Chapter 10

Role of Systems Biology in Brain Injury Biomarker Discovery: Neuroproteomics Application

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Abstract

Years of research in the field of neurotrauma have led to the concept of applying systems biology as a tool for biomarker discovery in traumatic brain injury (TBI). Biomarkers may lead to understanding mechanisms of injury and recovery in TBI and can be potential targets for wound healing, recovery, and increased survival with enhanced quality of life. The literature available on neurotrauma studies from both animal and clinical studies has provided rich insight on the molecular pathways and complex networks of TBI, elucidating the proteomics of this disease for the discovery of biomarkers. With such a plethora of information available, the data from the studies require databases with tools to analyze and infer new patterns and associations. The role of different systems biology tools and their use in biomarker discovery in TBI are discussed in this chapter.

Key words Neurotrauma, Traumatic brain injury TBI, Biomarkers, Systems biology tools, UCHL1, SBDPs, NSE, GFAP, S100β

1 Introduction

As systems biology and the field of proteomics continue to rapidly evolve, fundamental changes are being catalyzed toward the future of health care worldwide [1]. Research in these fields holds major implications in medicine, especially in enhancing the ability to improve diagnosis and treatment of diseases. We are currently witnessing an increased interest in personalized medicine; therefore, bridging the gap between basic research and clinical applications becomes imperative. One research-based proteomic tool at the forefront of personalized medicine is biomarkers. Biomarkers are quantitative physiological indicators of a biological disease or injury state that allow for diagnosis and assessment of the disease process and help monitor the response to treatment [2]. In clinical

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medicine, biomarkers have uses in diagnosis, prognosis, and determination of physiological status. They can manifest through vital signs, X-rays, and other imaging modalities as well as through laboratory analysis of biological indicators such as ribonucleic acid (RNA), metabolites, lipids, peptides, proteins, or autoantibodies against proteins released from the diseased/injured tissue [3]. Interestingly, much of medical practice involves interpreting and monitoring biomarkers, the diagnostic accuracy of which is quantitatively denoted by sensitivity and specificity.

Traumatic brain injury (TBI) is a neurotrauma caused by mechanical force applied to the head. It is of great concern since it is a leading cause of death worldwide [2, 4]. While traffic accidents and assault are the main causes of TBIs in younger populations, falls are the predominant reason for TBIs in older individuals, followed by traffic accidents [5–7]. A subset of the adult population in the USA, deployed military servicemen and women, are particularly vulnerable and are at high risk for TBI. They are often exposed to a variety of combat traumas. In fact, recent studies report that approximately 20% of Operation Enduring Freedom/Operation Iraqi Freedom veterans have clinical diagnosis of TBI [8]. More than 30,000 military personnel suffered a TBI in 2012. Another 13,000 or more people had a TBI in 2013 [9]. In addition, this population often exhibits comorbidities such as posttraumatic stress disorder (PTSD) or depression that can lead to an increased risk of misdiagnosis [10–14].

TBI does not describe a physical injury to the head, such as laceration, contusion, or fracture, but rather the change in brain function as a result of damage from an external force to the brain. This can be caused by various ways. One example is the case of rapid backward and forward motion caused by rapid acceleration and deceleration, such as that experienced during motor vehicle accidents or shaken-baby syndrome [15]. Another way is through impact due to falling, especially among the elderly, or caused by sporting injuries. TBIs can also result from blunt force trauma such as an assault or from exposure to blasts resulting in rapid changes in pressure. Penetration wounds to the head caused by high-velocity projectiles can also cause TBI [15, 16].

TBI is heterogeneous, as it is highly variable and characterized by several severities (mild, moderate, severe) in addition to multiple injury types (concussive, nonpenetrating, penetrating). It occurs in two phases: first as primary injury which then leads to secondary injury. Upon impact, primary injuries occur when there is deformation of the gray and white matter of the brain, causing a disruption of cell membranes and the release of intracellular contents [15]. Hours and days following the initial insult, secondary injuries occur as a result of brain edema, free radical formation, or the release of inflammatory mediators. These secondary injuries may exacerbate the initial injury through the mediation of cell damage or death

resulting in a poor neurological outcome. Brain damage may include excessive neuronal activity caused by unregulated glutamate release, changes in neurotransmitter levels, hemorrhage, changes in cerebral blood flow, damage to axons, and/or disruptions to the blood–brain barrier (BBB) [16]. After the incidence of primary injuries, the focus of TBI patient management becomes prevention or reduction of the extent of secondary injuries.

