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Neuronal adhesion and synapse organization in recovery after brain injury

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Abstract

Few specific therapeutic targets exist to manage brain injury, despite the prevalence of stroke or traumatic brain injury. With traumatic brain injury, characteristic neuronal changes include axonal swelling and degeneration, and the loss of synapses, the sites of communication between neurons. This is followed by axonal sprouting and alterations in synaptic markers in recovery. The resulting changes in neuronal connectivity are likely to contribute to the effects of traumatic brain injury on cognitive functions and the underlying mechanisms may represent points of therapeutic intervention. In agreement, animal studies implicate adhesion and signaling molecules that organize synapses as molecular players in neuronal recovery. In this article, the authors focus on the role of cell surface interactions in the recovery after brain injury in humans and animals. The authors review cellular and synaptic alterations that occur with injury and how changes in cell adhesion, protein expression and modification may be involved in recovery. The changes in neuronal surface interactions as potential targets and their possible value for the development of therapeutics are also discussed.

Keywords

brain injury; cellular adhesion; dendritic spines; neuronal adhesion proteins; recovery; repair; synapse organizing proteins; synapses; traumatic brain injury

Traumatic brain injury (TBI) is a devastating problem worldwide. Approximately 2 million head injuries occur each year in the USA, which lead to over 50,000 deaths and approximately 80,000 individuals who survive with severe and permanent neurological dysfunction [1]. Unlike other types of brain injury such as stroke, TBI affects individuals of a broad range of ages. The mainstay of management of acute TBI is regulation of blood pressure and intracranial pressure to avoid secondary injury; however, few specific therapeutic targets exist for improvement of outcomes, such as cognitive deficits or post-traumatic epileptic seizures [2]. Approximately 43% of patients with severe injury develop

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cognitive dysfunction, as measured at 6-months follow-up, lasting for years after injury [3,4]. It is estimated that upwards of 40–50% of patients with severe injury develop post-traumatic seizures in as little as 1 week after injury with epilepsy lasting for years postinjury. Recent clinical trials show promise for potential therapeutics, including amantadine and progesterone [5,6]. However, studies on new and more specific clinical targets resulting in other therapeutics to treat TBI are warranted [7]. The authors propose, based on evidence provided in the studies below, that possible targets for new specific therapeutics include neuronal surface molecules and their signaling pathways. In this review, the authors discuss neuronal adhesion proteins in brain injury, and whether they may be potential targets for treatment after brain trauma.

Neuronal & synaptic changes after brain injury

Depending on the type and severity of injury, the brain regions and cellular components that are affected have been described in humans and animal models [8,9]. There can often be brain swelling, increased intracranial pressure and ischemic damage. After closed head injuries, such as concussion, diffuse brain injury can occur. Diffuse brain injury, as opposed to a focal injury, is widespread and often has no macroscopic findings on brain imaging. However, there is diffuse microscopic damage, such as axonal injury, in multiple regions of the brain. Regions affected by diffuse injury include the cerebral white matter, corpus callosum and the brainstem. In these regions axons are damaged in as little as 2–3 h after injury and damage to synapses, the sites of connections between neurons, can occur. Accumulation of microglia and glial cellular swelling is present within hours after injury, and astrocytosis occurs diffusely within days to weeks. In addition, within hours after injury neuronal cell death can be detected. With focal injury, where the initial insult occurs in a specific area, the brain regions that are subsequently affected include the cortex (i.e., the region of direct injury), the hippocampus and the thalamus (areas affected by secondary injury after TBI) (Figure 1) [10]. Over time, there is cortical tissue loss at the site of injury. Over hours to days, axonal degeneration occurs, and neuronal cell bodies can appear shrunken and surrounded by swollen astrocytes. After 7 days, axonal sprouting occurs in areas of focal injury, indicating recovery after TBI [11].

In addition to axonal injury, there are changes in synapses and dendrites that occur in neurons that survive the initial injury. Multiple studies have shown significant loss of synapses in the days after brain injury, including in the brain regions connected to the site of initial injury, such as the hippocampus [12–14]. Dendritic spines are the postsynaptic protrusions through which neurons receive most of their excitatory input. Gao *et al.* showed in a mouse model that 72 h after TBI, there are fewer dendritic synaptic spines in the hippocampus [12]. The reduction in synaptic spine density after TBI reflects a loss of synapses. In addition, dendritic arbor complexity decreases. These results agree with earlier studies using various models of brain injury in rats, which demonstrated loss of synapses in the cortex and hippocampus after focal brain injury [13,14]. In addition to axonal and synaptic damage, there are changes in mitochondrial morphology, which indicate changes in cellular energy metabolism. Further discussion of these changes are reviewed elsewhere [15].

After brain injury, neuronal plasticity mechanisms required for recovery are only beginning to be understood. Post-traumatic plasticity involves aspects of neurogenesis, angiogenesis, axonal sprouting and synaptic formation and remodeling. Scheff *et al.* and Semchenko *et al.* both showed that synapse number after TBI begins to recover at approximately 10–14 days postinjury, and is nearly completely recovered at 1-month postinjury [13,14]. Regulation of synaptic proteins is most likely involved in postinjury functional adaptation of neurons through improvement of the efficacy of neurotransmitter release from remaining presynaptic

nerve terminals or structural remodeling in terms of new and increased numbers of synaptic terminals [16,17]. Cell adhesion molecules instruct these cellular processes, and are potential targets involving post-traumatic plasticity [16–18]. They comprise a number of select proteins that are present on neuronal processes and synapses. They participate in cell–cell and cell–matrix interactions and can guide the development and structural maintenance of neurites and synapses [19,20]. However, the specific roles of individual cell adhesion molecules in recovery after brain injury are unknown.

By contrast, roles of synaptic adhesion in neuronal development are increasingly understood. These studies have shown that select adhesion molecules span the synaptic cleft of developing and mature synapses, creating an interaction and signaling network between the pre- and post-synaptic membranes of neighboring neurons. These cell surface interactions are critical for proper neuronal communication by organizing developing and mature synapses [20,21]. Appropriate synapse formation is required for the integrated function of the CNS and aberrant dendritic spine formation is associated with cognitive dysfunction and the development of seizures [22,23]. For these reasons, cell adhesion molecules are a promising group of proteins to examine for roles in neuronal recovery after brain injury.

Models of injury

Rodent models of injury & relevance to the human condition

It is critical to understand the need for and basis of experimental injury that models the human condition in order to target potential therapeutics for TBI. The element of TBI in humans that greatly hinders the development of effective therapeutic targets is the enormous heterogeneity of injuries on a macroscopic scale [24]. Animal models of mild, moderate and severe TBI can provide the basis to further understand the cellular and molecular mechanisms of brain injury. The animal models, which are used to replicate human TBI, control for type and severity of injury, age and sex of animals, recovery period and homogeneity of genetic background. While the findings from one animal model cannot be applicable for all types of injuries, animal models will continue to be the cornerstone for discovery and testing of therapeutic targets in humans [25]. Selection of the proper animal model is critically dependent on the type of molecular or pathophysiological question asked. The authors limit this review to the use of rodents as animal models for human brain injury as studies in rats and mice allow for the mechanistic analysis of recovery processes that is the focus of this survey. When making comparisons among studies, differences in pathology and behavioral tests among strains of mice and rats, after TBI, should be considered [26,27].

