REVIEW

Targeting the Neurovascular Unit in Brain Trauma

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SUMMARY

Although the neurovascular unit was originally developed as a conceptual framework for stroke, it is now recognized that these cell–cell interactions play critical roles in many other CNS disorders as well. In brain trauma, perturbations within the neurovascular unit may be especially important. Changes in neurovascular coupling may disrupt blood flow and metabolic regulation. Disruption of transmitter release-reuptake kinetics in neurons and astrocytes may augment excitotoxicity. Alterations in gliovascular signaling may underlie blood–brain barrier disruptions and traumatic edema. Perturbations in cell–cell signaling between all neuronal, glial, and vascular compartments may increase susceptibility to cell death. Finally, repairing the brain after trauma requires the integrated restoration of all neural, glial, and vascular connectivity for effective functional recovery. Just as in stroke, saving neurons alone may also be insufficient for treating brain trauma. In this minireview, we attempt to briefly highlight some of these pathways to underscore the importance of rescuing the entire neurovascular unit in brain trauma.

Introduction

Over the past two decades, various molecular mechanisms of neuronal death after traumatic brain injury (TBI) have been dissected by many groups. These mechanisms often involve complex combinations of necrosis, apoptosis, necroptosis, and autophagy [1,2]. Defining these pathways offer the hope that effective therapeutic targets can be identified. However, it is now increasingly recognized that in addition to neuronal death, responses in glial and vascular compartments should also play a key role in the progression of secondary injury after TBI. Indeed, when TBI patients are in the intensive care unit, major clinical challenges are often centered on cerebrovascular instability perhaps related to glial swelling, blood–brain barrier leakage, and disruptions in flow-metabolism regulation. Taken together with emerging data in a wide range of experimental models, it is likely that developing therapies for brain trauma should require a careful rescue of the entire neurovascular unit, comprising interactions between all cell types in the damaged brain.

Cerebral Blood Flow and Metabolism

After TBI, the regulation of cerebral blood flow and metabolism can become disordered in dispersed brain regions, with the suppression of glucose metabolism along with reductions in cerebral blood flow (CBF). However, it is unclear whether metabolism is reduced because of insufficient flow or flow is reduced because of decreased demand in injured neurons. Evidence for actual "ischemia" post-TBI remains rare and controversial [3]. But it is likely that simultaneous disruption in neuronal metabolism and vascular flow occurs.

In terms of organ injury, CBF that is too low or too high can both be deleterious. Hyperperfusion may lead to increased capillary leakage and/or bleeding. Hypoperfusion may lead to dangerous metastable states of oligemia or, if CBF levels drop far enough, may even trigger outright ischemia in already vulnerable and traumatized brain tissue. It has also been proposed that CBF response after TBI is nonlinear, and acute hypoperfusion can be followed by secondary hyperperfusion [4]. Finally, traumatic vasospasm may also occur, leading to delayed hypoperfusion again at even later timepoints [4]. If true, then targeting these multiphasic CBF profiles after TBI may be extremely challenging.

From a functional viewpoint, these perturbations in metabolism and CBF may be due in part to traumatic effects on autoregulation. The brain is a high-energy organ. So, autoregulation provides a critical mechanism for maintaining balanced levels of energy supply and demand. Once the system is damaged by trauma, autoregulation may be impaired, although autoregulatory failure may not always be correlated with injury severity [5]. In rodent models of TBI, CBF may no longer be able to respond to

changes in blood pressure, hyperventilation, or hypercapnia [6–8]. The underlying mechanisms will surely be complex and multifactorial. For example, TBI can trigger widespread microthrombosis in a disseminated manner, either due to activation of coagulation cascades in blood or upregulation of adhesion molecules in affected endothelium [9]. Recent studies further suggest that endothelin signaling may be involved. Endothelin receptor antagonists may be able to prevent upregulation of vasoconstrictive smooth muscle actin in microvessel pericytes post-TBI [10]. Regardless of the exact molecular mechanisms involved, data from many experimental models now strongly suggest that dispersed and widespread alterations in microvascular perfusion occur after trauma.

Although the spatiotemporal profiles and underlying mechanisms of CBF response after TBI are complex and remain to be fully elucidated, many studies have suggested that in human patients, CBF-metabolic coupling can sometimes predict long-term outcomes [11,12]. Hence, finding ways to ameliorate CBF and metabolic dysregulation should be an important therapeutic direction for TBI. Because CBF metabolism function is fundamentally regulated by the entire neurovascular unit, this simply underscores the importance of targeting all neural, glial, and vascular elements to treat traumatized brain.