The transfer of energy that occurs following the insult can cause structural, pathological, and functional changes in the brain that may yield neurological, cognitive, and behavioral symptoms that can be long lasting. Symptoms of TBI may include confusion, concussion or altered levels or loss of consciousness, seizure, coma, focal sensory deficits, or motor neurologic deficits. The long-term effects of TBI may include depression, anxiety, psychiatric disorders, memory loss, reduced motor function, reduced social functioning, impaired vision, insomnia, dizziness, mood disturbances, and deficits in cognition. Moreover, substance abuse was found to be associated with individuals who have experienced a TBI, and for many patients, family life and relationships may be adversely affected [15]. Prominent neurological symptoms include headache, vomiting, nausea, imbalance, vision, dizziness, fatigue, drowsiness, sensitivity to light or noise, and sleep disturbances. Of the cognitive symptoms, problems with attention, concentration, memory, processing speed, and executive functions (e.g., working memory and decision making) are most frequently reported. Existing literature indicates that in the majority of patients, these symptoms will resolve within 10 days to 2 weeks of the injury [17]. In more than 25 % of the cases, however, symptomology can continue long beyond this timeframe [18–20].

In this book chapter, we will tackle the role of systems biology tools, bioinformatics, and biomarker research in the area of TBI. In particular, we will underline the need for biomarker discovery in TBI and how the major advances in the field of proteomics will further aid this quest for enhanced TBI patient care management.

2 Putting It All Together: Data Mining

Enormous amounts of data generated from high-throughput technologies require data mining tools to analyze data and visualize patterns, which are otherwise tedious and sometimes impossible to detect. An example of data mining methods is correspondence analysis which investigates the relation between features and data samples. Feature selection is another method that allows visualization and comprehension of data patterns. The use of these methods in TBI biomarker discovery has been documented in several reports.

A Multiple Correspondence Analysis (MCA) can be used to detect relationship patterns in data collected on multiple variables pertaining to the participants. These data points and variables are projected on graphs known as principal components that help visualize the clustering of data points and account for the highest amount of variance in the data. Points that cluster in proximity are indicated to have similarities while those that cluster further away from each other have more differences. Martinez et al. performed MCA on data collected from chronic TBI patients undergoing either cognitive training or a control program. The analysis was done by grouping the patients based on the type of head injury they suffered and the corresponding patterns in cognitive performance including assessment of memory, attention, and task switching. The analysis yielded 53% of variance detected by the first principal component based on cognitive performance in all assessments. The second principal component detected 8. 79% of variance based on assessment of memory between the different injury types. Moreover, principal component projections for individuals with blast-related injuries were clustered in the low cognitive performance side compared to projections of other injury types that were less clustered and more evenly distributed between high and low cognitive performances. This shows that MCA accurately clustered cognitive deficits detected in individuals suffering from blast-related injuries. This clustering is quite logical given the complex nature of this trauma that includes the initial shockwave followed by acceleration and deceleration shearing forces, and hence the devastating cognitive damage [21].

Recently, Ou et al. analyzed microarray data previously published by Shojo et al. [22] in Gene Expression Omnibus (GEO) database for differential gene expression profiles in rat models of TBI. After normalizing gene expression intensities with a robust multiarray average (RMA) algorithm, differentially expressed genes (DEGs) between control rats and those subjected to moderate fluid percussion of different durations were identified. This was done through implementing a *t*-test to calculate the probability of DEGs between different groups and the respective *p*-values. In turn, the *p*-values were analyzed in R [23] using a *q*-value package [24] to compute the false discovery rate. Significant GEDs were chosen based on a q-value $< 5\%$. In this study, microarray data was obtained on a TBI model from Gene Expression Omnibus (GEO) database and analysis of the altered gene expression profile was conducted. Results suggested that gene expression profiles were significantly altered in the late period after TBI. These altered genes were mainly involved in steroid biosynthesis, cell cycle, metal ion transport, inflammation, and apoptosis [25].

Given the enormity and heterogeneity of raw data generated from basic science research, there is a need to accelerate the translation of preclinical knowledge into clinical therapeutics. Accordingly,

Nielson et al. have recently developed a database for translational neurotrauma research dubbed Visualized Syndromic Information and Outcomes for Neurotrauma-SCI (VISION-SCI) [26]. In this study, syndromic analysis on data from several species published in the last two decades was collected, which allowed the identification of conserved biological mechanisms of recovery that can be used in monitoring of therapy of neurotrauma patients.