While cellular processes are similar in the rodent and human brain, there are some striking differences that should be noted. First, the rodent brain is not gyrencephalic, with sulci and gyri, like the human brain. Instead, its cortex is smooth, or lissencephalic. Second, regional brain proportions and positions, connectivity between brain areas and percentages of gray and white matter are markedly different in the rodent versus the human brain. While the physiologic relevance of these differences with respect to human brain injury is not known, the reproducibility of currently used injury models and the generation of data that correlate with many aspects of the human condition support the continued use of rodents in modeling TBI.

Performing & assessing brain injury in rodents

The relevance of different TBI models can be determined by drawing parallels between findings in the human disease process and in different animal experimental models [8]. TBI models are designed to mimic human physiological and pathological conditions with brain injury [25]. A complete discussion of each of the models of TBI is beyond the scope of this

article, and the authors refer the reader to three excellent papers for in-depth review [25,28,29]. Briefly, the most commonly used methods of TBI in experiments reviewed here are direct impact models using penetrating injury with direct contact to the brain or nonpenetrating head injury where the skull remains intact [28]. There are also models of indirect injury, such as blast wave (explosion) injury [30]. Of note, in all these studies the animals are anesthetized to ensure the ethical use of animals in research.

The most commonly used model of direct TBI is fluid percussion injury (FPI) method through a craniotomy. The FPI model causes injury by a piston striking a reservoir of fluid to the surface of intact dura, creating a fluid pressure pulse. Using FPI models in rodents, animals develop: brain edema; intra cranial hemorrhage; neuronal loss; and expansion of injury to other brain regions, including the hippocampus, by 1-week postinjury [31]. Apart from neuronal loss, axons of the remaining neurons are swollen. Synaptophysin, a presynaptic vesicle marker, accumulates at synapse terminals, although the overall level of synaptophysin does not change [32], indicating changes in the cellular trafficking of synaptic proteins. In addition, there is significant spine density loss in the cortex and the dentate gyrus of the hippocampus 24 h after FPI, which provides histological evidence for synaptic dysfunction after TBI [33]. After FPI, animals develop lasting impairments in learning and memory as in humans with brain injury [13,34].

The controlled cortical impact (CCI) model causes injury by a direct impact from a piston to the surface of the intact dura through a craniotomy. An advantage of CCI over FPI is greater control over injury parameters [35]. The histopathology that develops with FPI also develops post-CCI, including significant loss of dendritic spines [12]. Furthermore, because of the fine control over the severity of injury, there is a measurable graded change in pathology and cognitive functions that directly correlates with the degree of CCI [36].

Nonpenetrating injury models mimic closed head injuries. Blast injury models are employed as military personnel are exposed to injury sustained with detonations [30]. With blast injury models, anesthetized animals are typically placed in a compression-driven shock tube. Weight-drop models mimic concussions and a focal blunt head injury is delivered by a weight dropped from a standard height onto the anesthetized animal's intact skull. Both models cause CNS pathophysiology and behavior changes in animals that resemble those found in humans [37].

Different types of brain injury: similarities between models of ischemic stroke & trauma

Much of the cellular and molecular studies on elevated intracranial pressure, hemorrhage and neuronal tissue injury (as seen in TBI) are derived from experimental work from models of cerebral ischemia after stroke [9]. The initial mechanisms of injury for the two types of complex disease processes of stroke and TBI are very different, but there are striking similarities with respect to subsequent pathophysiology.

Stroke, most frequently caused by a thrombotic disease of arteries, results in severe and acute decreases in blood flow to brain tissue [38]. Ischemic injury to neurons ensues because they do not store alternative energy sources; metabolic imbalance quickly follows. With metabolic stress, there is failure of membrane ionic pumps and cellular swelling results. Cellular/axonal swelling is detrimental, causing increases in intracranial pressure and further decreases in cerebral blood flow. Focal brain ischemia, which occurs in ischemic stroke in humans, can be modeled by occlusion of the middle cerebral artery (MCAO) in rodents [39]. The cellular pathology and physiology that result from this model of cerebral ischemia include: elevated intracranial pressure; neuronal loss; axonal swelling; accumulation of synaptophysin at synapse terminals; and importantly, a marked loss of synaptic spines directly related to the severity of ischemic injury [40]. In this review, we will include studies

on models of cerebral ischemia and cell adhesion molecules because of the similarities between injury caused by ischemia and trauma on the cellular level.

Cell adhesion molecules in brain injury & recovery

Even though TBI consequences are highly heterogeneous on a macroscopic scale, the shared molecular and cellular alterations suggest that general points of intervention exist. Specifically, changes in the types of transmembrane proteins that serve as neuronal adhesion molecules, as described below, have been measured in models of brain injury (Table 1). The alterations of cell adhesion and signaling molecules in response to injury point to the potentially important roles they may play in postinjury pathophysiology and recovery (Figure 2). Beyond the scope of this review are non-neuronal vascular and glial cell adhesion proteins, extracellular matrix adhesion proteins and a variety of secreted proteins that have been implicated in TBI-associated changes in histopathology, physiology or behavior in animals. We refer the reader to two excellent papers on these classes of proteins [41,42].

Plexins/semaphorins/neuropilin signaling complexes

Plexins are a family of transmembrane molecules present in neurons that function as signaling receptors together with the coreceptors neuropilin-1 and -2 [43]. The primary ligands of plexins are semaphorins, including soluble and transmembrane forms of the protein family [43,44]. This group of signaling molecules is implicated in a variety of important functions, including but not limited to axon guidance, axonal pruning, spine morphogenesis and the restriction of synapse formation [45,46]. All three molecule families, plexins, neuropilins and semaphorins, have been implicated in recovery after brain injury.

The role of semaphorins in brain injury and recovery in the adult mammal is only starting to be revealed. In a functional study by Pekcec *et al.*, adult mice were subjected to MCAO injury, and 7 days later were treated with the soluble neuropilin-1 ligand, semaphorin 3A, which was injected into the striatum [47]. A total of 7 days after semaphorin 3A treatment, measurement of cortical injury volume showed that semaphorin 3A treatment causes an approximate 50% increase in tissue injury volume compared with controls. Tentatively, these results indicate that elevated semaphorin 3A negatively impacts recovery after cerebral ischemia and brain injury. Consistent with the disease relevance of this result, another study employed a more severe model of cerebral ischemia, the four vessel occlusion model, and found a significant upregulation of semaphorin 4C in both the dentate gyrus of the hippocampus and the sub ventricular zone at 7 and 14 days postinjury [48]. This increased expression returned to normal in the hippocampus or even decreased compared with controls in the subventricular zone by 30 days postinjury. While it is unclear if this increase is beneficial or detrimental postinjury, these data support the hypothesis that semaphorins are playing a significant role in the days after TBI. Besides those discussed here, few current functional studies on semaphorins after brain injury exist; however, functional studies on semaphorins after spinal cord injury have already been performed. Kaneko *et al.*, performed complete transection of spinal cords of adult rats, and treated the postlesioned cord with intrathecal semaphorin 3A inhibitor for 4 weeks after injury [49]. Treatment with the semaphorin 3A inhibitor not only increased axon regeneration, but also improved functional recovery as measured by hind limb movement after cord transection.

