Review Article

Traumatic Brain Injury, Microglia, and Beta Amyloid

Rebekah C. Mannix1,2 and Michael J. Whalen2,3

1 Division of Emergency Medicine, Department of Medicine, Children’s Hospital Boston, Harvard Medical School, Boston, MA 02124, USA
2 Neuroscience Center, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA 02129, USA
3 Department of Pediatrics, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA 02129, USA

Correspondence should be addressed to Rebekah C. Mannix, rebekah.mannix@childrens.harvard.edu

Received 30 November 2011; Accepted 2 March 2012

Copyright © 2012 R. C. Mannix and M. J. Whalen. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Recently, there has been growing interest in the association between traumatic brain injury (TBI) and Alzheimer’s Disease (AD). Data from both AD and TBI studies suggest that microglia play a central role in beta amyloid (Aβ) accumulation after TBI. This paper focuses on the current research on the role of microglia response to Aβ after TBI.

1. Introduction

Recently, there has been growing interest in the association between traumatic brain injury (TBI) and Alzheimer’s Disease (AD). The interest grew from several lines of evidence, including epidemiological studies that demonstrated an association of TBI and the development of AD later in life [1–7] and autopsy studies that showed acute and chronic AD-like pathology in TBI victims [8, 9]. While most of the studies investigating the association of AD and TBI have focused on the accumulation and clearance amyloid-β (Aβ) [2, 8, 9], chronic neuroinflammation is also a common feature of AD and TBI, and microglia likely play a central role [10, 11]. In AD, microglia are recruited to newly formed Aβ plaques, where microglial activation functions as a double-edged sword, promoting beneficial responses such as Aβ clearance [12–14] while also eliciting a proinflammatory response [12]. Similar patterns of microglia activation have been demonstrated both acutely and chronically after TBI [15, 16].

This paper will explore the current research on the role of microglia response to Aβ after TBI. Although there are few studies that directly examine microglial reaction to trauma-induced Aβ, data from TBI and AD experimental and human studies will be used to make an argument for a central role of microglia in acute and chronic responses to Aβ-mediated secondary injury after TBI.

2. General Microglial Response after TBI

TBI is a disease process in which mechanical injury initiates cellular and biochemical changes that perpetuate neuronal injury and death over time, a process known as secondary injury. Secondary injury begins minutes after injury and can continue years after the initial insult. Mechanisms implicated in secondary injury after TBI include glutamate excitotoxicity, blood-brain barrier disruption, secondary hemorrhage, ischemia, mitochondrial dysfunction, apoptotic and necrotic cell death, and inflammation [17].

As the primary mediators of the brain’s innate immune response to infection, injury, and disease, microglia react to injury within minutes. In fact, microglia may represent the first line of defense following injury [18]. Microglial activation has been demonstrated as early as 72 hours after injury in human TBI victims and can persist for years after injury [15, 16, 19, 20]. Experimental models have recapitulated these findings, with chronic microglial activation being demonstrated weeks to months after injury [21–24].

Gene-profiling studies also strongly implicate early microglial activation after TBI. Markers of microglial activation (CD68, MHC-II), stress responses (p22phox, heme oxygenase 1), and chemokine expression (CXCL10, CXCL6) have been shown to markedly increase after experimental models of TBI [25]. Consistent
Many as 30% of TBI victims (including children) [8, 9]. The and can appear within a few hours after injury [9, 36]. TBI-to those observed in the early stages of AD, develop rapidly plaques found in TBI patients, which are strikingly similar with increases in the enzymes necessary for Aβ and the intra-cellular domain of APP (AICD) [44]. Further evidence suggests that increases in the numbers of neurons with elevated B-APP concentrations after TBI correlate with increases in the number of activated microglia expressing IL-1α and that clusters of dystrophic neurites containing β-APP are nearly universally associated with activated microglia expressing IL-1α [45]. Microglia containing Aβ have also been described in association with TBI-induced Aβ plaques, suggesting that phagocytic clearance of plaques may occur [46].

In addition to the temporospatial relationship of microglial and Aβ after TBI, much of the evidence regarding the important role of microglia in the modulation of TBI-induced Aβ is indirect. Most of this indirect evidence is derived from drug studies, which, while not designed to demonstrate the important interaction of microglial with TBI-induced Aβ, have served to demonstrate this vital interaction. Many of the studies that have indirectly elucidated the interaction of microglia and Aβ after TBI have focused on therapeutics targeting postinjury inflammation. Minocycline, a compound whose anti-inflammatory properties (including attenuating microglial activation) have been widely demonstrated in different models of TBI [47, 48], has also been shown to preclude formation of Aβ through restoration of the nonamyloidogenic α-secretase pathway of APP processing [49]. Interestingly, it has been shown that some other anti-inflammatory compounds that exert neuroprotective effects in TBI, such as nonsteroidal anti-inflammatory drugs, cholesterol-lowering drugs, and steroid hormones, also enhance the α-secretase pathway [50–53]. It is unclear from these studies whether the anti-inflammatory and proα-secretase effects are merely parallel processes, although certainly diversion of APP from the production of Aβ, which has known proinflammatory properties including stimulation of microglial activation, may itself adequately explain both the anti-inflammatory and anti amyloidogentic effects.

Additional studies support the observation that suppression of microglial activation after TBI is also associated with decreases in injury-induced Aβ. Apo mimic peptides, liver X-receptor (LXR) agonists, and 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) have all been shown to attenuate microglial activation and mitigate increases in Aβ after TBI [54–56]. It should be noted, however that none of these earlier studies can definitively lead one to conclude whether Aβ is a cause, product, or mere marker of microglial activation and secondary injury after TBI. However, what can be concluded is that Aβ is an excellent indicator of microglial activation following TBI.

### 4. Conclusions and Future Directions

The link between trauma, microglial activation, and Aβ is likely to be extremely complex, and work in this field remains

---

**Figure 1**: Schematic depiction of the beneficial and detrimental effects of the interaction Aβ- genesis and microglia after traumatic brain injury.
in its infancy. Much of the work is derived from studies in AD, though the time course and long-term sequelae of TBI and AD may require separate lines of investigation. One recurring issue is the role of Aβ in the pathogenesis of microglial activation after brain injury which parallels the increasing emphasis on microglial function in the pathogenesis of AD.

Prior studies in AD suggest that microglial clearance of Aβ declines with aging [12]. It is therefore important to understand how TBI-induced Aβ alters long-term microglial function and Aβ-clearance. Future work should focus on whether blocking Aβ-genesis after TBI alters short- and long-term microglial activation. In addition, therapeutics targeting microglial-mediated Aβ clearance, such as the new AD therapeutic bexarotene [57], may hold promise as new modalities to treat TBI patients.

In this paper, we have attempted to show how a mechanistic understanding of the interaction of Aβ and microglia after TBI could have significant implications for therapeutics, especially for those at the highest risk for TBI, including those in the military and those who engage in contact sports. Furthermore, the advancement of drug discoveries in the field of TBI, such as sex steroids or Apoe mimetics which alter both microglial function and Aβ metabolism, may have potentially important roles in TBI as well as other neurodegenerative diseases. Finally, as we advance our mechanistic understanding of the interaction between microglia and Aβ after TBI, it is important to understand whether therapeutic interventions targeting microglia and Aβ will have any effect on long-term cognitive sequelae in TBI victims.

References


