Please cite this article in press as: Raad M et al. Autoantibodies in traumatic brain injury and central nervous system trauma. Neuroscience (2014), http://dx.doi.org/10.1016/j.neuroscience.2014.08.045

Neuroscience xxx (2014) xxx–xxx

REVIEW

AUTOANTIBODIES IN TRAUMATIC BRAIN INJURY AND CENTRAL NERVOUS SYSTEM TRAUMA

M. RAAD,[a] E. NOHRA,[b] N. CHAMS,[a] M. ITANI,[g] F. TALIH,[c*] S. MONDELLO[d] AND F. KOBAISSY[e,f*]

[a] *Faculty of Medicine, American University of Beirut Medical Center, Beirut, Lebanon*

[b] *Department of Surgery, Division of General Surgery, American University of Beirut, Lebanon*

[c] *Department of Psychiatry, American University of Beirut Medical Center, Beirut, Lebanon*

[d] *Department of Neurosciences, University of Messina, Messina, Italy*

[e] *Faculty of Medicine, Department of Biochemistry and Molecular Genetics, American University of Beirut Medical Center, Beirut, Lebanon*

[f] *Department of Psychiatry, Center for Neuroproteomics and Biomarkers Research, University of Florida, Gainesville, FL, USA*

[g] *Faculty of Medicine, Saint George University of London, Nicosia, Cyprus*

Abstract—Despite the debilitating consequences and the widespread prevalence of brain trauma insults including spinal cord injury (SCI) and traumatic brain injury (TBI), there are currently few effective therapies for most of brain trauma sequelae. As a consequence, there has been a major quest for identifying better diagnostic tools, predictive models, and directed neurotherapeutic strategies in assessing brain trauma. Among the hallmark features of brain injury pathology is the central nervous systems' (CNS) abnormal activation of the immune response post-injury. Of interest, is the occurrence of autoantibodies which are produced following CNS trauma-induced disruption of the blood–brain barrier (BBB) and released into peripheral circulation mounted against self-brain-specific proteins acting as autoantigens. Recently, autoantibodies have been proposed as the new generation class of biomarkers due to their long-term presence in serum compared to their counterpart antigens. The diagnostic and prognostic value of several existing autoantibodies is currently being actively studied. Furthermore, the degree of direct and latent contribution of autoantibodies to CNS insult is still not fully characterized. It is being suggested that there may be an analogy of CNS autoantibodies secretion with the pathophysiology of autoimmune diseases, in which case, understanding and defining the role of autoantibodies in brain injury paradigm (SCI and TBI) may provide a realistic prospect for the development of effective neurotherapy. In this work, we will discuss the accumulating evidence about the appearance of autoantibodies following brain injury insults. Furthermore, we will provide perspectives on their potential roles as pathological components and as candidate markers for detecting and assessing CNS injury. © 2014 Published by Elsevier Ltd. on behalf of IBRO.

Key words: autoantibodies, humoral immune response, traumatic brain injury, spinal cord injury, biomarkers, CNS trauma, immune system.

Contents

INTRODUCTION

Traumatic brain injury (TBI) is a major health concern with an incidence of 1.7 million cases per year in the United States. TBI is characterized with long-term consequences and debilitating post-injury disabilities (Selassie et al., 2008; Wolf et al., 2009; Corrigan et al., 2010). TBI refers to a spectrum of focal and diffuse cerebral insults resulting from sudden shock, blunt or transmitted force, hypoxia, intoxication, and vascular injuries to the brain (Malkesman et al., 2013). The immediate phase of injury arises from direct mechanical injury; while the secondary latent phase arises from systemic biochemical and physiological changes involving excitotoxicity, energy failure, ischemia, cell death, edema, delayed axonal injury, and inflammation (Diamond et al., 2013; Malkesman et al., 2013). Importantly, TBI, and even mild injuries, have been linked to serious long-term complications, including

*Corresponding authors. Address: American University of Beirut Medical Center, PO Box 110236, Cairo Street, 1107 2020 Beirut, Lebanon. Tel: +961-1-350000x5650; fax: +961-1-749209 (F. Talih). Address: 4000 SW 23[rd] Street, Apt 5-204, Gainesville, FL 32608, USA. Tel: +961-01-350000x4805 (F. Kobeissy).
E-mail addresses: ft10@aub.edu.lb (F. Talih), firasko@gmail.com (F. Kobaissy).

Abbreviations: ACR, acetylcholine receptor; BBB, blood–brain barrier; BDPs, break down products; CSF, cerebrospinal fluid; GFAP, glial fibrillary acid protein; IgM, immunoglobulin M; MBP, myelin basic protein; NMDA, N-methyl-D-aspartate; SCI, spinal cord injury; TBI, traumatic brain injury; UCH-L1, ubiquitin carboxy-terminal hydrolase L1.

http://dx.doi.org/10.1016/j.neuroscience.2014.08.045
0306-4522/© 2014 Published by Elsevier Ltd. on behalf of IBRO.

chronic traumatic encephalopathy, neuropsychiatric and movement disorders and early onset dementia (Angoa-Perez et al., 2014; Bazarian et al., 2014).

