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REVIEW ARTICLE

Transcriptional Factors and Protein Biomarkers as Target Therapeutics in Traumatic Spinal Cord and Brain Injury

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Abstract: Traumatic injury to the spinal cord (SCI) and brain (TBI) are serious health problems and affect many people every year throughout the world. These devastating injuries are affecting not only patients but also their families socially as well as financially. SCI and TBI lead to neurological dysfunction besides continuous inflammation, ischemia, and necrosis followed by progressive neurodegeneration. There are well-established changes in several other processes such as gene expression as well as protein levels that are the important key factors to control the progression of these diseases. We are not yet able to collect enough knowledge on the underlying mechanisms leading to the altered gene expression profiles and protein levels in SCI and TBI. Cell loss is hastened by the induction or imbalance of pro- or anti-inflammatory expression profiles and transcription factors for cell survival after or during trauma. There is a sequence of events of dysregulation of these factors from early to late stages of trauma that opens a therapeutic window for new interventions to prevent/restrict the progression of these diseases. There has been increasing interest in the modulation of these factors for improving the patient's quality of life by targeting both SCI and TBI. Here, we review some of the recent transcriptional factors and protein biomarkers that have been developed and discovered in the last decade in the context of targeted therapeutics for SCI and TBI patients.

Keywords: Transcription factors, biomarkers, biofluid, regeneration, repair, spinal cord injury, brain injury, inflammation.

1. INTRODUCTION

Traumatic spinal cord injury (SCI) affects millions every year worldwide [1]. As a consequence, patients suffer from permanent impairment or loss of voluntary motor function and sensation below the level of injury. Clinical treatments are limited to prevent further damage to the injured spinal cord [2]. Two phases of damage occur after SCI, primary damage that is mechanically induced and secondary damage of the spinal cord which occurs from weeks up to years after injury and that is triggered by inflammation, disruption of ionic and neurotransmitter homeostasis, ischemia, edema and leakage of the blood-spinal cord-barrier [3]. These various types of mechanisms that damage the spinal cord affect gene expression in several different ways. These changes in gene expression can cause more harm by mediating secondary damage such as apoptosis, inflammation, demyelination, microgliosis, and astrogliosis, or they can be neuroprotective and even beneficial for regeneration [4, 5]. A promising approach to improve recovery after SCI would be a combined therapy down-regulating transcription factors that are involved in secondary damage and, on the other hand, up-regulating transcription factors that are involved in neuroprotective and regenerative processes such as neurite outgrowth and remyelination.

On the other hand, TBI is also one of the major health problems rendering high mortality and disability rates across the globe even in patients younger than 45 years of age. It is affecting more than 2.5 million people in Europe and the USA every year [6]. TBI is a common injury related to sports, military and domestic environments, with these settings accounting for more than 90% of brain injuries in the USA. It affects neuronal function and cognitive abilities for years [7]. Multiple complex mechanisms are involved in the progression of TBI, including inflammatory responses, altered cerebral perfusion, oxido-nitrosative stress, apoptosis, ionic imbalance and glutamate excitotoxicity [8]. There are no clinically useful therapeutic agents available due to the complexity of secondary pathologies induced by TBI. Therefore, it is of utmost importance to explore pharmaco-therapeutics which may be useful in the modification of post-TBI complications. Studies have demonstrated that various transcription factors play an important role in the TBI-induced pathological damages by regulating mechanisms including apop-

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tosis, inflammation, oxido-nitrosative stress and microglia activation. Further, these transcription factors could be useful therapeutic targets to develop drugs for the management and treatment of TBI and its complications [6].

Since clinical manifestations are preceded by molecular changes in the injured tissue, detecting earlier or more accurate indicators to predict treatment response and recovery potential represents a clear yet unmet clinical challenge. A recent study indicated that cerebrospinal fluid (CSF) biomarker analyses are more predictive of neurological recovery than magnetic resonance imaging (MRI) analyses [9]. In this review, we described the laboratory and clinical research related to the transcription factors and protein biomarkers in the affected tissues and biofluid samples. There are different cell death, inflammation, apoptotic, myelination and regeneration associated transcription factors and protein biomarkers (NSE, S100-β, Tau, TNF-α, IL-6, MMPs, NF, GFAP, MBP, UCH-L1) discussed after SCI (NF-kB, SMAD1, ATF-3 & ATF-4, c-JUN, Olig1, Arpc1b) and TBI (NF-kB, CEBPD, Pax6, Spi1).