Blood–Brain Barrier

Perturbations in BBB function have been extensively documented after TBI in both experimental models and human patients [13]. From a clinical perspective, BBB leakage is most often associated with edema and brain swelling, which may lead to detrimental elevations in intracranial pressure (ICP) and corresponding reductions in cerebral perfusion pressure (CPP) [14]. From a molecular perspective, BBB permeability can be affected by TBI in multifactorial ways [13,15]. Many BBB-modifying factors can be upregulated after injury, spanning the range from damaging free radicals and inflammatory cytokines to BBB gene modifiers and neurovascular matrix proteases. Additionally, after TBI, mechanical impact may induce immediate BBB damage; microbleeding, vascular inflammation, and secondary ischemia/hypoxia may induce prolonged BBB dysfunction [13,15,16].

TBI is known to enhance the generation of reactive oxygen species (ROS) that can damage cerebral endothelium [17]. Downregulation of tight junction proteins has also been described in various models of TBI [16]. Under some conditions, TBI may upregulate matrix metalloproteinases (MMPs) that degrade both tight junction proteins and associated neurovascular matrix substrates [18]. Correspondingly, a wide spectrum of therapeutic approaches may protect the BBB post-trauma, at least in experimental model systems. For example, free radical scavengers reduced Evans blue leakage in rat-controlled cortical impact [19], blocking the effects of inflammatory cytokines with neuregulin appears to decrease endothelial tight junction permeability [20], and deleting the gene for MMP9 improved outcomes in transgenic mice [21].

Ultimately, the BBB phenotype is dependent on cell–cell signaling between neuronal, glial, and vascular cell types. Hence, BBB disruptions after TBI may be best interpreted as an integrative response within the entire neurovascular unit. Emerging findings now demonstrate that astrocytes and pericytes are essential for promoting BBB maturation in cerebral endothelium [22–24]. Cell–cell signaling mechanisms in this regard are complex, but broadly involve TGF-beta cascades [25]. More recently, it has also been proposed that oligodendrocyte precursor cells (OPCs) may also contribute to BBB function [26]. Hence, any disruption of neurovascular unit signaling may end up interrupting vital cross talk between cerebral endothelium and associated astrocytes, pericytes, and OPCs, thus affecting BBB homeostasis after TBI.

Cell–Cell Signaling Within the Neurovascular Unit

As a conceptual construct, the neurovascular unit emphasizes the importance of cell–cell signaling between all cells in neural, glial, and vascular compartments [27]. Historically, the cell type most recognized for its neurosupportive function is the brain astrocyte. Without astrocytes, release-reuptake kinetics for various neurotransmitters cannot be refined for effective neurotransmission. Any disruption of release-reuptake profiles will surely affect neurotransmitter networks and overall brain function after trauma. Furthermore, because dysregulated glutamate handling may be a key event in TBI, rescuing astrocyte function may represent a logical target for ameliorating secondary excitotoxicity in traumatized brain tissue. Proof-of-concept studies using microdialysis demonstrated that extracellular glutamate levels are rapidly elevated following traumatic injury [28]. Simple cell culture studies demonstrate that the presence of astrocytes can defend neurons against glutamate overload [29]. Hence, upregulating astrocytic glutamate transporters may represent a potential therapeutic target for neuroprotection [30]. In addition to buffering glutamate imbalance, astrocytes may also be neuroprotective via antioxidative mechanisms as these cells can express relatively high levels of antioxidant genes such as superoxide dismutase and glutathione [31]. Because excitotoxic and oxidative injury are key components of TBI pathophysiology, targeting astrocytes may be an important direction for pursuing future therapeutic approaches.

An essential part of cell–cell communication in the neurovascular unit comprises gliovascular signaling. Without proper signaling between the astrocytic endfeet and microvessel endothelium, BBB function cannot be maintained. After trauma, astrocyte dysfunction is a major event that underlies BBB leakage and vasogenic edema [32]. Some reports suggested that aquaporin channels may underlie some of these pathophysiological responses in TBI [33]. Furthermore, outright astrocyte swelling may also contribute to cytotoxic forms of brain edema [34], and targeting different types of astrocyte channels may prevent cytotoxic edema [35]. More recently, pericytes have also been recognized as being important contributors to CNS function and dysfunction. In developing brain, pericytes assist with BBB maturation [36]. In adult brains, pericytes may assist with vasoregulation for CBF control [37]. Hence, changes in pericyte signaling after TBI may further disturb BBB and CBF regulation. Altogether, disruption of signaling between astrocytes, pericytes, and endothelium may underlie gliovascular pathophysiology that further exacerbates secondary injury.

