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ORIGINAL RESEARCH

Maresin 1 Alleviates Seizure Symptoms by Modulating the Crosstalk Between Inflammation and Ferroptosis

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Background: Epilepsy is among the most common neurological disorders in children. The persistent challenges of drug-resistant epilepsy and the adverse effects associated with antiepileptic drugs highlight the need for innovative therapeutic approaches for pediatric epilepsy. Both ferroptosis and neuroinflammation have been identified as key mechanisms in the development of epilepsy. Recent studies suggest that Maresin1 may hold therapeutic promise for neurological diseases. However, the neuroprotective effects of Maresin1, particularly through the ferroptosis pathway in the context of seizures, remain insufficiently explored.

Objective: This study aimed to investigate the protective effects of MaR1 against seizures, with a focus on its regulatory role in neuroinflammation and neuronal ferroptosis.

Methods: Seizure severity was evaluated using the modified Racine scale. Cognitive abilities were assessed via the Morris Water Maze and Novel Object Recognition tests. Magnetic Resonance Imaging was used to determine hippocampal iron accumulation. Nissl staining quantified neuronal density, while Transmission Electron Microscopy examined mitochondrial ultrastructure. Western blotting was performed to analyze protein expression changes across experimental groups.

Results: Pretreatment with MaR1 or a ferroptosis inhibitor significantly reduced seizure severity and improved cognitive performance in epileptic mice.

Conclusion: These findings demonstrate that MaR1 can attenuate both seizure severity and cognitive impairment in epilepsy models, potentially through modulation of neuroinflammation and the ferroptosis pathway.

Keywords: epilepsy, Maresin1, neuroinflammation, ferroptosis

Introduction

Epilepsy is a common and debilitating neurological disorder that affects an estimated 0.5% to 1% of children worldwide, making it one of the most significant health challenges in the pediatric population.[1] The clinical management of pediatric epilepsy presents significant challenges, particularly given that drug-resistant epilepsy affects a substantial proportion—up to 25%—of these vulnerable patients.[2] Beyond the immediate neurological manifestations, the long-term consequences of epilepsy in children are multifaceted and concerning.[3] Seizure-induced cognitive impairments represent a major burden, while the chronic administration of conventional antiepileptic medications frequently results in neurotoxic effects that can further compromise cognitive development and neurological function, especially in the developing brains of young patients.[4] These compounding factors underscore the critical and urgent necessity for

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developing novel, more effective therapeutic approaches that can simultaneously prevent seizure occurrence and minimize treatment-related adverse effects in the pediatric epilepsy population.

The mechanisms behind the development of epilepsy are now understood to be highly complex and involve many interacting cellular and molecular pathways. In addition to well-known factors like excitotoxicity, oxidative stress, and synaptic dysfunction, new research highlights the importance of various neuroprotective and neurodegenerative processes in the onset and spread of seizures.[4] Neuroinflammation is now seen as a key factor that increases neuronal hyperexcitability and helps trigger and spread seizures. In particular, abnormal immune responses in microglia have been identified as important contributors to seizure risk and the formation of epileptic networks.[5] Our previous research has shown that ferroptosis, a unique, iron-dependent form of regulated cell death driven by ROS-induced lipid peroxidation and membrane damage, is a key pathological mechanism in epileptogenesis and seizure-related neuronal injury. Targeting ferroptosis is especially important because traditional neuroprotective strategies aimed at apoptosis, necroptosis, or pyroptosis have had limited success in treating epilepsy clinically.[6–8] Increasing evidence shows that ferroptotic cell death is closely linked to inflammatory processes, and both play major roles in the cognitive decline seen in epilepsy and other neurological diseases. Moreover, the specific metabolic weaknesses of ferroptosis, such as glutathione depletion and disrupted lipid metabolism, offer unique therapeutic targets that are different from those of standard antiepileptic drugs.[9]

Maresin1 (MaR1) is a potent lipid mediator derived from docosahexaenoic acid (DHA), an essential omega-3 fatty acid, and is primarily produced by human macrophages during the resolution phase of inflammation.[10,11] MaR1 plays a crucial role in terminating inflammation by limiting neutrophil recruitment, enhancing the clearance of apoptotic cells by macrophages, and promoting the shift of macrophages towards an anti-inflammatory, tissue-repairing phenotype.[12] Beyond suppressing inflammatory responses, MaR1 actively facilitates their resolution, making it a promising candidate for the treatment of neurological diseases. Previous studies have demonstrated that MaR1 can reduce disease severity and improve outcomes in conditions such as Alzheimer's disease, spinal cord injury, and multiple sclerosis. In Alzheimer's models, MaR1 promotes amyloid-beta clearance, reduces pro-inflammatory mediators, and improves cognitive function.[13] In spinal cord injury, it aids recovery by attenuating inflammation and promoting tissue repair, while in multiple sclerosis, MaR1 accelerates the resolution of autoimmune inflammation and protects against neurological decline.[14] Additionally, MaR1 has been shown to protect against surgery-induced neuroinflammation and cognitive dysfunction by preventing glial activation, maintaining blood-brain barrier integrity, and reducing immune cell infiltration into the brain.[15] Overall, MaR1's ability to regulate immune responses and promote tissue repair highlights its therapeutic potential for various neurological disorders. However, its neuroprotective role in seizure disorders remains largely unstudied, leaving a major gap in current knowledge. Although there is strong evidence for MaR1's anti-inflammatory and pro-resolving effects in other neurological conditions, its specific impact on seizure-induced neuronal damage and epilepsy development has not been systematically explored.