1.1. Transcriptional Factors as Therapeutic Targets in SCI

In this review, we describe the inflammatory and apoptotic factor nuclear factor kappa B (NF-κB), the anti-inflammatory and regenerative factor Arpc1b, (Actin Related Protein 2/3 Complex Subunit 1B) the anti-apoptotic factor JUN, the transcription factor Olig1 that is associated with myelination, and neuritogenic transcription factors SMAD1, activating transcription factor-3 (ATF-3), and ATF-4. These are the main transcription factors that can be related to the development of stage-specific targeted treatment for functional recovery in patients after SCI. These transcription factors and others have been studied at different time points after SCI by various groups of researchers; we have summarized them in the following sections.

1.1.1. NF-κB

NF-κB is expressed in most mammalian cells and can occur as a homo and heterodimer that can be assembled from five subunits: p50, p52, p65 (RelA), RelB, and c-Rel [10, 11]. The transcription factor NF-κB is one key molecule in secondary damage caused by inflammation after an injury [12, 13]. NF-κB is essential for the inflammatory response of macrophages, microglia and astrocytes [10, 14, 15], induces apoptosis in neurons [16, 17] and regulates myelination in the central nervous system (CNS) [18]. NF-κB occurs in rats that underwent contusion SCI and is activated from 30-minute up to at least 72 h after injury in macrophages/microglia, endothelial cells, and neurons at the lesion site. One month after injury, TRAF2-TRAF6 (TNF Receptor Associated Factor) centered signaling network activates NF-κB activity [19]. NF-κB was co-localized with the inflammatory marker inducible nitric oxide synthase, which indicates a functional effect of the NF-κB occurrence [20]. Triptolide improved the functional recovery and reduced microglial activation in rats that underwent SCI. After triptolide treatment, micro-RNA96 expressions increased which leads to downregulate the translation of IκB kinase α and β [21]. IκB kinase α and β are known to activate the transcription factor NF-κB [22]. Paeoniflorin improved motor function recovery of rats after SCI by inhibition of NF-κB activity [23]. It is reported that celastrol reduces the expression of NF-κB, attenuates inflammation and microglia activation and improves functional recovery after SCI in rats [24]. Hyperbaric oxygen therapy after SCI promoted neurological function and decreased the NF-κB level in the blood of SCI patients [25].

1.1.2. ATF-3 and ATF-4

ATF3 and ATF4 are members of the cAMP response element-binding (CREB) transcription factor family. ATF3 was found to be upregulated in motor and sensory neurons after axotomy and ATF4 was overexpressed after ischemia in the brain and the spinal cord [26, 27]. ATF3 is activated after inducing stress. The expression of ATF-3 increased over time after nerve root injury [28]. Also, activating transcription factor 3 promoted regeneration in adult zebrafish [29].

Neural cell adhesion molecules (NCAM) like L1 play an essential role in neural development and repair after injury of the CNS. For example, triggering the L1 function after SCI improves functional recovery [30]. CREB is an essential transcription factor for the L1 function [31]. Several small organic compounds were identified as L1 agonists that bind to it with the function of activating binding sites and triggering an L1 function [32]. Thus, it is reasonable to hypothesize that these L1 agonists activate CREB. From these L1 agonists, duloxetine, piceid, trimebutine, tacrine, and phenelzine had beneficial effects on functional recovery in mice and/or zebrafish [32-34].

1.1.3. SMAD1

The transcription factors of the SMAD protein family mediate the cell signaling of the TGF-β superfamily growth factors. The TGF-β superfamily is divided into two subfamilies, the BMPs, and TGF-βs. SMAD1 belongs to the group of receptor-regulated SMADs which are bound to membrane-bound serine/threonine kinase receptors [35]. Lai *et al*. suggested SMAD1 as one of the major transcription factors at two weeks after SCI [19]. SMAD1 can be phosphorylated and activated by the bone morphogenetic protein receptor kinase which might lead to enhanced axonal growth of dorsal root ganglion neurons [36]. This indicates a direct role of SMAD1 in sensory axon regeneration after thoracic SCI. Smad1 can be activated by TGF-β [37] and by BMP7 type I receptor ALK2 which leads to increased Erk1/2 phosphorylation [38]. BMP signaling plays an essential role in the development of the CNS and ALK2 is expressed in the brain and spinal cord [39]. Thus, it may be promising to screen for ALK2 agonists which activate specifically SMAD1 and trigger neurite outgrowth after SCI. However, neurogenic heterotopic ossification occurs in 10-53% of SCI patients. Neurogenic heterotopic ossification is a complication after SCI, in which formations of new extraosseous bone in the soft tissue surrounding peripheral joints occur [40]. Heterotopic ossification occurs in a mouse mutant that has a constitutively active form of ALK2 which can be blocked by the retinoic acid receptor-γ agonist [41, 42]. Thus, treating SCI patients with an ALK2 agonist might cause heterotopic ossification if it does not apply very dose and time specified manner in the CNS.

