

**ENDOTHELIAL MONOCYTE ACTIVATION
POLYPEPTIDE II, A BIOMARKER FOR USE
IN DIAGNOSIS AND TREATMENT OF BRAIN
INJURY**

[0001] This application claims priority of provisional application No. 60/809,986 filed May 18, 2006.

[0002] The invention described herein may be manufactured, used and licensed by or for the U.S. Government.

BACKGROUND OF THE INVENTION

[0003] 1. Field of the Invention

[0004] The invention apprise to the use of a polypeptide, Endothelial-monocyte activating polypeptide II (EMAP-II) as a biomarker to determine the presence and type of brain injury.

[0005] 2. Brief Description of Related Art

[0006] Traumatic brain injury is a leading cause of death and disability in the United States. One to 1.5 million Americans incurs a traumatic brain injury (TBI) each year. TBI is also a significant health problem for the uniformed services. Accurate diagnosis of brain-injury, severity and prognosis cannot be determined without skill and equipment typically located at an Echelon III facility (usually 1-8 hours after injury). Combat medics are not equipped with the requisite skills to accurately diagnose and triage brain-injured casualties. Therefore, a biomarker or biomarkers that can determine the severity and type of brain injury would be very useful both in combat and during sporting events.

[0007] Recent attention has focused on the development of protein biomarkers for the diagnosis and treatment of brain injury. Acute brain injury can induce a variety of signaling cascades, involving changes in post-translational protein modifications and expression of multiple genes that can lead to secondary injury (Lu et al., 2004). Differentiation of the pathological mechanisms underlying traumatic and ischemic brain injuries has been difficult due to the involvement of overlapping cellular and molecular pathways, presenting a great challenge for developing injury-specific therapeutics or management protocols. As such, improvements in methodology for the diagnosis/prognosis of the brain-injured patient can be of immense therapeutic value to define optimal neuroprotection strategies.

[0008] Two main categories of experimental models used to study brain injury are those due to a predominately ischemic-type injury (i.e., arterial occlusion models) or traumatic-induced injury (i.e. fluid percussion, cortical impact, cortical stab or penetrating missile wound models). Using these models, post-injury expression of numerous proteins have been independently identified and reported. Many cytoskeletal components, transcription factors, programmed cell death proteins, and protein kinase regulators are expressed predominantly in neurons, and are candidate biomarkers for selective detection of brain damage (Ingebrigsten and Romner, 2002). These proteins become accessible in body fluids following brain injury and associated blood-brain-barrier (BBB) disruption permitting minimally-invasive quantification, an essential characterization for their use as diagnostic and prognostic markers of brain injury. Consequently, increasing efforts have been devoted to the development of high-throughput differential techniques for detection of injury-mediated changes in proteins.

[0009] To date, several proteins have been studied as potential biomarkers including creatine kinase, glial fibrillary acidic protein, lactate dehydrogenase, myelin basic protein, neuron-specific enolase, S-100 protein, as well as others (Ingebrigtsen and Romner, 2002); however, all of these proteins have been ineffective as stand-alone markers of brain injury (Kobeissy et al., 2006). In response, recent efforts have been aimed at the development of a panel of biomarkers including not only surrogate markers related to injury outcome (Ingebrigtsen and Romner, 2002) but also markers providing specific information about the molecular mechanism of injury (i.e., true biochemical markers) (Liu et al., 2006a&b).

[0010] In previous studies, we characterized brain-injury changes in rat gene expression using real-time PCR and microarray techniques (Berti et al., 2002; Yao et al., 2002; Lu et al., 2004) and demonstrated the relevance of such data by using therapies specifically targeting aberrant gene transcription (Williams et al., 2004). However, PCR and microarray techniques focus on changes in gene expression at the mRNA level and do not necessarily reflect protein changes, for example due to degradation of transcriptional machinery in injured cells.

[0011] What is needed is a biomarker protein that is present in brain injury. What is also needed is a biomarker protein that is differentially regulated based on the type of brain injury. The biomarker needed could differentiate between an ischemic injury or traumatic injury.

[0012] These needs have become the objects of the present invention. The inventors observed changes in 30 out of 998 proteins following acute focal injuries to the brain. They found that one protein, EMAP-II was differentially expressed between two types of brain injury (traumatic vs. ischemic). EMAP-II is known to be an inflammatory cytokine involved in apoptotic processes. It was found that EMAP-II in brain and CSF are to significantly increased 1.6-1.8 fold following penetrating ballistic brain injury but decreased 2.1-2.3 fold after ischemic injury compared to uninjured animals. The differential expression of EMAP-II is useful for diagnosis of traumatic vs. ischemic brain injury and provides valuable information for directing injury-specific therapeutics. Additionally, the inventors have found that EMAP-II levels were elevated in CSF in human patient suffering from traumatic brain injury, when compared to uninjured controls.

SUMMARY OF THE INVENTION

[0013] The present invention is directed to a diagnostic tool and method of diagnosing brain injury and brain injury type (traumatic vs. ischemic) by detecting the level of expression of endothelial monocyte-activating polypeptide II (EMAP-II) as compared to control levels. Elevated post-injury levels of EMAP-II indicate the presence of a penetrating/traumatic type brain injury. In contrast, a decrease in EMAP-II protein level would indicate the presence of a primarily ischemic type of brain injury.

BRIEF DESCRIPTION OF THE FIGURES

[0014] FIG. 1 is a series of coronal sections of rat brains 24 hours following PBBI or MCAo injury;

[0015] FIG. 2a is a power blot template of PBBI (A) brain tissue 24 hours post-injury;

[0016] FIG. 2b is a power blot template of the sham (B) brain tissue 24 hours post-injury;