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Invited Review

Cellular players that shape evolving pathology and neurodegeneration following traumatic brain injury

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ABSTRACT

Traumatic brain injury (TBI) is one of the leading causes of death and disability worldwide, and has emerged as a critical risk factor for multiple neurodegenerative diseases, particularly Alzheimer's disease (AD). How the inflammatory cascade resulting from mechanical stress, axonal shearing and the loss of neurons and glia following initial impact in TBI, contributes to the development of AD-like disease is unclear. Neuroinflammation, characterized by blood-brain barrier (BBB) dysfunction and activation of brain-resident microglia and astrocytes, resulting in secretion of inflammatory mediators and subsequent recruitment of peripheral immune cells has been the focus of extensive research in attempts to identify drug-targets towards improving functional outcomes post TBI. While knowledge of intricate cellular interactions that shape lesion pathophysiology is incomplete, a major limitation in the field is the lack of understanding of how distinct cell types differentially alter TBI pathology. The aim of this review is to highlight functional differences between populations of bone marrow derived, infiltrating monocytes/-macrophages and brain-resident microglia based on differential expression of the chemokine receptors CCR2 and CX_3CR1. This review will focus on how unique subsets of mononuclear phagocytes shape TBI pathophysiology, neurotoxicity and BBB function, in a disease-stage dependent manner. Additionally, this review summarizes the role of multiple microglia and macrophage receptors, namely CCR2, CX_3CR1 and Triggering Receptor Expressed on Myeloid Cells-2 (TREM2) in pathological neuroinflammation and neurodegeneration vs. recovery following TBI. TREM2 has been implicated in mediating AD-related pathology, and variants in TREM2 are particularly important due to their correlation with exacerbated neurodegeneration. Finally, this review highlights behavioral outcomes associated with microglial vs. macrophage variances, the need for novel treatment strategies that target unique subpopulations of peripheral macrophages, and the importance of development of therapeutics to modulate inflammatory functions of brain-resident microglia at specific stages of TBI.

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1. Introduction

Traumatic Brain Injury (TBI) is defined by The Centers for Disease Control and Prevention (CDC) as the functional disruption of the brain from an impact or penetrating injury (Centers for Disease C, Prevention, 2013), resulting in apoptotic and necrotic cell death of neurons and glia, disruption of the blood-brain barrier (BBB) with subsequent infiltration of the injured brain by peripherally-derived, immune cell populations such as neutrophils and macrophages. This is accompanied by phenotypic activation of brain-resident glia, namely astrocytes and microglia (McKee and Lukens, 2016; Jassam et al., 2017; Ramlackhansingh et al., 2011). Approximately 10 million people experience some form of TBI every year (Hyder et al., 2007). In the United States, 1.4 million people suffer from TBI each year, with approximately 235,000 patients requiring hospitalization and specialized healthcare. Strikingly, TBI accounts for approximately 50,000 mortalities each year, along with over 90,000 individuals facing a lifetime of permanent post-injury impairment (Centers for Disease C, Prevention, 2013). Post-injury disabilities can encompass a myriad of cognitive, motor, and emotional deficits and result in healthcare costs that range into the upper millions to billions of dollars. Of particular importance is the fact that TBI has been identified as a significant risk factor for the development of Alzheimer's disease (AD) related pathological changes including intra-neuronal neurofibrillary tangles (NFTs) of hyperphosphorylated tau (pTau) and deposits of extracellular amyloid-β (Aβ) (Scott et al., 2016). It is important to note that single occurrence brain injuries are predominantly associated with AD, Parkinson's disease, and Amyotrophic Lateral Sclerosis (ALS), while Chronic Traumatic Encephalopathy (CTE) is the most prevalent disease associated with repetitive TBI. Given the increasing prevalence of AD worldwide, and that it is currently classified as the most common form of dementia, this review will focus on the development of AD/AD-like pathology following single occurrence TBI. Although there is a growing need to understand disease mechanisms resulting in CTE, these remain beyond the scope of this review.

