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Review

Traumatic brain injury: A risk factor for Alzheimer's disease

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ABSTRACT

Traumatic brain injury (TBI) constitutes a major global health and socio-economic problem with neurobehavioral sequelae contributing to long-term disability. It causes brain swelling, axonal injury and hypoxia, disrupts blood brain barrier function and increases inflammatory responses, oxidative stress, neurodegeneration and leads to cognitive impairment. Epidemiological studies show that 30% of patients, who die of TBI, have Aβ plaques which are pathological features of Alzheimer's disease (AD). Thus TBI acts as an important epigenetic risk factor for AD. This review focuses on AD related genes which are expressed during TBI and its relevance to progression of the disease. Such understanding will help to diagnose the risk of TBI patients to develop AD and design therapeutic interventions.

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1. Introduction

National Head Injury Foundation (1988) has defined traumatic brain injury (TBI) as "an insult to the brain caused by an external force that may produce diminished or altered states of consciousness, which results in impaired cognitive abilities or physical functioning". About 1.4 million people suffer from TBI every year in the United States alone (Zohar et al., 2011). The yearly cost of acute care and rehabilitation for new cases in the United States is between $9 and $10 billion (NIH Consensus Development Panel, 1999). TBI affects all age groups with particular prevalence among children and young adults (Fins, 2003; Kövesdi et al., 2010). It is the leading cause of acquired disability in children (Cronin, 2001). Survivors of TBI suffer from a wide variety of pathologies such as neurological deficits, short and long term brain damage, cognitive, behavioral and emotional impairments, all of which depend on the severity of injury. Neurological deficits in cognition are due to atrophy of hippocampus and damage of white matter tract as evident from functional imaging studies (Atkins et al., 2009).

TBI can be classified as (i) focal damage, which occurs in localized area and causes damage to the underlying brain tissues and vessels, and (ii) diffuse damage, which is not restricted but widespread throughout the brain. Diffuse type mainly involves axonal injury also called diffuse axonal injury (DAI), brain swelling and hypoxia (Hellewell et al., 2010; Laurer et al., 2000). Axonal injury is an almost universal sequel of TBI (Li et al., 2006; Smith, 2000) and a powerful predictor of morbidity and mortality (Czeiter et al., 2008). In axons, it causes an accumulation of proteins, including

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amyloid precursor protein (APP), which is carried by fast anterograde axonal transport and serves as a sensitive marker of axonal damage. This may result in axonal disconnection leading to loss of axonal function and structure (Chen et al., 2004). TBI is one of the most consistent candidates for initiating the molecular cascades that result in Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (Gavett et al., 2010).

2. TBI initiates a disease process

Although many patients survive the initial insult, TBI initiates a chronic disease process that may ultimately contribute to their deaths months to years later (Masel and DeWitt, 2010). Cell death after TBI is a major cause of neurological deficits and mortality (Stoica and Faden, 2010; Yu et al., 2008). TBI is a disease process with an initial injury that induces biochemical and cellular changes which in turn contribute to continuing neuronal damage and death over time. This continuing damage is known as secondary injury, and as a part of this process, multiple apoptotic and inflammatory pathways are activated (Loane et al., 2009). Although many cells may lose their functions during this phase, they are not necessarily irreversibly damaged or disrupted. The state of post injury cerebral environment and resultant secondary responses to TBI ultimately determine the final outcome. If a favorable milieu is created, brain cells and tissues may recover; if it is unfavorable, they may die. Following TBI, there is a major shift in the balance between pro-apoptotic and anti-apoptotic protein synthesis machinery, promoting either cell death or survival (Lotocki et al., 2003; Sullivan et al., 2005). The lack of brain injury diagnostic biomarkers has been identified as a significant roadblock to therapeutic development for TBI. The application of proteomic methodology may serve as a potential means for biomarker discovery (Kobeissy et al., 2008). Thus understanding the biological relevance of these altered proteins would provide insight into some of the possible mechanisms underlying TBI pathology. A great challenge is to identify what constitutes a damaging environment versus a healing environment and then to prevent further damage. Future advances in TBI will depend on prevention and scientific analysis to improve the diagnosis and treatment.