In the present comprehensive investigation, we endeavored to systematically elucidate the protective effects of MaR1 on seizure activity and to characterize its regulatory influence on both inflammatory and ferroptotic pathways in experimental epilepsy models. Our extensive experimental findings demonstrate that MaR1 treatment not only significantly alleviates hippocampal neuronal injury and substantially reduces seizure severity but also produces marked improvements in cognitive performance and behavioral outcomes. The observed neuroprotective effects of MaR1 appear to be mediated through multiple complementary mechanisms, including the targeted inhibition of pro-inflammatory cytokine release and the effective suppression of ferroptotic cell death pathways. Taken collectively, these compelling results highlight MaR1 as an exceptionally promising therapeutic candidate for the clinical management of epilepsy and potentially other related neurological disorders, offering new hope for patients suffering from treatment-resistant forms of epilepsy.

Methods

Acquisition of Human Brain Gene Expression Data

To elucidate the potential involvement of crosstalk between inflammation and ferroptosis in the pathophysiology of epilepsy, we retrieved and analyzed human brain gene expression data from the Gene Expression Omnibus (GEO)

database, building upon our previous research findings.[16,17] To assess the overall variation in gene expression between the epilepsy and control groups, principal component analysis (PCA) was performed, enabling visualization of the distinct clustering patterns and global transcriptomic differences. Differentially expressed genes (DEGs) were identified using stringent criteria: a fold change (FC) ≥ 1.5 and a P-value < 0.05, ensuring statistical robustness and biological relevance. To further illustrate the distribution of upregulated and downregulated genes, volcano plots were generated, providing a clear graphical representation of the magnitude and significance of gene expression changes. For comprehensive functional annotation and pathway exploration, Gene Ontology (GO) enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis were conducted on the identified DEGs. These analyses facilitated the identification of key biological processes, molecular functions, cellular components, and signaling pathways significantly associated with epilepsy-related gene expression alterations. Additionally, the expression levels of inflammation-related and ferroptosis-related genes were specifically examined and visualized using box plots. Inflammatory markers including IL-6R, TNF, IL1B, and NFKB1 were compared between groups, alongside core ferroptosis-associated genes such as NFE2L2 (Nrf2), SLC7A11, and GPX4. This targeted analysis provided further insight into the interplay of inflammatory and ferroptotic mechanisms in the epileptic brain, laying the groundwork for subsequent mechanistic investigations.

Determination of Sample Size

The sample size for animal experiments was rigorously established through a formal statistical power analysis to ensure adequate statistical power while adhering to the principles of the 3Rs (Replacement, Reduction, and Refinement) in animal research ethics. The power analysis was conducted using the standard formula for two-sample comparisons:

$$\text{Sample Size} = \frac{2 \times (Z_{\alpha/2} + Z_{\beta})^2 \times \sigma^2}{d^2}$$

The parameters were set according to established conventions in biomedical research: A significance level (α) of 0.05, corresponding to a Z-score ($Z\ \alpha/2$) of 1.96. A statistical power (1-β) of 80%, corresponding to a Z-score ($Z\ \beta$) of 0.84. An anticipated effect size (d) of 1.7σ, where σ is the standard deviation. Based on these parameters, the calculation resulted in $n \approx 5.43$. To be conservative, this value was rounded up, establishing that a sample size of n=6 animals per group was sufficient for the study and this study used n=8 animals per group.

Animals and Drug Treatment

To investigate the potential pathways mediating Maresin1's neuroprotective properties against seizure intensity, four-week-old C57BL/6J mice were employed to model pediatric epileptic episodes, consistent with our established methodology.[7,8,17] All experimental procedures were approved by the Animal Ethics Committee of Jiangnan University (JN.No20231030c0320115 [498]) and conducted in strict accordance with the Regulations on the Administration of Laboratory Animals of the People's Republic of China (GB/T 35892–2018).[18] Comprehensive measures were implemented to minimize animal suffering and reduce the total number of subjects required. The Maresin1 concentration was established at 100 ng/kg, based on previous investigations demonstrating this dose significantly attenuates neutrophil recruitment, enhances macrophage efferocytosis, accelerates tissue regeneration, and provides organ protection across multiple preclinical paradigms.[19] Animals were randomly allocated into four experimental cohorts: 1) KA + Mar1 cohort (n = 8): received daily intraperitoneal Maresin1 administration (100 ng/kg) for seven consecutive days, subsequently challenged with a single intraperitoneal kainic acid injection (20 mg/kg) to trigger seizure activity; 2) KA cohort (n = 8): treated with kainic acid alone (20 mg/kg, intraperitoneally); 3) Control cohort: administered equivalent saline volume; 4) KA + CD + Fer-1 cohort (n = 8): beyond Maresin1 treatment, these subjects received the ferroptosis antagonist ferrostatin-1 (3 mg/kg, intraperitoneally) once daily for one week preceding kainic acid challenge, following our previously validated protocols.[7,8,17]

Behavioral Scoring

To assess the therapeutic effect of Maresin1, seizure severity was evaluated using the Racine scale. Seizure intensity was graded across five stages: (1) rhythmic mouth and facial movements; (2) head nodding; (3) forelimb clonus; (4) rearing with forelimb clonus; and (5) loss of postural stability with generalized tonic-clonic seizures. A score of Stage 3 or higher (≥3) was defined as a pronounced motor seizure.[7,8] Additionally, two independent observers, blinded to the experimental groups, recorded the frequency and duration of all seizure events within a 4-hour period following KA administration to provide a comprehensive analysis of seizure activity.

Novel Object Recognition (NOR) Test

Recognition memory was evaluated using the Novel Object Recognition (NOR) test to investigate the effects of Maresin1 on kainic acid-induced cognitive impairments, following our established protocol.[4] The time mice spent exploring a novel object (N) versus a familiar object (F) was recorded. The discrimination index (DI) was then calculated as (N–F)/(N+F)×100% to provide a quantitative measure of learning and memory.

