Chapter 5

Traumatic Penumbra: Opportunities for Neuroprotective and Neurorestorative Processes

Andrea Regner, Lindolfo da Silva Meirelles and Daniel Simon

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.72156

Abstract

Traumatic brain injury (TBI) is a major cause of morbidity and mortality worldwide. Understanding the pathophysiology of TBI is crucial for the development of more effective therapeutic strategies. At the moment of the traumatic impact, transfer of kinetic forces causes neurologic damage; this primary injury triggers a secondary wave of biochemical cascades, together with metabolic and cellular changes, called secondary neural injury. These areas of ongoing secondary injury, or areas of "traumatic penumbra," represent crucial targets for therapeutic interventions. This chapter is focused on the interplay between progression of parenchymal injury and the neuroprotective and neurorestorative processes that are emerging and developing subsequently to traumatic impact. Thus, we emphasized the role of traumatic penumbra in TBI pathogenesis and suggested a crucial contribution of the neurovascular units (NVUs) and paracrine effects of exosomes and miRNAs in promoting neurological recovery.

Keywords: traumatic brain injury, traumatic penumbra, neural injury, pericytes, neurovascular unit, neurorestoration

1. Introduction

Worldwide, injuries account for 15% of the burden of death and disability, while traumatic brain injury (TBI) accounts for up to half of all deaths from trauma [1–6], and often causes severe and long-lasting functional impairment in survivors [7]. TBI affects individuals of all age groups with a bimodal distribution in adolescents and elderly [8, 9], with a major predominance in the male population [10, 11]. Blunt trauma accounts for about 88–95% of TBI cases, whereas the remaining 5–12% of cases are the result of penetrating injuries [12]. Because of the high-impact nature of trauma-inducing accidents, patients commonly suffer

concomitant injuries to multiple body regions and organs, otherwise known as multitrauma or polytrauma, that are capable of modifying the pathobiology and outcomes of TBI [13].

TBI is classified by different methods; in the 1970s, Teasdale and Jennett introduced the Glasgow Coma Scale (GCS) to objectively assess the degree of impaired consciousness [14]. Based on GCS, TBI is classified into mild (GCS score 14–15), moderate (9–13), and severe (3–8) [15]. At present, GCS is the most used method for TBI classification, however, has a number of limitations [15, 16]. A recent study reported that normal GCS did not indicate an absence of head injury, as among patients with GCS 15 in the Emergency Department, 26% had serious/critical TBI [17]. Therefore, stratification of severity and prediction of death and functional outcome is essential for determining treatment strategies and allocation of resources for patients with TBI. Among the most studied predictors of TBI outcome, age is a consistent predictor, as well as GCS scores and pupillary parameters [18]. Recent studies show a series of either tissue-specific or circulating biomarkers that are useful in the clinical status evaluation of these patients [19–22].

Intracranial hypertension is the main cause of death in patients with TBI and contributes to secondary brain injury if not managed correctly [23–25]. Therefore, the management of TBI focuses on the control of intracranial pressure (ICP) and maintenance of adequate cerebral perfusion, oxygenation, and metabolism attempting to limit secondary injury progression [26–28]. Mortality rates have decreased in the last decades, largely due to improvements in trauma systems and supportive critical care [29]. Yet, case fatality rates in severe TBI have not decreased significantly since 1990 [30], remaining with an outstanding mortality, because up to 50% of the patients will still die and nearly all survivors will present some degree of sequelae [3, 4, 6, 31–33]. To the present, regardless of over dozens of phase III clinical trials, there are no specific treatments known to improve TBI outcomes [13]. Hence, TBI is heterogeneous in terms of pathophysiology, clinical presentation, and outcome, with case fatality rates ranging from <1% in mild TBI up to 50% in severe TBI. A key issue in TBI care is the temporal progression of injury cascades and the design of therapeutic approaches to improve functional recovery after TBI.

This chapter is focused on the interplay between progression of parenchymal injury and the neuroprotective and neurorestorative processes that are emerging and developing subsequently to traumatic impact. Thus, we emphasized the role of traumatic penumbra in TBI pathogenesis and suggested a crucial contribution of the neurovascular units (NVUs) and paracrine effects of exosomes and miRNAs in promoting neurological recovery.

2. Mechanisms of neural injury in the traumatic penumbra

TBI is unique since it results from an external force, which can inflict devastating effects to brain vasculature, neighboring neural tissue, and blood-brain barrier (BBB) [34]. Together, neurons, vascular cells (endothelial cells) and perivascular components of the BBB (astrocytes and pericytes) form the neurovascular unit (NVU). NVU is at the basis of neurovascular coupling, which allows cerebral blood flow to local regulation according to neuronal

activity in specific areas of the brain [34]. TBI may cause mechanical deformation and damage to the entire NVU [20, 35, 36], compromising barrier integrity and leading to dysautoregulation of brain vessels and BBB disruption. In this context, brain edema may occur and result in increased ICP and decreased cerebral perfusion [37]. In fact, compensatory mechanisms are exceeded as brain volume increases due to edema, and ICP rises exponentially and correlates with increased mortality and poor functional outcomes [20, 38–40]. The impact of trauma causes mechanical forces that engender deformation of the brain tissue, resulting in immediate neural damage, called primary injury [40]. This primary injury triggers a secondary wave of biochemical cascades, together with metabolic and cellular changes, occurring within seconds to minutes after the trauma and lasting for days, months or years [40]. The ongoing brain damage characteristic of secondary injury culminates in notable cell death [24, 40, 41]. Typically, initial neuronal death following acute brain injury occurs by necrosis, on a time scale of minutes, then, a second wave of delayed cell death occurs mostly by apoptosis [13, 42–45]. Indeed, this protracted course of cell death following TBI may represent a unique opportunity for therapeutic intervention. Following TBI, brain lesions are not limited to the site of the primary trauma, but expand progressively and centrifugally. Therefore, secondary brain injury develops and progresses in the traumatic penumbra, that is, the potentially salvageable brain tissue surrounding the primary lesion [46, 47]. Indeed, clinical studies have demonstrated that expansion of the penumbra impairs cerebral blood flow and leads to edema and compromised local metabolism, resulting in clinical deterioration [48–50].

