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Neuroinflammation in animal models of traumatic brain injury

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ABSTRACT

Traumatic brain injury (TBI) is a leading cause of mortality and morbidity worldwide. Neuroinflammation is prominent in the short and long-term consequences of neuronal injuries that occur after TBI. Neuroinflammation involves the activation of glia, including microglia and astrocytes, to release inflammatory mediators within the brain, and the subsequent recruitment of peripheral immune cells. Various animal models of TBI have been developed that have proved valuable to elucidate the pathophysiology of the disorder and to assess the safety and efficacy of novel therapies prior to clinical trials. These models provide an excellent platform to delineate key injury mechanisms that associate with types of injury (concussion, contusion, and penetration injuries) that occur clinically for the investigation of mild, moderate, and severe forms of TBI. Additionally, TBI modeling in genetically engineered mice, in particular, has aided the identification of key molecules and pathways for putative injury mechanisms, as targets for development of novel therapies for human TBI. This Review details the evidence showing that neuroinflammation, characterized by the activation of microglia and astrocytes and elevated production of inflammatory mediators, is a critical process occurring in various TBI animal models, provides a broad overview of commonly used animal models of TBI, and overviews representative techniques to quantify markers of the brain inflammatory process. A better understanding of neuroinflammation could open therapeutic avenues for abrogation of secondary cell death and behavioral symptoms that may mediate the progression of TBI.

Contents

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1. Background

Traumatic brain injury (TBI) is a leading cause of death and long-term disability in the developed world. Each year, approximately 10 million people suffer a TBI event worldwide (Hyder et al., 2007; Ruff and Riechers, 2012). Predictive analyses indicate that TBI will constitute the third greatest portion of the total global disease burden by 2020 (Hyder et al., 2007). Within the US alone, some 1.7 million people sustain a TBI annually, and around 5.3 million people live with a TBI-associated disability (Langlois et al., 2006; Prins and Giza, 2012). Of those TBIs that occur, by far the majority are mild to moderate in nature and comprise 80–95% of cases, with severe TBI accounting for the balance (Tagliaferri et al., 2006). Consequent to increases in survival rate after initial injury, TBI can give rise to substantial and lifelong cognitive, physical, and behavioral impairments that necessitate long-term access to health care and disability services (Tagliaferri et al., 2006; Shi et al., 2013). Exceptionally vulnerable are the elderly, in which the very same injury can cause greater disability and can induce a dramatic rise in the risk of neurodegenerative (Gardner et al., 2014; Barnes et al., 2014) and neuropsychiatric disorders (Chen et al., 2014). Although TBI symptoms can intermittently resolve within a year after injury, some 70–90% of patients endure prolonged and often permanent neurocognitive dysfunctions. It is now established that TBI represents a process, that once initiated can extend either silently or symptomatically to neurodegeneration. This process can lead to early onset of dementia (Gardner et al., 2014; Barnes et al., 2014) as well as Parkinson's disease (PD) and other degenerative conditions (Gardner et al., 2015; Gardner and Yaffe 2015). Particularly notable, TBI is a strong environmental risk factor for development of Alzheimer's disease (AD). Recent gene expression studies have delineated the up regulation of key pathways leading to AD and PD provoked by mild, let alone moderate or severe forms of TBI (Greig et al., 2014; Tweedie et al., 2013a,b; Goldstein et al., 2012). Consequent to a current lack of any available therapeutic options (Moppett, 2007), it is imperative to understand the mechanisms that underlie head injury and the ensuing neuronal dysfunction and cognitive impairments to successfully develop possible therapeutics.

2. TBI-triggered pathological processes

TBI instigates complex pathological processes that involve a broad spectrum of cellular and molecular pathways. TBI-associated brain damage can be classified into two main phases. First, an initial primary damage phase occurs at the moment of insult. This can involve contusion and laceration, diffuse axonal injury, brain swelling and intracranial hemorrhage, and invariably results in immediate (necrotic) cell death (Greig et al., 2014; LaPlaca et al., 2007; Cheng et al., 2012). This is followed by an extended secondary phase that involves cascades of biological processes initiated at the time of injury that may endure over much longer times, from days to numerous weeks (Maas et al., 2008; Zhang et al., 2008). This delayed phase, caused by a variety of cellular and molecular responses instigated in an effort to potentially restore the cellular homeostasis of the damaged tissue, is not particularly well controlled and often will lead to exacerbation of the primary injury damage, progressive neurodegeneration and delayed cell death (Kabadi and Faden, 2014; Lozano et al., 2015). Hallmarks of the secondary insult response can include blood-brain barrier (BBB) breakdown, oxidative stress, glutamate excitotoxicity, and neuroinflammation, which all can occur time-dependently following the primary mechanical insult (Bains and Hall, 2012; Das et al., 2012; Maas et al., 2008; Zhang et al., 2008).

Neuroinflammation is present in both primary (acute) and secondary (chronic) stages of TBI (Lozano et al., 2015) and appears to be responsible for both detrimental and beneficial effects, contributing to primary insult and secondary injury but also facilitating tissue repair (Woodcock and Morganti-Kossmann, 2013). In this regard, following the primary insult, cellular endogenous inflammatory responses are triggered at the injury site with the aim to repair the damaged tissue; however, the often excessive production of pro-inflammatory cytokines appear to become an important driving force for the pathological progression in TBI.

Consequent to recent medical and media interest in sport and military concussions, the concept of chronic neuroinflammation and white matter (WM) injury has been highlighted within the context of TBI. Historically, chronic neuroinflammation was generally associated with chronic neurological diseases, such as occurs in multiple sclerosis, rather than with acute injury, as occurs with TBI. However, recent reports linking single and repeated TBI events to chronic WM outcomes have fortified association between TBI and neuroinflammation. Neuropathological studies of pre-clinical and clinical TBI cases has provided evidence that glial cells are a central component of the chronic WM degenerative process (Glushakova et al., 2014; Mouzon et al., 2014; Sajja et al., 2014).

3. Neuroinflammation in TBI

3.1. TBI neuroinflammation is characterized by reactive gliosis

The development of neuroinflammation that follows TBI involves a complex process of cumulative changes that occur within the brain. Following a TBI insult, quiescent glial cells of multiple types become rapidly activated via a process termed "reactive gliosis". This process involves activated microglia initiating and sustaining astrocytic activation via the generation and release of inflammatory mediators that, in turn, act on surrounding glia and neurons. Post-traumatic cerebral inflammation is characterized by glial activation, leukocyte recruitment, and upregulation and secretion of mediators such as cytokines and chemotactic cytokines (chemokines). (Morganti-Kossmann et al., 2001) (Fig. 1).

These inflammatory mediators not only impact surrounding glia and neurons but additionally act to recruit peripheral immune cells, such as neutrophils, macrophages and lymphocytes, into brain. Thus acute neuroinflammation following an initial TBI insult not only functions to regulate both damaging and reparative events in the injured and recovering brain, but can also sensitize neurons to enable long-term degenerative processes (Mrak and Griffin, 2005; Streit et al., 2004; Tweedie et al., 2013a,b; Tweedie et al., 2016a,b). Glial activation induces morphological and functional alterations within the cells that impact neural–glial and glial–glial interactions. This change can cause dysfunction of synaptic connections, neurotransmitter homeostasis imbalance, and potential axonal degeneration and neuronal death (Bal-Price and Brown, 2001). Astrocytes become activated (termed reactive astrogliosis) in response to CNS injury (Buffo et al., 2010). Moreover, astrocytes are responsible for encapsulating damaged areas after injury,