TBI is a serious problem in geriatric population, as advancing age is an important factor influencing prognosis after injury. In the last decade, there has been 21% increase in TBI cases in individuals over 65 years (Anderson et al., 2009; Cekic and Stein, 2010; Rapoport et al., 2008). In elderly trauma patients, outcomes are notoriously poor, recovery is incomplete and unsatisfactory, and the mortality and functional disability rates are twice that of younger patients (Sandhir and Berman, 2010; Tokutomi et al., 2008). Recent studies have shown exacerbated inflammatory responses associated with increased number of dying neurons and a deficit in behavioral recovery following brain injury in aged rodents (Glimer et al., 2010).

2.1. Axon and its role during TBI

Axon regeneration in the mature mammalian central nervous system (CNS) is extremely limited after injury (Huebner and Strittmatter, 2009). Consequently, functional deficits persist after spinal cord injury (SCI), TBI and stroke. Clinical studies have shown that axonal injury may cause significant learning and memory dysfunction. Patients with DAI are more likely to develop persistent coma and are less likely to return to previous level of functioning (Maxwell et al., 1997; Povlishock, 1993). Alteration in cellular protein synthesis is a key part of the pathological response and repair following TBI. Cellular injury results in up-regulation of genes that code for some proteins and down-regulation of others. Mediators of injury such as cytokines play a role in modulating cellular protein production. Posttranslational modifications of proteins may produce changes in protein levels that can be detected in serum or cerebrospinal fluid (CSF). This holds some promise in the development of biomarkers to assess the severity of TBI and also to understand some of the cellular processes that may occur in the injury and post injury period (Greve and Zink, 2009). Understanding protein regulation and response following TBI may lead to future interventions to reduce secondary injury (Kochanek, 2008). Calpains, proteases that under normal cellular conditions have a variety of regulatory functions including cytoskeletal maintenance, play a significant role in TBI as key enzymes targeting axonal proteins which lead to cytoskeletal breakdown and disruption of axonal transport (Saatman et al., 2010). Targeted inhibition of these enzymes has shown great promise in limiting secondary injury to axons (Ray et al., 2003).

3. TBI and Alzheimer's disease

TBI is a strong epigenetic risk factor for AD (Fleminger et al., 2003; Magnoni and Brody, 2010; Plassman et al., 2000) which is a neurodegenerative disorder characterized by the presence of extracellular senile plaques and intracellular neurofibrillary tangles (NFTs) (Slemmer et al., 2011). Senile plaques are formed of aggregates of amyloid beta (Aβ) peptides, whereas NFTs are composed of bundles of pathological fibrils called paired helical filaments (PHFs), which are made up of aberrantly phosphorylated tau microtubule associated proteins. There are many pathological features common to both acute brain injury and AD, including Aβ deposition, tau phosphorylation, neurite degeneration, synapse loss and microgliosis (Ikonomovic et al., 2004; Uryu et al., 2007). Neuroinflammatory responses may serve as a common denominator between these two entities, and play a central role in mediating secondary neuronal injury in both chronic neurodegenerative diseases and acute brain injury. In the acute setting, glial activation results in up-regulation of APP as well as other inflammatory mediators. This increase in APP expression and neuroinflammatory response following injury may contribute to a cycle of Aβ deposition and microglial activation that ultimately result in chronic neuropathology. Although TBI is associated with AD (Fig. 1), the role played by TBI in the mechanism of disease development and progression is not clearly understood. Primary feature of TBI is axonal damage and it is clear from many studies that axonal defect is a key disease manifestation of AD and responsible for its symptoms (Tang, 2009). There is little doubt that axonal/presynaptic trafficking of APP and its processing enzymes occur in normal and dystrophic neurons. TBI deregulates the expression patterns of α-synuclein, APP, BACE1, tau and ApoE4 genes. These genes and their cleaved products are implicated in neurodegenerative disorders, axonal pathology and apoptosis. TBI also induces caspase-3 which in turn is involved in APP processing contributing to AD. APP, BACE1 and PS1 often accumulate in damaged axons following TBI (Chen et al., 2004; Uryu et al., 2007), probably resulting from axolemmal disruption and impaired axonal transport. Injury to axons causes the formation of axonal spheroids, focal swellings that result from blocked transport. The accumulation of APP and its processing enzymes in these focal injuries result in increased APP processing and Aβ generation (Gentleman et al., 1993). These together with other factors associated with brain injury, trigger a cascade of events that might increase tau phosphorylation and NFT formation. Cumulative axonal transport defects leading to AD pathogenesis is attractive, but further understanding of the underlying process involved in transition from axonal defect to AD is needed. A better understanding of molecular and physiological responses to TBI is essential to develop future therapies which can