The traumatic penumbra is characterized by metabolic changes as a consequence of neural injury progression [51–53] culminating in cell death [26, 54]. In this scenario of metabolic crisis, astrocytes may exert a neuroprotective action supplying substrates of glycogen metabolism for the survival of ischemic neurons and oligodendroglial cells [49]. Thus, astrocytes also play crucial roles in the injury site after TBI, as they exert homeostatic mechanisms critical for maintaining neural circuit function, such as buffering neurotransmitters, modulating extracellular osmolarity, and calibrating neurovascular coupling [55]. Accordingly, astrocytes are thought to exert many beneficial effects post-TBI [56] as providing neurotrophins that support and guide axons in their recovery [57], increasing cell proliferation, and promoting the long-term survival of neurons by inhibiting apoptosis [58, 59]. However, when the presence of astrocytes is too large and they become over activated, they may build a dense physical and chemical barrier surrounding the injury site (glial scar), which encapsulates and isolates the axons. This not only protects the remaining healthy brain from the neurotoxic environment of the injury site but also interferes and prevents the regeneration and repair of the damaged tissue [60, 61].

We will resume some of the phenomena involved in cellular injury in the traumatic penumbra. Particularly, excitotoxicity, oxidative stress, mitochondrial dysfunction, and neuroinflammation are processes that contribute to neurological damage and impairment of neural recovery following TBI (**Figure 1**). In the injured brain, excitotoxicity derives from an acute increase in extracellular glutamate levels due to excessive release from depolarized neurons, leakage from neuronal and glial cells exhibiting damaged membranes, or the extravasation through a disrupted BBB [53, 62–64]. TBI also involves enhanced glutamatergic activity at

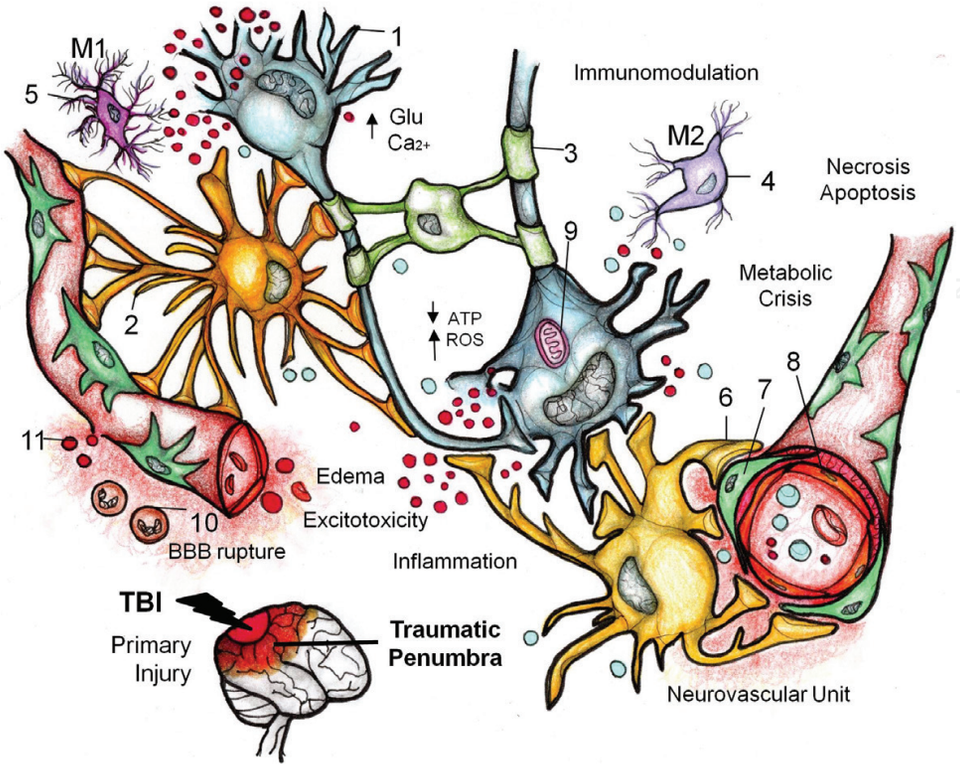

Figure 1. Schematic representation of mechanisms of neural injury in the traumatic penumbra. The neural tissue disruption of primary injury triggers a cascade of cellular events that result in areas of traumatic penumbra characteristic of secondary injury, leading to necrosis and apoptosis. Secondary injury progression can either evolve to edema that culminates in an uncontrollable increase of intracranial pressure leading to brain death or trigger mechanisms of neural tissue survival and recovery. The first 96 hours after the trauma are critical for the cellular processes involved in ongoing secondary neural injury. Various cellular components are involved in secondary injury progression in the traumatic penumbra: (1) neuron, (2) reactive astrocyte, (3) oligodendrocyte, (4) microglia M2 anti-inflammatory phenotype, (5) microglia M1 pro-inflammatory phenotype, (6) astrocyte endfoot, (7) pericyte, (8) endothelial cells, (9) mitochondria, (10) peripheral immune cells, and (11) signaling molecules. Excitotoxicity is a central mechanism of injury and triggers a cascade of events, such as increase in calcium influx, cellular damage mediated by ROS, and mitochondrial dysfunction resulting in metabolic crisis and culminating in cell death. A pro-inflammatory phase occurs in the first hours and days. In that microenvironment, microglia polarize into a M1 pro-inflammatory phenotype. Reactive astrocytosis occurs and contributes both to injury and neurorestoration. Acutely after TBI, in the neurovascular unit, swelling of perivascular astrocytes occur and the swollen endfeet constrict capillaries, leading to a reduction in oxygen availability. Also, focal microhemorrhages contribute to inflammatory processes. In this scenario, pericytes contribute to alterations in BBB permeability, angiogenesis, clearance of toxic metabolites, and hemodynamic responses. BBB rupture is evident and contributes to inflammation and edema of the neural tissue.

extrasynaptic sites due to failure of glutamate uptake, gliotransmission, reverse operation of the glutamate transporters, increase in presynaptic glutamate release or increase in the number and/or stability of glutamatergic receptors [53, 62, 65, 66]. The increase in glutamate levels occurs several minutes after the primary trauma, peaks in about 10 minutes and stays increased for several days [45, 64]. Excitotoxicity also causes calcium influx and overload [67, 68], resulting in cellular damage due to several mechanisms (i.e. activation of destructive calcium-dependent proteases, oxidative stress, mitochondrial impairment and transition pore formation, and apoptotic events) [51, 53, 62, 69–71]. Noteworthy, the massive influx of calcium causes production of reactive oxygen species (ROS) in mitochondria. The calcium overload leads to swelling and compromised function of mitochondria, instigating impaired

energy metabolism [51, 72]. Conversely, the damaged tissue needs more energy for its repair than under physiological conditions, resulting in what has been termed a "flow/metabolism mismatch," a factor that aggravates injury in the traumatic penumbra [62, 73]. Furthermore, increased glutamatergic release into the extracellular milieu following injury causes marked increases in glucose use and accumulation of extracellular lactate [53, 74–79]. This deregulated cerebral metabolism leads to decreased ATP production causing the failure of ATP-dependent ion channels and proteins leading to ionic osmotic alterations that result in cell swelling and culminating in necrosis [80]. Mitochondrial dysfunction may be central to the pathophysiology of TBI through metabolic derangements, oxidative stress, and apoptosis. In fact, a recent study showed mitochondrial ultrastructural alterations at progressive distances from the center of the penumbra in tissue samples from TBI patients [81]. In the setting of TBI, the production of ROS is enhanced [82–84], and the neuroprotective systems become overwhelmed and result in oxidative cell damage. Furthermore, ROS can contribute to disruption of the BBB, edema, and neuroinflammation [34].