1.1.4. c-JUN

The c-Jun amino-terminal kinases 1 and 2 are members of the mitogen-activated protein kinases family and positive regulators for c-Jun [43]. c-Jun was the first described oncogene. Jun can form a heterodimer with Fos *via* their leucine zipper domains and forms the transcription factor AP-1 [44]. c-Jun can also form a dimer with the activating transcription factor 3 and induces the anti-apoptotic factor Hsp27. Consequently, protein kinase B is activated which inhibits apoptosis and induces nerve elongation. Houle *et al*. found that cervical, but not thoracic SCI increases the c-Jun expression in brain stem neurons [45]. Application of a gel foam saturated with ciliary neurotrophic factor triggered a further increase of the c-Jun expression in the brain stem. Phosphorylation of c-Jun by c-Jun amino-terminal kinases leads to apoptosis. Oleanolic acid improves functional recovery after SCI attenuates the blood-spinal cord barrier leakage, reduces apoptosis and inflammation in the spinal cord, and attenuates the phosphorylation of c-Jun N-terminal kinase [46].

1.1.5. Olig1

In the CNS, oligodendrocytes are the myelinating glia cells and the basic-helix-loop-helix transcription factors Olig1 and 2 are essential for their maturation and myelination of axons [47]. After SCI, a long-term death of oligodendrocytes occurs which leads to widespread demyelination of spared axons after the injury [48]. This implies considering the activation of transcription factors that trigger the remyelination of axons in combined therapy to improve recovery after SCI. The transcription factor Olig1 is essential for the differentiation of oligodendrocytes in the mouse brain [49]. Olig1 was a downregulated transcription factor at three days and one week after SCI [50]. It was found to be expressed during the maturation and regeneration of human oligodendrocytes and it is associated with the repair of the central nervous system in mice [51, 52]. If rats were transfected with Olig1 DNA after SCI, moderate remyelination was observed, but if the animals were transfected with Olig2 DNA, tumor growth was observed. Only if the rats were transfected with Olig1 and Olig2 DNA was a robust effect on remyelination observed and the animals had also an improved functional recovery and no tumor growth [53]. Thus, a treatment that activates both, Olig1 and Olig2, might have the most promising effect on remyelination after SCI.

1.1.6. Arpc1b

Jin *et al*. suggested that Arpc1b is one of the main transcription factors responsible for the upregulation of differentially expressed genes at three days and two weeks after SCI [54]. Arpc1b is a part of the actin-related protein (Arp2/3) which mediates the formation of branched actin filaments in the cytoplasm and promotes the actin polymerization in the nucleus. Arpc1b regulates with its latter function gene transcription and repair [55]. Besides, Arpc1b binds directly to and activates Aurora A, and together with PAK1 and Aurora A, Arpc1b is involved in cell cycle regulation [56]. Arpc1b-deficiency causes severe inflammation and infection which indicates anti-inflammatory properties of this transcription factor [57]. Besides, Arpc1b is important for generating F-actin bundles and Arpc1b deficiency leads to impaired function of $CD8^+$ cytotoxic T lymphocytes. Especially in these T lymphocytes, it is essential to have a rapid reassembling of the F- actin cytoskeleton network. Patients with mutations in the Arpc1b have fewer $CD8^+$ cells and have an immunodeficiency. Since $CD8^+$ T lymphocytes that express perforin attenuate the functional recovery and prolonged the leakage of the spinal cord-blood barrier, it might be beneficial to block Arpc1b in T lymphocytes [58].

1.2. Transcriptional Factors as Therapeutics Target in TBI

Numerous studies have demonstrated the dysregulation of various transcription factors including CEBPD, Pax6, Spi1, Tp73, and NF-kB post-TBI. Further, transcription factors such as Tcf7l2 and CEBPD influence the gene networks in the brain regions of TBI patients [7]. Thus, we can speculate that transcription factors regulate the post-TBI pathological damages such as inflammation, apoptosis, oxidative stress, and microglial activation. In this section, we will discuss various transcription factors, their role in the pathogenesis of TBI, and how these factors might be useful as therapeutic targets for the management and treatment of TBI and post-TBI pathologies (Table **1**).

1.2.1. CEBPD (CCAAT/enhancer-binding Protein Delta)

CEBPD belongs to the CCAAT/enhancer-binding protein family, and functions as transcription factors in many biological processes, including cell differentiation and growth, cell death, metabolism, inflammation and immune responses [59]. It is induced by a variety of extracellular stimuli such as interleukin-1 (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), lipopolysaccharide (LPS), and prostaglandin-E2 [60-62]. These inflammatory stimuli activate the CEBPD through various signaling pathways such as phosphatidylinositol 3-kinase, p38, JAK, JNK, and PKA signaling pathways [63-67]. The study of Wang *et al*. suggested that IL-1β in astrocytes activates CEBPD which causes Sod1 gene stimulation leading to oxidative stress through ROS generation [68]. It performs different functions depending on cell type and their environment and accommodates according to the situation. CEBPD (also known as NF-IL6β) is a transcriptional factor that regulates immune-inflammatory responses. Studies have revealed that CEBPD and its target gene IGF-1 are up-regulated in the cortex in various TBI experimental models, including a controlled cortical impact mouse model [69] and a weight-drop rat model [70].