Morris Water Maze (MWM) Test

To determine the role of Maresin1 in kainic acid–induced cognitive decline in epileptic mice, we executed the Morris water maze (MWM) test following our previously validated protocol.[20]

Magnetic Resonance Imaging (MRI)

A noninvasive T2-weighted MRI method was adopted to approximate brain iron load.[6] With it, we examined the influence of Maresin1 on kainic acid–evoked disruptions in iron homeostasis.

Transmission Electron Microscopy (TEM)

Established TEM protocols from our prior work were adopted.[6–8] Using them, we surveyed the hippocampus for changes in mitochondrial architecture.

RNA Sequencing Analysis

To elucidate molecular pathways by which Maresin1 modulates seizure severity in experimental epilepsy, we performed RNA-seq–based transcriptomic profiling using previously described procedures.[16] Differential expression was analyzed with DESeq2, defining significant transcripts as those with $P < 0.05$ and $|\log2FC| \geq 0.58$; functional interpretation of DEGs employed GO and KEGG enrichment via the OECloud platform (https://cloud.oebiotech.cn).

Malondialdehyde (MDA) and Glutathione Levels (GSH) Level

Following our prior procedures,[6–8] oxidative stress in the hippocampus after kainic acid exposure was evaluated by measuring malondialdehyde (MDA) and glutathione (GSH) with commercial kits (S0131S, S0053; Beyotime, Shanghai, China) to examine Maresin1's regulatory effect.

Nissl Staining

To probe Maresin1's neuroprotective potential in a kainic acid model, hippocampal neuronal integrity was examined by Nissl staining as previously described.[6–8]

Iron Concentration Analysis

To evaluate how Maresin1 influences hippocampal iron accumulation, we quantified iron using a commercial assay kit (Solarbio, BC4355) following previously established methods.[6,7]

Western Blot Analyses

To assess changes in hippocampal protein expression, Western blotting was carried out following earlier protocols,[6–8,17] with chemiluminescence used for band visualization and quantification.

Quantitative Real-Time Reverse Transcription PCR (qRT-PCR)

To determine how Maresin1 modulates ferroptosis-related mRNA expression, qRT-PCR was conducted per prior protocols,[6–8,17] and the primers used are detailed in Table 1.

Statistical Analysis

Data are reported as mean ± SD. Normality was assessed using the Shapiro–Wilk test. Normally distributed data were compared with unpaired Student's t tests (two groups) or one-/two-way ANOVA followed by Tukey's post hoc test. Non-normal data were analyzed using the Mann–Whitney *U*-test (two groups) or Kruskal–Wallis test (multiple groups). Analyses were performed in GraphPad Prism with $P < 0.05$ considered significant. To minimize observer bias, statistical analyses were performed in a blinded fashion by two independent investigators who were not involved in the experimental procedures. To ensure transparency and reproducibility, all analysis code and visualization scripts have been made publicly available in our GitHub repository (https://github.com/PediatricLab-Jiangnan/Maresin1-and-Seizures)

Results

Maresin1 Attenuates Seizure Severity and Seizure-Induced Cognitive Impairment

In this study, we initially explored the potential crosstalk between inflammation and ferroptosis in the pathophysiology of epilepsy by analyzing human brain gene expression profiles from the Gene Expression Omnibus (GEO) database. Specifically, we utilized the GSE256068 dataset, which comprises bulk RNA-sequencing data from brain tissues of seizure patients (n = 135) and matched healthy controls (n = 27).[21] As illustrated in Figure 1A and B, a total of 2,494 significantly upregulated and 169 significantly downregulated differentially expressed genes (DEGs) were identified (absolute LogFC > 0.58 and $P < 0.05$). Gene Ontology (GO) enrichment analysis revealed significant enrichment in biological processes and molecular functions related to phospholipid binding, a key molecular trigger of ferroptosis, and cytokine binding, which plays a central role in inflammatory responses. Consistently, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis highlighted the biosynthesis of unsaturated fatty acids and the TGF-β signaling

Table 1 The Detailed Information of Primer Sequences Utilized in This Study

Name	Sequence (5′-3′)
IL-6 forward:	GGCGGATCGGATGTTGTGAT
IL-6 reverse:	GGACCCCAGACAATCGGTTG
TNF-α forward:	CCAACATGCTGATTGATGACACC
TNF-α reverse:	GAGAATGCCAATTTTGATTGCCA
NF-κB forward:	CTGGGCACCAGTTCGATGG
NF-κB reverse:	GACAGCATAAGGCACACACTT
Nrf2 forward:	CTTTAGTCAGCGACAGAAGGAC
Nrf2 reverse:	AGGCATCTTGTTTGGGAATGTG
SLC7A11 forward:	GGCACCGTCATCGGATCAG
SLC7A11 reverse:	CTCCACAGGCAGACCAGAAAA
GPX4 forward:	TGTGCATCCCGCGATGATT
GPX4 reverse:	CCCTGTACTTATCCAGGCAGA
PTGS2 forward:	TTCCAATCCATGTCAAAACCGT
PTGS2 reverse:	AGTCCGGGTACAGTCACACTT
GAPDH forward:	AGGTCGGTGTGAACGGATTTG
GAPDH reverse:	GGGGTCGTTGATGGCAACA