Another important glial reaction to injury comprises microglial activation. Activation of these resident CNS inflammatory cells is well documented in TBI. In animal models, microglia can release a wide spectrum of neurotoxic cytokines that further contribute to neuroinflammation and cell death [38]. In humans, rapid microglia activation occurs within hrs and can even persist for up to months or years after injury [39,40]. Because microglia are known to play a role in pruning and maintaining synaptic homeostasis, it is attractive to hypothesize that dysfunctional microglia can contribute to prolonged neuronal dysfunction in TBI. Although blocking microglia may offer therapeutic opportunities for TBI, it is now appreciated that not all of these cells are damaging, and biphasic properties may emerge in injured brain tissue as part of an endogenous inflammatory/wound-healing response. Experimental findings now suggest that deleterious M1-like phenotypes can be contrasted against prorecovery M2-like phenotypes in CNS disorders [41]. Defining the pathways that regulate the microglial switch may be an important target for TBI.

Although glial interactions are well dissected in gray matter, it is increasingly recognized now that analogous cell–cell signaling pathways may be essential for understanding function and dysfunction in white matter. In TBI, white matter damage is especially important. In this regard, oligodendrocyte precursor cells (OPCs) may be significant targets for TBI. OPCs are thought to comprise a general stem/progenitor pool for maintaining mature oligodendrocyte populations in white matter [42]. Therefore, TBI-mediated damage to these cells may compromise the ability of damaged white matter to heal. Furthermore, OPCs may also support BBB function [26], so any disruption of oligovascular cross talk may lead to edema in traumatized white matter.

After TBI, severely injured neurons in the core die rapidly. Then, over the course of hrs to days or even weeks, secondary pathways of injury often occur. The standard hypothesis and hope has been that blocking intraneuronal mechanisms of cell death should be the logical therapeutic target. Increasingly, however, both clinical and experimental data now strongly suggest that much of the pathophysiology of TBI is not only due to neurons dying, but also mediated by perturbations in cell–cell signaling in the entire neurovascular unit. Hence, restoring the homeostasis of these signals should offer important therapeutic directions in TBI.

Remodeling the Neurovascular Unit

The concept of the neurovascular unit has been mostly applied in the context of acute brain injury and neurodegeneration. However, it is increasingly recognized that analogous cell–cell cross talk between neural, glial, and vascular elements is absolutely required for repair and remodeling as well [43,44]. In the mature mammalian brain, neurogenesis is mostly inactive, except for pockets of ongoing neuroblast activity in the subventricular and subgranular zones. After TBI, neurogenesis may be increased in these areas as the damaged brain attempts to heal itself. In experimental models of cortical impact or fluid percussion injury, neuroblasts can be observed to migrate from these subventricular and subgranular regions toward traumatized areas [45]. Recently, emerging data now support the notion that after acute brain injury from either stroke or trauma, neurogenesis and angiogenesis appear to be tightly co-regulated, especially

during the recovery phase. Migrating neuroblasts move along perivascular pathways [46]. Promoting neurogenesis seems to augment angiogenesis and vice versa [47]. Indeed, many mediators that assist with neurogenesis and neural patterning may also assist with angiogenesis and vessel guidance as well, including semaphorins, netrins, VEGF, and BDNF [48].

A prominent example of multicellular cross talk in the neurovascular unit involves the interactions between the brain microvessel and surrounding glia (astrocytes, pericytes, and OPCs) that support BBB maturation. During recovery, BBB function also needs to be restored. But this may require careful attention to the biphasic effects of some neurovascular and gliovascular signals. For example, while VEGF promotes potentially beneficial angiogenesis, incorrect timing of VEGF signals may increase BBB leakage and worsen edema [49]. As a general principle, many mediators that are activated after TBI may follow this biphasic rule, that is, deleterious in the acute phase while beneficial in the delayed phase. In this regard, the neurovascular unit may provide a conceptual framework for defining the shifting profiles of pathophysiology over time.

Beyond CBF and BBB function, cerebral microvessels may also subserve many other CNS functions. Recently, the concept of the vasculome has been proposed, which states that the cerebral endothelium may not just comprise "empty pipes" for blood flow [50]. Instead, the entire microvessel network may represent an intricate paracrine organ that supports neuronal function and homeostasis [51,52]. Hence, protecting the vasculome in TBI may ultimately defend neurons against cell death as well as augment neurorecovery as the entire neurovascular unit attempts to rebuild itself. Furthermore, the cerebral microvascular system may act as sensors and integrators of brain injury and dysfunction, releasing measurable signals into the circulation [53]. Therefore, mining the vasculome may also provide a database for TBI biomarkers [50].