According to Lipponen *et al*. [6], the Library of Integrated Network-Based Cellular Signatures (LINCS) studies demonstrated that the expression of the CEBPD transcription factor is upregulated by numerous compounds. Tranylcypromine, an MAO-I antidepressant, showed a neuroprotective effect in a mouse model of TBI [71]. CEBPD upregulation with fluspirilene and chlorpromazine also showed promising neuroprotective effects against ischemia in a rat model [72]. Compounds such as vorinostat, valproate, and tamoxifen also provided protection against neurodegeneration and improved neurological imbalance in a rodent model of TBI, ischemia, and stroke by up-regulating the expression of CEBPD [73-75]. Importantly, these studies indicate that

Table 1. Summary of transcription factors as therapeutic targets in TBI.

TF	Expressing Cells/tissue		Role of TF	TF Modulator	Major Findings	Refs.
	Brain Area	Cells				
CEBPD	Cortex Thalamus Hippocampus	Astrocytes Glial cells Macrophages	Inflammation Immune response Oxidative stress	Tranylcypromine	Upregulated CEBPD expression	[71, 119]
				Fluspirilene Chlorpromazine	Upregulated CEBPD expression in all 3 brain areas after 3 months in lateral FPI induced-TBI in rats	[72]
				Vorinostat	Neuroprotection and improved neurological behavior Downregulated glial activation after 24 h in an intracerebral hemorrhage stroke model in mice	[73]
				Valproate	Neuroprotection, anti-inflammatory, and anti-apoptotic action in a rat model of TBI and ischemia by up-regulating pCREB and CEBPD	[6, 75]
				Tamoxifen	Reduced expression of ERα and CEBPD in neuronal and glial cells	[6, 74]
Pax6	Cortex Thalamus Hippocampus	Astrocytes Microglia Dentate gyrus	Brain development Adult neurogenesis Brain patterning Neuronal migration Neural circuit formation processes	SKF-96365	Decreased BBB permeability in an *in vitro* model of bovine brain microvessel endothelium	[81]
				Thioproperazin Methylphenidate	Improved spatial memory Increased dopamine Enhanced Pax6 expression	[82, 120]
				Rolipram	Decreased infarct size and improved neurological behavior Decreased pro-inflammatory cytokines after focal cerebral ischemia	[84]
				Apicidin	Decreased Pax6 expression Enhanced apoptosis of MCF-7 cells Reduced NO and iNOS expression	[6]
				Proadifen	Downregulated Pax6 in cortex, thalamus, and hippocampus	[6]
Spi1	Cerebral cortex	Microglia	Microglial survival T cells B cells Neutrophils Monocytes Macrophage differentiation/ development	U0126	Decreased expression of Spi1 Decreased infarct size in MCAO model Microglial activation in SCI	[90]
				Genistein	Neuroprotection against various models of brain injury by down-regulating Spi1 expression	[92]
Tp73	Cortex		Cell cycle regulation Apoptosis Neurological development Ciliogenesis Fertility	Wortmannin	Akt (Protein kinase B) inhibitor beneficial against TBI	[6]
				Trimipramine	Decreased neuroinflammation and oxidative stress-induced neurotoxicity Reduced TNF-α & NO levels in brain Upregulated Tp73 transcription factor	[121]
NF-kB	Cerebral Cortex Hippocampus Amygdala Cerebellum Hypothalamus	Olfactory lobes	Inflammatory response Cell cycle Cell survival Neuronal differentiation	ω-3 PUFA	ω-3 PUFA supplementation attenuated inflammation by altering microglial activation through NF-κB downregulation leading to neuroprotection in TBI models	[106]
				Astaxanthin	Attenuated inflammation and apoptosis post-TBI in cultured astrocytes by inhibiting NKCC1 and NF-κB expression	[122, 123]
				Metformin	Inhibited microglial activation-mediated inflammation by downregulating NF-κB and MAPK signaling thereby improving neurobehavioral function post-TBI	[124]
				Resveratrol	Reduced neuronal autophagy and inflammatory cascade by inhibiting IL-1β, TNF-α, and NF-κB in rat TBI	[125]
				Dexmedetomidine	Neuroprotective action in acute TBI Downregulated NF-κB and NLRP3	[126]

(Table 1) contd….

