post-lesion *in vivo*, involving administration of chABC-soaked Gelfoam immediately after injury in adult rats, established that CSPG could be digested *in vivo* [59]. This result illustrated the potential for chABC administration as a therapeutic strategy for the treatment of spinal cord lesions. More recently, exciting progress has been made with *in vivo* chABC-mediated treatment with promising results. These studies revealed that chABC administration promoted axonal regeneration following spinal cord lesions (hemisections and contusions) in rodents [14,151-154] and cats [155] with subsequent improvements in recovery of limb mobility and dexterity. However, for all its successes, this strategy has yet to be tested on NHP models of CNS injury. Moreover, limited literature exists describing the effect of chABC in the injured brain as well as potential cytotoxic side effects from chABC administration therapies. These issues will need to be addressed before any translational outcome for treatment of SC and brain injuries in human is achieved.

Targeted molecular therapies

Another method currently employed as a potential therapeutic strategy, is the use of molecular agents (peptides, antibodies, nucleotides), targeted against the specific inhibitors of regeneration and repair. By targeting these inhibitory cues directly, several studies have demonstrated the ability of the injured CNS to rewire damaged connections resulting in improved functional recovery.

Nogo-A mAb and NgR antagonists.

Treatment of rodent [60,62,156] and NHP [157-159] models of SCI using a monoclonal antibody against Nogo-A. These studies resulted in significant increase in regenerative collateral axonal sprouting [160,161] as well as improvements in locomotion and forelimb dexterity compared to untreated controls, permitting greater regenerative capacity of damaged connections through sprouting of regenerative/ compensatory neurites to re-establish damaged connections. Similarly, the NgR antagonist NEP1-40 (Nogo extracellular peptide, residue1-40 [160,162]) has also been demonstrated to promote functional recovery and axonal sprouting after spinal cord [161,163] and brain injuries [164] in rodents. The success of these experiments in both rodent and NHP models has inspired the development of phase I clinical trials (commenced in 2006; see [165]) to investigate the therapeutic potential of the anti-Nogo-A antibody in human patients with SCI.

Suppression of EphA4 activation

The strategy of blocking EphA4 activation that is significantly upregulated on astrocytes at the site of injury (in rodents [102], and primates [33]), has been proposed to attenuate astrogliosis, glial scarring and promote axonal regrowth. Previous studies demonstrated that neurons cultured on astrocytes extended neurites that were significantly shorter than those on EphA4$^{-/-}$ astrocytes. However when blocked with unclustered, monomeric ephrin-A5-Fc, which binds with high affinity to EphA4 receptors, EphA4 activation was effectively blocked. This resulted in significantly longer neurite outgrowth from cultured neurons on monomeric ephrin-A5-Fc-treated compared to those grown on EphA4-/- astrocytes [102] or following clustered ephrin-A5-Fc treatment [33,166,167]. *In vivo* experiments in rodents through administration of unclustered ephrin-A5-Fc, EphA4-Fc [168] or a blocking peptide (KYLPYWPVLSSL [169]) demonstrated improved axonal regeneration and functional recovery after CNS injury, with notable reduction in astrogliosis. Recent studies have also identified novel small-molecule EphA4 inhibitors that shows promising results in limiting astrogliotic wound closure *in vitro* [170] putting greater emphasis on the therapeutic potentials of EphA4 inhibition following CNS injury.

Exogenous administration of growth factors

In the normal brain, growth factors regulate synaptic plasticity and transmission, neuronal survival and neurite growth. Administration of growth factors has been suggested as a therapeutic strategy to promote repair and functional recovery following ABI and SCI by promoting survival of neurons and regeneration of damaged axons. Experiments using either transient or continuous exogenous administration of transforming growth factor-α (TGFα), brain- and glial cell-derived neurotrophic factors (BDNF; GDNF) and fibroblast growth factor-2 (FGF-2) has had some success in promoting axonal regeneration following injury.

