Traumatic Brain Injury and Secondary Neurodegenerative Disease

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Traumatic brain injury (TBI) is a devastating event with severe long-term complications. TBI and its sequelae are one of the leading causes of death and disability in those under 50 years old. It is clear that neurotrauma can incite chronic neurodegenerative processes. Chronic traumatic encephalopathy, Parkinson's disease, and many other neurodegenerative syndromes have all been associated with a history of traumatic brain injury.

neurotrauma secondary mechanisms neurodegeneration

1. Introduction

Neurodegeneration following traumatic brain injury is a complex process that is initiated by several distinct pathways which overwhelm homeostatic stress responses and trigger cellular degeneration and death. Recent studies have demonstrated a progression of neurodegenerative processes months and even years after traumatic brain injury, termed secondary neurodegeneration. Secondary neurodegeneration can manifest in many ways depending on specific etiology and affected neuroanatomy. Chronic traumatic encephalopathy (CTE) is a well-known disease closely associated with repeated traumatic brain injuries (TBI) [1][2]. Parkinson's disease (PD), frontotemporal dementia (FTD), and other neurodegenerative diseases are less common but can also be induced as a consequence of TBI [3][4][5]. The precise incidence of CTE is hard to quantify due to diagnostic limitations; however, it has gained notoriety due to the prominence of repeated mild TBI in professional sports [1][6]. On the other hand, severe TBI with greater than 1 h loss of consciousness triples the risk of eventually developing PD [3]. Investigation into neurodegenerative disease secondary to TBI is rapidly evolving due to its complex pathophysiology and important public health implications.

2. Mechanisms of Neurodegeneration after TBI

The inciting mechanisms of secondary neurodegeneration after TBI are an interdependent set of pathological changes initiated by the primary traumatic injury (**Figure 1**). The temporal evolution of brain injury after TBI is multidimensional and complex but can be conceptualized as overlapping phases. The "acute injury" phase after TBI is characterized by the predominance of mechanical damage resulting from the initial trauma while the "secondary injury" phase is characterized by the delayed emergence of dysregulated metabolism and inflammation pathways [7][8][9]. The acute phase is generally defined as the first week post-TBI before transitioning into the

secondary injury phase that can last months to years [7][10]. Some also advocate for a “subacute” phase as an intermediary that occurs up to 3 months post-TBI [11]. In any case, oxidative stress seems to be a key mediator in the secondary injury phase, as glutamate excitotoxicity, mitochondria dysfunction, and endoplasmic reticulum (ER) stress all contribute to increased reactive oxygen species (ROS) [12][13][14]. Depolarization of glutaminergic neurons after TBI results in increased calcium ion influx through NMDA and AMPA receptors [15]. Excess intracellular calcium increases mitochondrial ROS production through several mechanisms including activation of Ca^{2+}-calmodulin pathways and disruption of the electron transport chain [16]. Endogenous oxidative stress responses are coordinated by the transcription factor Nrf2 [17]. Nrf2 promotes the expression of many cytoprotective proteins including HO-1, NQO-1, and GCLM, among others. These systems can be overwhelmed and become insufficient to prevent ROS-mediated cellular injury [18]. ROS can cause protein damage and misfolding (discussed further below) but may also be especially harmful through lipid peroxidation [19]. Dysregulation of membrane structures such as caveolae in mice is associated with increased markers of neurodegeneration and neuroinflammation [20]. Increased tissue markers of oxidative stress including lipid peroxidation have been observed as far as 12 weeks post-TBI in rats, indicating these pathological mechanisms do not resolve in the acute phase after TBI [21].

