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REVIEW

Research Progress on Th17/Treg Cell Imbalance in Epileptic Seizures

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Abstract: Epilepsy is associated with widespread neurological circumstances due to aberrant neuronal discharges in the brain, which have significant adverse effects on patient's quality of life and increase their risk of death. Immune imbalance, particularly disruption of the Th17/Treg cell balance, has gained increasing attention in the pathophysiology of epilepsy as our understanding of neuroimmune interactions improves. This paper examines the potential therapeutic effects and thoroughly discusses the processes by which the Th17/Treg cell imbalance contributes to the development of epilepsy. The primary emphasis is on the mechanism by which this imbalance impairs blood–brain barrier integrity, neuroinflammation, and other elements. On the therapeutic front, targeting the Th17/Treg axis for immune regulation—through approaches such as ketogenic diets, nanomaterials, and gene editing—shows promising prospects for restoring immune balance. By furthering our knowledge of the connection between Th17/Treg cell imbalance and epilepsy etiology, this work offers a crucial theoretical foundation for creating innovative immunotherapy approaches.

Keywords: epilepsy, Th17/Treg cell balance, neuroinflammation, immune regulation, neuroimmune regulation

Introduction

Approximately 70 million people worldwide have epilepsy, one-third of whom have drug-resistant epilepsy. This therapeutic challenge has driven researchers to explore the novel mechanisms underlying epilepsy to identify more effective treatment strategies.[1,2] A recent study demonstrated that immunological imbalance is significantly correlated with the pathophysiology of epilepsy. Studies have identified a marked imbalance in the Th17/Treg cell ratio in patients with epilepsy;[3] an excessive increase in pro-inflammatory helper T cell 17 (Th17) cells and a substantial decline in regulatory T cells (Tregs), which have immunoregulatory functions, are hallmarks of this imbalance.[4]

Tregs and Th17 cells are essential for preserving the equilibrium of the immune system. Th17 cells primarily disrupt the blood–brain barrier (BBB) by secreting various pro-inflammatory factors.[3,5] In contrast, Tregs maintain immune homeostasis by suppressing the overactivation of Th17 cells.[6] Reduced Treg cell function or quantity causes improper proliferation of Th17 cells, which, in turn, induces tissue damage and autoimmune reactions. According to research, an imbalance in Th17/Treg cells plays a vital pathogenic role in neurological pathologies, such as multiple sclerosis (MS) and experimental autoimmune encephalomyelitis (EAE), as it promotes BBB disruption and escalates neuroinflammatory reactions.[7–10] Notably, patients with epilepsy frequently display comparable immunological imbalance mechanisms in the peripheral blood and cerebrospinal fluid.[4,11] Based on these studies, adjustments to the Th17/Treg cell balance have generated remarkable therapeutic benefits in EAE and MS.[12,13] This finding opens new avenues for epilepsy treatment, suggesting that restoring the Th17/Treg cell balance through immunomodulation could become a novel intervention target for drug-resistant epilepsy.

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Recent clinical research has shown that immunomodulatory strategies targeting the Th17/Treg axis have achieved preliminary success. The ketogenic diet (KD), as a non-pharmacological treatment, demonstrates significant immunomodulatory effects in patients with refractory epilepsy. Studies have indicated that a ketogenic diet can significantly reduce the proportion of Th17 cells and interleukin (IL)-17A levels in the peripheral blood of children with refractory epilepsy while increasing the number of Treg cells and forkhead box protein 3 (Foxp3) expression, thereby restoring the Th17/Treg balance.[4] This restoration of immune balance was positively correlated with reduced seizure frequency. Moreover, peripheral Treg cells and γδT cells play opposing roles in the pathogenesis of refractory epilepsy in children, and enhancing the function of Treg cells can significantly suppress seizures.[14] These findings suggest that therapeutic strategies aimed at regulating the Th17/Treg cell balance have a solid theoretical basis and show promising prospects in clinical practice, particularly for patients with drug-resistant epilepsy.

This review explores the essential role of the Th17/Treg cell imbalance in the pathophysiology of epilepsy. A thorough understanding of this mechanism is crucial to establish new therapeutic approaches. In particular, ketogenic diets, as a primary approach, have demonstrated favorable clinical efficacy in epilepsy treatment within the realm of immunomodulatory therapies. Moreover, emerging therapeutic approaches, such as gene editing technologies and the use of nanomaterials for targeted drug delivery, have shown promising application prospects.