A role for the semaphoring coreceptor, neuropilin, in recovery after injury was supported by a second MCAO study. Whitehead *et al.* measured neuropilin-1 in the ipsilateral and contralateral cortices of adult mice and found that neuropilin-1 was elevated by 1-h postinjury and remained elevated at 6-h postinjury compared with the contra lateral cortex and sham animals [50]. However, by 24 h, the levels were returned to sham-operated levels,

although it did appear that the ipsilateral cortical levels remained slightly elevated above the contralateral side at that time point. Neuropilin-1 is involved in axon guidance and pruning during brain development. Considering the potential contribution of proteins that serve in axonal development to the recovery after TBI, one may therefore speculate that regulating signals for axonal pruning may be important immediately after injury of the adult brain.

Neuropilin-2 has also been shown to regulate axonal guidance and pruning in the hippocampus [46]. Svetlov *et al.* employed various blast injury paradigms in adult rats and measured the levels of neuropilin-2 both in the hippocampus and in serum at 1 and 7 days postinjury [51]. They found that neuropilin-2 protein amounts were increased in the hippocampus compared with naive animals at both 1 and 7 days. Neuropilin-2 was also increased in the serum at 1 and 7 days, indicating that compromise of the blood–brain barrier soon after blast injury may allow the measurement of neuropilin-2 in the serum and allow for its use as a biomarker of TBI. It needs to be noted that plexin A3 mRNA was reported to be decreased at 4 and 24 h after CCI in the ipsilateral hippocampus. While changes in mRNA do not linearly track changes in protein expression, this indicates dynamic changes in the molecular composition of these signaling complexes after TBI that can involve up- and down-regulation of its components.

Taken together, these results indicate that this group of important proteins, plexins, neuropilins and semaphorins, plays a role in both the acute phase 24 h after injury, and the recovery phase 7–14 days after injury.

Neural cell adhesion molecule and polysialylated neural cell adhesion molecule

Neural cell adhesion molecule (NCAM) is a transmembrane cellular adhesion protein, with its extracellular portion composed of immunoglobulin-like domains for binding [17]. NCAM can be enzymatically modified by the addition of large polysialic acid (PSA) carbohydrate moieties to an extracellular immunoglobulin domain to generate PSA-NCAM [52]. NCAM binds homophilically and it also binds other cell adhesion molecules (heterophilic binding), while the PSA modification interferes with adhesion. NCAM and PSA-NCAM are involved in proper neurite outgrowth and network connectivity in the developing rodent brain [53,54].

PSA-NCAM also plays a role in recovery after TBI. Emery *et al.* performed moderate FPI in adult rats and measured PSA-NCAM-positive neurons in the dentate gyrus of the hippocampus at specific time points after injury [55]. They found a fourfold increase in the number of PSA-positive neurons at 48-h postinjury compared with uninjured control animals. PSA-positive neurons remained elevated at 2-weeks postinjury. At 1-month postinjury, the number of PSA-NCAM-expressing neurons had returned to control levels. This surge in PSA-NCAM-expressing neurons indicates that this surface protein may contribute to cellular remodeling in the hippocampus after brain injury. Similarly, Budinich *et al.* performed an extensive study on PSA-NCAM after brain injury in adult mice [56]. Their results in a CCI model confirm that PSA-NCAM is increased in the ipsilateral cortex and hippocampus at 1-week postinjury, and this persists up to 3 weeks.

An increase in PSA-NCAM also occurs postinjury in the middle cerebral artery occlusion model. Cerebral ischemia caused an increase in neuronal expression of PSA-NCAM in the cortex of rats at 1-h postinjury and PSA-NCAM remained elevated for at least 3 days postinjury [57]. Given the consistent increase in PSA-NCAM across three models of brain injury, it is possible that this upregulation is a general physiologic response to injury. More studies need to be undertaken, perhaps on conditional knockout mice lacking NCAM- or PSA- modifying enzymes, to understand the consequences of dysregulation of these adhesion molecules and their post-translational modification in brain injury.

Of note, NCAM-dependent responses to injury may not only include cellular remodeling, but also effects on neuronal migration. Decker *et al.* showed that in both NCAM-deficient mice and in PSA-depleted mice there is an enhanced migration of neuronal progenitor cells to the site of lesions [58]. Furthermore, Battista *et al.* reported that PSA depletion causes increased recruitment and migration of neuroblasts to sites of injection [59]. Together, these studies support the idea that PSA-NCAM contributes to promoting recovery after brain injury.

Eph receptors & ephrins

Eph receptors are transmembrane receptor tyrosine kinases that bind ephrins [60,61]. This signaling system has roles in axon guidance and regulation of synaptic function by modulating dendritic spine formation and synaptic strength [19,60–62]. Owing to the accumulation of Ephs and ephrins at lesions of the CNS, they were hypothesized to regulate recovery of neuronal function after injury [63,64].

Indeed, two separate studies using models of cerebral injury and ischemia have reported changes in Ephrin/Eph levels. Li *et al.* used a four-vessel occlusion model of cerebral ischemia in adult rats and measured Ephrin3A and EphA4 protein levels in the CA1 region of the hippocampus [65]. Ephrin3A increased by approximately 2.5-times and EphA4 more than tripled at 6 h, and both remained elevated at 24 h. In this same study, neuronal cell death was measured in the hippocampus 72 h after ischemic injury, and the authors found that using an EphA4-blocking antibody, they were able to attenuate apoptosis. However, Doeppner *et al.* showed that loss of EphrinB3 in mice results in a significant increase in ischemic injury after MCAO [66]. This apparent difference in outcome to the block of EphA4 function may reflect the different biological roles of these proteins. Furthermore, there is enhanced neurogenesis after MCAO in EphrinB3-knockout mice [66]. These results indicate that improved neurogenesis after injury may worsen functional outcomes.

Interestingly, a report on human brain tissue after TBI showed an upregulation of EphA4 density by immunohistochemistry that seemed to predominate in GFAP-positive astrocytes [67]. Furthermore, phospho-EphA4 was upregulated in a time-dependent fashion after injury, indicating signaling changes in disease. This study implicates EphA4 in glia as a potential mediator of plasticity after brain injury in humans.

Biervert *et al.* used a rat model of subdural hematoma, which frequently occurs with TBI, to survey mRNA levels of different Eph isoforms in the cortex of injured rats [68]. They found that mRNA for EphB1 was increased at 7 days, but trended toward normal by 18- and 28 days postinjury. These findings indicate that therapeutics targeting this signaling pathway may be of value in treating tissue injury after the development of subdural hematoma.

Theus *et al.* showed that after moderate CCI in adult mice, EphB3 expression in the subventricular zone decreased; this was paired with an increase in cell proliferation in the same area [69]. In this same study, after moderate CCI in EphrinB3- or EphB3-knockout mice, there was an increase in stem cell proliferation, indicating that Ephrins and EphB3 may be involved in cell death regulation, and repair and regeneration after TBI. While the models of injury are different in these studies described, each show alterations in the Eph/ephrin signaling pathway, indicating that these molecules are involved in recovery after injury.