3 Deciphering Molecular Mechanisms of Neurotrauma Using Proteomics

Proteins are major effectors driving cell behavior. Accordingly, the field of proteomics was established and devoted entirely to the systemic study of proteins [1]. The goal of proteomics research is to understand the expression and function of proteins on a global level which requires more than simply cataloguing the proteome; it involves the characterization of protein structure, function, and interaction in all its complexities. The ability to capture and compare all of this information between two cellular states is essential for understanding cellular responses [1]. Thus, proteomics is becoming a well-established approach for protein biomarkers discovery with the ability to identify proteome dynamics in response to experimental stimuli [27]. The collective number of published reports and citations utilizing proteomics in brain injuries is steadily increasing [9].

TBI neuroproteomics studies have used biofluids and injured tissue to identify clinical markers that may correlate with injury severity and may be able to determine therapeutic response [28]. In one study, altered differential proteins were evaluated in normal human postmortem cerebrospinal fluid (CSF) [29]. Since postmortem CSF resembles a model of massive brain injury and cell death, its use could allow for identification of protein markers of injury through comparison of the protein profile of postmortem CSF with that of the CSF of individuals with brain injuries. In this study, 172 of the 229 proteins identified were novel and not previously described. Postmortem CSF was thus used to evaluate altered protein levels similarly occurring after traumatic insult. Additionally, differential proteins of intracellular origin were identified in the CSF. This corroborates the suggestion that protein leakage into the CSF occurs following brain injury [30, 31]. Since neuronal-specific proteins leak from injured brain directly to the CSF, this is crucial to identifying protein markers [27].

CSF in a rat model of TBI was also evaluated in another proteomic study by Siman et al. [32] In this study, tau protein fragment of 17 kDa, αII-spectrin breakdown product of 150 kDa, and collapsing response mediated protein-4 were released as a general response to brain insult. The findings from the experiments may suggest surrogate biomarkers for injury severity and may have

the potential for increasing our understanding of the mechanism of brain injury by shedding light on the process of how these proteins are observed in the CSF biofluid at specific time points [32]. In another study, Waybright et al. [33] characterized the proteome of human ventricular CSF obtained from hydrocephalic patients. They were able to identify more than 1500 unique proteins which were then compared with the Human Proteome Organization serum proteome database. Human ventricular CSF was then concluded to contain a large array of proteins unique to CSF [33].

Studies undertaking the catalog of cellular elements under various conditions and in various organisms are well underway and becoming increasingly possible with the maturity of global technologies. This is where systems biology should rise to meet the demand of high-throughput data by helping understand how the elements discovered are coordinated to form functional biological systems. Though systems level integration of data is still in its infancy, a number of new concepts have emerged (such as those discussed earlier). The importance of this data integration is twofold: (1) it allows for minimization of noise inherent in data generated through the high-throughput biology and (2) it serves to reveal new biological phenomena not readily apparent from any single analysis [1]. Ultimately the goal is to characterize the information flow through protein networks that reflect the interconnection between the extracellular microenvironment and gene regulatory networks in response to effector functions of development and physiological responses.

Studies conducted by Kobeissy et al. used Pathway Studio to construct a functional interaction map linking 59 proteins significantly increased or decreased post-TBI [4, 34]. The altered pathways were found to be associated with inflammation, cell survival/proliferation, and synaptic plasticity. In another recent study by Feala et al. [35], around 32 TBI biomarker candidates from the literature were analyzed. These biomarkers' associations with four KEGG pathways were found to be statistically significant, three of the four of which (apoptosis pathway, amyotrophic lateral sclerosis pathway, and Alzheimer's disease pathway) were relevant to TBI or the nervous system. By performing a PPI network analysis, they were able to show that the 32 TBI biomarker candidates were tightly connected to each other on a PPI network of over ten thousand proteins.

4 Inferring Molecular Biomarkers in Neurotrauma

Systems biology study of neurotrauma is moving toward revealing the complex molecular processes induced by brain trauma [36]. The field of proteomics serves as a powerful tool in this endeavor, showing great promise in the identification of specific proteins

implicated in TBI. Proteomics can lead toward the discovery of many candidate biomarkers to help ascertain the mechanisms of TBI. Already biomarkers have demonstrated great success and reliability in diagnosis of some diseases such as in cardiac injury. For instance, cardiac troponin proteins (T and I) and various forms of brain natriuretic peptide (BNP) are routinely used to facilitate accurate diagnosis of congestive heart failure and myocardial infarction in patients presenting with chest pain.