Currently, there are few effective therapies targeted against the latent manifestations of TBI (Beauchamp et al., 2008; Loane and Faden, 2010; Maas et al., 2010; Wheaton et al., 2011) exacerbated by the fact that there are no diagnostic approaches that can identify those who will develop severe complications later. A better understanding of CNS trauma and its pathogenic processes are major components to develop improved diagnostic tools that allow for accurate disease characterization and phenotyping. These enhanced tools have a direct impact toward establishing novel targeted patient management and better neurotherapeutic strategies. Advanced prognostic capabilities, determination of injury severity and prediction of long-term complications are also required for better injury management. These advances may be provided by identifying accurate biological molecular signature markers, referred to as biomarkers.

Biomarkers refer to detectable components liberated by tissues in a disease state, or better defined as biological parameters that are in an altered state different from those in a healthy individual (Raad et al., 2012). An ideal biomarker involves detection, diagnosis and prognosis of a disease state. The five phases proposed by the National Institute of Health in the evaluation of biomarkers are in sequence (NIH, 1998): (1) discovery using genomics or proteomics, (2) developing an assay that is portable and reproducible, (3) measuring sensitivity and specificity, (4) affirming the measurement in a large cohort, and (5) determining the risks and benefits of using the new diagnostic biomarker.

The current available protein and gene biomarkers are now regarded as early generation biomarkers that suffer from several limitations, such as low specificities and sensitivities (Papa et al., 2013). Therefore, a search for a novel family of biomarkers in this field is essential; and currently, both microRNAs and autoantibodies are under investigation. In this review, we highlight the potential use of autoantibodies as candidate blood biomarkers discussing their potential roles in the secondary progression of CNS trauma and its underlying pathology.

THE IMMUNE RESPONSE AFTER CNS INJURY

After brain injury, the immune system is engaged acutely to contain the injured cells, and chronically to support spontaneous brain regenerative processes, including neovascularization, axonal sprouting, and neurogenesis (Peruzzotti-Jametti et al., 2014). The degree of recovery may be dependent on the success of these molecular mechanisms.

Autoinflammation involves inflammasomes, multioligomeric proteins that initiate the innate immune response and an uncontrolled production of cytokines coupled with the activation of myeloid cell lineages (e.g., monocytes/macrophages and neutrophils), and self-reactive lymphocytes. On the other hand, autoimmunity occurs due to activation or survival of self-reactive lymphocytes with enhanced synthesis of autoantibodies directed against one or more of the individual's own self proteins. Both pathways have been implicated in progression of secondary injury after CNS injury (Archelos and Hartung, 2000; Jones et al., 2005; Trivedi et al., 2006; de Rivero Vaccari et al., 2008; Diamond et al., 2009). Autoimmune recognition plays a pivotal role in tuning the strength of the immune activation by presenting and processing self-antigens. The nature and degree of activation determine whether the response is beneficial or detrimental to recovery (Trivedi et al., 2006).

Importantly, both B and T lymphocytes appear to contribute to CNS injury and repair (Ankeny et al., 2006, 2009; Popovich and Longbrake, 2008). Ankeny et al. discussed the contribution of B-cell activation and its associated autoantibodies in the area of spinal cord injury (SCI) pathogenesis proposing new sites for neuro-therapeutic targeting for patients suffering from SCI (Ankeny et al., 2006, 2009; Ankeny and Popovich, 2009, 2010). B-lymphocytes involved in such pathogenesis are shown to develop from bone marrow and specifically from hematopoietic stem cells at its immature phase (Dalakas, 2008a,b).

Upon the entrance of a "non-self" alien antigen, the immune system mounts an immune response where plasma cells, which are mature B-cells, are paired with T cells stimulation. Nonetheless, when the confronted antigen is a self or a host-derived (DNA, Peptide or protein), then the immune response elicited is called an autoimmune response (Ankeny et al., 2009). Typically, during the developmental stages, negative-selection abolishes highly reactive lymphocytes whereas, positive-selection keeps "sub-threshold" stimulation of lymphocytes that identify self/host antigens and increase sensitivity to alien antigens (Stefanova et al., 2002). This machinery of positive-selection has a crucial role in controlling the immune reaction and regulating it; nonetheless, when the threshold level is crossed then an abnormal condition of autoimmunity is elicited (Stefanova et al., 2002). When stimulation of its correlated antigens occurs, B-cells differentiate into antibody-secreting plasma cells and afterward into the long-lived antibody secreting plasma cells (Dalakas, 2008a,b). B-cells can play the role of antigen-presenting cells as well as antibody secreting cells (Waubant, 2008; Dalakas, 2008b). These activated B-cells make their way to the secondary lymphatic system, to the bone marrow, and to the CNS (Dalakas, 2008b).

Recent studies have provided conflicting evidence about which immune mechanisms are beneficial and which are detrimental (Ankeny et al., 2006, 2009; Popovich and Longbrake, 2008). Some autoantibodies produced against CNS cells have been shown to be beneficial since they activate intracellular repair pathways (Wright et al., 2009). Furthermore, natural autoreactive monoclonal antibodies, especially the immunoglobulin M (IgM) isotype that are produced at early phases of immune response, may have some neurotherapeutic potential in CNS disease by promoting CNS protection and repair (Schwartz and Raposo, 2014). IgM antibodies are thought to enhance re-myelination, neurite growth and prevention of neuronal apoptosis as shown in mouse models of multiple sclerosis (Wright et al., 2009). In addition, these

Please cite this article in press as: Raad M et al. Autoantibodies in traumatic brain injury and central nervous system trauma. Neuroscience (2014), http://dx.doi.org/10.1016/j.neuroscience.2014.08.045