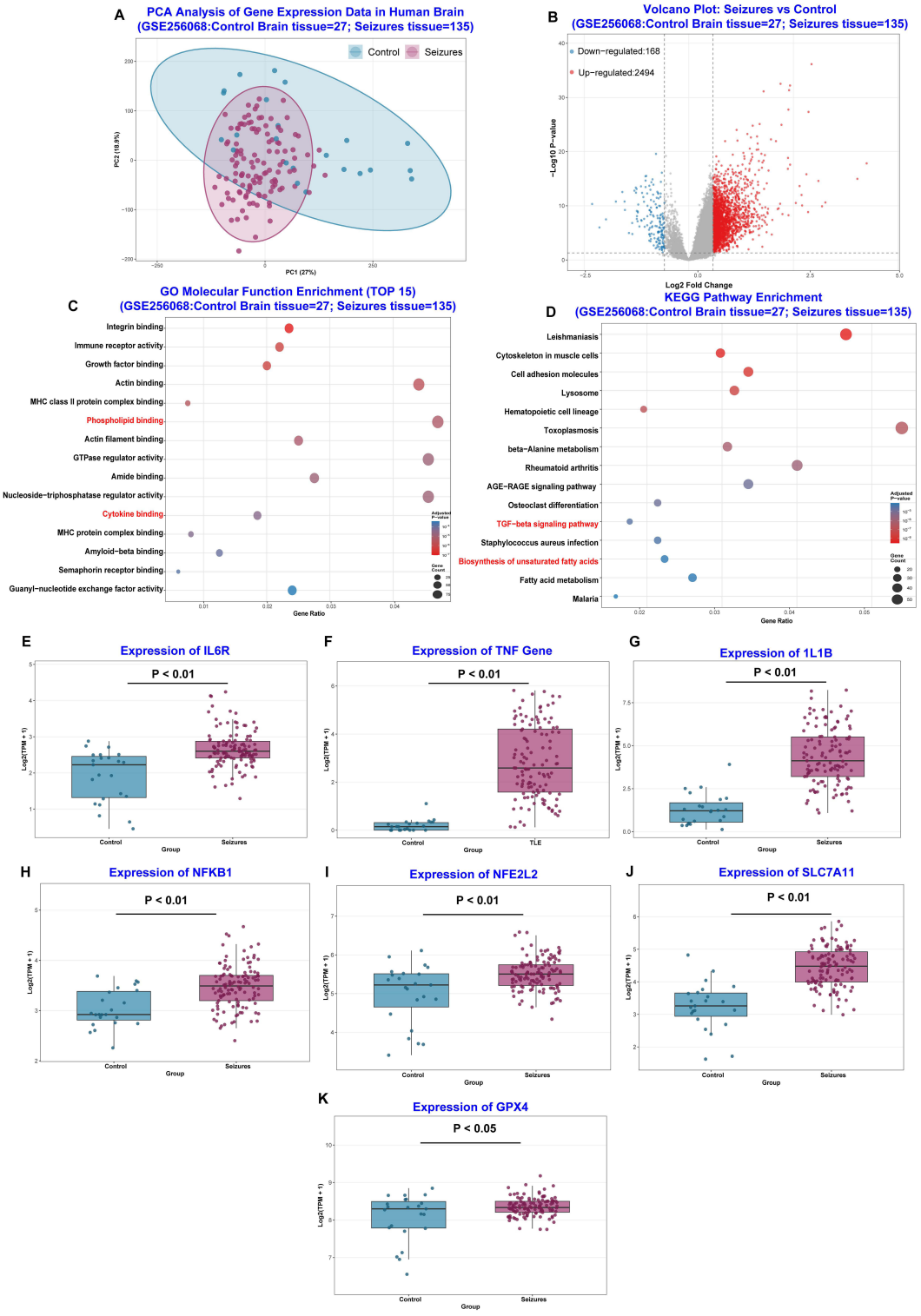

Figure 1 Bioinformatics analysis of human brain tissue from the GSE256068 dataset, comparing seizure patients (n=135) with controls (n=27). (**A**) Principal Component Analysis (PCA) plot illustrating the overall difference in gene expression profiles between the Seizures group and the Control group. (**B**) Volcano plot displaying differentially expressed genes. Compared to the control group, 2494 genes were significantly up-regulated (red) and 168 genes were significantly down-regulated (blue) in the seizures group. (**C**) Bubble chart of Gene Ontology (GO) enrichment analysis, showing the top 15 enriched molecular functions among the differentially expressed genes. (**D**) Bubble chart of Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis, highlighting the signaling pathways significantly enriched with differentially expressed genes. (**E**–**K**) Box plots showing the expression levels (Log2(TPM+1)) of seven key genes: IL6R, TNF, IL1B, NFKB1, NFE2L2, SLC7A11, and GPX4. The expression of all listed genes was significantly different between the two groups ($P < 0.05$).

pathway as significantly enriched (Figure 1C and D), further implicating lipid metabolism and immune regulation in the interplay between ferroptosis and neuroinflammation in epilepsy. Furthermore, we compared the expression levels of inflammatory markers (IL-6R, TNF, IL1B, and NFKB1) and core ferroptosis-associated genes (NFE2L2/Nrf2, SLC7A11, and GPX4) between the epilepsy and control groups. The results demonstrated significant differences in the expression of these genes, as depicted in Figure 1E–K, indicating a robust involvement of both inflammatory and ferroptotic pathways in epilepsy. Collectively, these findings suggest that the crosstalk between inflammation and ferroptosis plays a pivotal role in the pathophysiology of epilepsy. Based on this mechanistic insight, we hypothesized that MaR1, a specialized pro-resolving mediator, may attenuate seizure severity by modulating the interaction between these two pathways.