Neurexins & neuroligins

Neurexins are presynaptic adhesion molecules at excitatory and inhibitory synapses of the CNS [19,70,71]. The binding of neurexins to different partners across the synaptic cleft,

such as neuroligins, guides the maturation of excitatory and inhibitory synapses. Based on these findings, it is plausible to test for changes in neurexins and neuroligins with neuronal repair and remodeling after brain injury. Indeed, two groups employed gene array technology to measure changes in multiple potential targets in the hippocampus and cortex after a moderate to severe brain injury [72,73]. Both studies utilized the CCI model of TBI, and found that neurexin 1- β mRNA is decreased after 24 h. Brain injury may not only alter the expression of adhesion molecules but also impact their extracellular interactions as indicated by a study of Li *et al.* [74]. This study provides evidence of a rapidly increased interaction between neurexin and neuroligin-1 in a model of cerebral ischemia.

Cadherins

Cadherins, specifically N-cadherin, are a family of abundant cell adhesion molecules in the brain. N-cadherin is a transmembrane glycoprotein that spans the synaptic cleft presynaptically to bind homophilically to postsynaptic N-cadherin. N-cadherin is involved in synapse maturation and remodeling once synapses are formed [75–77].

Using either unilateral entorhinal cortex injury or a combined FPI with bilateral entorhinal cortical lesions, Warren *et al.* measured N-cadherin levels after recovery [78]. They showed that 2 and 7 days postinjury, N-cadherin protein is decreased in the ipsilateral rat hippocampus in animals with only entorhinal cortical lesions. At 15 days, this decrease is reversed, with N-cadherin increasing by approximately 25%. In the injury model employing both FPI and entorhinal cortical lesions, N-cadherin is also decreased at 2 and 7 days postinjury and its level returns to baseline after this injury, without a subsequent increase. These results suggest that N-cadherin is involved in recovery after TBI, and that this protein may play different roles in synaptic modulation after injury.

N-cadherin also plays a role in ischemic injury. Using an MCAO model of cerebral ischemia, Jang *et al.* delivered a 1-h ischemic injury to the rat brain, followed by reperfusion; the experimenters measured N-cadherin in the cortex 24 h postinjury [79]. They found that there was a significant increase in the extracellular cleaved portion of N-cadherin, but not total N-cadherin, on the ipsilateral side of injury. The authors speculate that in the intact, injured animal brain, cleavage of N-cadherin may be critical for repair of damaged neurons and for neuronal plasticity in recovery after ischemic injury or trauma. Warren *et al.* found that there were decreases in full-length N-cadherin after 2 days postinjury, which could be linked to this increase in the extracellular portion reported by Jang *et al.* and agrees with the possibility that rapidly increased proteolytic processing of N-cadherin occurs after injury [78,79].

Other potential adhesion molecules as targets in TBI

It is likely that other molecules involved in neuronal cell adhesion, synaptogenesis and synaptic remodeling are critical in recovery after TBI. Specifically, adhesion proteins that are targets of matrix metalloproteinases may be involved in synapse reorganization and recovery after brain injury [78]. In experiments on N-cadherins described above, Warren *et al.* measured the increase of a matrix metalloproteinase, ADAM-10, for which N-cadherin is a substrate. ADAM-10 levels were elevated at 2 and 7 days postinjury (MCAO) during the same period when N-cadherin was decreased [78]. These results suggest an important role for matrix metalloproteinases in neuronal surface remodeling and point to roles of other metalloproteinase substrates after TBI. Therefore, it may be beneficial to specifically study other substrates of ADAM-10 and matrix metalloproteinases, including the synapse-inducing adhesion proteins SynCAM1 and -2 [80]. SynCAM1 stabilizes nascent synaptic contact sites [81], and elevated SynCAM1 increases functional excitatory synapse number in the mature nervous system, while loss of SynCAM1 decreases the number of excitatory

synapses [82]. The fact that SynCAM1 can also be modified with PSA may contribute to the effects of PSA removal on neuronal recovery [83]. Although no studies on brain injury have specifically examined alterations in SynCAMs, there have been studies on motor neuron injury in the spinal cord. Zelano *et al.* showed that SynCAM1 expression decreased after motor neuron injury prior to synapse loss and then increased prior to the formation of new synapses in recovering neurons [84,85]. This indicates that SynCAM1 may play roles in neuronal recovery after injury.

Conclusion

This review assesses current brain injury models and the value of neuronal and synaptic cell adhesion molecules as potential targets for future therapeutics. The use of models such as FPI and CCI are critical for our understanding of the cellular, molecular and physiologic events that occur with TBI far away from the actual injury site. These models allow for exquisite control over injury parameters such as animal type, injury severity, days post injury and brain regions studied. From the data reviewed here, the common theme emerging is that brain injury can cause significant changes in the expression and processing of neuronal surface proteins, including those that are present at synapses. These cell adhesion and signaling molecules are likely to be critical in the wave of neuronal and synaptic remodeling that must occur for individuals to recover after brain insult. While further studies are warranted to determine the potential of these synaptic adhesion molecules as therapeutic targets, these results support the hypothesis that proteins that organize developing synapses also have roles in the recovery of adult neurons after injury. Of particular interest will be to test whether the signaling pathways downstream of these molecules can be targeted to improve outcomes in humans after TBI [21].

Future perspective

The investigation of neuronal adhesion molecules in human brain injury is in its early stages. While there are multiple studies referenced here that touch upon their expression after experimental TBI, the functional contributions of these molecules to neuronal recovery or functional recovery remain to be defined. While few such studies in TBI are available, there are at least two functional studies in spinal cord injury that implicate cell surface molecules that mediate neuronal signaling in functional recovery after injury. First, as mentioned above, Kaneko *et al.* show that Semaphorin 3A inhibition improves spontaneous limb movement 14 weeks after spinal cord transection [49]. Second, Goldshmit *et al.* show that blocking EphA4 after spinal cord hemisection improves walking, climbing and grip strength in animals 6 weeks after injury [86]. Clearly, functional studies after TBI are needed, especially considering the repeated failures of less specific types of therapies that have been trialed in human medicine [7,24,87].

One important benchmark for future work will be to gain insight into the relationship of cell adhesion molecules and their roles in synaptic remodeling after injury. Moreover, while general studies on cognitive deficits and post-traumatic epilepsy in animal models are available, the role of cell adhesion molecules in these sequelae remains to be addressed. An important consideration is that most studies of animal pathophysiology and behavior are limited to periods ranging from 1 day to 2 weeks of injury, with maximum time courses extending out to 1–2 months. However, cognitive deficits and post-traumatic epilepsy are present at months and very often years after the primary injury. Therefore, studies that extend several months in animals will allow us to better understand the roles of cell surface interactions in recovery.

In terms of potential therapeutic strategies and interventions, the data presented here inspire multiple ideas. As described above, there are already two potential inhibitors for semaphorin 3A and EphA4 that have been employed in spinal cord injury. These compounds could now be used in one of the models of TBI presented above to determine whether these are effective compounds for treatment. In addition, blocking antibodies for adhesion proteins such as Syn-CAM1 are commercially available and have the potential to be therapeutics. As shown by Decker *et al.*, compounds that remove PSA could also be employed in models of injury to test whether functional outcomes are improved [58].