Plastic cross talk can also be found between neurons and astrocytes. Regulation of neurotransmitter release–reuptake kinetics cannot take place without coordinated interactions between neurons and astrocytes. During the remodeling phase post-TBI, astrocytic cross talk may be important as neuronal circuits are reconstructed. Traditionally, reactive astrocytes are thought to be deleterious because they underlie the inhibitory glial scar [31,32]. However, emerging data now suggest that their roles may be more complex. Under some conditions, astrocytes can be helpful for brain repair [31,32]. Transgenic mice that suppress astrocyte GFAP activation surprisingly show improved outcomes after cortical impact injury [54]. The underlying mechanisms may be complex. For example, astrocytes release thrombospondin-1 which promotes synaptic function and maturation [55], and tissue plasminogen activator which contributes to dendritic plasticity in recovering neurons [56]. Indeed, several studies have suggested that the therapeutic benefits of stem cell therapies may depend in part on the ability of astrocytes to amplify the effects on neuronal remodeling [57]. Ultimately, the roles of activated glia will surely be complex comprising both damaging and beneficial effects over time as the entire neurovascular unit attempts to heal itself.

For the large human brain, what happens in white matter may be even more important. Emerging data now suggest that besides a neurovascular niche, an analogous oligovascular niche may also

exist. Astrocytes and cerebral endothelial cells secrete many trophic factors that support oligodendrocyte precursor cells and vice versa [58]. And after injury, vascular endothelial growth factor (VEGF)-mediated endothelial recovery is linked with the proliferation and migration of oligodendrocyte precursor cells [59]. Oligodendrogenesis and angiogenesis are intricately linked. Without proper remodeling in white matter, the recovering brain cannot reconnect.

Finally, accumulating data is beginning to suggest that non-cell-autonomous mechanisms may extend beyond the narrow confines of the CNS itself. The neurovascular unit does not stand in isolation. It is in constant communication with the entire systemic physiology as well. For example, peripheral tissue injury and inflammation can alter BBB function [60]. After focal brain injury, reactive astrocytes can also release HMGB1 as a signal to promote endothelial progenitors for neurovascular remodeling [61]. After brain injury, detectable responses should be present in circulating blood cells and components. Beyond the obvious implications for biomarkers, these systemic blood responses may also have therapeutic implications. Modifying circulating blood responses may potentially influence neuroinflammation and secondary brain pathophysiology. Cross talk between multiple cell types in CNS and non-CNS compartments will be exceedingly complex (Figure 1). In the end, a systems biology approach may be required to truly dissect the mechanisms involved.

Conclusions and Opportunities

Neuronal death provides a cell biology correlate for neurological dysfunction after TBI. However, emerging data in both experimental models and patients now clearly demonstrate that a singular focus on neurons alone may not be enough. Pure neuroprotection (even if it is effective) may not translate into improved outcomes. What may be required is a rigorous consideration of the entire neurovascular unit. In this minireview, we attempted to briefly survey and highlight examples of cell–cell signaling phenomenon relevant for neuronal, glial, and vascular responses after TBI. Targeting these multicellular interactions may provide opportunities for developing therapeutics for ameliorating acute injury as well as promoting delayed repair.
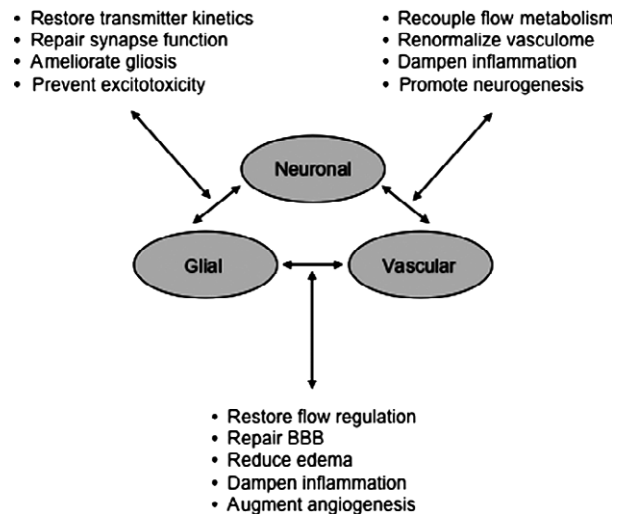

Figure 1 Cross talk between multiple cell types in CNS and non-CNS compartments after TBI. After TBI, perturbations in cell–cell signaling between all neuronal, glial, and vascular compartments may increase susceptibility to cell death. Changes in neurovascular coupling may disrupt blood flow and metabolic regulation. Disruption of transmitter release-reuptake kinetics in neurons and astrocytes may augment excitotoxicity. Alterations in gliovascular signaling may underlie blood–brain barrier disruptions and traumatic edema. Finally, repairing the brain after trauma requires the integrated restoration of all neural, glial, and vascular connectivity for effective functional recovery.

Acknowledgments

Conflict of Interest

The authors declare no conflict of interest.

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