Importantly, neuroinflammation is known to be important for the short- and long-term consequences of TBI [85]. Various factors influence the inflammatory response of the brain to TBI. These factors include activation of resident central nervous system (CNS) immune cells and cerebral infiltration of peripheral immune cells (through a disrupted BBB); these cells mediate inflammatory processes through secretion of a variety of inflammatory cytokines, chemokines, adhesion molecules, ROS, and complement factors [86, 87]. Immediately following injury, the levels of various cytokines change drastically in the brain parenchyma and take approximately 48 hours to return to normal [45]. Accordingly, regional, intrathecal, and systemic concentrations of various inflammatory cytokines (interleukin-1, -1β, -6, -8, -10, -12, and tumor necrosis factor-alpha) are altered shortly after TBI in humans and experimental models [88–94]. Even though neuroinflammation is generally considered to have negative effects on the neural tissue, interleukins may actually exert beneficial effects on the injured brain by triggering mechanisms of response to tissue injury. Clearly, the beneficial effects of these cytokines are dependent on their concentrations and the timing/conditions of their expression following TBI [53]. The dual role of these cytokines on TBI is observable during the pro-inflammatory phase (in the first hours and days after TBI) as well as through the reparative phase, which lasts for days to months after TBI [95]. Of these cytokines, IL-1β is of special importance because its action on astrocytes makes them release of matrix metalloproteinases (MMPs) [96] that cause further BBB breakdown by promoting and prolonging neuroinflammation [97]. Modulating these inflammatory cells by changing their phenotype from pro-inflammatory to anti-inflammatory would likely promote therapeutic effects on TBI [42, 59, 98]. Additionally, peripheral injuries of the multi-injured patient may increase circulating levels of many of the inflammatory cytokines worsening TBI outcomes [13, 68].

As the major cellular component of the innate immune system in the central nervous system (CNS) and the first line of defense whenever injury or disease occurs, microglia play a critical role in neuroinflammation through the production of various cytokines, proteases, and ROS [45, 99]. In the injured brain, microglia can produce neuroprotective factors, clear cellular debris, and orchestrate neurorestorative processes that are beneficial for neurological recovery after TBI [100, 101]. Microglia can polarize into distinct phenotypes, depending on

the microenvironment in which they are activated. The macrophage/microglial populations are shown to result in a mix of pro-inflammatory M1 and anti-inflammatory M2 microglia/macrophage populations following TBI [56, 102]. It is thought that M1 microglia/macrophage populations are responsible for the production of oxidative species, increased synthesis of pro-inflammatory cytokines, low levels of anti-inflammatory cytokines, and much of the phagocytic activity. As a result, they may contribute to injury progression. M2 populations on the other hand are believed to play a role in angiogenesis, remodeling of the extracellular matrix, and support regeneration following injury [103]. When appropriately queued, microglia can also release neurotrophins to augment neuronal growth and survival [104]. Deficits in the ability of microglia to perform these functions or to appropriately switch between M1 and M2 phenotypes detrimentally affect brain function [105]. Microglial activation within the injured area is observed within 6–48 hours post injury [99] but evidence has shown that microglia can maintain a primed or pro-inflammatory profile for weeks to months after the acute effects of injury have dissipated [106]. Recently, it was shown that extracellular vesicles may exchange pro-inflammatory molecules between brain immune cells, as well as to the systemic circulation, as pathways of inflammation propagation following TBI [107].

Notwithstanding the previous characterization of the pathophysiologic responses to TBI, these biologic responses occur in individuals who possess biologic differences that can modify their response to injury [53, 108]. Over the last years, evidence has showed that the brain is capable of significant structural and functional repair, plasticity, and regeneration. Approaches for accomplishing this include reawakening the growth potential of the surviving neurons or antagonizing the inhibition of axonal growth and synaptogenesis. Alternatively, cellular replacement is achievable in certain brain regions that possess nascent neural stem cells [25, 43, 109–111]. Thus, the discussed concept of traumatic penumbra imbues the transition between injury and repair at the NVU with profound implications for selecting the appropriate type and timing of neuroprotective interventions [34]. In this scenario, it is instigating to investigate which cellular pathways in the traumatic penumbra could play key roles for neurorestoration and, therefore, represent novel therapeutic opportunities for TBI.

2.1. The neurovascular unit in the traumatic penumbra

NVU comprises vascular cells (endothelial cells), perivascular constituents of the blood-brain barrier (pericytes and astrocytes) and their associated neurons, as well as extracellular matrix components [112]. NVU also includes microglial cells, vascular smooth muscle cells located around blood vessels, specialized cellular compartments such as the endothelial glycocalyx, the endothelial lining of cerebral capillaries, capillary tight junctions, and the capillary basement membrane [113]. Together, the components of NVU detect physiological needs of the neural tissue and respond accordingly to supply these demands [112]. Consequently, under normal conditions, cerebral blood flow is maintained constant despite wide changes in perfusion pressure [114], a phenomenon called autoregulation of cerebral blood flow [115].

Traumatic cerebral vascular injury (TCVI) is a major feature of TBI disease. While the complex molecular and cellular mechanisms responsible for functional deficits after TBI are not fully understood, substantial data indicate that TCVI underlies a significant fraction of TBI-related disability. Therefore, in view of its physiological function, the NVU plays an important role

in the pathogenesis of TBI, whether responding to physical trauma or participating in the cascade of events that leads to secondary injury in the traumatic penumbra [116]. Endothelial cells, for example, respond to hemodynamic forces by releasing factors that promote constriction or dilation. Neurons associated with the neural cerebral vasculature release neurotransmitters (e.g. norepinephrine and serotonin for vasoconstriction, and acetylcholine, substance P, and vasoactive intestinal polypeptide for vasodilation) that diffuse into the tunica media and act on receptors in the smooth muscle cell layer to elicit either vasoconstriction or dilation. Based on local activity and needs, basal forebrain neurons release vasoactive mediators on cortical microvessels and supporting astrocytes to modulate microvascular tone [113]. Consequently, neuronal metabolism and activity are tightly coupled to local cerebral blood flow [117].