While compounds targeting adhesion and signaling proteins are exciting potential therapeutics, one also must consider other mechanisms of therapy after brain injury that have been shown to improve outcomes after TBI, notably environmental enrichment [88]. The mechanism by which environmental enrichment improves outcomes after injury is not known, but may involve the remodeling of synaptic connectivity [89], and it is likely that cell adhesion molecules, such as PSA-NCAM, are playing a role [90]. Therefore, a more complete survey of adhesion proteins after TBI in the setting of environmental enrichment to improve outcomes is warranted.

The list of cell adhesion proteins, which may be critical players in recovery after brain injury, is probably incomplete. Furthermore, molecules that perform post-translational modifications or proteolytic processing of these membrane proteins may be important as well. As described above, data suggest an important role for matrix metalloproteinases in neuronal surface remodeling and point to roles of other metalloproteinase substrates in injury response. We suggest these may be among the targets upon which to focus in studies on TBI.

Together, functional studies can now test the emerging theme that neuronal adhesion proteins that guide developmental processes may be involved in injury and recovery responses of neurons in the adult brain. The progress reviewed here allows us to address important new questions. These questions include whether cell adhesion molecules are cleaved in the acute phase of brain injury as damaged cells, whether tissues undergo remodeling and to what extent synapse-organizing adhesion and signaling proteins contribute to the restoration of neuronal connectivity in later stages.

References

Papers of special note have been highlighted as:

■ of interest

■ ■ of considerable interest

1. Rosenfeld JV, Maas AI, Bragge P, Morganti-Kossmann MC, Manley GT, Gruen RL. Early management of severe traumatic brain injury. *Lancet*. 2012; 380(9847):1088–1098. [PubMed: 22998718]
2. ■ ■. Brain Trauma Foundation; American Association of Neurological Surgeons; Congress of Neurological Surgeons. Guidelines for the management of severe traumatic brain injury. *J Neurotrauma*. 2007; 24(Suppl 1):S1–S106. Excellent review of evidence-based clinical practice for clinicians treating individuals with severe traumatic brain injury.
3. Tate RL, Broe GA, Lulham JM. Impairment after severe blunt head injury: the results from a consecutive series of 100 patients. *Acta Neurol Scand*. 1989; 79(2):97–107. [PubMed: 2711827]
4. Lowenstein DH. Epilepsy after head injury: an overview. *Epilepsia*. 2009; 50(Suppl 2):4–9. [PubMed: 19187288]

5. Giacino JT, Whyte J, Bagiella E, et al. Placebo-controlled trial of amantadine for severe traumatic brain injury. *N Engl J Med*. 2012; 366(9):819–826. [PubMed: 22375973]
6. Ma J, Huang S, Qin S, You C. Progesterone for acute traumatic brain injury. *Cochrane Database Syst Rev*. 2012; 10:CD008409. [PubMed: 23076947]
7. Maas AI, Marmarou A, Murray GD, Teasdale SG, Steyerberg EW. Prognosis and clinical trial design in traumatic brain injury: the IMPACT study. *J Neurotrauma*. 2007; 24(2):232–238. Excellent overview of trials for the treatments of head injury. [PubMed: 17375987]
8. Hardman JM, Manoukian A. Pathology of head trauma. *Neuroimag Clin N Am*. 2002; 12(2):175–187. vii.
9. Bramlett HM, Dietrich WD. Pathophysiology of cerebral ischemia and brain trauma: similarities and differences. *J Cereb Blood Flow Metab*. 2004; 24(2):133–150. [PubMed: 14747740]
10. Chen S, Pickard JD, Harris NG. Time course of cellular pathology after controlled cortical impact injury. *Exp Neurol*. 2003; 182(1):87–102. [PubMed: 12821379]
11. Harris NG, Mironova YA, Hovda DA, Sutton RL. Pericontusion axon sprouting is spatially and temporally consistent with a growth-permissive environment after traumatic brain injury. *J Neuropathol Exp Neurol*. 2010; 69(2):139–154. [PubMed: 20084019]
12. Gao X, Deng P, Xu ZC, Chen J. Moderate traumatic brain injury causes acute dendritic and synaptic degeneration in the hippocampus dentate gyrus. *PLoS ONE*. 2011; 6(9):e24566. [PubMed: 21931758]
13. Scheff SW, Price DA, Hicks RR, Baldwin SA, Robinson S, Brackney C. Synaptogenesis in the hippocampal CA1 field following traumatic brain injury. *J Neurotrauma*. 2005; 22(7):719–732. Comprehensive study examining synapse changes after controlled cortical impact model of injury in rodents. [PubMed: 16004576]
14. Semchenko VV, Bogolepov NN, Stepanov SS, Maksimishin SV, Khizhnyak AS. Synaptic plasticity of the neocortex of white rats with diffuse-focal brain injuries. *Neurosci Behav Physiol*. 2006; 36(6):613–618. [PubMed: 16783514]
15. Balan IS, Saladino AJ, Aarabi B, et al. Cellular alterations in human traumatic brain injury: changes in mitochondrial morphology reflect regional levels of injury severity. *J Neurotrauma*. 2013; 30(5):367–381. [PubMed: 23131111]
16. Keyvani K, Schallert T. Plasticity-associated molecular and structural events in the injured brain. *J Neuropathol Exp Neurol*. 2002; 61(10):831–840. [PubMed: 12387449]
17. Kiss JZ, Troncoso E, Djebbara Z, Vutskits L, Muller D. The role of neural cell adhesion molecules in plasticity and repair. *Brain Res Rev*. 2001; 36(2–3):175–184. [PubMed: 11690614]
18. Yakovlev AG, Faden AI. Molecular biology of CNS injury. *J Neurotrauma*. 1995; 12(5):767–777. [PubMed: 8594206]
19. Missler M, Sudhof TC, Biederer T. Synaptic cell adhesion. *Cold Spring Harb Persp Biol*. 2012; 4(4):a005694. Excellent overview of the molecules discussed in this review.
20. Giagtzoglou N, Ly CV, Bellen HJ. Cell adhesion, the backbone of the synapse: ‘vertebrate’ and ‘invertebrate’ perspectives. *Cold Spring Harb Persp Biol*. 2009; 1(4):a003079.
21. Biederer T, Stagi M. Signaling by synaptogenic molecules. *Curr Opin Neurobiol*. 2008; 18(3):261–269. [PubMed: 18725297]
22. Penzes P, Cahill ME, Jones KA, Vanleeuwen JE, Woolfrey KM. Dendritic spine pathology in neuropsychiatric disorders. *Nat Neurosci*. 2011; 14(3):285–293. [PubMed: 21346746]
23. Prince DA, Parada I, Scalise K, Graber K, Jin X, Shen F. Epilepsy following cortical injury: cellular and molecular mechanisms as targets for potential prophylaxis. *Epilepsia*. 2009; 50(Suppl 2):30–40. [PubMed: 19187292]
24. Saatman KE, Duhaime AC, Bullock R, Maas AI, Valadka A, Manley GT. Classification of traumatic brain injury for targeted therapies. *J Neurotrauma*. 2008; 25(7):719–738. [PubMed: 18627252]
25. Xiong Y, Mahmood A, Chopp M. Animal models of traumatic brain injury. *Nat Rev Neurosci*. 2013; 14(2):128–142. [PubMed: 23329160]
26. Tan AA, Quigley A, Smith DC, Hoane MR. Strain differences in response to traumatic brain injury in Long-Evans compared with Sprague-Dawley rats. *J Neurotrauma*. 2009; 26(4):539–548. [PubMed: 19216636]