TF	Expressing Cells/tissue		Role of TF	TF Modulator	Major Findings	Refs.
	Brain Area	Cells				
ATF3	PNS Cortex Hippocampus	Astrocytes Microglia Macrophages	PNS axon regeneration Inflammatory processes	NNZ-2566	Exhibited anti-inflammatory and neuroprotective action by enhancing expression of ATF3 *in vitro*	[127]
				Laquinimod	Upregulated Atf3 transcription factor in microglial cells in TBI model	[128]
Nrf2	Cortex Hippocampus Striatum Amygdala	Neurons Astroglial cells Microglia	Antioxidant response Anti-inflammation	SFN	Reduced oxidative stress and neuronal damage in TBI animals by up-regulating Nrf2 expression in cortex	[129]
				tBHQ	Reduced TBI-induced brain edema and neurologic deficits Up-regulated Nrf2	[130]
				Baicalin	Neuroprotective effect *via* activation of Akt/Nrf2 pathway	[131]
				N-acetylcysteine amide	Improved neurobehavioral/neuroprotection by activating Nrf2-ARE	[132]
				Valproic acid	Exhibited neuroprotection and reduced neurological deficits, brain edema by preventing microglial activation and inflammatory responses through up-regulation of autophagy and antioxidative enzymes *via* activation of Nrf2/ARE pathway in a TBI rat model	[133]
				Asiatic acid	Neuroprotective effect against TBI *via* reducing oxidative stress and enhancing Nrf2 and HO-1 expression in rats	[134]

the upregulation of CEBPD expression might ameliorate post-TBI pathologies.

1.2.2. Pax6

Pax6, a highly conserved pro-neurogenic transcription factor belonging to the paired box family, is profoundly expressed in reactive astrocytes after ischemic stroke. It plays an important role in brain development and the conversion of astrocytes into neurons (adult neurogenesis). It is also involved in brain patterning, neuronal migration, and neural circuit formation processes [76]. Pax6 has regenerative potential after ischemic injury in the hippocampus by controlling the differentiation and migration of neuronal progenitor cells (NPC). It is an important neurogenic factor used as a marker of neural precursor status and differentiates fibroblast cells into neuronal progenitor cells. It is highly expressed in adult neural progenitor cells of the subventricular zone of the olfactory bulb and the subgranular zone of the dentate gyrus [77]. Pax6 expression is involved in adult neurogenesis in the damaged area after brain injury. Pax6 is overexpressed in the sub-granular zone cells in transient forebrain after ischemic brain injury model [78].

These findings suggest that the conversion of astrocytes to neurons in ischemic brain injury is governed by the upregulation of PAX6, thus it might be a potential therapeutic target for TBI treatment. Shen *et al*. reported that ischemic stroke enhanced the expression of PAX6 thereby favoring the conversion of astrocyte to neuron in astrocytes of adult rat brain through vascular endothelial growth factor (VEGF) [79]. Mo *et al*. found that enhanced expression of Pax6 induced neurogenesis in astrocytes and attenuated brain injury in a transient middle cerebral artery occlusion (MCAO) model of cerebral ischemic injury in adult rats [80]. Transcriptomics analysis carried out by Lipponen *et al*. revealed that SKF-96365, thioproperazine, and rolipram are strong up-regulators of Pax6 in ischemic stroke models [6]. SKF-96365, a calcium channel blocker, decreased the blood-brain barrier permeability (a major TBI pathology) in an *in vitro* model of bovine brain microvessel endothelial cells [81].

Preclinical studies have shown that there is a decrease in dopamine levels after TBI in the rat CCI model. Thioproperazin, a neuroleptic drug, enhanced dopamine release thereby improving the behavioral anomalies in the rat CCI model [82]. Further, rolipram also upregulates Pax6 gene expression and decreases cytokine release in both human and animal T cells. Animal studies demonstrated that rolipram prevented hippocampal neuronal damage, reduced infarct area, attenuated neuroinflammation, and improved the neurological symptoms in cerebral ischemia models [83-85]. Findings demonstrated that the up-regulation of the Pax6 transcription factor is a potential therapeutic approach for TBI by reducing neuroinflammation and preventing reduced dopamine levels. Moreover, both CEBPD and Pax6 upregulation could be beneficial therapeutic targets for the treatment of TBI and associated pathologies.

1.2.3. Spi1

The ETS-family transcription factor SPI1 (also referred to as PU.1) is highly expressed in microglia and important for its survival [86]. Transcriptomics studies revealed that Spi1 and its gene target Lsp1are upregulated in microglia and cortex after TBI. Further, Lsp1expression is also enhanced in the cerebral cortex of the rat brain in a controlled cortical impact-induced TBI model [69, 70]. Myeloid and B-lymphoid cells play an important role in the progression of the inflammatory pathway after TBI. Spi1 plays a significant role in T cell, B cell, neutrophil, monocyte, and macrophage differentiation and development. Thus, it is speculated that Spi1 is one of the important transcription factors involved in TBI pathogenesis [87, 88].