Microvascular injury is observed in animal models of TBI, whether the injury is caused by impact acceleration, fluid percussion or controlled cortical impact (CCI). Immediately after TBI, endothelial cells are damaged; subsequently, secondary injury extends to the other components of the NVU; decreased blood flow and focal hypoxia disturb the NVU, and various pathophysiological events, such as BBB disruption, edema, and focal ischemia, take place [118]. The NVU response to these events include the increased production of nitric oxide and consequent increase of blood flow right after TBI followed by a period of decreased production of NO and consequent decrease of blood flow [119]. Another aspect of the response of the NVU to these events is the release of damage-associated molecular patterns that trigger secretion of pro-inflammatory mediators such as tumor necrosis factor, interleukin-6, and interleukin-1β by glial cells [120]. The trade-off to this response consists of unwanted side effects such as BBB disruption, edema, hypoperfusion, and oxidative stress, all of which contribute to increase severity of the secondary injury.

Ultrastructural changes in endothelial cells at acutely injury sites are observable 3 hours after TBI and are still present 1 week later [121]. During this, time swelling of perivascular astrocytes is evident; their swollen endfeet constrict capillaries, which leads to a redistribution of capillary blood flow that can reduce oxygen availability to cerebral tissue even if ischemia is not obvious [122]. Data from experimental TBI models indicate that increased extravasation of the contents of blood vessels through microhemorrhages is evident between 3 and 12 hours after the injury [116]. Most of these focal hemorrhages occur in pericontusional tissue, while some occur within the contusion itself and diffusely throughout the ipsilateral, noncontused cerebral hemisphere; intravascular microthrombi, in turn, peak at 48 hours after TBI but persist for at least 9 days [123]. Focal microhemorrhages are accompanied by activation of microglia, reactive gliosis, and recruitment of macrophages; 3 months after the injury, these microbleed sites are surrounded by glial scars and are characterized by major loss of myelin [124].

Clearly, endothelial cells are not alone in the response to TBI. During necrotic phases, cytokines, such as TNF and IL-1, are released by astrocytes, microglia, endothelial cells, and neurons and contributed to the initiation of neuroinflammation [125]. These cytokines induce microglial activation and expression by endothelial cells of adhesion molecules, such as intercellular adhesion molecule 1, aka CD54 (ICAM-1), vascular cell adhesion protein 1, aka CD106 (VCAM-1), P-selectin (CD62P), and E-selectin (CD62E), which in turn allow attachment of leukocytes (neutrophils and

monocytes) to the endothelium and their passage across the BBB. These events lead to increased production of proinflammatory factors at the injured tissue, and leukocytes start releasing MMPs [125]. These MMPs, which include MMP-2, MMP-3, and MMP-9, degrade extracellular matrix proteins and tight junction proteins that join endothelial cells with each other, which results in increased permeability of the BBB. Not surprisingly, the levels of some of these TBI-associated molecules in the blood, as is the case of MMP-9 [126], have been associated with the outcome of TBI and may become important tools for patient screening at the emergency unit in the future.

2.2. Pericytes in the traumatic penumbra

Another cell of the NVU, the pericyte, has been recognized as a component of the BBB more than a century ago [127]. Functions attributed to pericytes in the CNS include regulation of the BBB permeability, angiogenesis, clearance of toxic metabolites, and capillary hemodynamic responses [128]. Through the past two decades, pericytes have been increasingly receiving attention from researchers around the world owing to growing knowledge on their properties, which suggested they could behave as stem or progenitor cells not only in the mesodermal tissues [129–132] but also in the CNS [133]. Indeed, various types of evidence suggest that pericytes behave as mesenchymal stem cells in vivo [134], especially the fact that pericytes isolated through various techniques give rise to cultured cells with mesenchymal stem cell characteristics [135–137]. Experiments in which the progeny of cells expressing certain pericyte markers was genetically labeled indicate that pericytes give rise to differentiated progeny in situ in various tissues [138–142], while a recent fate tracing study indicates that does not happen [143]. Albeit in contrast with previous findings in this area, this latter study confirmed that isolated pericytes give rise to cultures with mesenchymal stem cell characteristics.

Most of the knowledge on mesenchymal stem cells comes from in vitro studies that used cultured cells with mesenchymal stem cell characteristics. The International Society for Cellular Therapy has proposed that these cultured cells be called mesenchymal stromal cells (MSCs) unless they are proved to be stem cells using strict criteria [144], and many studies on this cell population use this terminology, although it may be inaccurate. Even though MSCs, owing to their ability to differentiate into various mature cell types, may be used for tissue engineering, it is their ability to secrete trophic and immunomodulatory molecules [145–147] that render them so interesting for cell therapies. Therefore, the acronym "MSC" has been proposed to be used in reference to these cells, but under the designation of "medicinal signaling cells" [148] or any other that does not include "stem cells" [149].

Even though the question as to whether or not pericytes are able to give rise to mature cell types in situ warrants further experimentation, it is likely that pericytes may still be important for regenerative purposes even if they do not behave as stem cells in the body. Pericytes can give rise to cultured cells able to secrete a wide range of trophic and immunomodulatory molecules; consequently, it is possible that pericytes can secrete these types of molecules in vivo too. When tissue injury occurs, pericytes undergo a process called activation—their gene expression profile changes and they become proliferative. As MSC cultures endowed with the ability of secreting trophic molecules can be derived from prospectively isolated pericytes, it is likely that these MSCs possess characteristics of activated pericytes. An early study has

shown that some pericytes detach from blood vessels and migrate toward the cerebral tissue after CCI in rats [150]. Pericytes have been shown to become activated in a CCI model and progress to a state of *reactive pericytosis* [151] in reference to the well-known reactive gliosis observed in various types of CNS injuries. In that study, the number of pericytes in the pericontusional area decreased drastically after the injury, remained lower than normal up to 3 days after the injury, and doubled 5 days after the injury; additionally, the authors found that these activated pericytes remained limited by an area of reactive gliosis. Pericytes were shown to undergo apoptosis in a cortical organotypic slice culture subjected to hypoxia [152]. More recently, cells with characteristic pericyte markers have been detected and isolated from necrotic cerebral tissue affected by stroke; these cells were able to establish MSC cultures [153]. Human brain pericytes cultured under hypoxic conditions were shown to upregulate the expression of neurotrophin-3, which boosted NGF produced by astrocytes under hypoxia, contributing to a neuroprotective effect [154]. Whereas, noncultured pericytes isolated from human adipose tissue express message not only for neurotrophin-3 but also for other neurotrophic factors, such as NGF, BDNF, GDNF, and persephin [155].