There is an increased recognition for the need of biomarker discovery which has led to the Biomarkers Consortium launched in October of 2006 as a public–pharmaceutical industry partnership that includes the National Institutes of Health (NIH), the Food and Drug Administration (FDA), the Centers for Medicare and Medicaid Services, in addition to pharmaceutical industry representatives, nonprofit organizations, and advocacy groups [37]. Importantly, an NIH workshop on improving diagnosis of TBI for targeting therapies stressed the need for biomarker identification [38].

However, despite the efforts in brain injury research, there are no clinically validated biomarkers to diagnose TBI. The efforts to identify sensitive, universal, and specific biomarkers are hindered mainly by challenges such as brain tissue complexity and the heterogeneous nature of brain injury models [27, 39]. Even though extensive studies are being pursued to move protein biomarkers to clinical validation, the work is still under development.

Biomarkers can be discovered through traditional strategies such as knowledge-driven or discovery-driven methods, which are also called "top-down" and "bottom-up" methods [36]. While the knowledge-driven strategy infers biomarkers through understanding disease pathology and molecular mechanism, it is restricted by our knowledge of diseases. Due to the lack of understanding of the molecular mechanisms of action of TBI, it is a less effective approach in the search for TBI biomarkers. On the other hand, the discovery-driven strategy employs high-throughput technologies to screen a large number of genes and proteins to determine those whose abundance change could indicate TBI. The limitations to this approach may be inherent noise and the semiquantification nature of high-throughput technologies may lead to false positives passing the screening [36].

In 2006, Kobeissy and colleagues identified 59 proteins 48 h post-TBI using a rat model and they found that proteins that were decreased in abundance included CRMP-2, glyceraldehyde-3-phosphate dehydrogenase, microtubule-associated proteins MAP2A/2B, and hexokinase [34]. Proteins that were upregulated included C-reactive proteins, transferrin, and breakdown products of CRMP-2, synaptotagmin, and αII-spectrin. The changes in these proteins were confirmed by western blotting. This study generated candidate biomarkers that can aid in the evaluation of the severity and progression of injury as well as in the development of possible therapies.

The use of a systems biology-based approach to drug discovery and development for TBI based on the advances in genomics, proteomics, bioinformatic tools, and systems biology software has been shown [28]. In 2012, Boutte and colleagues conducted a proteomic analysis and brain specific systems biology in a rodent model of penetrating ballistic-like brain injury (PBBI) where they used a combination of 2D-gel electrophoresis and Mass Spectrometry (MS) to screen for biomarkers. After identifying 321 upregulated and 65 downregulated proteins 24 h post PBBI compared to sham controls, pathway analysis indicated that these proteins were involved in neurite outgrowth and cell differentiation. Among these proteins that indicated consistent increase in the brain tissue and CSF at several time points post PPBI were UCHL1, tyrosine hydroxylase, and syntaxin-6.

While systems biology is interested in complex biological processes as they are governed by the interactions of multiple genes and proteins, it may seem that the intention to search for a TBI biomarker candidate from TBI-relevant pathways or interaction network is against the principle of systems biology. This is why a panel of biomolecules serving as TBI biomarker profiles should be suggested by systems biology [36]. In fact, GFAP and UCHL1 have been proposed together as TBI biomarkers [40]. There are huge numbers of possible combinations of multiple proteins in which systems biology will prove useful in identifying most effective combinations of proteins for TBI biomarker panels.

Soluble biomarkers ideal for use in the diagnosis of TBI should be absent in the peripheral tissue unless the brain tissue has been injured [10]. The ideal biomarker should be a small molecule that can be rapidly measured in the serum or CSF for a reasonable period after injury. Additionally, it would be ideal for the biomarker to have a level that corresponds to the degree of brain injury.

5 Traumatic Brian Injury Candidate Biomarkers Identified After Applying Systems Biology Concepts to Neuroproteomics

Listed below are examples of the most studied candidate protein biomarkers for TBI and have shown high sensitivity and specificity in independent studies (Table 1). UCHL1, SBDPs, and neuron-specific enolase (NSE) are neuronal and axonal protein biomarkers whereas GFAP and S100β are glial-specific markers [41]. Combining neuroproteomic methods with relevant animal models, systematic assessments have been made to identify additional protein biomarkers for TBI [34, 42–45].