Physiological Role of the Th17/Treg Cell Balance

Th17 cells, as a critical subset of CD4+ T lymphocytes, undergo differentiation primarily driven by the synergistic effects of cytokines, such as transforming growth factor-β (TGF-β), IL-6, IL-1β, and IL-23. Numerous effector compounds, which include interferon-γ (IFN-γ), granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-22, IL-17, and IL-21, are secreted by mature Th17 cells and are vital for host defense responses and the etiology of autoimmune disorders (Figure 1).[8,15–17]

Tregs, another important subset of CD4+ T lymphocytes, have unique functions in maintaining immune system homeostasis and self-tolerance. High expression of the characteristic transcription factor Foxp3 is crucial for recognizing self-antigens and preventing autoimmune responses. Additionally, under the regulation of TGF-β, Treg cells effectively modulate the progression of chronic infections and allergic reactions.[6,18–20] Treg cells block Th17 cell activation and proliferation by direct cell-to-cell contact or by secreting inhibitory cytokines, including IL-10, IL-35, and TGF-β, which dampens overactive immune responses;[6] on the other hand, they mediate apoptosis of effector T cells, antigen-presenting cells, and natural killer (NK) cells by expressing perforin and granzyme B, thereby further regulating immune responses (Figure 1).[21,22] This multilayered immune regulatory network ensures the dynamic balance of the immune system.

Neuroimmune Regulatory Role of Th17/Treg Imbalance in the Pathogenesis of Epilepsy

Th17/Treg Imbalance Regulates the Immune Microenvironment in Epilepsy: Pathogenic Mechanisms

The local immunological milieu of the central nervous system (CNS) may undergo substantial alterations due to epileptic seizures. These changes are not only a consequence of seizures; they may also contribute to the worsening of epilepsy.[23] Research has indicated that individuals with epilepsy have markedly higher levels of several cytokines in their serum and cerebrospinal fluid.[23] Among these, key inflammatory factors secreted by Th17 cells include IL-17A, IL-6, GM-CSF, and TNF-α. These inflammatory factors activate glial cells, induce oxidative stress and excitotoxicity, and ultimately cause neuronal damage.[14,24] Notably, IL-17A increases neuronal excitability and indirectly regulates nervous system function by affecting satellite cells and immune cells, thereby promoting the onset and progression of epilepsy.[25,26] Nonetheless, by secreting anti-inflammatory substances like IL-10 and TGF-β or by competitively consuming IL-2 to halt Th17 growth and function, Tregs can reduce inflammation in the CNS; however, in patients with epilepsy, this inhibitory effect is significantly weakened.[4,27,28]

Treg cells were shown to significantly infiltrate the brain tissue in a pilocarpine-induced temporal lobe epilepsy animal model, with a significant negative correlation observed between the number of Treg cells in the brain and the frequency of seizures.[24] Anti-CD25 monoclonal antibodies have been shown to systematically diminish brain Treg cells,

