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Mini Review

Microglia-Related Differences in Inflammation Between Genders after Traumatic Brain Injury

Jian Shi[1]*, Jialing Liu[2] and Midori Yenari[1]

[1]*Department of Neurology, Veterans Affairs Medical Center, University of California, USA*

[2]*Department of Neurosurgery, Veterans Affairs Medical Center, University of California, USA*

***Corresponding author:** Jian Shi, Department of Neurology, University of California, San Francisco, CA 94121, USA

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Introduction

Traumatic brain injury (TBI) is a heterogeneous disorder with variable outcomes, as evidenced by recent studies, which also vary by sex. There are many variations between sexes after TBI, including inflammation, microglia, dopamine systems, some behavioral impairments, and more [1,2]. All these variations lead to different outcomes between sexes. Here, we focus on differences in inflammation associated with microglia after TBI between sexes.

Microglia are the main target for many treatments to suppress secondary inflammation and enhance post-TBI protection [3]. In male rats, moderate-to-severe TBI caused robust and pronounced cortical microglial activation, showing a significant increase in Iba1 and CD11b positive microglia from 4 h to 7 days [4,5]. Villapol et al. reported that male mice exhibited enhanced astrogliosis, neuronal death, and increased lesion volume within 7 days after TBI compared to female mice [6]. In contrast, TBI caused less robust microglial activation in female mice during this period [6,7]. In addition, the macrophages of male but not female TBI mice can rapidly infiltrate the injured brain. In fact, in the normal brain, microglia represent anatomical and developmental differences between sexes [8], which might be the primary mechanism of the different responses of both sexes after TBI, whose responsive profiles include changes to their cytokine expression, metabolic profile, and immunophenotype. They may exacerbate brain damage that occurs in male animals during the acute phase after TBI [4-6]. Usually, activated microglia and infiltrated macrophages produce some proinflammatory cytokines after brain injury, including interleukin 1 beta (IL-1β), IL-6, and tumor necrosis factor (TNF-α). Cytokines such as IL-1β, IL-6, and TNF-α have been shown to promote inflammatory responses in the primary and secondary phases after TBI. In addition, elevated levels of these proinflammatory cytokines have been observed in the cerebrospinal fluid (CSF) of the injured brain from animals and patients [9-11]. Therefore, these facts, mainly derived from animal studies, suggest that differences in microglial activation between sexes may lead to differences in cytokine-responsive release and to different damage and recovery following TBI.

In experimental TBI, microglia inhibitors and hormonal treatments have been administrated to male animals due to microglia-related mechanisms and sex differences. Minocycline, as an inhibitor of microglia, inhibited microglial activation and significantly reduced impairments of spatial learning and memory in male TBI rats [12,13], and this treatment also showed some sex differences in cytokine expression [14]. For hormonal treatments, the application of estrogen and progesterone to TBI male or ovariectomized female rats showed a decreased intracranial pressure, improved cerebral perfusion, and increased neurological function scores [15]. In these processes, the neuroprotective effects of progesterone may be partially caused by the reduction of TNF-α and IL-6 levels in the primary or second phases after TBI. The neuroprotective effect of estrogen may be due in part to decreasing IL-1β levels in the second phase.

For clinical studies, sex differences after TBI have been reported, but compared to animal studies, this study is very rare, and the mechanisms associated with microglia are unclear. However, elevated cytokines including TNF, IL-1β, and IL-6 in CSF suggest central synthesis by microglia or other immune cells [16,17], partially extending the experimental TBI studies. Different from experimental TBI, many studies have shown that women have worse clinical outcomes than men after TBI [18-20], but in a meta-analysis of moderate-severe TBI [21], outcomes were better for most women, especially for adolescents [22], suggesting that due to elevated sex hormone levels. Some clinical studies are contrary to animal TBI studies, possibly because these studies are long-term clinical results, which is much longer than the time of animal

studies. In addition, over 6.5 years of observation of TBI patients, there was no significant difference between sexes, including mild, moderate, or severe TBI [23]. Even so, there are still some behavioral differences between sexes following TBI. For cognitive recovery in TBI patients, men generally recover better on verbal tasks, while women can restore spatial orientation more quickly [24,25]. Some researchers have proven the female advantage in recognizing emotion [26], suggesting that females may be protective against social impairment after TBI, although there are opposite results in animal experiments. Since social communication and other cognitive behaviors of animals are much more straightforward, species may cause differences between humans and animals [27].

In conclusion, there is growing evidence that biological sex can greatly influence inflammatory activity following TBI, while the overall mechanisms underscoring these sex differences remain unclear, and more research is needed to understand these sex differences, especially in microglia-associated differences. Therefore, the correlation, treatment, and research of the inflammatory responses after TBI should consider gender differences as an important a

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