To systematically evaluate the therapeutic potential of MaR1, we employed continuous video monitoring combined with Racine scale scoring to assess seizure severity in animal models. As shown in Figure 2A–C, animals in the KA-induced epilepsy group exhibited significantly higher Racine scores, prolonged seizure durations, and increased seizure frequencies compared to controls ($P < 0.05$), confirming the pronounced severity of KA-induced seizures. Notably, pretreatment with MaR1 or the ferroptosis inhibitor ferrostatin-1 (Fer-1) resulted in a substantial reduction in all three metrics ($P < 0.05$), demonstrating that both interventions effectively mitigate seizure severity. These results collectively indicate that MaR1 exerts a neuroprotective effect by alleviating seizure severity, potentially through modulation of the crosstalk between inflammation and ferroptosis. This provides a promising avenue for the development of novel therapeutic strategies targeting epileptic pathology.

To further investigate the potential of MaR1 to ameliorate cognitive deficits associated with epilepsy, we conducted the NOR and MWM tests. In the NOR test (Figure 2D and E), mice subjected to KA-induced seizures spent significantly less time exploring the novel object and demonstrated a lower discrimination index relative to controls ($P < 0.05$), indicative of impaired recognition memory and cognitive dysfunction.[6] Remarkably, administration of MaR1 or Fer-1 prior to seizure induction significantly improved performance in both measures ($P < 0.05$), suggesting a protective effect on cognitive function. In the MWM test, analysis of swimming speed among groups revealed no significant differences ($P > 0.05$, Figure 3A), confirming that motor abilities remained intact and did not confound cognitive assessments. During the spatial learning phase, the KA group exhibited a substantial increase in escape latency compared to controls, reflecting deficits in spatial learning and memory. Pretreatment with MaR1 or Fer-1 significantly shortened escape latencies ($P < 0.05$, Figure 3B), as further illustrated by representative swim trajectories (Figure 3C). In subsequent probe trials, the KA group showed a significant decrease in both the time spent in the target quadrant and the number of platform crossings ($P < 0.05$, Figure 3D and E), indicating impaired spatial memory retention. Notably, both MaR1 and Fer-1 administration effectively restored these parameters to near-control levels.

Collectively, these comprehensive behavioral analyses demonstrate that MaR1 not only reduces seizure severity but also confers significant protection against seizure-induced cognitive deficits. The parallel efficacy observed with Fer-1 suggests that the neuroprotective actions of MaR1 may be mediated, at least in part, through inhibition of ferroptosis pathways. These findings support the therapeutic potential of MaR1 as a multi-target intervention for epilepsy, capable of addressing both acute seizure manifestations and long-term cognitive outcomes.

Maresin1 May Suppress Kainic Acid-Induced Inflammatory Response

To elucidate the molecular mechanisms underlying the neuroprotective effects of Maresin 1 in epileptic mice, comprehensive transcriptomic profiling was conducted using RNA-sequencing. As depicted in Figure 4A and B, GO enrichment analysis identified a significant enrichment of genes associated with cytokine activity, while KEGG pathway analysis highlighted the involvement of the TNF signaling pathway and cytokine-cytokine receptor interactions. These results indicate that MaR1 exerts a substantial regulatory effect on inflammatory processes, with particular emphasis on pathways known to be critical in the pathogenesis of epilepsy. Notably, several pro-inflammatory cytokines, including IL-6 and TNF-α, were found to be closely associated with disease progression.[5] Further supporting this, gene set enrichment analysis (GSEA) revealed that MaR1 treatment led to a significant downregulation of the TNF signaling pathway (Figure 4C).

To corroborate the transcriptomic findings, we performed RT-qPCR and Western blot analyses to assess the expression of key inflammatory mediators. As shown in Figure 4D–F, mRNA levels of NF-κB, IL-6, and TNF-α were