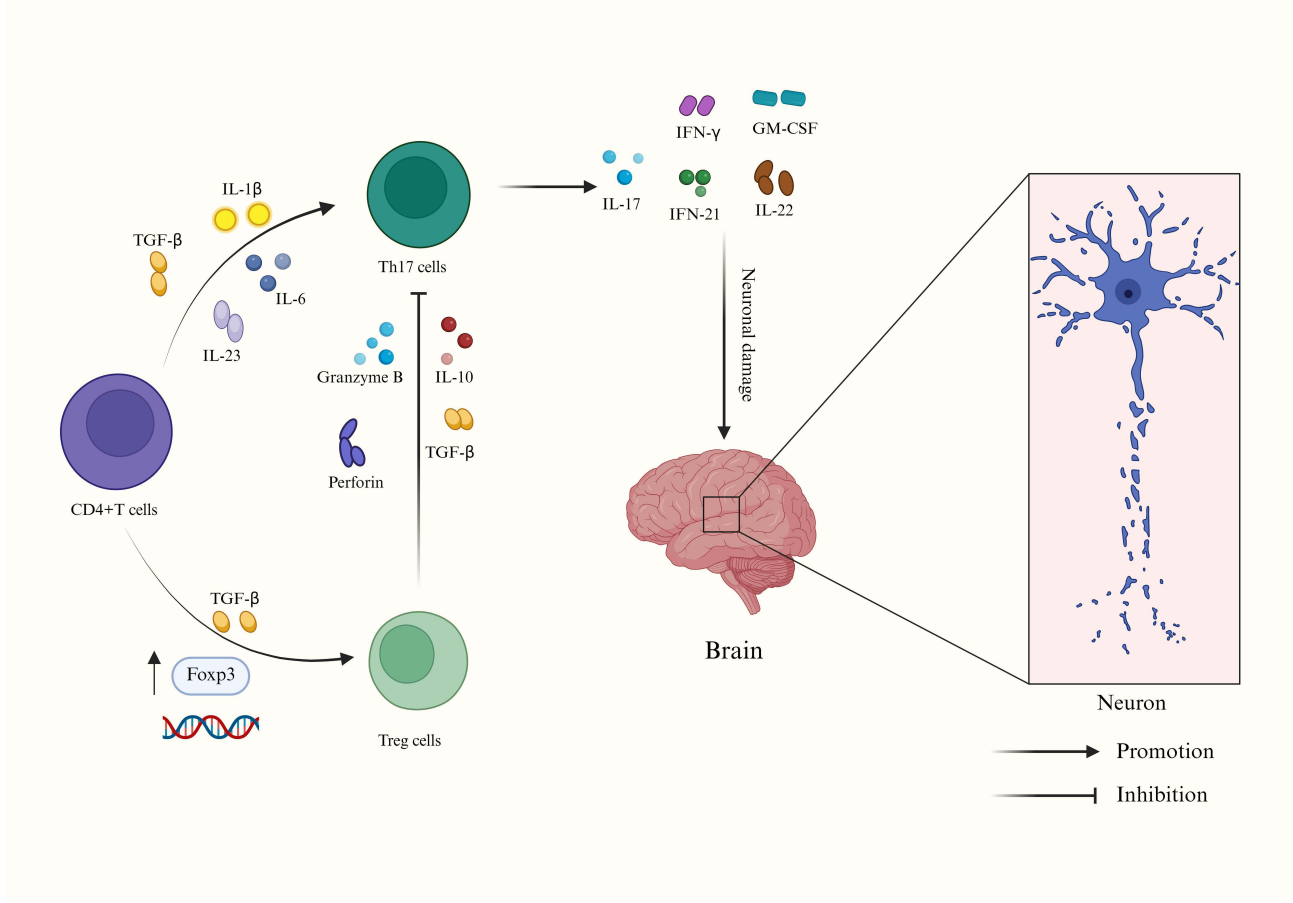

Figure 1 $CD4^+$ T cells differentiate into two subtypes, Th17 cells and regulatory T (Treg) cells, under the regulation of different environmental factors and cytokines. The differentiation of Th17 cells is stimulated and regulated by pro-inflammatory cytokines, such as interleukin (IL)-6, IL-1β, and IL-23. They primarily secrete cytokines, such as IL-17, IL-21, IL-22, interferon-γ (IFN-γ), and granulocyte-macrophage colony-stimulating factor (GM-CSF), which play a crucial role in tissue inflammatory responses by promoting the recruitment of immune cells and the release of inflammatory factors in tissues, thereby exacerbating inflammatory pathological processes. In contrast, the differentiation of Treg cells is supported by the regulation of transforming growth factor-β (TGF-β) and the expression of the forkhead box protein 3 (FOXP3) gene. These cells primarily secrete inhibitory molecules, such as IL-10, granzyme B, perforin, IL-35, and TGF-β. These molecules help maintain immune homeostasis in the body by inhibiting the activation of effector T cells, reducing the release of inflammatory factors, and regulating the balance, thereby preventing excessive inflammatory responses and the development of autoimmune diseases. Created in BioRender. MU, I. (2025) https://BioRender.com/ahykxiv.