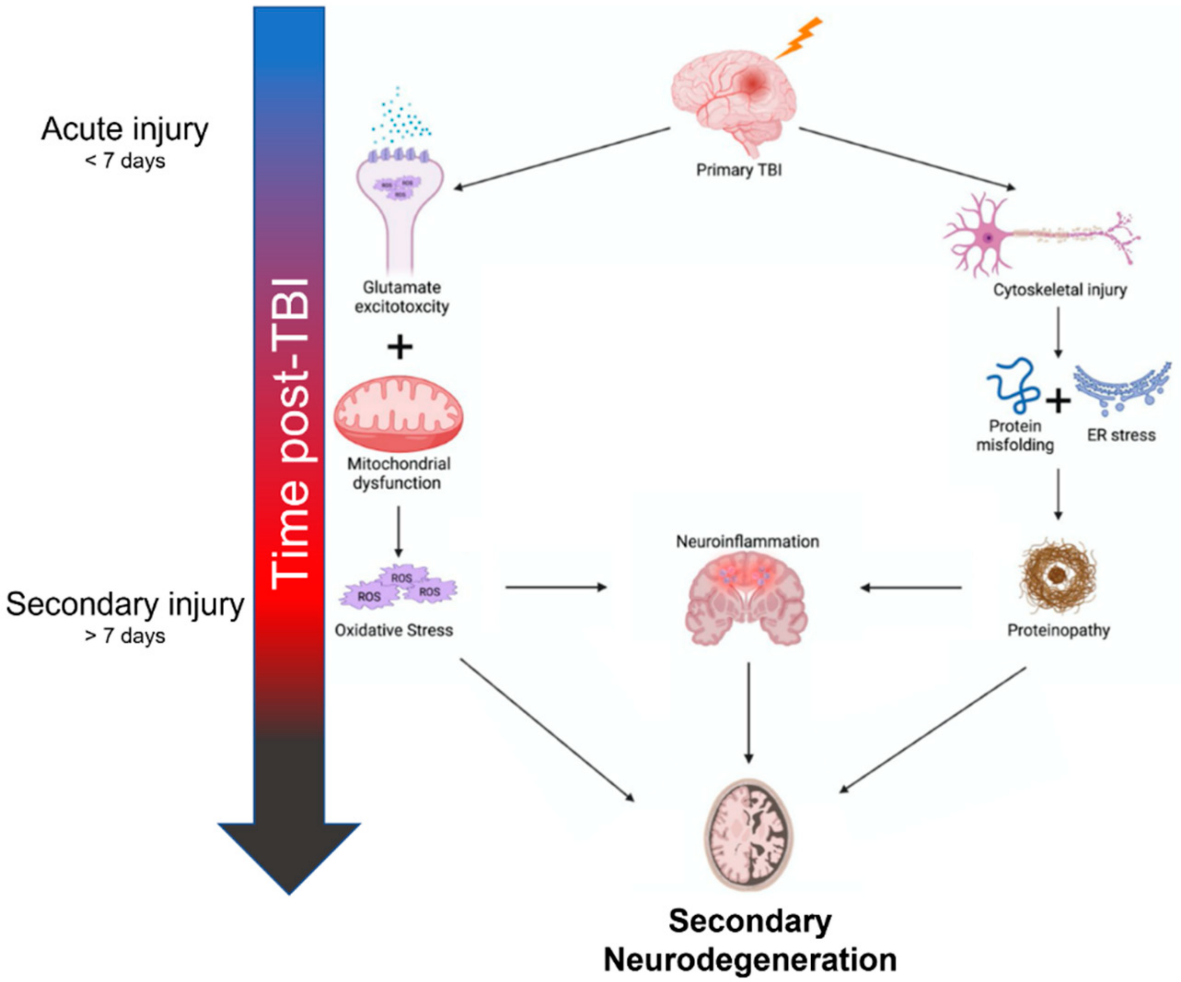

Figure 1. Summary of mechanisms contributing to secondary neurodegeneration following traumatic brain injury.

Another central element of secondary neurodegeneration is pathological changes to neuronal cytoskeletal dynamics. Axons, especially within the white matter, are particularly susceptible to damage from tensile strain during traumatic injuries due to their unique cellular anatomy [22]. The cytoskeleton of these axons can be completely severed during trauma; however, axonal transport may be disrupted even with mild cytoskeletal damage [22]. This type of injury, often termed diffuse axonal injury (DAI) is common after TBI; however, is likely underreported due to the limitations of imaging techniques and the inability to perform brain biopsies in this patient population [23]. Disrupted axonal transport is one of several mechanisms that impede neuronal homeostatic mechanisms and lead to activation of neuroinflammatory pathways (NFκB– and inflammasome-mediated increases in IL-1β, IL-6, TNFα, etc.) and cell death (caspase-3-mediated apoptosis) [24][25][26]. Pro-inflammatory signals begin locally in damaged neurons but quickly promote reactive gliosis and widespread propagation of the neuroinflammatory cascades by microglia and astrocytes [10][24]. Vascular tissues affected by ROS and pro-inflammatory cytokines are at risk of defective autoregulatory function which can decrease cerebral blood flow and compound cerebral injury [10][25]. These pathological changes result in high protein turnover, particularly in neurons, and may alter ER function by stressing proteostatic mechanisms [27]. ER stress, particularly activation of the unfolded protein response (UPR), is a critical mediator of neurodegenerative change [12][28]. Proteinopathies that occur as a result of misfolding including tauopathies, amyloid plaques, Lewy bodies, and TDP-43 have all been observed after TBI [29][30][31]. Severe (i.e., associated with >1 h loss of consciousness) TBI triples the risk of developing of Lewy bodies in the substantia nigra [3]. ROS can be both a product and contributing factor to axonal degeneration and neuroinflammation, highlighting the interconnections between mechanisms of secondary neurodegeneration.