27. Fox GB, Levasseur RA, Faden AI. Behavioral responses of C57BL/6, FVB/N, and 129/SvEMS mouse strains to traumatic brain injury: implications for gene targeting approaches to neurotrauma. *J Neurotrauma*. 1999; 16(5):377–389. [PubMed: 10369558]
28. Cernak I. Animal models of head trauma. *NeuroRx*. 2005; 2(3):410–422. Exceptional review of currently used models of traumatic brain injury in animals. [PubMed: 16389305]
29. Laurer HL, McIntosh TK. Experimental models of brain trauma. *Curr Opin Neurol*. 1999; 12(6): 715–721. [PubMed: 10676754]
30. Cernak I, Noble-Haeusslein LJ. Traumatic brain injury: an overview of pathobiology with emphasis on military populations. *J Cereb Blood Flow Metab*. 2010; 30(2):255–266. [PubMed: 19809467]
31. Hicks R, Soares H, Smith D, McIntosh T. Temporal and spatial characterization of neuronal injury following lateral fluid-percussion brain injury in the rat. *Acta Neuropathol*. 1996; 91(3):236–246. [PubMed: 8834535]
32. Shoji H, Kibayashi K. Changes in localization of synaptophysin following fluid percussion injury in the rat brain. *Brain Res*. 2006; 1078(1):198–211. [PubMed: 16497279]
33. Campbell JN, Register D, Churn SB. Traumatic brain injury causes an FK506-sensitive loss and an overgrowth of dendritic spines in rat forebrain. *J Neurotrauma*. 2012; 29(2):201–217. [PubMed: 21517673]
34. Hamm RJ. Neurobehavioral assessment of outcome following traumatic brain injury in rats: an evaluation of selected measures. *J Neurotrauma*. 2001; 18(11):1207–1216. [PubMed: 11721739]
35. Dixon CE, Clifton GL, Lighthall JW, Yaghami AA, Hayes RL. A controlled cortical impact model of traumatic brain injury in the rat. *J Neurosci Methods*. 1991; 39(3):253–262. [PubMed: 1787745]
36. Saatman KE, Feeko KJ, Pape RL, Raghupathi R. Differential behavioral and histopathological responses to graded cortical impact injury in mice. *J Neurotrauma*. 2006; 23(8):1241–1253. [PubMed: 16928182]
37. Garman RH, Jenkins LW, Switzer RC 3rd, et al. Blast exposure in rats with body shielding is characterized primarily by diffuse axonal injury. *J Neurotrauma*. 2011; 28(6):947–959. [PubMed: 21449683]
38. Barash, PG.; Cullen, BF.; Stoelting, RK.; Cahalan, MK.; Stock, MC. Clinical anesthesia. 6th. Wolters Kluwer, Lippincott Williams & Wilkins; PA, USA: 2009.
39. Chen ST, Hsu CY, Hogan EL, Maricq H, Balentine JD. A model of focal ischemic stroke in the rat: reproducible extensive cortical infarction. *Stroke*. 1986; 17(4):738–743. [PubMed: 2943059]
40. Zhang S, Boyd J, Delaney K, Murphy TH. Rapid reversible changes in dendritic spine structure *in vivo* gated by the degree of ischemia. *J Neuroscience*. 2005; 25(22):5333–5338.
41. Knobloch SM, Faden AI. Administration of either anti-intercellular adhesion molecule-1 or a nonspecific control antibody improves recovery after traumatic brain injury in the rat. *J Neurotrauma*. 2002; 19(9):1039–1050. [PubMed: 12482117]
42. Chen G, Shi J, Hu Z, Hang C. Inhibitory effect on cerebral inflammatory response following traumatic brain injury in rats: a potential neuroprotective mechanism of *N*-acetylcysteine. *Mediators Inflamm*. 2008; 2008:716458. [PubMed: 18483565]
43. Kolodkin AL, Tessier-Lavigne M. Mechanisms and molecules of neuronal wiring: a primer. *Cold Spring Harb Persp Biol*. 2011; 3(6) pii: a001727.
44. Pasterkamp RJ. Getting neural circuits into shape with semaphorins. *Nat Rev Neurosci*. 2012; 13(9):605–618. [PubMed: 22895477]
45. Tran TS, Rubio ME, Clem RL, et al. Secreted semaphorins control spine distribution and morphogenesis in the postnatal CNS. *Nature*. 2009; 462(7276):1065–1069. [PubMed: 20010807]
46. Bagri A, Cheng HJ, Yaron A, Pleasure SJ, Tessier-Lavigne M. Stereotyped pruning of long hippocampal axon branches triggered by retraction inducers of the semaphorin family. *Cell*. 2003; 113(3):285–299. [PubMed: 12732138]
47. Pekcec A, Yigitkanli K, Jung JE, et al. Following experimental stroke, the recovering brain is vulnerable to lipoxygenase-dependent semaphorin signaling. *FASEB J*. 2013; 27(2):437–445. Demonstrating that semaphorin 3A treatment worsens brain injury volume after occlusion of the middle cerebral artery model of stroke. [PubMed: 23070608]