which sets off a cascade of neuroimmune reactions, such as astrocyte proliferation, microglial activation, upregulation of pro-inflammatory factors (IL-1β, TNF-α, IL-6), and marked increases in markers of oxidative stress (malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE)).[14,29–31] These changes result in substantial neuronal loss in the CA1 and CA3 regions of the hippocampus, ultimately leading to an increased frequency of spontaneous seizures and the exacerbation of chronic temporal lobe epilepsy (TLE)-related behavioral disorders. The protective role of Treg cells in the pathophysiology of epilepsy is further strengthened by the intracerebroventricular injection of chemokine ligand 20 (CCL20), which increases the number of Treg cells in the brain and significantly suppresses seizures.[24] This Th17/Treg imbalance-induced alteration of the immune microenvironment not only exacerbates neuroinflammatory responses but may also promote the onset and progression of epilepsy through multiple mechanisms.

Abnormalities in Treg cells are not only characterized by a reduction in their numbers, which is negatively correlated with seizure frequency; they are also closely associated with functional impairments, jointly contributing to the onset and progression of epilepsy.[14,32] Peripheral blood Treg cells in patients with epilepsy exhibit significant functional abnormalities, which primarily manifest as the increased production of anti-inflammatory factors, such as IL-10.[33] This compensatory increase reflects the body's attempt to suppress neuroinflammatory responses by enhancing Treg cell function; however, this compensatory mechanism is often insufficient to control disease progression.

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At the molecular level, abnormally activated Th17 cells secrete large amounts of inflammatory factors in patients with epilepsy. These inflammatory factors directly participate in neuroinflammatory responses and lead to significant functional abnormalities in Treg cells. These functional impairments arise mainly from the synergistic disruption of multiple signaling pathways. Vital components of Treg induction are the prostaglandin E2 (PGE2) and IL-10 receptor coactivation pathways. PGE2 binds to EP2/EP4 receptors and, in conjunction with the IL-10 receptor, stimulates the maturation of naïve CD4+ T cells into Treg cells.[5,34,35] Excessive inflammatory factors inhibit PGE2 synthesis and interfere with IL-10 signaling, resulting in downregulation of Foxp3 expression and weakened Treg function.[34] Specifically, IL-17 secreted by Th17 cells and elevated levels of TNF-α can disrupt the epigenetic foundation required for maintaining high Foxp3 expression in Treg cells by upregulating histone deacetylase (HDAC) activity, which perturbs the Foxp3 gene promoter region.[36] Additionally, the Smad-dependent and Smad-independent pathways of TGF-β play essential roles in stabilizing Treg function. The Smad2/3-Smad4 complex directly activates Foxp3 transcription while maintaining the epigenetic modifications of the Foxp3 gene by inhibiting the PI3K/AKT/mTOR signaling pathway.[37,38] However, in patients with epilepsy, high levels of IL-6 and IL-17 seriously interfere with TGF-β signaling pathways, leading Treg cells to develop into effector T cells or even pro-inflammatory Th17 cells. This creates a vicious cycle that worsens the immunological imbalance.[5,39–41]

Currently, the causal relationship between the Th17/Treg cell imbalance and the pathogenesis of epilepsy remains unclear and may be bidirectional.[42,43] Under normal conditions, Th17 and Treg cells maintain a dynamic balance, which can be disrupted through two pathways. First, seizures are brought on by a surge in Th17 cells or a decline in Treg cells, which boosts neuroinflammatory components. Secondly, seizures damage neurons and activate glial cells, which release inflammatory factors (such as IL-2 and IL-6) that further encourage Th17 cell proliferation and impair Treg function, thereby initiating a vicious cycle.[24,44–47] This complex feedback mechanism limits the effectiveness of single therapeutic strategies, necessitating further research on the interplay of these factors.

Th17/Treg Imbalance Regulates BBB Function in Epilepsy: Pathogenic Mechanism

An essential component for preserving the stability of the CNS is the BBB. Studies have demonstrated an intricate connection between neuroinflammation and BBB integrity.[48,49] T-cells are crucial for this process because they are an indispensable component of the adaptive immune system.