Studies have suggested that the downregulation of Spi1 could be a therapeutic target for the treatment of TBI. To

support this hypothesis, researchers showed that U0126 has a beneficial effect in various animal models of brain injury such as by reducing the infarct area in middle cerebral artery occlusion in rats, lesion size in controlled cortical impact model in mice, and preventing microglial activation in SCI-induced ischemia in rats [89, 90]. Further, Genistein, a phytoestrogen with wide pharmacological activities, also showed a protective effect against cerebral ischemia and TBI-induced behavioral anomalies in animals [91, 92]. Transcription factor Tp73 and its target genes are also up-regulated in the cortex region of the brain after TBI. It is a p53 related protein important for cell cycle regulation and apoptosis after DNA damage. It is also involved in neurological development, ciliogenesis, and fertility processes [93].

Preclinical studies have reported that Tp73 up-regulation in the cortex of the rat brain regulated the metabolic and inflammatory response in the lateral fluid percussion injury model of the TBI [94]. Both *in vitro* and *in vivo* studies have indicated that Wortmannin and Trimipramine upregulate Tp73 and inhibit the pro-inflammatory cytokines and increase the anti-inflammatory cytokines. Tp73 could be a therapeutic target since its upregulation showed beneficial effects against TBI [6].

1.2.4. NF-kB

The NF-kB family of transcription factors plays a significant role in the inflammatory response, cell survival and neuronal differentiation in the CNS. Stimuli, such as oxidative stress, cytokines, chemokines, neurotransmitters, neurotrophic factors, neurotoxins, and experimental injury induce NF-kB in neuronal and glial cells [95, 96]. NF-kB activation performs different functions in different cells; for example, NF-kB activation in glial cells is responsible for mediating the inflammatory response whereas in neurons it is involved in differentiation, synaptic plasticity, and neuronal development and survival [97-102].

Preclinical and clinical studies have demonstrated that NF-kB levels are increased in fluid percussion brain injury in humans and brain tissue of rats after the controlled cortical impact [103, 104]. Elevated levels of NF-kB increased brain injury size and altered blood-brain barrier function in controlled cortical impact trauma model in transgenic mice [105]. These studies indicate that the type of cell and nature of trauma is the deciding factor in exerting beneficial or harmful effects in the case of NF-kB signaling. Therefore, activation of NF-kB in microglia provides a detrimental effect while in neurons it exerts a beneficial action. Chen *et al*. showed that ω-3 PUFA prevented TBI-induced microglial activation and neuroinflammatory response by regulating the HMGB1/NF-κB signaling pathway [106]. Taken together, these studies have suggested that NF-κB could be a potential therapeutic target for developing drugs to treat TBI and associated pathologies.

1.3. Protein Biomarkers as Target Therapeutics in the Traumatic SCI and TBI

Protein biomarkers in the biofluid are playing a significant role in identifying and targeting windows for treating SCI and TBI patients. There are several clinical trials also undergoing studying the role of these protein biomarkers in blood, CSF, *etc*. (https://clinicaltrials.gov). The current state and need for biofluid biomarkers in SCI and TBI have been extensively summarized in numerous recent reviews [107-111]. For example, in their review of SCI biomarkers, Kwon *et al*. focus on protein biomarkers' potential utility in clinical trials and highlight three main uses: injury severity stratification at the acute stage when physical examinations may not be possible, long-term monitoring and prognostic prediction, and serving as a clinical endpoint and/or marker of treatment efficacy [108]. Similar applications apply to TBI, such as identifying cases of mild TBI (mTBI, *i.e*. concussion), determining the need for a CT scan, and prognostic prediction in both mild and severe TBI [112]. Other potential applications include the identification of possible drug targets and pathways, understanding the molecular mechanisms of injury, and predicting the onset of associated conditions (urinary tract infections; UTIs, pressure ulcers; PUs, polytrauma) [113, 114]. Studies involving biomarkers in TBI are much more numerous than those in SCI, though the shared neuropathologies of both types of injury have allowed the former to influence the direction of the latter. For this review paper, we are only highlighting human studies that target protein biomarkers in SCI and TBI. Some of the most studied biomarkers in TBI and SCI are included in Table **2**, though this is not an exhaustive list.

While all of the listed biomarkers are elevated in cases of TBI and/or SCI, it should be emphasized that the "Possible Indications" given for each are not always conclusive, due to limited study sizes and time points analyzed, confounding variables (explained in detail below), and often contradictory findings between studies. These biomarkers are drawn from CSF or blood components (sera, plasma), though there is evidence for the presence of biomarkers like S100-β in saliva as well [115]. In general, biomarkers are often present in both types of fluids. While blood-based biomarkers are desirable over CSF-based ones due to the easy accessibility of peripheral blood, they suffer from limitations including dilution and low concentrations in the blood, increased degradation and clearance *via* hemolysis, lymphatic, renal, and hepatic pathways, and lack of specificity due to the expression of some of these biomarkers by non-CNS tissues [109]. In contrast, molecules in CSF present a more representative and exclusive indication of the state of the CNS.

