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Interaction Between Neuroimmune Activation Mechanisms in Epilepsy: the S100b Signaling Network and Brain-gut-bio-axis

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Abstract. Epilepsy is a syndrome characterized by abnormal firing in the brain, with numerous risk factors. Autoimmune central nervous system diseases are currently being widely explored; however, the neuroimmune processes involved in epilepsy have not been fully elucidated. This disorder is associated with the rise in the blood protein S100b concentration; hence, S100b levels are considered damage markers. From a recent review, we discovered the interaction of epilepsy with neural immunity and intestinal immunity. Neural immunity in epilepsy is associated with S100b generation and consumption. Therefore, we expect that S100b can be used as immune activation material to amplify immune responses in epilepsy simultaneously with intestinal immune suppression. The symbiotic relationship with intestinal biological immune upregulates the intestinal immune function, alleviating adverse outcomes of neural immunity in local brain regions.

Keywords. Epilepsy neuroimmune activation, Epilepsy, S100b network signaling pathway, Brain-gut-bio-Axis

1. Introduction

The blood-brain-barrier (BBB) and brain lymphatics are crucial anatomic structures of the neuroimmune system [1]. The abnormal discharge of neurons can adversely affect nerve tissues in epilepsy. Platelets were the first components to repair neural tissue lesions, while innate immune cells help platelets release S100b, which activates neuroimmune function and regulates intestinal immunity [2]. Epilepsy is an unusual clinical syndrome characterized by highly synchronized abnormal discharge in a group of neurons. The position of these abnormal neurons and the range of electrical waves could lead to different clinical manifestations. Because the electrical injury is challenging to detect unambiguously using microscopy, epilepsy pathology could centrally exhibit two aspects.

On the one hand, pathological complications such as traumatic brain injury (TBI) were the primary study objectives of cytopathology. On the other hand, neuron-based molecular screening, such as GABA metabolism, provided evidence of NMDA-based autoimmune mechanisms [3]. Electrical waves could

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directly injure substances on the cell surface, such as ion channel proteins affecting transmembrane transport and leading to cell death. Imaging pathology has revealed that the brain area in epilepsy has neuronal loss of pyramidal cells in the Cornu Ammonis regions and dentate hilar [4]. Tracing damage markers such as S100b could explore the pathogenesis of epilepsy [5] S100b is released by innate immune cells such as microglia and macrophages and can activate neuroimmune function via the S100b signaling pathway [2]. The glymphatic system is a significant site for brain metabolism, such as β protein clearance [6]. In 2015, researchers discovered lymphatic vessels of the dura mater using tracers [7]. T cells were found in cerebrospinal fluid (CSF), which played an essential role in neuroimmune interactions in epilepsy. S100b could thus impact the innervation of adipose tissue [8].

2. Neuroimmune activation mechanism of epilepsy

2.1. S100b signal network and innate immune cells

Figure 1 shows S100b signal Network. Conventional views believed that the brain provided exemptions from immunization and bad immunosurveillance. However, the discovery of lymph systems in the brain refuted this perspective [7]. This anatomical finding could support the hypothesis of epilepsy nerve immunity. With diffusing intermittent electric waves, cells suffer from epilepsy. First, the injury may be caused by changing ion concentration gradients in ion channel proteins. Cells suffer from physical attacks releasing damage markers, which can be sensed by innate immune cells. Innate immune cells would release cytokines after phagocytoses, such as IL-1β, IL-6, and TNF-α. S100b, released by innate immune cells, could positively affect prognosis [5]. S100b can resist the deposition of α and β proteins, which have crucial implications for preventing Alzheimer's and Parkinson's disease formation [9]. S100b via the NFκB pathway can induce gut immunity [10].