48. Wu H, Fan J, Zhu L, et al. *Sema4C* expression in neural stem/progenitor cells and in adult neurogenesis induced by cerebral ischemia. *J Mol Neurosci.* 2009; 39(1–2):27–39. [PubMed: 19189244]
49. Kaneko S, Iwanami A, Nakamura M, et al. A selective *Sema3A* inhibitor enhances regenerative responses and functional recovery of the injured spinal cord. *Nat Med.* 2006; 12(12):1380–1389. [PubMed: 17099709]
50. Whitehead SN, Gangaraju S, Slinn J, Hou ST. Transient and bilateral increase in Neuropilin-1, *Fer* kinase and collapsin response mediator proteins within membrane rafts following unilateral occlusion of the middle cerebral artery in mouse. *Brain Res.* 2010; 1344:209–216. [PubMed: 20493826]
51. Svetlov SI, Prima V, Glushakova O, et al. Neuro-glial and systemic mechanisms of pathological responses in rat models of primary blast overpressure compared with ‘composite’ blast. *Front Neurol.* 2012; 3:15. [PubMed: 22403567]
52. Colley KJ. Structural basis for the polysialylation of the neural cell adhesion molecule. *Adv Exp Med Biol.* 2010; 663:111–126. [PubMed: 20017018]
53. Takei K, Chan TA, Wang FS, Deng H, Rutishauser U, Jay DG. The neural cell adhesion molecules L1 and NCAM-180 act in different steps of neurite outgrowth. *J Neuroscience.* 1999; 9(21):9469–9479.
54. Seki T, Rutishauser U. Removal of polysialic acid-neural cell adhesion molecule induces aberrant mossy fiber innervation and ectopic synaptogenesis in the hippocampus. *J Neuroscience.* 1998; 18(10):3757–3766.
55. Emery DL, Raghupathi R, Saatman KE, Fischer I, Grady MS, McIntosh TK. Bilateral growth-related protein expression suggests a transient increase in regenerative potential following brain trauma. *J Comp Neurol.* 2000; 424(3):521–531. [PubMed: 10906717]
56. Budinich CS, Chen H, Lowe D, Rosenberger JG, Bernstock JD, McCabe JT. Mouse brain PSA–NCAM levels are altered by graded-controlled cortical impact injury. *Neural Plast.* 2012; 2012 Article ID 378307. Comprehensive study of polysialic acid–neural cell adhesion molecule levels in neurons of different brain regions at varying timepoints and injury severity after traumatic brain injury.
57. Hayashi T, Seki T, Sato K, et al. Expression of polysialylated neural cell adhesion molecule in rat brain after transient middle cerebral artery occlusion. *Brain Res.* 2001; 907(1–2):130–133. [PubMed: 11430894]
58. Decker L, Durbec P, Rougon G, Baron-Van Evercooren A. Loss of polysialic residues accelerates CNS neural precursor differentiation in pathological conditions. *Mol Cell Neurosci.* 2002; 19(2):225–238. [PubMed: 11860275]
59. Battista D, Rutishauser U. Removal of polysialic acid triggers dispersion of subventricularly derived neuroblasts into surrounding CNS tissues. *J Neuroscience.* 2010; 30(11):3995–4003.
60. Hruska M, Dalva MB. Ephrin regulation of synapse formation, function and plasticity. *Mol Cell Neurosci.* 2012; 50(1):35–44. [PubMed: 22449939]
61. Klein R. Bidirectional modulation of synaptic functions by Eph/ephrin signaling. *Nat Neurosci.* 2009; 12(1):15–20. [PubMed: 19029886]
62. Kayser MS, Nolt MJ, Dalva MB. EphB receptors couple dendritic filopodia motility to synapse formation. *Neuron.* 2008; 59(1):56–69. [PubMed: 18614029]
63. Du J, Fu C, Sretavan DW. Eph/ephrin signaling as a potential therapeutic target after central nervous system injury. *Curr Pharm Des.* 2007; 13(24):2507–2518. [PubMed: 17692019]
64. Goldshmit Y, Mclenachan S, Turnley A. Roles of Eph receptors and ephrins in the normal and damaged adult CNS. *Brain Res Rev.* 2006; 52(2):327–345. [PubMed: 16774788]
65. Li J, Liu N, Wang Y, Wang R, Guo D, Zhang C. Inhibition of EphA4 signaling after ischemia-reperfusion reduces apoptosis of CA1 pyramidal neurons. *Neurosci Lett.* 2012; 518(2):92–95. [PubMed: 22580205]
66. Doeppner TR, Bretschneider E, Doebring M, et al. Enhancement of endogenous neurogenesis in ephrin-B3 deficient mice after transient focal cerebral ischemia. *Acta Neuropathol.* 2011; 122(4):429–442. [PubMed: 21779764]

67. Frugier T, Conquest A, Mclean C, Currie P, Moses D, Goldshmit Y. Expression and activation of EphA4 in the human brain after traumatic injury. *J Neuropathol Exp Neurol*. 2012; 71(3):242–250. [PubMed: 22318127]
68. Biervert C, Horvath E, Fahrig T. Semiquantitative expression analysis of ephrine-receptor tyrosine kinase mRNA's in a rat model of traumatic brain injury. *Neurosci Lett*. 2001; 315(1–2):25–28. [PubMed: 11711206]
69. Theus MH, Ricard J, Bethea JR, Liebl DJ. EphB3 limits the expansion of neural progenitor cells in the subventricular zone by regulating p53 during homeostasis and following traumatic brain injury. *Stem Cells*. 2010; 28(7):1231–1242. [PubMed: 20496368]
70. Sudhof TC. Neuroligins and neuroligins link synaptic function to cognitive disease. *Nature*. 2008; 455(7215):903–911. [PubMed: 18923512]
71. Huang ZJ, Scheiffele P. GABA and neuroligin signaling: linking synaptic activity and adhesion in inhibitory synapse development. *Curr Opin Neurobiol*. 2008; 18(1):77–83. [PubMed: 18513949]
72. Raghavendra Rao VL, Dhodda VK, Song G, Bowen KK, Dempsey RJ. Traumatic brain injury-induced acute gene expression changes in rat cerebral cortex identified by GeneChip analysis. *J Neurosci Res*. 2003; 71(2):208–219. [PubMed: 12503083]
73. Matzilevich DA, Rall JM, Moore AN, Grill RJ, Dash PK. High-density microarray analysis of hippocampal gene expression following experimental brain injury. *J Neurosci Res*. 2002; 67(5):646–663. [PubMed: 11891777]
74. Li C, Han D, Zhang F, Zhou C, Yu HM, Zhang GY. Preconditioning ischemia attenuates increased neuroligin-1-PSD-95 interaction after transient cerebral ischemia in rat hippocampus. *Neurosci Lett*. 2007; 426(3):192–197. [PubMed: 17904739]
75. Jungling K, Eulenburg V, Moore R, Kemler R, Lessmann V, Gottmann K. N-cadherin transsynaptically regulates short-term plasticity at glutamatergic synapses in embryonic stem cell-derived neurons. *J Neuroscience*. 2006; 26(26):6968–6978.
76. Mendez P, De Roo M, Poglia L, Klauser P, Muller D. N-cadherin mediates plasticity-induced long-term spine stabilization. *J Cell Biol*. 2010; 189(3):589–600. [PubMed: 20440002]
77. Bozdagi O, Wang XB, Nikitczuk JS, et al. Persistence of coordinated long-term potentiation and dendritic spine enlargement at mature hippocampal CA1 synapses requires N-cadherin. *J Neuroscience*. 2010; 30(30):9984–9989.
78. Warren KM, Reeves TM, Phillips LL. MT5-MMP, ADAM-10, and N-cadherin act in concert to facilitate synapse reorganization after traumatic brain injury. *J Neurotrauma*. 2012; 29(10):1922–1940. [PubMed: 22489706]
79. Jang YN, Jung YS, Lee SH, Moon CH, Kim CH, Baik EJ. Calpain-mediated N-cadherin proteolytic processing in brain injury. *J Neuroscience*. 2009; 29(18):5974–5984.
80. Bajor M, Michaluk P, Gulyassy P, Kekesi AK, Juhasz G, Kaczmarek L. Synaptic cell adhesion molecule-2 and collapsin response mediator protein-2 are novel members of the matrix metalloproteinase-9 degradome. *J Neurochem*. 2012; 122(4):775–788. [PubMed: 22694054]
81. Stagi M, Fogel AI, Biederer T. SynCAM 1 participates in axo-dendritic contact assembly and shapes neuronal growth cones. *Proc Natl Acad Sci USA*. 2010; 107(16):7568–7573. [PubMed: 20368431]
82. Robbins EM, Krupp AJ, Perez de Arce K, et al. SynCAM 1 adhesion dynamically regulates synapse number and impacts plasticity and learning. *Neuron*. 2010; 68(5):894–906. [PubMed: 21145003]
83. Galuska SP, Rollenhagen M, Kaup M, et al. Synaptic cell adhesion molecule SynCAM 1 is a target for polysialylation in postnatal mouse brain. *Proc Natl Acad Sci USA*. 2010; 107(22):10250–10255. [PubMed: 20479255]
84. Zelano J, Wallquist W, Hailer NP, Cullheim S. Down-regulation of mRNAs for synaptic adhesion molecules neuroligin-2 and -3 and synCAM1 in spinal motoneurons after axotomy. *J Comp Neurol*. 2007; 503(2):308–318. [PubMed: 17492651]
85. Zelano J, Berg A, Thams S, Hailer NP, Cullheim S. SynCAM1 expression correlates with restoration of central synapses on spinal motoneurons after two different models of peripheral nerve injury. *J Comp Neurol*. 2009; 517(5):670–682. [PubMed: 19827159]