Another important characteristic of pericytes that can be inferred from their relationship to MSCs is the ability to secrete molecules that interfere with the action of immune system cells, blocking inflammation [156]. However, it should be noted that pericytes do not become activated immediately upon TBI, and during the initial stages of the response to this injury, they may contribute to the recruitment of inflammatory cells. Some studies have presented evidence that pericytes may contribute to neuroinflammation owing to their ability to perceive infection-related or pro-inflammatory signals and respond through secretion of chemokines that recruit inflammatory cells [157]. In contrast, cultured pericytes have also been shown to be immunosuppressive, as they can inhibit the proliferation of T cells to the same extent as MSCs isolated through traditional methods [136]. It is likely, therefore, that pericytes display a pro-inflammatory phenotype at the onset of TBI, but become immunosuppressive as they undergo activation, thus contributing to maintenance of a balanced level of inflammation as the response to injury progresses.

Together, the information depicted above indicates that, under injury conditions such as TBI or stroke, a number of pericytes die; whereas, the surviving ones become activated, increase in number, and secrete a number of molecules that exert trophic and immunomodulatory effects on their surroundings, contributing to mitigate tissue damage caused by the insult, as previously suggested [155]. While further experimentation is warranted to gain insight into the details of this process, some questions, such as what is the mode of delivery of these soluble factors, are yet to be elucidated. Not long after the introduction of the concept that MSCs exert their reparative effects by means of paracrine factors, microvesicles were found to work as vehicles for the delivery of trophic molecules secreted by MSCs in acute tubular injury [158]. The same principle could well apply to activated pericytes in TBI, but that requires validation. On the other hand, this proposed action of pericytes during the response to TBI suggests that this process could be explored for the purpose of diagnostics and intervention. On one hand, the detection of pericyte-related molecules in the blood could provide information on the status of the lesion in acute TBI patients. On the other hand, knowledge on the main pericyte-derived molecules involved in trophic support of the surrounding cells in

the injured cerebral tissue may allow the development of novel pharmacological approaches to minimize tissue damage during the early stages of TBI. These pharmacological approaches could be further enhanced with the use of microvesicles as delivery vehicles.

3. Neuroprotective and neurorestorative processes in the traumatic penumbra

TBI triggers adaptive and maladaptive reactions to injury as damaged tissue attempts to recover [159]. The secondary injury events initiated in the traumatic penumbra lead to cellular dysfunction and death and determine the extent of brain damage. There may be overlapping signals and substrates between the initial trigger of injury and the subsequent endogenous mechanisms of neurorestoration and remodeling (**Figure 2**). The extended nature of these events and the multiplicity of targets offer opportunities for innovative therapeutic interventions [34, 160]. Undeniably, with therapeutic options centered on supportive care, trauma-related mortality and morbidity is an area with unlimited scope for advancement. Therefore, modulating endogenous repair mechanisms through enhancing neurogenesis could be an attractive approach for novel therapies for TBI [161].

Neurogenesis was once thought to be discontinued after brain development in mammals. However, certain areas of the brain retain the ability to generate neurons and glia [162, 163]. In these areas, neural stem cells (NSC) continue the developmental mechanisms to replace and replenish damaged cells. Neurogenic response includes three different phases: proliferation or generation of new cells, migration of new cells to target areas, and differentiation into proper cell types [164]. Many factors may affect adult neurogenesis, such as growth factors, exercise, enriched environment, or stress [161]. Studies have shown that TBI induces an upregulation of neurogenesis in varying types of TBI models [165]. In that sense, strategies such as supplementing varying types of trophic factors (i.e. BDNF, VEGF, S100β), manipulating transcriptional regulators, or other pharmacological approaches targeting different aspects of the endogenous neurogenic response have shown promising results improving functional recovery following experimental models of TBI [45, 155, 161, 165]. The potential use of cellular therapies to prevent secondary neural injury and promote recovery of injured tissue in trauma is an area of emerging investigation. Preclinical data indicate that restorative therapies targeting multiple parenchymal cells, including cerebral endothelial cells, neural stem/progenitor cells, and oligodendrocyte progenitor cells, enhance TBI-induced angiogenesis, neurogenesis, axonal sprouting, and oligodendrogenesis [45, 161, 166, 167].

Cellular therapies fall into two main categories of cell types: adult multipotent cells and pluripotent embryonic stem cells (ESCs). Adult multipotent cells, such as mesenchymal stem cells, multipotent adult progenitor cells (MAPCs), hematopoietic stem cells (HSCs), and bone marrow mononuclear cells (BMMNCs), have the capacity to generate a limited number of terminally differentiated cell types [168]. Cell-based therapies have been shown to improve outcomes in preclinical studies of trauma-related conditions via several mechanisms, which include: (i) production of soluble factors that regulate the exacerbated cell damage through