Under typical physiological conditions, the BBB is not substantially disrupted by Th17 cells; however, pathological alterations occur when there is excessive inflammation in the central and peripheral nervous systems and insufficient Treg function or number. This viewpoint is supported by the observation of a considerable increase in the proportion of Th17 cells in the peripheral blood of individuals with drug-resistant epilepsy (DRE). These cells impact brain microvascular endothelial cells by secreting inflammatory molecules, such as IL-17 and IL-22, which lower the expression of tight junction proteins, such as claudin-5 and occludin, ultimately improving BBB permeability.[4,50,51] Additionally, Th17 cells can trigger endothelial cell death via the TRAIL-DR5 signaling pathway, further exacerbating BBB damage.[49]

Recent studies have highlighted the potential role of ferroptosis, an iron-dependent form of regulated cell death, in modulating the immune microenvironment and inflammatory responses. Ferroptosis-related gene signatures are associated with specific immune cell infiltration patterns and treatment responses in various diseases.[52] In the context of epilepsy, ferroptosis may contribute to BBB disruption and neuroinflammation,[53,54] potentially influencing the Th17/Treg balance and disease progression. Consequently, more peripheral immune cells, particularly Th17 cells, infiltrate the CNS. Activated astrocytes further promote T-cell infiltration by secreting chemokines such as CCL5. These infiltrating Th17 cells directly damage neurons and stimulate microglia and astrocytes to produce more pro-inflammatory factors, creating an "inflammatory storm". This vicious cycle ultimately increases neuronal excitability and the triggering of epileptic seizures.[55]

Disruption of the BBB allows more inflammatory cells and factors to enter the CNS and may promote the progression of epilepsy by altering the ion balance. Conversely, Treg cells, as immunosuppressive cells, prevent Th17 cells from becoming overactive by unleashing anti-inflammatory molecules, including TGF-β and IL-10, maintaining BBB homeostasis and reducing inflammatory damage. If Treg cell numbers or functions are impaired, the balance between Th17

cells and their pro-inflammatory effects is disrupted, making the BBB more susceptible to damage. This constitutes a key immunopathological mechanism underlying epilepsy.[56]

Advances in Research on Immune Regulatory Mechanisms Related to Th17/Treg Imbalance in Antiepileptic Treatment Strategies

Ketogenic Diet

One important non-pharmacological treatment for refractory epilepsy is the ketogenic diet, a high-fat, moderate-protein, and low-carbohydrate diet; studies have confirmed its remarkable clinical efficacy and immunomodulatory effects.[57] Regarding the immune regulatory mechanism, the ketogenic diet can alter the proportion of T cell subsets, reducing Th17 cells and increasing Tregs in the circulation of children with refractory epilepsy. This shift is accompanied by the downregulation of IL-17A and RORγt expression, as well as the upregulation of regulatory T cell factors, such as Foxp3, GITR, and CTLA-4, potentially achieved through inhibition of the mTOR/HIF-1α signaling pathway.[4,14]

At the molecular level, a ketogenic diet regulates the expression of neuregulin 1 (NRG1) by influencing histone acetylation levels, which are critical for its antiepileptic effect.[58] This suggests that a ketogenic diet may modulate neuroimmune function through epigenetic modifications, thereby reshaping the Th17/Treg balance at the immunological level and providing new insights into its therapeutic mechanisms.

The gut–brain axis plays an important role in the therapeutic benefits of a ketogenic diet. Research published in the journal *Cell* has shown that a ketogenic diet significantly impacts the gut microbiota and its functions.[59] In children with refractory epilepsy undergoing treatment, reductions in *Bifidobacterium, Eubacterium*, and *Blautia* were observed, in addition to an increase in *Escherichia coli* and a concurrent decline in pathways related to carbohydrate metabolism.[60] These microbial changes are closely associated with seizure control. In addition, when the gut microbiota of treated subjects was transplanted into mice, the mice exhibited significantly enhanced seizure resistance.[61]

Multiple large-scale studies have yielded encouraging results regarding the clinical efficacy of a ketogenic diet. According to a randomized controlled trial that included 427 children and adolescents, up to 55% of patients following the traditional 4:1 ketogenic diet had a seizure-free status within 3 months, with a seizure reduction rate of up to 85%.[62] Another systematic review and network meta-analysis involving 907 patients confirmed these findings. The standard ketogenic diet, modified Atkins diet, and low glycemic index treatment were among the ketogenic diets compared in this study.[63] Results indicated that all these treatment approaches significantly reduced seizure frequency, with the low glycemic index treatment showing a superiority ratio of 24.7 (95% confidence interval (CI): 5.3–115.4), which was markedly better than conventional treatment approaches.[63]