Furthermore, S100b via TLR-amplified immune signals plays an essential role in the immune response. TRAF 6 via TLR7/8/9 could induce NFκB and MAP kinase leading to the acceleration and amplification of immune responses [11]. Immune cells receive signals from the immune system, and this information is gradually delivered to the bone marrow through the lymphatic system. Immune intake induces the generation of permanent memory cells in the bone marrow microenvironment, ultimately capable of immune memory. S100b regulates the interleukin family signaling networks leading to significantly activating leukocyte function. The IL-1 system, including a minimum of 21 molecular markers, could regulate inflammation, angiogenesis, hematopoiesis, and cognitive function. When inflammatory immune responses occur, the interaction between IL-1 and IL-IR2 on innate immune cells enhances the biological roles of innate immune cells. IL-1R2 promoter region presents binding sites for NF-κB, which provides more convincing evidence for the combined excitation of immune IL-1 family signals and NF-κB. Inhibition of IL-1 movement has been used as a therapeutic immune target for autoimmune diseases [12]. In addition, S100b could induce ERBB4 signal activation. ERBB4 likely plays a role in the proliferation of oligodendrocytes, differentiation of oligodendrocytes, and regeneration of the myelin sheath. **FIGURE 2** showed Target genes for epileptic seizures, which may provide supporting evidence for molecular regulation of the CD family.

CD3 and CD28 upregulate the expression of ERBB4 [13]. With the infiltration of inflammation, the BBB is damaged, leading shielding components in the blood to enter the brain tissue. We hypothesize that those shielding components induce remarkable immune responses from the increasing number of T cells in the brain. Therefore, platelets adhere to the shielding material, leading to their activation—the granules released recruit inflammatory cells such as astrocytes, microglia, macrophages, and neutrophils. C3 and C3b stored in platelets could clear the shielding material via alternative pathways. However, research thus far has depicted that the local brain area responsible for immune responses deregulates peripheral immune function, thus disrupting the homing of lymphocytes, which increases the chance of infection. Immune responses negatively affect immune information stored by immune cells in the brain and could lead to *Streptococcus pneumoniae* lung infections associated with respiratory burst-depletion

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of lysosomes [14].

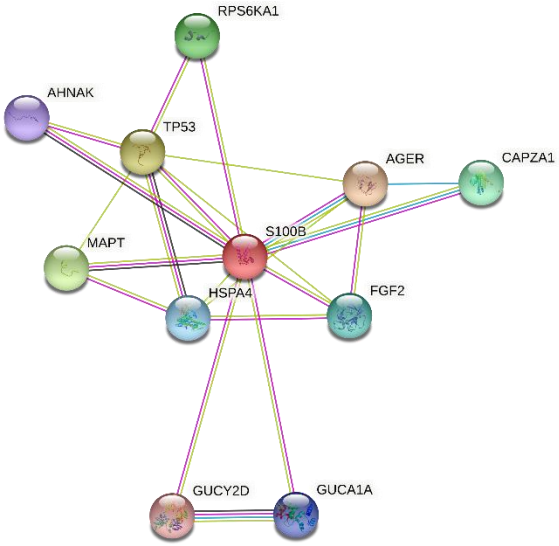

Figure 1. After we analyzed S100b by protein function, we showed the mutual network diagram of S100b and other proteins.