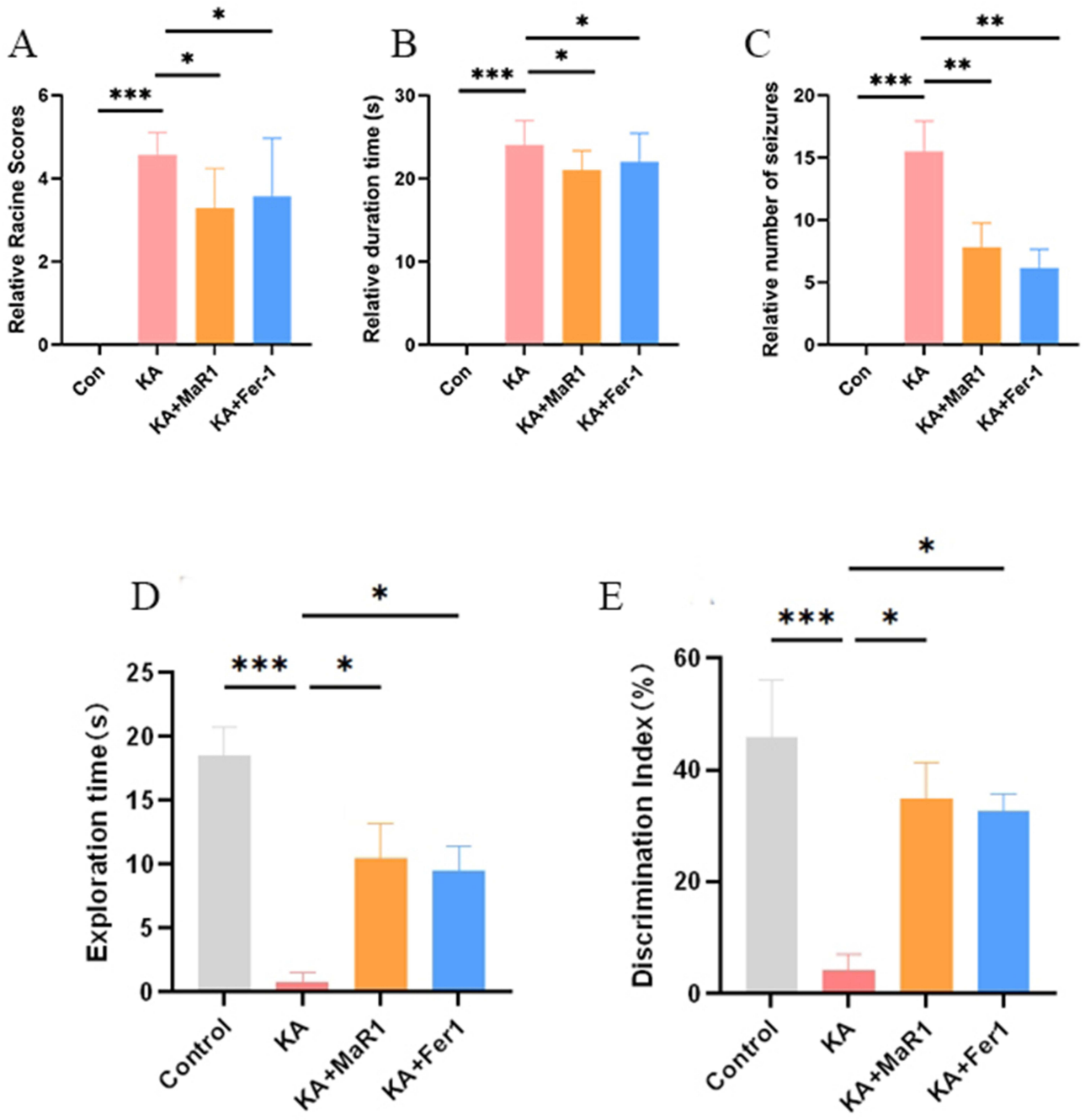

Figure 2 Impact of maresin1 treatment on epileptic seizure characteristics across experimental cohorts.(**A–C**) Statistical evaluation of normalized Racine scale ratings, seizure occurrence rates, and seizure episode length across all treatment groups. (**D**) Recognition discrimination coefficient derived from novel object recognition behavioral assessment for each experimental cohort. (**E**) Duration of investigative behavior directed toward the unfamiliar object exhibited by mice within each treatment group. *P < 0.05, **P < 0.01, ***P < 0.001.

significantly elevated in the KA-induced epilepsy group compared to controls (P < 0.05). Strikingly, pretreatment with either Maresin 1 or Fer-1 resulted in a marked reduction in the expression of these pro-inflammatory markers (P < 0.05). These mRNA-level changes were mirrored at the protein level, as demonstrated by Western blot results (Figure 5A–D), further confirming the anti-inflammatory action of Maresin 1. Taken together, these data demonstrate that MaR1 effectively suppresses KA-induced neuroinflammation in epileptic mice. The observed attenuation of inflammatory signaling—particularly through inhibition of the TNF pathway—likely contributes to the reduction in seizure severity