86. Goldshmit Y, Spanevello MD, Tajouri S, et al. EphA4 blockers promote axonal regeneration and functional recovery following spinal cord injury in mice. *PLoS ONE*. 2011; 6(9):e24636. [PubMed: 21931787]
87. Narayan RK, Michel ME, Ansell B, et al. Clinical trials in head injury. *J Neurotrauma*. 2002; 19(5):503–557. [PubMed: 12042091]
88. Johnson EM, Traver KL, Hoffman SW, Harrison CR, Herman JP. Environmental enrichment protects against functional deficits caused by traumatic brain injury. *Front Behav Neurosci*. 2013; 7:44. [PubMed: 23734108]
89. Caroni P, Donato F, Muller D. Structural plasticity upon learning: regulation and functions. *Nat Rev Neurosci*. 2012; 13(7):478–490. [PubMed: 22714019]
90. Rizzi S, Bianchi P, Guidi S, Ciani E, Bartesaghi R. Impact of environmental enrichment on neurogenesis in the dentate gyrus during the early postnatal period. *Brain Res*. 2011; 1415:23–33. [PubMed: 21885039]

Executive summary

Traumatic brain injury has few specific & targeted therapeutics

- Multiple clinical trials have been executed, and while a few have shown promise, many have failed to show benefits for post-traumatic sequelae.
- Cell adhesion molecules may represent a novel class of therapeutic targets to improve outcomes after brain injury.

Cerebral edema occurs with middle cerebral artery occlusion in a similar manner to that of traumatic brain injury

- Occluding the middle cerebral artery in rodents is a model for ischemic stroke, and postischemic pathophysiology develops in a manner similar to traumatic brain injury (TBI), including edema, increased Intracranial pressure and changes in synaptic markers.

Cell adhesion & signaling molecules are potential targets for improving neurologic deficits after TBI

- Based on various models, time points and brain regions, there are significant alterations in proteins from one of five groups: plexins, neural cell adhesion molecule, ephrins, neuroligins/neurexins and N-cadherins. These results have implications for synaptic plasticity and neuronal recovery after injury.

Conclusion

- The cell surface proteins described here and their signaling pathways are potential targets for the development of novel therapeutics that could improve neurologic deficits after TBI.

Future perspective

- More complete studies of the cell adhesion and signaling molecules described in this article are needed.
- Future studies should include more chronic phases of TBI recovery and should include behavioral studies as functional measures for improvement after TBI.
- A more complete survey of the importance of other types and classes of cell adhesion molecules in TBI is needed, and the possibility of cell adhesion molecules as therapeutic targets after TBI is warranted.

Figure 1. Regions of the brain affected by diffuse or focal-type injuries

A coronal section of mouse brain is shown. The figure depicts a representative injury isolated to the cortex. Cortical injury causes indirect cellular damage in the corpus callosum (yellow), hippocampus (red), thalamus (green) and brainstem (not shown).

Figure 2. Molecules that are altered with traumatic brain injury

A coronal section of mouse brain is represented in the top left corner. The hippocampus, while not directly damaged by the cortical impact, is shown below and its neurons exhibit cellular changes that have been mostly analyzed in the CA1 region. Notably, axonal swelling occurs together with a loss of synapses that can be transient. Two representative neurons are depicted, one is presynaptic (green) and the other is postsynaptic (red, with a swollen axonal segment indicated). A synaptic connection, with pre- and post-synaptic sites and the synaptic cleft, is enlarged to depict the cellular proteins that have been shown to change after traumatic brain injury. The inset shows a depiction of various domains and moieties that are present on the molecules presented in the figure.

AChE: Acetylcholinesterase; DG: Dentate gyrus; EphR: Eph receptor; LNS: Laminin, neurexin and sex hormone-binding globulin-like folding units; NCAM: Neural cell adhesion molecule; PSA: Polysialic acid.

Table 1

Overview of results from experiments reviewed, including summary of molecules studied, injury type and time course.

Protein name	Result	Brain injury type	Subject	Brain area surveyed	Measurement	Time postinjury [†]	Ref.
Plexins and neuroligins	↑ Neuropilin-2 in hippocampus/serum	Blast injury	Rats	Hippocampus/serum	Protein	1 and 7 days	[51]
Semaphorins	↑ Neuropilin-1 in cortex	MCAO	Mice	Cortex	Protein	1, 6 and 24 h	[50]
	Semaphorin 3A treatment worsens injury	MCAO	Mice	Cortex	Tissue volume loss	7 days	[52]
	↑ Semaphorin 4C	Four-vessel occlusion model	Rats	Hippocampus, SVZ	Protein	7 and 14 days	[53]
NCAM	↑ PSA-NCAM-positive neurons	FPI	Rats	Hippocampus	Protein	2 and 14 days	[56]
	↑ PSA-NCAM protein	CCI	Mice	Cortex	Protein	7 and 21 days	[57]
	↑ PSA-NCAM-positive neurons	MCAO	Rats	Cortex	Protein	1 h and 3 days	[58]
Ephrins	↑ Ephrin3A and EphA4	Four-vessel occlusion model	Rats	Hippocampus	Protein	6 and 24 h	[64]
	↑ EphA4	Post-mortem tissue	Humans	Cortex	Protein	6–122 h	[65]
	↑ EphB1	Subdural hematoma	Rats	Cortex	mRNA	7 days	[66]
	↓ EphB3	CCI	Mice	SVZ	Protein	3 and 7 days	[67]
Neurexin/NLG	↓ Neurexin-1β only at 24 h	CCI	Rats	Cortex	mRNA	3, 9 and 24 h	[70]
	↓ Neurexin-1β only at 24 h	CCI	Rats	Hippocampus	mRNA	24 h	[71]
	↑ Neurexin-NLG 1	MCAO	Rats	Hippocampus	Protein	5 min	[72]
Cadherins	↓ N-cadherin, 2 and 7 days	FPI	Rats	Hippocampus	Protein	2, 7 and 15 days	[76]
	↓ N-cadherin	MCAO	Rats	Cortex	Protein	24 h	[77]

[†]Changes that happened occurred at all timepoints listed.

↑: Increase in the measurement; ↓: Decrease in the measurement; CCI: Controlled cortical impact; FPI: Fluid percussion injury; MCAO: Middle cerebral artery occlusion model; NCAM: Neural cell adhesion molecule; NLG: Neuroligin; PSA: Polysialic acid; SVZ: Subventricular zone.