While mechanisms that govern the pathophysiology of TBI lesions and result in AD-like neurodegenerative changes are poorly understood, increasing experimental and clinical data implicate chronic post-injury neuroinflammation as a potential catalyst for TBI-related neurodegeneration and cognitive decline. The lack of a clear understanding of the complexity of the inflammatory response following TBI has been a significant hindrance to the development of successful therapeutics to minimize and/or ameliorate post-injury deficits. The unique pathological and inflammatory features of TBI vary based on the severity (mild vs. moderate vs. severe) and duration (single vs. repetitive) of the injury (McKee and Lukens, 2016; Jassam et al., 2017; Ramlackhansingh et al., 2011). This, in combination with the evolving nature of TBI lesions as injury becomes chronic, has added to the dilemma of failed treatment paradigms. Lastly, extensive research has been dedicated towards development of anti-inflammatory drugs targeting functional responses of immune cell populations, namely the blood derived macrophages and the brain-resident microglia. However, an incomplete understanding of their unique contributions to TBI pathogenesis in a disease-stage dependent manner has led to several failed clinical trials and ineffective treatment strategies (Chakraborty et al., 2016). This review seeks to outline what is currently known about cellular mechanisms that shape inflammatory responses post moderate to severe single occurrence TBI, with a particular focus on defining functional differences between activated peripheral macrophage populations and brain-resident microglia, and how they relate to development of AD-like, neurodegenerative pathology post TBI.

1.1. The problem with 'immune privilege' in TBI.

The central nervous system (CNS), composed of terminally differentiated neurons and highly specialized glial cells, the astrocytes, microglia and oligodendrocytes, comprises a unique neuroimmunologic niche. Complex interactions between various populations of glia and neurons are critical for the functional integrity of the CNS. Based on homeostatic mechanisms involving critical immune interactions evolved to limit immune-mediated damage and loss of CNS function, the CNS is considered 'immunologically privileged' where responses with a potential to cause bystander injury to healthy tissue are selectively restricted and those that promote repair and homeostasis are preserved and/or enhanced (Louveau et al., 2015; Romo-González et al., 2012).

Specialized draining lymphatics and the recently discovered, glial-dependent glymphatic system that allow for controlled cellular and molecular egress into the deep cervical lymph nodes (Romo-González et al., 2012; Plog and Nedergaard, 2018), and limited cellular expression of major histocompatibility complex (MHC) molecules limit endogenous antigen presentation (Louveau et al., 2015; Romo-González et al., 2012). Constitutive expression of soluble immune-suppressive factors like TGFβ, macrophage migratory inhibition factor (MIF) and neurotrophins results in tolerance-inducing antigen presenting cells (APCs) leading to overall T-cell suppression and inhibition of Natural Killer (NK) cell-mediated cytolysis. Furthermore, bi-directional signaling between neurons and microglia via fractalkine (CX_3CL1), CD200 and neurotransmitter signaling actively maintains microglia in their homeostatic activation state (Eyo and Wu, 2013). Finally, blood vessels lining the CNS are composed of specialized endothelial cells with restricted expression of adhesion molecules and presence of tight junction proteins that act to restrict the access of large molecules and peripheral immune cells (Jassam et al., 2017; Abbott and Hansson, 2006). The basement membrane separates the endothelium from the brain parenchyma, and is juxtaposed with pericytes, astrocytic endfeet and microglia. This neurovascular unit is collectively called the 'blood-brain barrier (BBB)' and is the final, important factor in CNS immune privilege (Abbott and Hansson, 2006).

This neurological milieu presents a unique challenge following trauma or injury. Pro-inflammatory immune signaling is critical for the resolution and containment of pathogens, but also causes bystander, immune-mediated cell death. Although heightened anti-inflammatory responses can minimize bystander damage, early inhibition of inflammation can lead to chronic pathology and lesion spread. Thus, the CNS immune response has to be finely tailored to a) allow for a controlled pro-inflammatory response that effectively resolves initial pathology and limits the expansion

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