http://dx.doi.org/10.5772/intechopen.72156

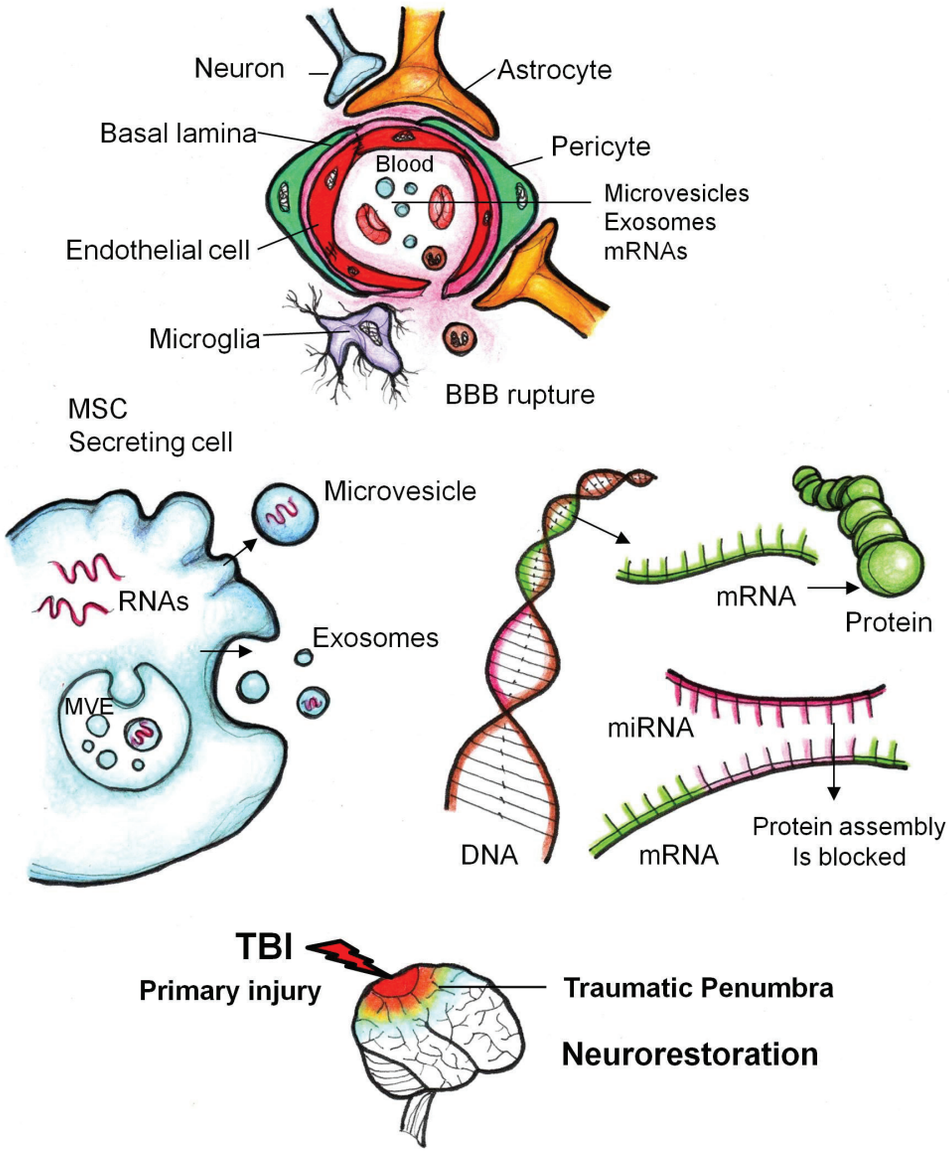

Figure 2. Schematic representation of neurorestorative mechanisms in the traumatic penumbra. Secondary injury progression in the traumatic penumbra can trigger mechanisms of neural tissue survival and recovery. After TBI, a pro-inflammatory phase occurs in the first hours and days and is followed by a reparative phase lasting from days to months. Secondary injury progression involves a cascade of events that results in cellular damage through diverse signaling pathways. In this scenario, components of the neurovascular unit may orchestrate several neurorestorative mechanisms in the traumatic penumbra. Of particular interest are the neurorestorative mechanisms associated to cellular therapies using mesenchymal stem cells (MSCs). MSCs may exert paracrine effects through secretion of microvesicles and exosomes, evoking endogenous reparative mechanisms, and functional recovery following TBI. Indeed, microvesicles and exosomes can deliver miRNAs to recipient cells, promoting gene regulation and enhancing neuroplasticity.

anti-inflammatory and cell-protective effects (i.e., growth factors, cytokines, microvesicles, exosomes); (ii) replacement of lost cells by differentiating and integrating into the damaged tissue microenvironment; and (iii) stimulation of endogenous regeneration of the injured tissue [167]. A multitude of cell types derived from a variety of tissues are currently under preclinical and clinical investigation for applications in trauma [167]. Multipotent MSCs have shown promise as an effective therapy for brain injuries in experimental models of acute brain

injury [165, 169–172] and potentially in clinical settings [173, 174]. However, previous studies show that only a small proportion of transplanted MSCs actually survive and few MSCs differentiate into neural cells in injured brain tissues. It seems that the predominant mechanisms by which MSCs participate in brain remodeling and functional recovery are likely related to their secretion-based paracrine effect rather than a cell replacement effect [45, 175–178] (**Figure 2**).

In effect, MSCs secrete or express factors that reach neighboring parenchymal cells either via a paracrine effect or a direct cell-to-cell interaction, or MSCs may induce host cells to secrete bioactive factors, which promote survival and proliferation of the parenchymal cells (brain remodeling) and thereby improve functional recovery [178, 179]. In addition to their soluble factors, therapeutic effects of MSCs may be attributed to their generation and release of exosomes [178]. Exosomes are endosomal origin small membrane vesicles released by almost all cell types and contain not only proteins and lipids but also messenger RNAs and microRNAs (miRNAs) [180]. Recent evidence indicates that exosomes have a crucial role in cell-to-cell communication. In contrast to transplanted exogenous MSCs, nanosized exosomes derived from MSCs do not proliferate and are less immunogenic and easier to store and deliver than MSCs [181–183]. Exosomes generated from MSCs improved functional recovery in rats after TBI [45, 175]. Exosomes play an important role in intercellular communication and are promising therapeutic agents because their complex cargo of proteins and genetic materials has diverse biochemical potential to participate in multiple biochemical and cellular processes, an important attribute in the treatment of complex diseases with multiple secondary injury mechanisms involved [45]. The refinement of MSC therapy from a cell-based therapy to cell-free exosome-based therapy offers several advantages, as it eases the arduous task of preserving cell viability and function, storage, and delivery to patient [175–178]. Further exploring the mechanisms by which the secretion-based paracrine effect of MSCs participates in neurorestoration and functional recovery following TBI is an outstanding opportunity for research. The development of cell-free exosome-based therapies for TBI may allow to deliver targeted regulatory genes (miRNAs) to enhance neuroplasticity and to amplify neurological recovery in TBI.