Regarding safety, the ketogenic diet generally demonstrated good tolerability. Although some gastrointestinal-related adverse effects, such as abdominal pain and diarrhea, may occur, these symptoms are typically short-term and manageable.[64] Notably, altered therapy modalities, such as low glycemic index therapy and a modified Atkins diet, preserved therapeutic efficacy while lowering the frequency of side effects.[57] A randomized controlled experiment with 170 children verified that patient adherence to treatment was better, and the occurrence of side effects was much lower in the low glycemic index therapy group (33.3%) than in the standard ketogenic diet group (56.4%).[57]

The immunomodulatory effects of the ketogenic diet require additional clinical data. The KIWE study highlights the need for in-depth research on long-term efficacy, age-related differences, and combination therapies.[64] Future research should concentrate on the effects on the patient's standard of life, the creation of individualized treatment regimens, and how the microbiome affects neuroimmunity via the gut–brain axis. More clinical data are required to provide tailored care for infants and toddlers aged 1–36 months.[65]

Immunomodulatory Antiepileptic Strategies Targeting the PD-1/PD-L1 Pathway

As a new therapeutic approach, immunomodulatory therapy has shown effectiveness in treating inflammatory conditions, such as MS and inflammatory bowel disease.[66–68] Research has shown that the function of Tregs is significantly regulated by programmed death receptor 1 (PD-1) and its ligand, PD-L1. This modulation is accomplished by influencing T-cell activation and proliferation signaling pathways.[69,70] PD-L1 expression was significantly positively correlated with FOXP3 mRNA levels and was closely associated with the proportion of peripheral blood Treg cells.[71–73] In the in vitro experiments, PD-L1 co-

stimulation increased the expansion rate of inducible Treg cells from 6.5% to 18.3%.[74] Subsequent investigations revealed marked dysregulation of the PD-1/PD-L1 pathway in individuals with epilepsy. Individuals with refractory epilepsy have higher serum and cerebrospinal fluid levels of PD-1, which are linked to the severity of the condition, particularly in status epilepticus. This pathway may serve as a diagnostic biomarker and therapeutic target, and modulating its function could potentially improve the prognosis.[75] In addition, during the pathological process of epilepsy, PD-1 may be involved in immunoregulatory mechanisms related to neurons and microglia. By influencing central immune inflammation and T-cell activation, the PD-1/PD-L1 pathway further affects the overall homeostasis of the CNS.[76,77] Thus, the PD-1/PD-L1 pathway may also be involved in the immunopathological mechanisms of epilepsy based on current studies on the regulatory function of Tregs in the development and progression of epilepsy. Interventions targeting this pathway may provide new insights into immunotherapy for epilepsy.

These findings demonstrate the dual function of the PD-1/PD-L1 pathway in immune regulation: on the one hand, it exerts immunosuppressive effects by inducing Treg cell proliferation and maintaining their function; on the other hand, excessive expression may disrupt the homeostatic balance of Treg cells, leading to functional impairment. Therefore, therapeutic strategies targeting the PD-1/PD-L1 signaling pathway require precise control of dosage and timing to achieve optimal therapeutic outcomes.[78] Small-molecule kinase inhibitors, such as Janus kinase (JAK) inhibitors, have demonstrated significant clinical efficacy and favorable safety profiles for the treatment of autoimmune diseases. This study provides an important theoretical foundation and technical approach for developing novel immunomodulatory drugs.[69]

Challenges of Other Treatments

Owing to their accessibility and safety, olfactory mucosa mesenchymal stem cells (OM-MSCs) have recently gained attention as a prospective cell source for treating intractable epilepsy. Studies have shown that OM-MSC treatment can significantly improve seizure type, frequency, and severity in patients with epilepsy, with no significant adverse reactions observed during an 8-year follow-up period. According to brain magnetic resonance imaging (MRI), patients with epilepsy may experience less reduction in brain volume after receiving autologous OM-MSC therapy.[79] OM-MSCs have been shown to restore neuronal networks, alleviate inflammation, attract Treg cells to the brain, and enhance cognitive, motor, and sensory abilities in animal models of epilepsy.[79] These findings provide experimental evidence supporting the use of OM-MSCs in the treatment of epilepsy. Small sample sizes and a dearth of randomized controlled trials continue to restrict research despite the positive prognosis. Although the 8-year follow-up shows safety, the long-term consequences need to be evaluated. Therefore, large-scale clinical trials are required to validate the therapeutic value of these drugs.