Grafting of BDNF expressing fibroblasts following an axotomy has been reported to promote axonal survival and regeneration [171-173], as well as rescue limb function after rat SCI [13,174]. Administration of TGFα, a mitogenic growth factor, either via intracatheter infusion [175] or via overexpression through adeno-associated virus injection [176] adjacent to the injury site in mice transformed reactive astrocytes to a neuroprotective, growth-supportive phenotype. TGFα treatment also enhanced proliferation and infiltration of these axonal-growth promoting astrocytes to the lesion site resulting in improved axonal regeneration. GDNF overexpression induced by gene delivery using adenoviral vectors has also been demonstrated to confer neuroprotective roles on neuronal survival and improved following TBI in rats [177,178]. FGF-2 treatment improved functional recovery following early-adolescent and neonatal injury to the rat motor cortex [179,180] as well as conferring neuroprotective roles against hypoxic-ischemic insult to the perinatal rat brain [181]. Although these studies demonstrate promising results for growth factor therapy following brain injury, further work will be required to determine if this strategy will indeed promote neuroprotection and axonal regeneration in the NHP models of injury before moving on to human clinical trials.

Stem/progenitor cells therapy: endogenous vs exogenous

Research over the last 15-20 years has overturned the dogma that the generation of neurons in the mammalian CNS is restricted to development. It is now firmly established that new neurons are generated in the subventricular zone (SVZ), and hippocampus

throughout adult life [182,183]. Just as significant, is the recent finding that non-neurogenic compartments of the uninjured adult rodent [184], marmoset [185] and human [186] neocortex contain multipotent neural precursor cells (NPCs) that exhibit latent neurogenic potential *in vitro*.

However, the presence of neurogenesis in the adult human CNS remains strongly disputed, citing evolutionary and interspecies differences in cellular mechanisms [187]. One study in particular, demonstrated an 18-month [188,189] window for postnatal neurogenesis and migration before subsiding and becoming non-existent in adult humans. It has been suggested that investigation of postnatal and adult neurogenesis in higher order apes, such as chimpanzees, will provide a clearer understanding as to whether or not reduced adult neurogenesis is a uniquely human trait [187].

Whether neurogenesis and subsequent integration of new neurons into existing neural circuits following an injury remains controversial. Recent findings demonstrated that that new neurons are generated in the adult rodent's neocortex following specific types of cortical injury [190,191]. Moreover, significant synaptic plasticity and neurogenesis occurs following CNS injury in higher order mammals, including NHP [192-194]. The significance of injury-induced neurogenesis in the NHP neocortex, an area that in humans is often damaged as a result of TBI and stroke, raises the exciting possibility that similar mechanisms could operate in the human. A rigorous understanding of endogenous regenerative mechanisms in the NHP neocortex could have a transformational influence on our attempts to potentiate CNS regeneration in the human.

Exogenous or autologous transplantation of embryonic or adult stem/progenitor cells as a therapeutic strategy following CNS injury has been proposed to improve functional recovery. It is hypothesized that implantation of exogenous/autologous stem/progenitor cells may promote recovery by forming bridging relays to re-established neural circuits, induce localized plasticity and promote axonal regeneration [195]. Experiments using transplanted human embryonic neural stem cells into monkey spinal cord following an SCI demonstrated the ability of the transplanted cells to survive and differentiate into cells with neuronal and oligodendroglial characteristics [196]. Grafting of engineered human neural stem cells onto the rat forebrain following hypoxic-ischemic injury promoted axonal sprouting and improved recovery [197,198]. Stem cell transplantation therapies have also been proposed for the treatment of retinal diseases [199], ischemic injuries [200] and TBI [201,202]. The capacity for autologous transplantation of adult stem cells to improve recovery following CNS injury has also been demonstrated, avoiding many of the ethical and immunological concerns of embryonic stem cells. Transplantation of adult-derived hemopoetic stem cells was successful in improving functional outcomes following ischemic stroke [203]. Human umbilical cord mesenchymal stem cells therapy in rats following SCI also provided evidence of improved functional recovery and axonal regeneration [204].