3.1. MicroRNAs

Previous studies have demonstrated that TBI induces extensive temporal changes in the expression of brain protein, mRNA and miRNA [184–186]. There has been a growing interest on the role of miRNA in normal CNS development and function, as well as in disease, including TBI, stroke, and neurodegenerative disorders. Mature, functional miRNA sequences are single-stranded RNA molecules composed of 20–25 nucleotides, which regulate gene expression post-transcriptionally through direct effects on 3′-untranslated region (3′ UTR) of mRNA, resulting in translation repression or mRNA degradation. One miRNA usually targets more than 100 genes [187]. In turn, a gene may be regulated by multiple miRNAs [188]. It is estimated that over 2000 miRNAs have been involved in the regulation of approximately 30% of the human protein-coding genes [189].

http://dx.doi.org/10.5772/intechopen.72156

Microarray analyses in animal models of TBI have shown a dynamic temporal regulation of miRNA expression. A report described that a peak of downregulated and upregulated miRNAs was observed after injury in rat cerebral cortex at 24 and 72 hours, respectively [190]. The research also revealed that a large number of miRNA was expressed at four different time points after injury: 136 at 6 hours, 118 at 24 hours, 149 at 48 hours, and 203 at 72 hours. In addition, only miR-21 expression was upregulated within all the four time points post injury, indicating that this miRNA may be involved in the complex process of TBI course. Another study analyzed changes in expression of 444 miRNAs within the hippocampus of rat TBI models at 3 and 24 hours after controlled cortical impact injury [184]. The results showed that 50 miRNAs had decreased expression levels and 35 miRNAs exhibited increased expression levels in the hippocampus after injury. A bioinformatic analysis of the predicted targets of a subset of the miRNAs with altered expression after TBI (miR-107, -130a, -223, -433-3p, -451, and -541) revealed that many of the target genes are involved in biological functions and processes that play a role in TBI pathophysiology, including transcription, proliferation, morphogenesis, and signal transduction. A study of microarray analyses of miRNA expression profile in rat hippocampus found that 10 of 156 reliably detected miRNAs were significantly and consistently altered from 1 hour to 7 days post injury [186]. Bioinformatic and gene ontology analyses revealed 107 putative target genes, as well as several biological processes that might be initiated by the dysregulated miRNAs, that include miR-144, miR-153, and miR-340-5p. Recently, a study analyzed the biological roles of about 600 genes that are targeted by 10 TBI-altered miRNAs [191]. Bioinformatic analysis suggested that neurodegeneration results from a global miRNA-mediated suppression of genes essential for maintaining proteostasis, the competing and integrated biological pathways that control the synthesis, folding, trafficking, and degradation of proteins. Notably, dysregulation of these essential genes would significantly impair synaptic function and functional connectivity of the brain.

MicroRNAs have emerged as novel serum diagnostic biomarkers for various diseases. The use of miRNA as biomarkers of brain injury in the serum or CSF could serve as tools for both diagnosing and stratifying TBI severity. As a biomarker of pathologic process, miRNA have several unique features, including cell-, tissue-, and disease-specific expression patterns [192, 193]. Studies of CSF in a rat model of mild blast TBI found a significant increase in levels of one miRNA, miR-let-7i, as early as 3 hours post injury [194]. Prediction analysis revealed that this miRNA targets TBI-related proteins, such as S100B and ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1), suggesting a possible role for miR-let-7i in regulating TBI pathology. Studies in patients with TBI have identified other miRNAs that may serve as diagnostic biomarkers for severe (miR-16, −92a, and −765) [195] and mild brain injury (mir143-3p and mir423-3p) [196]. A recent study using a microarray platform identified 14 miRNAs differentially expressed (10 upregulated and 4 downregulated) in CFS of severe TBI patients who remained unconscious for 2 weeks compared with controls [197]. Another study using microarray analyzed the expression of 754 miRNAs in serum of TBI patients with polytrauma aiming to find biomarkers able to discriminate between mild and severe TBI [198]. The analysis revealed two miRNAs (miR-425-5p and miR-502) that were downregulated in mild TBI at early time points and two miRNAs (miR-21 and miR-335)

that were upregulated in severe TBI. Moreover, miR-425-5p and miR-21 were predictors of 6-month outcome, but with differences regarding the timepoint when they were analyzed (miR-425-5p: until 1 hour and also between 4 and 12 hours from injury; miR-21: between 4 and 12 hours from injury). Overall, these studies have shown a potential role of miRNA as TBI biomarkers, but only miR21 has been identified as a candidate in more than one study [198, 199]. Given that pre-clinical optimism in finding good biomarkers in the past has not been successfully translated in clinical settings [200], further evaluation of these miRNAs with larger, multicenter patient cohorts is needed to explore their use as effective biomarkers applied to diagnosis and prognosis of TBI.

Besides the studies that evaluated miRNAs as TBI biomarkers, there was an interest about if miRNAs can be used as therapeutic targets. Hypothermia is a promising treatment for TBI patients because reducing body temperature attenuates neurological damage and improves functional outcomes [201]. A study presented an intervention on a specific miRNA-regulated pathway treating rats with an antagonist of miRNA-29c in an animal model of deep hypothermic circulatory arrest. The results showed that neurologic function, as assessed by vestibulomotor and cognitive performance tests, was improved in the pretreated animals as compared to the placebo group. Studies have shown that some miRNAs that show altered expression after TBI are also temperature sensitive and may be reduced under hypothermic conditions [202]. Since the pathways in which individual miRNAs can act are often numerous [203], further studies are needed to clarify the use of miRNAs in TBI therapy.

The analysis of miRNA in the TBI context may help in understanding the pathophysiology and possible treatments for TBI as it will provide insights into injury-related gene networks. However, the underlying molecular mechanisms of how miRNAs cause neurodegeneration or neurorestoration after TBI remains elusive. Investigating the role of miRNAs in neurological disorders is a new frontier for neurological research.

3.2. Extracellular vesicles and exosomes

MSCs have shown promise in the field of regenerative medicine, since exogenously administered MSCs target injured tissue, interact with brain parenchymal cells, and promote neurorestoration and recovery of neurological function after brain injuries [178, 191, 204, 205]. Despite the differentiation capacity of MSCs, the principal mechanism of their therapeutic action seems to be a robust paracrine capacity, related to their soluble factors as well as generation and release of microvesicles and exosomes [178, 205].

Extracellular vesicles (EVs) are membrane bound entities that transmit signals between cells via all cells and are found in all body fluids [206, 207]. The term "EV" includes microvesicles, exosomes, and oncosomes, among other vesicles that may be variously defined by origin, size, and markers [208–210]. EVs interact with target cells by binding to cell surface receptors, transfer of membrane proteins, membrane fusion, endosomal uptake, and cargo extrusion through vesicle-cell channels [206, 211, 212]. The EV protein and RNA compositions generally reflect that of progenitor cells [211]. Their ability to transport molecules and to target specific cell

populations raised possibilities for their development as therapeutic tools [212–214]. MSC-EVs seem to exert positive impacts on tissue-specific stem cells, promote angiogenesis, and suppress oxidative stress and fibrosis, and, noteworthy, may suppress pro-inflammatory responses in brain injury [215, 216]. Indeed, it was shown that MSC-EVs are able to convert M1 into M2 macrophages and, therefore, by switching pro-inflammatory into tolerogenic environments, MSC-EV administration might promote regenerative processes [170, 205, 212, 215, 217–221]. These therapeutic potentials position EVs as highly competitive alternatives to stem cells, as the EVs are likely to be safer than their parental secreting stem cells [212].