Immunosuppressive therapy is the primary treatment for various autoimmune diseases; however, its long-term application faces significant challenges. Studies have shown that excessive use of immunosuppressants may lead to severe complications, including increased infection risk and higher tumor incidence.[80,81] Treg cells mostly preserve grafts by modulating immune responses. However, an increase in Th17 levels may cause acute rejection or persistent graft malfunction, which may arise from excessive Th17 cell suppression or anomalies in the number and function of peripheral Treg cells.[82,83] This imbalance may further exacerbate immune response dysregulation and impair graft function. Therefore, the precise regulation of Th17/Treg balance has become a critical challenge in the treatment of epilepsy.[84]

However, traditional immunosuppressive therapies lack specificity. For instance, calcineurin inhibitors (CNIs) influence the growth and function of Foxp3+CD4+CD25+ Tregs and prevent graft rejection by inhibiting IL-2.[85] Studies have shown that transplant recipients using CNIs exhibit a noteworthy increase in Th17 frequency and a decrease in Treg frequency in the peripheral blood, which may increase the risk of kidney dysfunction.[85]

Novel therapeutic strategies are being explored to achieve precise immunomodulation. For instance, compound 511 improves the Th1/Th2 and Treg/Th17 balance by regulating the PI3K/AKT/mTOR signaling pathway.[82] Recent studies have uncovered the complex interplay between different signaling cascades in epilepsy regulation: the AMPK/PGC-1α pathway has been shown to influence seizure susceptibility through mitochondrial fusion,[86] while the dynamic activation of the PI3K/AKT/mTOR pathway is critical for lymphocyte differentiation patterns.[83] These interconnected pathways are potential therapeutic targets for the comprehensive management of epilepsy. However, these treatments need to strike

a balance between maintaining efficacy and minimizing adverse effects. In addition, developing personalized treatment plans poses significant challenges, requiring careful consideration of the patient's specific circumstances and disease characteristics.[87]

Innovative Immunomodulatory Strategies: A New Dawn in Epilepsy Treatment

Th17/Treg balance is regulated by an insulin-like growth factor (IGF) system. The IGF1R exploits the AKT-mTOR pathway to suppress Treg production, promoting Th17 differentiation and exacerbating inflammatory responses. Mice lacking IGF1R exhibit alleviated symptoms of MS, suggesting that inhibiting IGF signaling may mitigate epilepsy-related inflammation by restoring the immune balance, thereby providing a novel therapeutic target.[88]

One important transcription factor that controls Th17 cell development and the release of pro-inflammatory molecules, including IL-17, is RORγt. As Th17 cells, γδT cells, and ILC3s consistently express it, it may serve as a target for epilepsy treatment.[89,90] Currently, progress has been made in developing RORγt inhibitors, including competitive antagonists and inverse agonists, which inhibit transcriptional activity by binding to the ligand-binding domain.[90,91] These inhibitors exhibit promising efficacy in autoimmune disorders, as evidenced by in vitro studies indicating a significant reduction in the development of Th17 and IL-17 expression levels without altering Th1 and Treg differentiation.[91,92] However, challenges remain for clinical application. RORγt is crucial for immune homeostasis, and long-term inhibition may increase the risk of infections, impair barrier function, and disrupt microbiota balance.[90,93] Additionally, its ability to penetrate the BBB and its pharmacokinetic properties require further validation.

In addition to inhibiting Th17 cell function, increasing the number of Tregs has become a research focus. Studies have shown that the modulation of Foxp3 can enhance Treg cell function. Recent research has indicated that CD4+CD25+CD226- Treg cells have significant advantages over traditional CD4+CD25+CD127lo/- Treg cells. After 14 days of culture, the proportion of FOXP3+Helios- cells is lower, their epigenetic characteristics are more stable, and they exhibit stronger suppressive functions. These cells can inhibit effector T cell proliferation while producing fewer pro-inflammatory factors and more TGF-β1.[94] Furthermore, the T-cell receptor (TCR) signaling pathway is critical for Treg differentiation and function. TCR activates transcription factors through the PI3K/AKT and MAPK pathways, promoting Foxp3 expression, which forms transcriptional complexes to regulate gene expression.[95] This regulatory mechanism maintains Treg cell stability and provides a foundation for developing new cell expansion strategies.