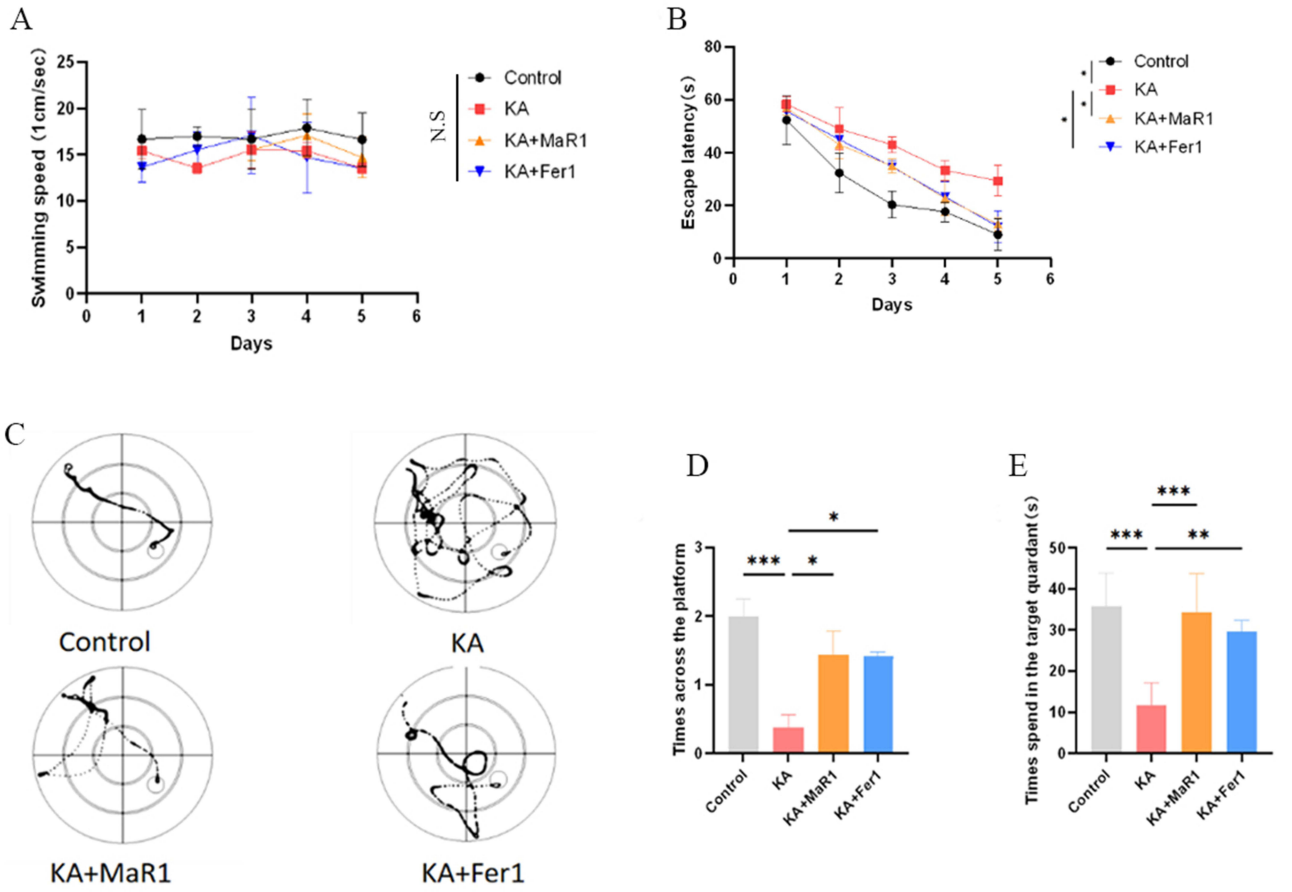

Figure 3 Maresin1 intervention on seizure-associated cognitive dysfunction evaluated through Morris Water Maze (MWM) behavioral paradigm. (**A**) Comparative locomotor velocities across all treatment cohorts. (**B**) Time-to-platform measurements documented throughout the spatial learning phase of MWM testing for each experimental group. (**C**) Exemplary trajectory patterns demonstrating navigational approaches employed by distinct groups during acquisition trials. (**D**) Platform crossing frequency quantified during memory probe sessions for each cohort. (**E**) Residence duration within the designated quadrant during probe testing across all experimental conditions. N.S. = not significant, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

and the preservation of cognitive function observed in MaR1-treated animals.[22] These findings highlight the potential of MaR1 as a therapeutic agent capable of modulating neuroinflammatory cascades in epilepsy.

Maresin1 May Mitigates Seizure-Induced Neuronal Ferroptosis

To thoroughly assess the impact of MaR1 on seizure-induced neuronal damage and disruptions in iron metabolism, we utilized both Nissl staining and T2-weighted MRI. Nissl staining, a well-established histological approach for evaluating neuronal structure and survival, revealed a significant reduction in hippocampal neuronal density in mice subjected to KA treatment compared to controls (Figure 6A–D, $P < 0.05$).[23] This notable neuronal loss underscores the susceptibility of hippocampal neurons to excitotoxic injury following epileptic seizures. Remarkably, animals pretreated with MaR1 or the ferroptosis inhibitor Fer-1 exhibited substantial preservation of neuronal populations, demonstrating potent neuroprotective effects of both interventions. In addition to neuronal integrity, we examined alterations in cerebral iron metabolism—an important contributor to both epilepsy progression and ferroptosis—using T2-weighted MRI.[24] Quantitative MRI analysis indicated a significant increase in iron accumulation within the hippocampus of the KA group, as reflected by pronounced signal hypointensity on T2-weighted MRI images (Figure 6E and F, $P < 0.05$). This pathological iron overload was effectively ameliorated by pretreatment with either MaR1 or Fer-1 ($P < 0.05$), indicating restoration of iron homeostasis. Taken together, these results provide compelling evidence that MaR1 not only mitigates seizure-induced neuronal loss but also prevents aberrant iron deposition in the hippocampus. The similar protective effects observed with MaR1 and Fer-1 further implicate the inhibition of ferroptosis as a key mechanism underlying the

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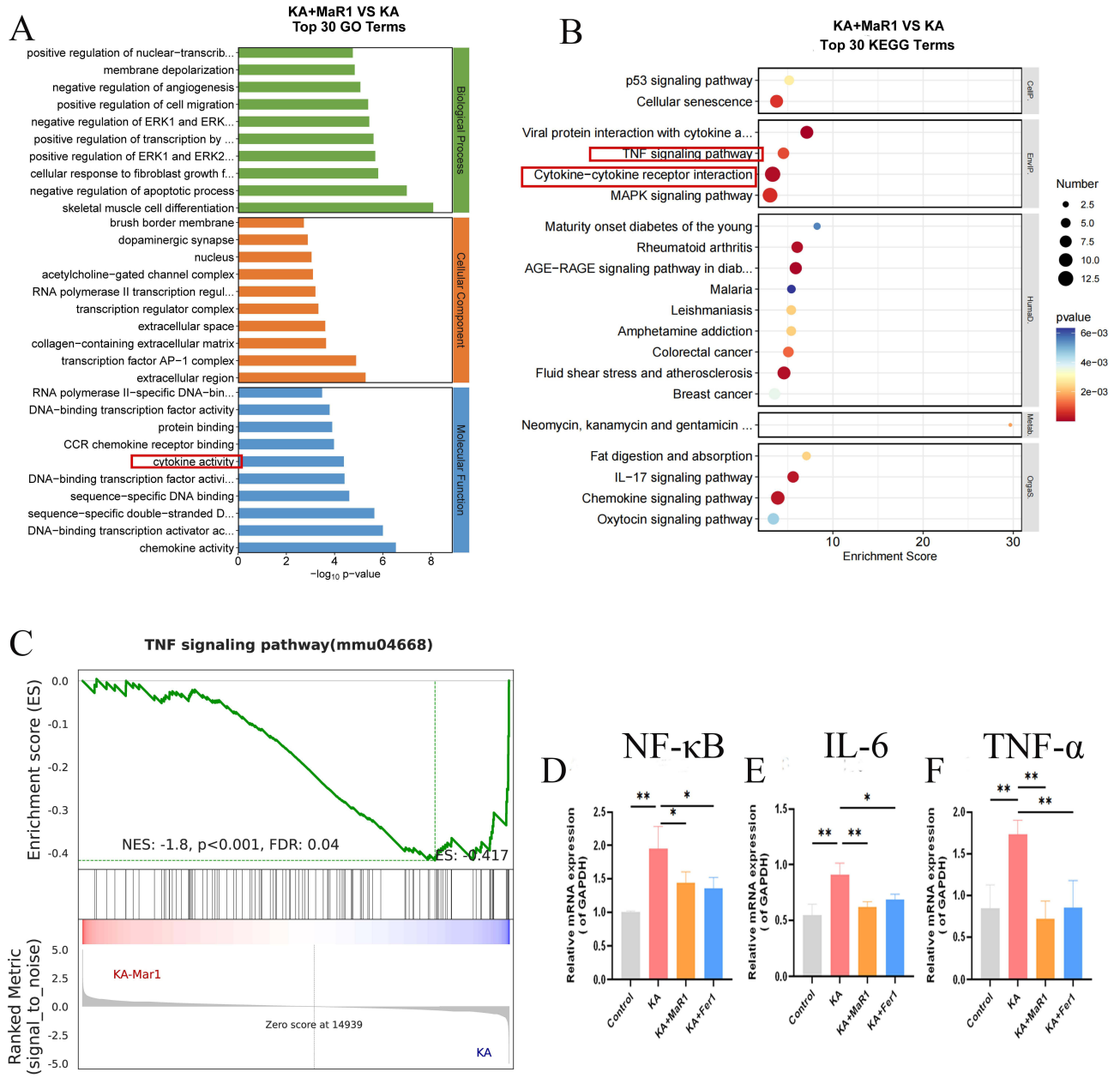