3. Imaging

Neuroimaging can be used to identify chronic pathological changes from TBI in addition to the acute injury. Generally, TBI disrupts white matter connections and results in cerebral atrophy [32]. This finding tends to be worst in frontotemporal and limbic areas [33], possibly due to trends in traumatic injury mechanisms [34]. Serial quantitative T1 magnetic resonance imaging (MRI) can evaluate neurodegeneration after TBI in a sensitive but non-specific way by assessing cerebral atrophy and volume loss. An increasing ventricle-to-brain ratio is associated with chronic cerebral atrophy in those with TBI after resolution of the acute phase (weeks to months) [35][36]. Generally, TBI-induced neurodegeneration leads to cerebral volumes comparable to that of older individuals with other neurodegenerative diseases; both demonstrating a yearly loss of 1.5% of cerebral volume occurring mostly in sulci and white matter tracts [32][37]. The frontotemporal and limbic areas, which are seated on the sharp sphenoid ridge and edge of the tentorium cerebelli, demonstrate the most severe degenerative changes as their location makes them vulnerable to mechanical deformation. Hippocampal atrophy is especially evident within the limbic system considering its location in the medial temporal lobe and high metabolic demand [38][39]. Patients with DAI-type TBI experience white matter degeneration for months to years following the acute injury as evidenced by studies utilizing MRI diffusor tensor imaging (DTI). DTI is a method for detecting structural changes by analyzing the fractional anisotropy (FA), mean diffusivity (MD), and radial diffusivity (RD) of water molecules. TBI with predominant axonal/white matter injury demonstrates reduced FA and increased MD and RD [40][41]. These findings

point to demyelination, loss of axonal integrity, and reduced axonal packing and coherence in frontotemporal and limbic structures such as the anterior limb of the internal capsule, corona radiata, optic radiations, and cingulum [42][43]. Furthermore, changes in these DTI indices are associated with poor neuropsychological performance, including executive function, memory, and functional outcomes [44][45][46][47].

Molecular imaging with positron emission tomography is an evolving modality to identify post-traumatic neurodegeneration in vivo in a specific manner. Following TBI, the PET tracer ^{11}C-Pittsburgh compound-B (^{11}C-PiB) binds amyloid-beta (Aβ) in cortical areas, the striatum, and posterior cingulate cortex similar to Alzheimer's disease (AD). Unlike AD, there are increased Aβ depositions in the cerebellum in TBI [48][49][50]. Additionally, several PET tracers specific to hyperphosphorylated tau (p-tau) previously used in AD are under investigation for use in TBI. FDDNP is the most well-studied biomarker. FDDNP levels are increased in the midbrain, thalamus, pons, and cingulate gyrus and demonstrate lower binding in temporal and parietal regions in military personnel with mild TBI exposure and football players with suspected chronic traumatic encephalopathy compared to patients with AD [51]; however, FDDNP is non-specific as it also binds Aβ. Other PET imaging biomarkers that bind tau include T801, AV1451, and flortaucipir. Studies are generally limited as they have small sample sizes, lack control groups, or are restricted to one subtype of TBI. While cortical tau tracer uptake varies within individuals with CTE-type TBI, studies have demonstrated consistent uptake in the temporal lobe and limbic system [47][52][53][54]. The current use of PET imaging biomarkers remains in the early stages. The Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) consortium is evaluating the efficacy of these imaging modalities alone and in combination with fluid biomarkers, radiogenomics, or with EEG. Furthermore, there is evolving research investigating magnetic resonance spectroscopy (MRS), functional MRI (fMRI), transcranial Doppler (TCD), single photon emission computed tomography (SPECT), and functional near-infrared spectroscopy) [53][55][56]. Early human and rodent studies evaluating the newly discovered glymphatic pathway reveal that mild, repetitive TBI alters glymphatic clearance rates examined with MRI [57][58][59][60].

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