Besides the choice of sample fluid, the time course and biokinetic profile of a biomarker is perhaps the most critical consideration when designing a diagnostic or prognostic assay. Biomarkers can be classed into acute, sub-acute, and chronic categories depending on the time of their emergence into CSF or blood following an injury. For example, concentrations of biomarkers such as AB42 and MBP are not elevated until 2-5 days post-injury, so studies or assays that attempt to detect such molecules during the acute phase of injury may suffer from misleading results [111, 116]. Additionally, biomarkers of any class may persist for months in the CSF, as has been found for S100β, GFAP, and NF-H [117], though this is less likely for blood-based biomarkers due to the aforementioned issues of clearance and degradation. The biokinetic profiles of certain biomarkers have also been correlated with prognostic outcomes, such as a rise in

Table 2. Protein biomarkers in SCI and TBI human studies.

Protein	Associated Pathologies	Physiological Source	Possible Indications	Refs.
NSE	SCI TBI	Neuronal injury Erythrocytes	• **SCI (CSF)**: Severity stratification and discrimination of motor complete (AIS A+B) and incomplete patients (C+D) • **TBI (CSF)**: Severity stratification; discrimination of inflicted and non-inflicted TBI (by concentration-time course)	[117, 118, 135, 136]
S100-β	SCI TBI	Astrocyte injury Marker of BBB disruption	• **SCI (CSF)**: Severity stratification and discrimination of motor complete (AIS A+B) and incomplete patients (C+D); Lower concentrations in AIS A patients who improved; Prognostic outcome prediction (in a panel of biomarkers) • **TBI (sera)**: Correlation with prognosis (death and/or favorability of outcome)	[107, 117, 137-139]
Tau P-Tau C-Tau	SCI, TBI Epilepsy Alzheimer's	Axonal injury Expression in liver, kidneys, and testis	• **SCI (CSF)**: Severity stratification; a prognostic outcome • **TBI (sera/plasma)**: Prediction of intracranial damage after mTBI (need for CT); prediction of severe outcomes/death; severity stratification	[112, 138, 140]
TNF-α IL-6 MMPs	SCI, TBI Autoimmune diseases	Neuroinflammation	• **SCI (CSF & sera)**: Severity stratification; clinical outcome prediction; higher levels may be correlated with complications such as UTI, PU, neuropathic pain • **TBI (CSF)**: Prognostic outcome associated with elevated levels and/or time trajectory; maybe correlation with injury type (isolated vs. polytrauma)	[112-114, 138, 141]
NF-H NF-L	SCI TBI	Axonal injury	• **SCI NF-H & pNF-H (CSF & sera)**: Severity stratification; Discrimination of motor complete (AIS A+B) and incomplete patients (C+D) • **SCI NF-L (CSF & sera)**: Good correlation with severity (motor complete vs. incomplete) and prognostic outcome; possible drug response marker (minocycline); classification of injury type; degree of neuronal damage • **TBI NF-H (sera)**: Increase in concentration linked to worse outcomes/death; severity stratification • **TBI NF-L (sera)**: Indicative of delayed recovery/PCS after mTBI	[112, 117, 118, 139, 142-146]
GFAP	SCI, TBI Stroke Diabetes mellitus Alzheimer's	Astrocyte injury	• **SCI (CSF & sera)**: Severity stratification, discrimination of Grade A+B from C+D; Prognostic outcome prediction (in a panel of biomarkers); Much higher concentrations in upper SCI than lumbar injuries • **TBI (sera)**: Correlation with prognosis (death and/or favorability of outcome); Severity stratification; Detection of intracranial lesions and need for CT scan	[112, 117, 118, 137-139, 147-150]
MBP	SCI TBI	Oligodendrocytes (myelination) Immune cells	• **TBI (sera)**: Correlation with prognosis and death	[151, 152]
UCH-L1	SCI TBI	Neuronal injury	• **TBI (sera)**: Detection of intracranial lesions (in a panel with GFAP); severity stratification; prognostic outcome prediction	[139, 148, 149, 153]

serum NSE concentration over 48 h being correlated with death in SCI patients [118] and a high IL-6 trajectory profile in CSF over 5 days linked to unfavorable outcomes in TBI patients [114]. For these reasons, studies aiming to establish new biomarkers or extrapolate upon the findings of those existing for TBI and SCI should consider taking samples from patients at multiple time points, including some for long-term (6-12 months) analysis.