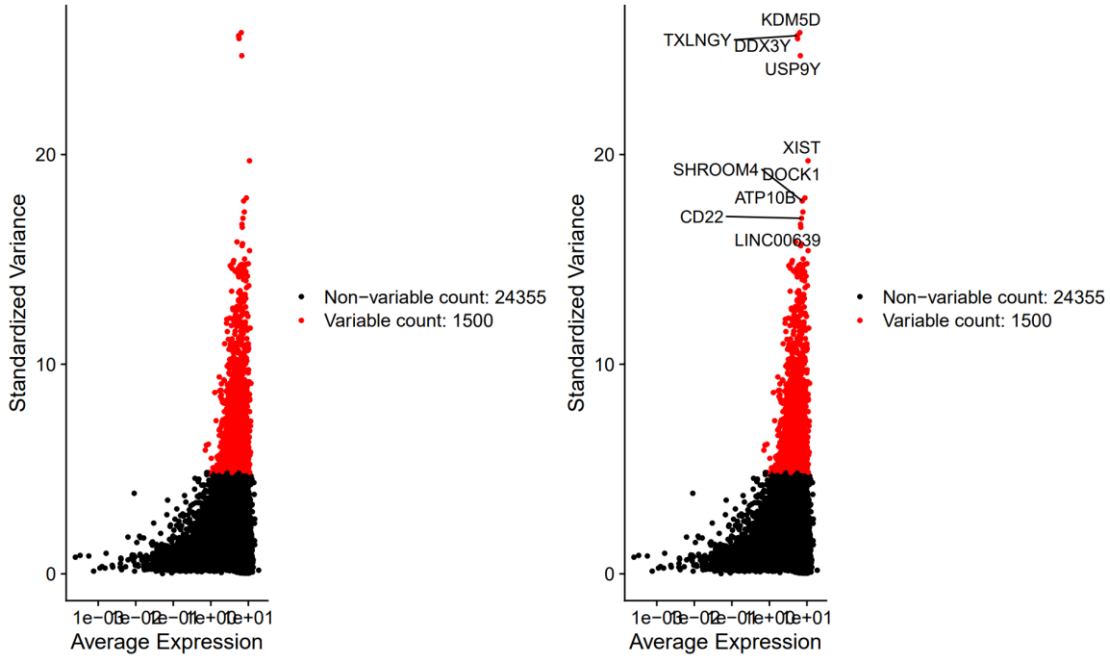

Figure 2. We performed single-cell sequencing analysis on lesion samples from patients with epilepsy. When we first isolated the gene of interest we found KDM5D, TXLNGY, DDX3Y, USP9Y, XIST, SHROOM4, DOCK1, ATP10B, CD22 and LINC0069.

2.2. Th1/Th2 axis and Th17/Treg axis

Injury caused by epilepsy gradually turns to immune damage when humoral immune responses shift to cellular immune responses. The synthesis and secretion of IL-17 and IL-23 by Th17 are essential for the immune pathway [15]. In subsequent studies, the Th1/Th2 axis was confirmed to tilt toward Th1, which confirmed this guess. However, the Th17/Treg axis was thought to be conclusive evidence of the association with activated Th17 across the BBB [16]. Many Th17 cells were detected in the injured brain

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area using animal experimentation. However, Th17 cells in the peripheral blood were absent after brain injury relief [17]. Th17 cells are associated with the expression of RORγ and STAT3.

Moreover, the secretion of IL-16, IL-22, IL-6, and IL-12 by Th17 played an essential role in inducing inflammation. Secretion of IL-17 by Th17 has different biological functions, such as regulating neutrophils, monocytes, and B cells and causing the release of cytokines [18][19]. Secretions of IL-22 by Th22 play a significant role in neural-immune functions, which is why IFN-β therapy is not ideal [20]. In addition, Th9 could regulate Th17 cells [21, 22]. Treg cells could regulate oligodendrocyte progenitor cells, thus leading to the repair of the injured myelin sheath, particularly the CCN3 protein. When studying cytokines, we discovered that the secretion of IL-22 by Th22 cells was detected in peripheral blood and cerebrospinal fluid, which mediated resistance to IFN-β treatment. Secretion of TNF-α and IFN-γ by Th1 cells can enhance cellular immunity response. Hence, the intestinal immune system would impact neural-immune interactions. In a study using animal models, CD4+ induced intraepithelial lymphocytes (IELs) across the inflammation of the brain and spine, which played a significant role in the remission of autoimmune encephalomyelitis (EAE).

Moreover, activating CD4+IELs was regulated by a positive feedback loop of the gut microbiota [23]. T cell populations played a crucial role in neural-immune functions. The concept could provide potential treatment pathways for improving local neural immunity. T cell activation promotes inflammation-associated injury neurons, and Treg cells could protect neuron tissue by inhibiting the inflammatory microenvironment [24]. Further, T cell populations depend on secondary recruitment leading to the activation of CD4+T and CD8+T cells, demonstrating why T cells are detected in cerebrospinal fluid.

2.3. B Cells

Researchers discovered lymphoid follicles in the brain when tracking B cells, which could provide a workplace for B cell clonal expansion. Hoffmann et al. detected polyclonal B cells in the central nervous system (CNS) and CSF, proving that B cells participate in CNS immune responses [25]. Meanwhile, B cells are also associated with generating IgG and IgM. A histological study of B cells across the BBB connected the peripheral and central immune systems. As secondary lymphoid tissue detected B cell maturation, related cytokines such as CD20, CD19, and CD52 could be therapeutic targets, potentially adding value to the neural-immune network [26]. Sustained immune responses may thus damage endothelial cells at the BBB. In contrast, injury to the BBB could weaken the ability to block the shielding material, which can be alleviated by gamma globulin [2].