Therapies for diseases of the CNS have advanced substantially in recent years owing to micro/nanocarrier technologies. Because micro/nanocarriers can effectively traverse the BBB, they can transport a variety of immunomodulatory medications, including immunoregulatory proteins and small interfering RNA (siRNAs). By employing brain-targeted modifications using transferrin receptor ligands or cell-penetrating peptides (such as TAT and Penetratin), these carriers can be actively transported across the BBB.[96,97] Utilizing pH- or enzyme-sensitive structures, they enable controlled release within the microenvironment of diseased tissues, allowing drugs to accumulate locally at epileptic foci. This approach reduces peripheral toxic side effects and enables precise regulation of the Th17/Treg balance, mitigating neuroinflammation-induced neuronal damage.[98] Although this technology is still in the exploratory stage in the field of epilepsy immunoregulation, its ability to cross the BBB has been demonstrated. Future preclinical studies are required to optimize their safety and targeting capabilities.

Additionally, researchers developed a modified IL-2 protein (mIL-2) that extends its half-life through H16L mutations and fusion with the Fc fragment. mIL-2 selectively activates the STAT5 signaling pathway in Treg cells, significantly expanding the Treg population in the peripheral blood, spleen, and lymph nodes without affecting the proliferation of CD8+ T cells and NK cells.[99,100] This offers a novel approach for restoring the Th17/Treg balance in epilepsy; however, whether mIL-2 can effectively cross the BBB to reach the CNS and exert its effects remains unclear, representing a key area for future investigation.

Recently, a research team developed an innovative "dual-lock" gene delivery system that achieves spatiotemporal control of IL-2 gene delivery through the GFAP astrocyte-specific promoter and a tetracycline-inducible switch. This system effectively expands the Treg population in the brain and exerts protective effects in various neurological disease models.[101] Studies have shown that brain-specific IL-2 delivery can prevent and improve age-related neurofunctional decline by activating the PI3K/AKT and JAK/STAT signaling pathways and restoring the molecular characteristics of glial cell compartments in the brain. This leads to significantly reduced expression levels of related markers compared to those in younger control groups.[102]

Another groundbreaking study revealed that EXO-PD-L1-HGF (exosomes modified with PD-L1 and hepatocyte growth factor) could be precisely targeted to areas of ischemic brain injury via CXCR4 upregulation after intravenous injection. This system modulates immune responses through multiple mechanisms, including inhibition of effector T cell proliferation and significantly increasing the number of CD8+CD122+IL-10+ Treg cells, thereby effectively reducing inflammation.[103] This novel therapeutic approach has the potential to significantly alter the immune microenvironment of brain cells and promote neuronal regeneration after stroke. In addition, multi-omics integration (such as genomics and transcriptomics) plays a critical role in deciphering the complex mechanisms of epilepsy. Identifying molecular biomarkers and epilepsy targets related to brain tumors provides new insights into immune-related mechanisms.[104] This approach is essential for studying the Th17/Treg imbalance in epilepsy and developing precise medical strategies to restore immune balance.

In summary, although immunomodulation therapy for epilepsy has achieved groundbreaking progress in various fields, challenges remain, including crossing the BBB, the risk of immunosuppression, and the lack of large-scale clinical trials. By focusing on the key role of Th17/Treg cell imbalance in the course of epilepsy, this study provides a new intervention strategy for patients with drug-resistant epilepsy and further demonstrates the importance of precise modulation of the immune microenvironment in neuroprotection and brain function remodeling. The integration of multi-omics technologies offers powerful tools for the deep analysis of the complex mechanisms of epilepsy and identification of potential targets, advancing personalized immunotherapy from concept to clinical practice. Future efforts should focus on increasing sample sizes, fostering multicenter collaborations, and optimizing technologies to achieve more precise and safer interventions, bringing new hope and improving the quality of life of patients with refractory epilepsy.

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