CONCLUSION

The most widely used predictors for functional recovery following trauma are based upon clinical observation and MRI imaging. These clinical observations cannot sufficiently predict a patient's response to drug candidates, nor are they useful in developing other potential treatments. Over the last decade, several groups of scientists have made exceptional progress in the field of SCI and TBI in terms of identifying the role of transcription factors and protein biomarkers at different stages of SCI and TBI progression of cell damage. These pro-apoptotic pathways have several functional components that may vary with the severity of injury and location of injury including cell to cell type. The common factors in neuronal loss/apoptosis pathways lead to the identification of the factors that are candidates for the exploration of the therapeutics for SCI and TBI. There are several candidates already identified and there is still a need to define the precise contribution of each transcription factor/protein biomarker to each stage after trauma including neuronal death and repair. Besides, protein biomarkers offer a new approach to patient care, with the potential to predict injury severity and assist in developing new clinical therapeutics.

Since clinical manifestations are preceded by molecular changes in the injured tissue, detecting earlier or more accurate indicators to predict treatment response and recovery potential represents a clear yet unmet clinical challenge. For these complex traumas such as SCI and TBI that involve several cell types, including neuronal or glial cells as well as other peripheral cells that migrated to the injury site, the precise or accurate stage-specific therapeutic approach may require identification of either the specific transcription factor and protein biomarker or a combination of these. To achieve maximal functional recovery in SCI and TBI patients, more studies are needed either in experimental or clinical settings as there are only a few clinical studies related to protein biomarkers only (https://clinicaltrials.gov). It will be useful and beneficial for the affected lives after SCI and TBI including patients, their caretakers, and family members.

LIST OF ABBREVIATIONS

AIS	=	Abbreviated injury scale
ALK2	=	Activin receptor-like kinase-2
AP-1	=	Activator protein 1
ARE	=	Antioxidant responsive element
Arpc1b	=	Actin Related Protein 2/3 Complex Subunit 1B
ATF3	=	Cyclic AMP-dependent transcription factor 3
BBB	=	Blood-brain barrier
BMPs	=	Bone morphogenetic proteins
cAMP	=	3',5'-cyclic adenosine monophosphate
CD8	=	Cluster of differentiation 8
CEBPD	=	CCAAT/enhancer-binding protein delta
CNS	=	Central nervous system
CREB	=	cAMP response element-binding
CSF	=	Cerebrospinal fluid
DNA	=	Deoxyribonucleic acid
Erk	=	Extracellular signal-regulated kinase
ERα	=	Estrogen receptor alpha
FPI	=	Fluid percussion injury
GFAP	=	Glial fibrillary acidic protein
HMGB1	=	High-mobility group protein 1
HO-1	=	Heme oxygenase-1
Hsp27	=	Heat shock protein 27
IGF-1	=	Insulin-like growth factor-1
IL-6	=	Interleukin-6
IκB	=	The inhibitor of nuclear factor-κB
JAK	=	Janus Kinase
JNK	=	c-Jun N-terminal kinase
L1	=	A transmembrane protein member of the L1 protein family (L1CAM)
LINCS	=	The library of integrated network-based cellular signatures
LPS	=	Lipopolysaccharide
MAO-I	=	Monoamine oxidase inhibitors
MAPK	=	Mitogen-activated protein kinase
MBP	=	Myelin basic protein
MCAO	=	Middle cerebral artery occlusion
MMPs	=	Matrix metalloproteinases
MRI	=	Magnetic resonance imaging
NCAM	=	Neural cell adhesion molecule
NF-H	=	Neurofilaments-heavy chain
NF-kB	=	Nuclear factor kappa-light-chain-enhancer of activated B cells
NKCC1	=	Na-K-Cl co-transporter 1
NPC	=	Neuronal progenitor cells
NSE	=	Neuron-specific enolase
Olig1	=	Oligodendrocyte transcription factor 1
PAK1	=	Serine/threonine-protein kinase PAK 1
PCS	=	Post-concussion syndrome
PGE2	=	Prostaglandin-E2
PKA	=	Protein Kinase A
PU	=	Pressure ulcer
PUFA	=	Polyunsaturated fatty acids
RNA	=	Ribonucleic acid
ROS	=	Reactive oxygen species
S100-β	=	S100 calcium-binding protein B
SCI	=	Spinal cord injury
TBI	=	Traumatic brain injury
TGF-β	=	Transforming growth factor-beta
TNF-α	=	Tumor necrosis factor-α
TRAF2	=	TNF receptor-associated factor 2
UCH-L1	=	Ubiquitin carboxy-terminal hydrolase L1
USA	=	The United States of America
UTI	=	Urinary tract infection
VEGF	=	Vascular endothelial growth factor

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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