3. Brain-gut-bio-axis

3.1. Th17-dependent biological immune regulation

Highly heterogeneous flora live in mammalian digestive tracts. These intestinal microorganisms and host genetics determine the local community and immune system balance, termed the biological immune system. Alterations in the gut mycobiome can regulate intestinal immune and neural-immune responses [27]. Th17 cells have been discovered in the intestinal lamina propria. Animal experiments using sterile mice showed resistance to experimental autoimmune encephalomyelitis without pathogenic T cells [28]. The gut commensal microflora alters Th17/Treg by inducing intestinal lamina propria Th17 leading to neural-immune regulation. The uptake of *S. thermophilus* and *Lactobacillus* via Th17/Treg caused Treg cells to regulate neural immune response, thus leading to the slow deterioration of epilepsy and brain injury [29]. Polysaccharide A released by *Bacteroides fragilis* could prevent the secretion of IL-17 and induce the secretion of IL-10 to increase the number of CD4+T cells [30].

3.2. Th17-dependent intestinal immune regulation

Vitamin D-depleted charcoal-stripped serum, certified for vitamin D LC-MS/MS applications, was used as a negative control matrix [31]. Vitamin D supplementation during pregnancy decreases the risks of

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MS in offspring. Double-blind experiments provided strong evidence that activated vitamin D (1, α25-dihydroxy vitamin D3) through increasing the intake could induce anti-inflammatory efficacy, which was likely to be associated with the deregulation of the Th17 pathway [32][33]. A recent study demonstrated the association of salt with immune responses in the brain. Increasing salt intake could upregulate the Th17/Treg pathway through salt-sensitive kinase [34][35]. Elevated brain white matter sodium concentration is conducive to forming damaged foci, likely correlated with axonal injury [36].

4. DAP of immune information

We predict a dominant assignment pattern (DAP) in the immune system. This DAP includes three parts. Firstly, the immune system distributes immune information only around the damaged organ or tissue when only one organ or local tissue is pathologically damaged. The immune information mainly refers to the blood and lymph circulation of immune cells and immune molecules. Secondly, immune information will distribute advantages to minor pathologically damaged organs or tissues when the two organs or local tissue have incurred damage. The response shows that minor damage can recover faster than heavier damage, which remains unchanged. Thirdly, the immune information will give priority to the distribution of the most serious damage when more than three organs or tissues are damaged.

5. Regulation of immune function by symbiotic bacteria metabolites

Recently, the gut commensal microflora and neural-immune had an interesting overview. The metabolites of the commensal microflora have a significant influence on the hypothalamic-pituitary-adrenal (HPA) axis. Short-chain fatty acids (SCFAs) could impact brain endothelial cells. The microbial metabolism of tryptophan could inhibit the activation of the microglia by deregulating the NF-κB pathway. Some studies regulated the lineage of commensal microflora using antibiotics, thus inhibiting γδT cells and improving the outcome in patients with cerebral stroke [37]. *S. salivarius* could directly kill *Corynebacterium diphtheriae* and *Neisseria meningitidis* through the secretion of hydrogen peroxide. The production of bacteriocins by *Escherichia coli* could kill anaerobe and Gram-positive bacteria. These microorganisms may likely damage the symbiotic intestinal immune barrier when antibiotics such as ofloxacin encephalitis treat brain infection with no favorable effects.

6. Conclusion

Innate immune cells help platelets repair tissue damage in epilepsy while releasing S100b to amplify neuroimmune via Th1/Th2 and Th17/Treg axis. Moreover, S100b indirectly uses the Th17 pathway to regulate biological immune and intestinal immunity. Symbiotic intestinal metabolism of substances can enhance the intestinal immune. Intake of probiotics can not only enhance the biological immune to a certain extent but also the neural-immune response. S100b-related immune pathways are a new direction for future epilepsy control.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Second Provincial People' s Hospital of Gansu. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Yan Bo researched topic and wrote the manuscript. Ren Sha analyzed the inspection data and contributed to the discussion. Yan Bo, Ren Sha and Haodong Yu reviewed and modified the manuscript. All authors contributed to the article and approved the submitted version.

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