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Does Sepsis-Associated Encephalopathy Begin and End with T Cells?

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Abstract

A recent study revealed that 20%-40% of sepsis survivors suffer from mental disorders, more than a year after being discharged from the hospital. Although sepsis-associated encephalopathy (SAE) is complicated by septic conditions and is critically associated with increased mortality, it also leads to neurological dysfunction, which includes mental impairments. Therefore, finding a suitable treatment for neurological dysfunction is of vital importance for the survival and long-term prognosis of patients who contracted sepsis. Neuro-inflammation is the major pathogenesis of SAE, which is caused by the infiltration of inflammatory monocytes into the brain and by the activation of glial cells. However, the mechanism by which T cells are involved in the pathogenesis of SAE remains unclear. This review attempts to understand the underlying mechanisms associated with glial cells and T cells in the development and recovery of SAE and mental impairment following sepsis.

Keywords: Sepsis-associated encephalopathy; T cell; Mental impairment; Microglia; Astrocyte

Abbreviations: SAE: Sepsis-Associated Encephalopathy; CNS: Central Nervous System; IL: Interleukin; TCR: T Cell Receptor; Th: Helper T cell; Treg: Regulatory T Cell; TNF: Tumor Necrosis Factor

Introduction

Sepsis is a life-threatening extreme response to infection, caused by a dysregulated host immune response [1,2]. Although sepsis remains one of the leading causes of Intensive Care Unit (ICU) morbidity and mortality worldwide, the survival rate has improved, especially in developed countries [3,4]. However, new concerns have been raised regarding the long-term mortality of sepsis survivors following their discharge from hospitals. Long-term mortality in septic patients is called “post-sepsis syndrome,” and is characterized by long-lasting mental, cognitive, and physical impairments [3]. These symptoms hinder the ability of sepsis survivors to return to society, and concurrently increase their risk of readmission to the hospital [5].

Sepsis is known to induce severe systemic inflammation, with the brain being the first organ to be affected by septic conditions [6], which are referred to as Sepsis-Associated Encephalopathy (SAE). Epidemiological studies have reported that up to 70% of septic patients develop SAE, and that it is associated with mortality [7,8]. Moreover, even though patients can recover from SAE, central nervous system disturbances (e.g., mental and cognitive impairment) may persist for more than a year in 20%-40% of patients [9]. Although the critical pathophysiological feature of SAE is neuroinflammation, it is a multifactorial disease. It increases the accumulation of pro-inflammatory cytokines, mitochondrial dysfunction, and oxidative stress. Moreover, it leads to changes in cerebral homeostasis (including metabolite neurotransmitters such as glutamate) and blood-brain barrier dysfunction [10-15]. Although it is known to cause such distress, the exact underlying mechanism of SAE unfortunately still remains unclear.

Recent studies suggest that the activation of two types of glial cells (microglia and astrocytes) is implicated in the development of SAE. Microglia are macrophage-like immune cells in the Central Nervous System (CNS) that maintain multiple neurological brain functions *via* inflammatory or anti-inflammatory cytokines [16,17]. Astrocytes are supporting cells within the CNS, and are the most abundant glial cells in the brain [18]. They help nerve cells survive by providing them with nutrients and by rapidly removing neurotransmitters (e.g., glutamate) [19-21]. Since they do not respond to electric stimulation, astrocytes were originally considered “silent cells” within the brain. However, recent findings have revealed that astrocytes express several kinds of neurotransmitter receptors in the steady-state, and various cytokines during infection [22,23]. Under septic conditions, these microglia and astrocytes are rapidly activated, leading to their proliferation, and subsequent uncontrollable production of inflammatory cytokines, which alters CNS homeostasis [16,24-26]. Therefore, these glial cells, especially microglia, represent therapeutic targets for SAEs [27,28].