Exosomes are endosome-derived small membrane nanosized vesicles (30–100 nm in diameter) generated by almost all cell types and released into extracellular fluids, playing a pivotal role in intercellular communication [178, 215]. MSC is the most prolific exosome producer among the cell types known to produce exosomes [204, 222]. Exosomes contain various molecular constituents including proteins and RNAs from maternal cells. Among these constituents are miRNAs, which play crucial roles in mediating biological function due to their prominent role in gene regulation. Via exosomes, MSCs transfer their therapeutic factors, especially miRNAs, to recipient cells, and thereby modify gene expression [205, 208]. Although all exosomes contain the constitutive array of proteins, lipids, and RNAs, their contents vary in accordance with the cellular origin and the physiological or pathological condition of the cell and of its extracellular environment [204]. Most of the studies have demonstrated that MSC-derived exosomes contain various miRNAs, which participate in the cell-cell communication and alter the fate of recipient cells [204, 223, 224].

Overall, it has been widely accepted that the exosome secretion is an efficient adaptive mechanism since environmental challenges (such as stress conditions) can influence its composition, biogenesis, and secretion [204, 205, 225]. In fact, through preconditioning or genetic manipulation of neural cells, their exosome secretion profile can be modified [205, 215]. Of note, hypoxia and endothelial activation may be reflected in RNA and protein exosome composition [226, 227]. Furthermore, stressed cells that released exosomes conferred resistance against oxidative stress to recipient cells, suggesting that cells modulate intracellular stress situations and modify the surrounding environment via the secretion of exosomes [225, 228]. Also, the MSC exosome profile can be modified by pretreatment. When MSCs were *in vitro* exposed to brain tissue extracted from rats subjected to middle cerebral artery occlusion, the miR-133b levels in the released exosomes from MSCs were significantly increased [229]. Thus, there is a feedback between the MSC and its environment, and through which ischemic conditions will modify the exosome contents, and consequently, the secreted exosomes affect and modify the tissue environment [205, 230]. Regarding the brain, impacts of MSC-EV treatment were mainly studied in models for ischemic stroke and TBI and reduced apoptosis rates in affected brains, while promoted angiogenesis and neurogenesis [175–177, 215, 231–236]. Both systemic pro-inflammatory and neuroinflammatory cues were reduced following MSC-EV treatment [107, 215].

Administration of cell-free exosomes derived from MSCs is sufficient to exert therapeutic effects of intact MSCs after brain injury [176, 231, 232, 234]. The exosomes transfer RNAs and proteins to other cells which then act epigenetically to alter the function of the

recipient cells [175, 178, 205, 215, 225]. Previous studies indicated that MSCs promised to be an effective therapy for brain injury in TBI [175–177, 215, 231–236]. Instead of brain remodeling and functional recovery by cell replacement effects, evidence suggests that the major effects of neurorestoration were due to the paracrine effects of secretion-based factors such as MSCs-derived exosomes that may reduce neuroinflammation, promote neurogenesis and angiogenesis, rescue pattern separation and spatial learning impairments, and improve functional recovery after TBI in animal models [107, 176, 178, 191, 204, 205, 215, 216, 235–237]. In addition, as exosomes contain various miRNAs, which play a key role in modifying the phenotype and/or the physiology and modulating the cellular processes of the recipient cell, and miRNAs such as miR-21 could be potential therapeutic targets for interventions after TBI, the combination of miRNAs and MSC-derived exosomes might be a novel approach for the treatment of TBI [238]. That is, MSCs-derived exosomes that carry and transfer their cargo such as miRNAs to parenchymal cells may mediate brain plasticity and improve functional recovery after TBI [204]. Furthermore, another potential application of brain endothelial-derived eMVs could be as biosignatures for monitoring the health of the BBB in CNS conditions associated with trauma and neuroinflammation [239].

Hence, MSC-derived exosomes play an important role in intercellular communication and have shown promise in the field of regenerative medicine including treatment of TBI. The refinement of MSC therapy from a cell-based therapy to cell-free exosome-based therapy offers several advantages, as it eases the arduous task of preserving cell viability, storage, and delivery to patient [178, 215]. Indeed, due to the nanosize of exosomes, they can across the BBB and present lower risk of vascular occlusion than intact stem cells [204]. Developing a cell-free exosome-based therapy for TBI may open up a variety of means to deliver targeted regulatory genes (miRNAs) to enhance multifaceted aspects of neuroplasticity and neurorestoration in TBI [178, 205].

4. Conclusions and perspectives

Despite the burden of the morbimortality of neurotrauma, currently, there are no single agent treatments known to improve TBI outcomes. Furthermore, the diverse etiology and complicated pathogenesis of TBI make it difficult for clinical diagnosis and prognosis of outcome. Since TBI acutely triggers adaptive and maladaptive reactions to injury while damaged tissue attempts to recover, understanding the mechanisms of neural injury and neurorestoration is crucial for the development of novel therapeutic approaches. The secondary injury events initiated in the traumatic penumbra lead to cellular dysfunction and death and determine the extent of brain damage. Nevertheless, recent evidence shows that response to injury may also trigger neurorestoration. In the above context, microvesicles and exosomes secreted by MSCs may induce intrinsic repair mechanisms that sustain post-traumatic recovery. Indeed, evidence shows that cell-free, exosome-based therapies for TBI may deliver molecules that regulate gene expressions to enhance neuroplasticity and neurorestoration following TBI.

Acknowledgements

The research in the authors' laboratories has been funded by Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul and Conselho Nacional de Desenvolvimento Científico e Tecnológico.

Author details

Andrea Regner[1,2]*, Lindolfo da Silva Meirelles[1,2] and Daniel Simon[1,2]

*Address all correspondence to: regner@uol.com.br

1 School of Medicine, Lutheran University of Brazil, Canoas, RS, Brazil

2 Graduate Program in Cellular and Molecular Biology Applied to Health (PPGBioSaúde), Lutheran University of Brazil, Canoas, RS, Brazil

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