5.1 Ubiquitin Carboxy-Terminal Hydrolase L1 Protein (UCHL1)

UCHL1 is a cysteine protease of relatively small size (around 25 kDa and comprises 1–2% of the total soluble protein in the brain) that is predominantly expressed in neurons, although it is also expressed in small amounts in neuroendocrine cells. UCHL1 is known to hydrolyze the C-terminal bond of ubiquitin or unfolded polypeptides [10,

Table 1
Putative biomarkers of traumatic brain injury

TBI biomarker	Source of sample	Origin cell type	Function	Use
UCHL1	Blood serum	Neurons	Ubiquitin	BBB disruption
	Blood plasma	Neuroendocrine	Hydrolysis	Injury outcome
	CSF	Tissue		
SBDPs	Blood serum	Neuron axons	Activation of intracellular proteases	Axonal damage
	Blood plasma	Presynaptic terminals		Injury severity
	CSF			
NSE	Blood serum	Neurons	Glycolytic pathway enzyme	Injury severity
	Blood plasma	Oligodendrocyte		
	CSF			
GFAP	Blood serum	Astroglia	Structural filament	Injury severity
	Blood plasma			Outcomes
	CSF			
S100β	Blood serum	Glial cells	Intracellular signaling	BBB disruption
	Blood plasma	Astrocytes	Calcium homeostasis	Injury severity
	CSF			

CSF cerebrospinal fluid, *BBB* blood–brain barrier, *NSE* neuron-specific enolase, *GFAP* glial fibrillary acidic protein, *UCHL-1* ubiquitin carboxy-terminal hydrolase L1, *TBI* traumatic brain injury, *SBDP* Alfa II spectrin breakdown product

41, 46]. Mutations in UCHL1 may be associated with Parkinson's disease and other neurodegenerative disorders [46]. Importantly, UCHL1 has previously been shown to be elevated in patients with severe TBI [10] and several publications have indicated that UCHL1 can be a biomarker for TBI. UCH-L1 CSF and serum levels were found to be elevated in patients with severe TBI correlating with the severity and outcome of injury [15, 47–49].

The elevation of levels of UCH-L1 post-TBI is proposed to be secondary to BBB dysfunction [50]. In addition, several recent studies also demonstrated the detectability of UCH-L1 in blood following mild TBI [51–53].

5.2 α II-Spectrin Breakdown Products (SBDPs)

Among the novel biomarkers studied for their clinical relevance in TBI, alpha II-spectrin is a cytoskeletal protein primarily found in neurons and is concentrated in axons and presynaptic terminals

[41, 54–56]. Though alpha II-spectrin is present in various nucleated cells, and most tissues, its high abundance and enrichment of brain qualifies it as a candidate biomarker, especially if combined with another brain-specific marker [37].

The breakdown products (SBDPs) of alpha II-spectrin is due to activation of intracellular proteases such as calpain and caspase in the brain after TBI, thus reflecting axonal damage [10, 54, 57]. While SBDP150 (molecular weight 150 kDa) and SBDP145 (molecular weight 145 kDa) are characteristics of calpain activation (associated in acute necrotic neuronal cell death), SBDP120 is produced by action of caspase-3 (associated with delayed apoptotic neuronal death) [10, 27]. Elevation levels of SBDPs in CSF were reported as a possible outcome predictor in patients with severe TBI, rather than mild TBI [54, 58–60]. Not only can SBDPs provide important information on severity of brain injury, but also on underlying pathophysiological mechanisms associated with necrotic and apoptotic cell death.

5.3 Neuron-Specific Enolase (NSE)

Highly expressed in neuronal cytoplasm, neuron-specific enolase (NSE) is a glycolytic pathway enzyme of different isoforms [10, 54]. The gamma-gamma homodimer isoform is highly enriched in the neuronal cell body [61], but is present in multiple other cell types, such as erythrocytes, platelets neuroendocrine cells, and oligodendrocyte [62]. NSE has been shown to have the sensitivity and specificity to detect neuronal cell death [63]. Increased CSF and serum levels of NSE have been reported after TBI, with levels that are detectable within six hours postinjury [2, 10]. Studies have also shown that NSE levels in CSF and serum correlate with severity of injury and clinical outcome [10, 41, 54, 64, 65]. However, the specificity and sensitivity of NSE have been reported as unsatisfactory [66–71]. The limitations on NSE as a biomarker of TBI may be due to the high sensitivity of NSE to hemolysis [72]. Therefore, it has been proposed that NSE is not to be used as a standalone screening biomarker for brain injury [71].