In 2010, the recruitment of patients into phase-I human clinical trials using engineered cells derived from human embryonic stem cells for the treatment of subacute SCI was announced by Geron [205,206], but has since been discontinued, citing funding and financial reasons [207]. Implantation of the NT2/D1 precursor cell line (human embryonic carcinoma-derived) has also been previously trialed in human stroke patients. Cells were implanted via stereotaxic-guided injection into the basal ganglia of stroke patients. Post-recovery functional/neurological assessments demonstrated trending improvements but were statistical insignificant [208].

Although the conceptual applications of stem/progenitor cell therapy seems promising, it is our opinion that further animal trials are still needed, especially in the NHP models of CNS injuries, to more thoroughly assess potential physiological and ethical pitfalls that may arise before further human clinical trials can be considered.

Combination strategies

Due to the numerous factors present at the lesion site that inhibit axonal regeneration and functional recovery following injury, therapeutic interventions incorporating more than one treatment strategy (combination strategy) may prove more beneficial to compared to individual therapies. For example, it has been demonstrated that physical training and rehabilitation [209], in combination with induced localized plasticity opens a window for plasticity [154] to improve locomotor functional recovery following SCI. In experiments using NgR blockers and inosine in combination with environmental enrichment successfully improved recovery of limb motility in rats after stroke [164]. Rats treated with chABC following SCI in combination with task-specific rehabilitation demonstrated improved limb motility and manual dexterity [154]. Cortically blind human patients (homonymous hemianopia) that underwent visual field rehabilitative training for 4-weeks revealed significant long-term improvements in reaction time and accuracy of target localization [210-212].

Combined delivery of NogoA antibody and the growth factor neurotrophin-3 (NT3) induced enhanced synaptic plasticity at the lesion site resulting in improved motor function following SC hemisection [213]. Other examples of combination therapies include combined administration of chABC with NT3 [214] as well as combined NT3 with NMDA receptor 2d subunit [215], demonstrated the compounded effect in promoting improved functional recovery compared to individual administration.

As individual treatment strategies only address a single aspect of inhibition, it stands to reason that strategies that combine the therapeutic effect of several different approaches may work synergistically to promote better functional outcomes following CNS injury. It is our opinion that combination treatment strategies may have the best translational potential for human clinical trials for the treatment of CNS injuries. However, further *in* vivo and *in* vitro research is required to identify the best strategy, time of delivery and route of administration to maximize the likelihood of significant functional outcomes.

Concluding remarks

Acquired CNS injury remains to date, a devastating condition for which there are yet no effective restorative or curative therapies. The indiscriminate epidemiology of CNS injuries also present issues of negative outlooks regarding quality of life and socioeconomic outcomes of those afflicted. However, the notion that axonal regeneration and functional recovery is possible following CNS injuries has prompted the development of animal models to investigate the anatomical, cellular, and molecular mechanisms underlying the process of repair inhibition following injury. These models also play pivotal roles for testing novel therapeutic techniques for the treatment of CNS injuries with potential translational clinical outcomes.

Although significant strides has been made recently in understanding repair inhibition as well as in the development of novel therapeutic strategies, the variations in types of injuries and their subsequent cellular and molecular response makes the development of a standard treatment strategy for all CNS injuries impossible. Furthermore, It is unlikely that individual therapies will be a solution due to the multifaceted source of repair inhibition present after CNS injuries. It is our opinion that tailored, personalized therapies combining aspects of cellular, molecular and rehabilitative techniques will be the best approach to improve regenerative capacity and functional outcomes following the various types of CNS injuries.

Nonhuman primates remain the best model for the study of CNS injury and repair due to the complexity of their brain as well as anatomical, pathophysiological and behavioral responses to CNS injuries that are more reflective of those in humans compared to non-primate species. To that end, further testing will be required, especially in the NHP models, before an effective therapy can be translated from experimental testing to clinical applications.

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