T cells, a type of lymphocyte, are crucial in the adaptive immune system. In vertebrates, two main T cell lineages, αβ and γδ, are defined by the expression of the αβ T Cell Receptor (TCR) and γδ TCR, respectively. As for αβ T cells, they are further divided based on their surface markers and function. They can either be CD4+ T cells or CD8+ T cells. Finally, CD4+ T cells are further divided based on secretion types, for example, Helper T (Th) 1 cells, Th2 cells, and Regulatory T cells (Tregs). In sepsis, long-lasting severe T cell reduction by apoptosis is observed in both human and mouse models, which are associated with poor outcomes, making it an ideal therapeutic target for sepsis-induced immunosuppression [29]. However, little is known about the involvement of T cells in the pathogenesis of SAE and the development of mental impairment following sepsis [30].

This literature review aims to summarize the current state of knowledge regarding the underlying mechanisms associated with glial cells and T cells in the development and recovery of SAE and mental impairment after sepsis.

Literature Review

Attenuation and alleviation of SAE and mental impairment

In a septic mouse model, sepsis-induced anxiety-like behaviours naturally recovered within approximately two months [31-40]. Surprisingly, an increase in the number of microglia was observed during this time. In fact, this increase was observed for at least 90 days following sepsis induction [32]. Microglia expresses a wide variety of receptors on their cell surface, one of which is the fractalkine receptor CX3CR1 (C-X3-C motif chemokine receptor 1). Expressed/unexpressed phenotype of microglia is involved in the development of mental impairment in mice. CX3CR1- microglia increased in the brains of mice following lipopolysaccharide (LPS)-induced endotoxin shock [41]. Moreover, CX3CR1-/- mice showed prolonged anxiety behavior following LPS administration [41]. With regards to sepsis, we observed an increase in the number of CX3CR1- microglia in the brains of septic mice, with the phenotype decreasing gradually with the alleviation of anxiety-like behaviours (unpublished data). These results suggest that it is essential to investigate the phenotype of microglia after the onset of sepsis, and to clarify how CX3CR1+ microglia are involved in the alleviation of mental impairments. The role of astrocytes in the recovery process of SAEs and mental impairment, however, is not well elucidated. In a previous study, we showed that astrocyte levels return to baseline levels in the chronic phase after an initial drop in the acute phase of sepsis [33]. How this recovery takes place, however, remains unclear.

Discussion

Interestingly, T cells (especially CD4+ T cells) in the brains of septic mice increased for at least 30 days following sepsis induction [33]. This observation prompted us to investigate whether it plays a role in the alleviation of mental impairment following sepsis. To test this, we treated septic mice with FTY720 to inhibit the infiltration of lymphocytes into the brain. This resulted in recovery from anxiety-behaviour being delayed in FTY720-treated septic mice. Moreover, FTY720-treated septic mice showed notably high mRNA levels of Il-1β and tumor necrosis factor-α in the brain even 30 days after the onset of sepsis. More importantly, we observed an increase in the number of CX3CR1- microglia and a reduction of astrocytes in treated mice, suggesting that infiltrated CD4+ T cells in the brain are involved in the alleviation of mental impairments *via* an anti-inflammatory response. Finally, we confirmed our phenotypic observations using flow cytometry, and found an increase in Th2 and Tregs cells in the brain after sepsis [33]. Collectively, increased levels of Th2 and Tregs cells, in the brain contributed to the attenuation of SAE and alleviation of mental impairment during the chronic phase of sepsis, *via* recovery of brain homeostasis, by resolving the imbalance of astrocytes and microglia [42,43].

Conclusion and Future Work

Our study showed that infiltration of Treg and Th2 cells in the brain is critical for the attenuation of SAE and alleviation of mental impairment. These results could contribute to the improvement of long-term prognosis and quality of life for sepsis survivors after their discharge from the hospital. It is important to determine the source of these T cells. Since the BBB might have been repaired during the chronic phase of sepsis, it is difficult to conceive of how T cells are circulating in the blood and infiltrating the brain. Anatomical studies have shown that the draining lymph nodes of the brain are superficial cervical lymph nodes (CLNs), deep CLNs, and meningeal lymph nodes (MenLNs). Clarifying the circulation of T cells in the axis of Brain-CLN-MenLN under sepsis conditions would be the first step in the treatment of SAE.

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