Editorial

Applications of Proteomics in Traumatic Brain Injury: Current Status and Potential Prospects

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Introduction

Traumatic brain injury (TBI), one of the most common causes of death and disability worldwide, has become a public health crisis. TBI can be classified as primary injury or secondary injury. The leading causes of primary injury are falls, motor vehicle traffic, and struck.[1] The delayed, secondary injury cascades with highly complex pathophysiological events occur following primary mechanical insults and are regarded as contributing factors influencing the recovery of TBI.[2] Over the past few decades, a considerable number of clinical trials and animal experiments have sought to develop therapeutic strategies.[3] The efforts to lower the risk of secondary injury and improve outcomes for TBI patients can be ascribed to the process of "squeezing oxygenated blood through a swollen brain".[4]

It is well accepted that accurately diagnosing and monitoring TBI is important for early care and rehabilitation. The clinical severity of TBI is traditionally categorized as mild, moderate, or severe on the basis of clinical features.[5] Neurological assessments (Glasgow Coma Scale [GCS], Acute Physiology and Chronic Health Evaluation II, Injury Severity Score, and Sequential Organ Failure Assessment) and neuroimaging techniques (computed tomography and magnetic resonance imaging) are consistently being applied as diagnostic tools. Unfortunately, diagnosing and predicting outcomes of TBI are still challenging due to the insufficient sensitivity and specificity of the available tools.[6] Neuron-specific enolase, S100B, glial fibrillary acidic protein, neurofilaments, tau, and several inflammatory cytokines have been identified as candidate protein biomarkers in TBI patients recently.[7,8] There is a growing need for reliable biomarkers that can reflect and track the TBI process; however, no Food and Drug Administration-approved biomarkers are currently available for TBI.[9] Emerging proteomics studies have proven to be powerful and have the potential for the discovery and validation of TBI biomarker candidates.[10] We try to present current status as well as the potential prospects of proteomics technology in both TBI patients and animal models in this article.

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Proteomics Studies in Traumatic Brain Injury Patients

With the ongoing development of proteomics technology, molecular signatures may be obtained and the possible mechanisms underlying TBI can be further elaborated.[10] Differentially expressed levels of proteins or peptides may be discovered for characterizing the pathological states of TBI, and new protein biomarkers should be identified. Clinical specimens from TBI patients, such as the brain tissue, cerebrospinal fluid (CSF) and blood (serum or plasma), are appropriate samples for proteomics analysis. Blood and CSF samples can be collected routinely, thus providing systematic protein profiling and valuable information about the status of injured brain suffering from the disruption of blood-brain barrier. Conversely, the brain tissues from human subjects are usually collected during brain biopsies or from the postmortem examination. The biggest advantage of brain tissue proteomics is the small area of the brain selected for analysis, which allows for a more specific and intuitive

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understanding of the injury process. Previous studies have revealed that these differentially expressed proteins might be predominantly associated with oxidative damage,[11] glial cell differentiation,[12] neurodegenerative processes,[13] acute phase response,[14] and complement cascade.[15]

The GCS has become a conventional diagnostic tool for grading TBI severity into three categories: mild (GCS: 13–15), moderate (GCS: 9–12), and severe (GCS: 3–8). Proteomics technology serves as a complementary approach for TBI severity stratification. A recent proteomics study from Ganesan's laboratory revealed serum protein biomarkers in patients with mild, moderate, and severe TBI.[16] Moreover, proteomics technology has been designed to identify possible markers present during the acute[13] and chronic[15] TBI phases. Candidate biomarkers for brain injury show their clinical utility in monitoring TBI-associated pathologies and distinguishing the different severity strata. Although the protein candidates have shown their diagnostic value, they fail to be independent from clinical measurements due to heterogeneity and complexity. Multiple proteomic biomarkers have been investigated in severe TBI patients,[12-15] which may provide efficient information for predicting recovery. Information relating to biomarkers in mild and moderate TBIs, by contrast, is relevantly scarce in published studies.

Proteomes from the pediatric population suffering from TBI have already demonstrated several biomarkers available for clinical utility.[17] Compared with adults, infants and adolescents are more likely to sustain a TBI and experience the late effects.[1] However, it can be difficult for the early and accurate diagnosis of pediatric TBIs due to the limited recognition of signs and symptoms. Thus, proteomics has the potential to identify and assess pathophysiological conditions in pediatric TBI patients. Nevertheless, proteomics studies in pediatric TBI are rarely undertaken.

Proteomics Studies in *In vivo* and *In vitro* Models of Traumatic Brain Injury

Investigators have developed numerous animal models of TBI, such as cortical impact injury, fluid percussion injury, weight drop injury, penetrating ballistic-like brain injury, and blast injury.[18] Animal models manifest cortical contusions in certain temporal and regional patterns and continue to expand the secondary injury cascades up to 1 year after the initial injury. Application of neuroproteomic strategies to TBI models allows researchers to identify key molecular elements and pathways in TBI pathophysiology. Global proteome analysis of the hippocampal tissue, cortical brain tissue, and plasma has been performed previously in animal models of TBI. Meanwhile, *in vitro* models of TBI have also been constructed in SH-SY5Y and HT-22 cells using the cell injury controller to develop biomarker research.[19] Erlandsson's laboratory reported the proteomic changes of astrocytes, oligodendrocytes, and neurons after trauma induced by scalpel cuts.[20]

Recently, progress toward understanding the underlying pathogenetic mechanisms has been made using TBI models. Various TBI models have been employed to assess post-TBI conditions associated with disease progression. In fact, sufficient preclinical data should be required before the translation into costly clinical trials. The proteomic response of TBI models has proven to be successful and convenient in identifying biomarkers at multiple time points and regions, among different injury types and severities, and relating to population-associated variables. However, physiological variables in many studies are poorly controlled, and no reliable measurements can be used for scoring injury in TBI models. In addition, current TBI models fail to mimic all types of clinical situations due to the complex pathogenesis of clinical brain injury. Thus, it is necessary to develop a novel, powerful technique to decipher the interactive biochemical patterns and facilitate the translation of data obtained from models into clinical TBI settings.

While major advances in proteomics techniques have been obtained, and growing attention has been paid to the precise diagnosis of TBI, proteomics-based biomarker discovery is currently a hotbed of research. Previous exploratory studies have revealed the possible biology and identified potential biomarkers by assessing global protein profiles in the TBI process. However, the limited size of datasets, difficulty in analyzing and interpreting proteomic data, and inconsistent and nonreproducible measurements represent significant challenges to collect valuable information in TBI proteomics studies. Continued researches will be required for validating and evaluating the candidate biomarkers in large cohorts eventually guiding the diagnosis and appropriate therapeutic interventions for TBI patients. In summary, this is an urgent and interesting investigation in exploring possible biomarkers following TBI, and additional researches are warranted to elucidate potential pathological mechanism in the future.

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