5.4 Glial Fibrillary Acidic Protein (GFAP)

Glial fibrillary acidic protein (GFAP) is an intermediate filament protein that forms networks that support the astroglial cells. First reported in 1971, GFAP is found exclusively in the astroglial cytoskeleton [54, 61, 73]. Of the candidate biomarkers available for TBI, GFAP has been assessed in different studies of clinical studies [74–77]. Part of what makes this an ideal biomarker candidate for TBI is that this protein is not found outside the central nervous system [78]. Even if the body is subjected to multiple forms of trauma, GFAP does not increase without brain injury [79, 80]. Thus, GFAP can be considered as a potential biomarker-specific glial injury.

GFAP was studied in both CSF and sera of patients with TBI [56, 66, 81–83]. Upregulation of GFAP follows damage to the astroglial cells (astrogliosis) [10]. Astroglial cells react during

injury by generating more GFAP. Evidence points to elevated serum GFAP levels in several types of brain damage, including TBI [79, 82, 84]. GFAP can also predict death or unfavorable outcomes [83, 85] and validation studies in humans are already ongoing [3] according to the proceedings of the military mild TBI diagnostic workshop [10].

5.5 S100β

One of the earliest and most extensively studied biomarkers of brain damage is S100β which belongs to a family of low molecular weight (9–13 kDa) calcium-binding S100 proteins important in intracellular calcium regulation [9, 86]. S100β is mainly found in astroglia and Schwann cells [87, 88]. S100β aids in cell homeostasis and prevents neuronal death by increasing cellular calcium concentrations [89]. It also acts as a neurotrophic factor, promoting neurite outgrowth and astrocytic proliferation [2]. Its potential as a biomarker for TBI is found in its increased concentration in the CSF and serum after injury [90]. This protein is not influenced by hemolysis and has a biological half-life of two hours. Studies have correlated this biomarker with injury and outcome [91–94]. The first study to emphasize the role of serum S100β in TBI patients was done by Ingebrigtsen et al. who showed that elevated serum S100β levels in patients with negative CT results are correlated with occurrence of postconcussive symptoms [95].

Several other studies have investigated the clinical prognostic value of elevated serum S100β levels in TBI patients with conflicting evidence [80, 83, 94, 96–104]. Interestingly, in 2010 Unden and Romner did a meta-analysis of studies on mild head injury in which CT findings and S100β were compared in the acute phase of injury [105]. In the 12 eligible articles (total 2466 patients) they discovered a high sensitivity of low levels of S100β in the prediction of negative CT findings. In fact, Unden and Romner suggested that a low serum S100β level (<0.10 μg/L) in the first three hours after injury has more than 90% negative predictive value of the presence of clinically relevant CT findings. These findings are further confirmed by other studies which also suggest the use of serum S100β as a substitute for CT in assessment of mTBI patients [106, 107]. S100β has also been studied as a useful indicator of patients with intracranial lesion [94].

However, even if those studies demonstrate the sensitivity of the use of S100β, there are several limitations on this biomarker candidate. Since S100β is not specific to the brain, it can show up outside the central nervous system [9, 39, 61, 108, 109]. Therefore, general trauma without brain injury can increase levels of this protein [110]. In fact, S100β can be elevated in bone fractures without head injury [111–113]. Despite the abundance of studies reporting serum S100β elevation, studies of CSF levels of S100β in TBI is still limited [56]. Additionally, elevated S100β occurs after hemorrhagic shock, correlating the concentration to shock severity

[91, 114, 115]. Because of this, S100β cannot be used as a single biomarker for TBI. The ratio of S100β against GFAP has been investigated, instead of S100β alone, and this was used to determine brain damage and prognosis [84].

6 Conclusion

The short-term and long-term effects of TBI, in the absence of any FDA approved treatment [116], highlight the urgency for detection of biomarkers to improve the quality of life and decrease mortality among patients with TBI. Multiple individual soluble biomarkers currently show promise in the diagnosis of brain injury, with the ability to predict degree of injury and clinical outcome. The breakdown products of α-II spectrin and the serum levels of UCH-L1 were found to change in a similar manner to that of S100β and GFAP postinjury. Hence all these putative biomarkers can be used as important predictors of outcome in patients with moderate-to-severe brain injury [55, 117]. Given the limitations in each biomarker, it is likely that no single biomarker will have adequate sensitivity and specificity for accurate diagnosis of TBI. The better approach may be in using bioinformatics to discover and combine biomarkers in order to improve diagnostic accuracy. The field of neuroproteomics is still in the developing stage and its full potential remains to be explored to reveal the integral molecular and cellular mechanisms of gene dynamics involved in brain injury.

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