Figure 4 Maresin1 protects against epilepsy-induced neuroinflammation by regulating key gene pathways. (**A**) GO analysis showing the main biological functions of genes that were altered by MaR1 treatment compared to the epilepsy-only group. (**B**) KEGG analysis identifying the specific cellular signaling pathways that MaR1 influenced. (**C**) Gene Set Enrichment Analysis (GSEA) confirming that MaR1 suppresses the pro-inflammatory TNF-α signaling pathway.(**D**–**F**) qPCR results validating that MaR1 treatment significantly decreased the levels of key inflammatory genes—NF-κB, TNF-α, and IL-6—in the hippocampus. *P < 0.05, **P < 0.01.

neuroprotective actions of MaR1. Overall, these findings highlight the therapeutic promise of MaR1 in targeting ferroptosis-related pathways to safeguard against seizure-associated brain injury.

The Neuroprotective Mechanism of Maresin1 Involves Cross-Talk Between Neuroinflammation and Ferroptosis

A comprehensive investigation was undertaken to delineate the impact of MaR1 on the ferroptosis pathway within the hippocampus. As illustrated in Figure 7A, the TEM analysis demonstrated that both MaR1 and the ferroptosis inhibitor Fer-1 effectively alleviated seizure-induced ferroptotic ultrastructural changes in hippocampal neurons. To further characterize ferroptosis, we measured several key biomarkers—including Fe^{2+}, malondialdehyde (MDA), glutathione

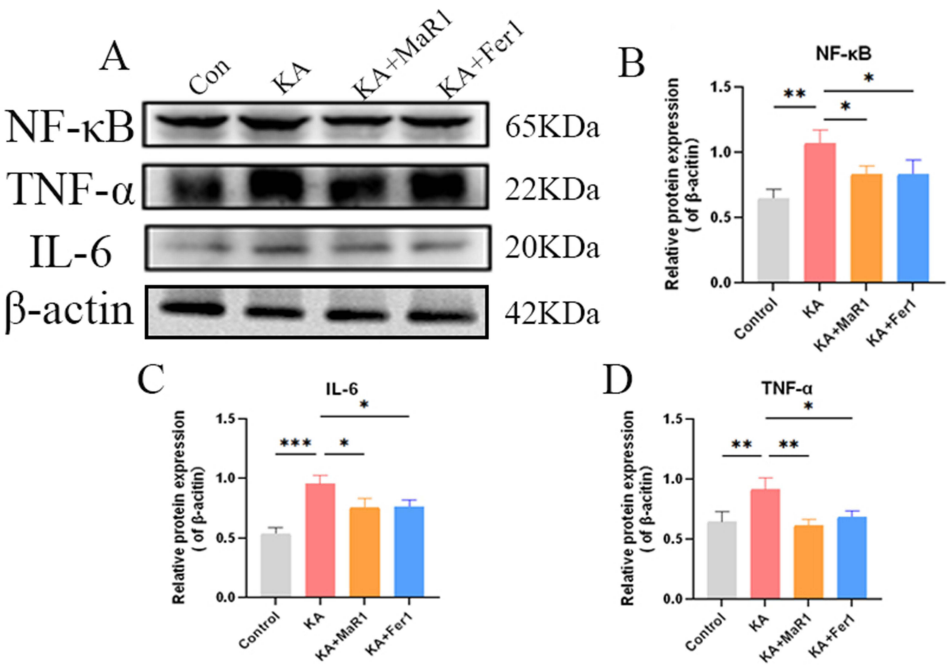

Figure 5 Maresin1 modulation of NF-κB, TNF-α, and IL-6 protein expression within hippocampal tissue of seizure-induced mouse models. (**A**) Immunoblot detection of NF-κB, TNF-α, and IL-6 protein abundance among experimental cohorts in epileptic mouse hippocampal regions. (**B**–**D**) Semi-quantitative densitometric evaluation of NF-κB, TNF-α, and IL-6 protein concentrations across treatment groups. *P < 0.05, **P < 0.01, ***P < 0.001.

(GSH), and prostaglandin-endoperoxide synthase 2 (PTGS2)—across all experimental groups (Figure 7B–E).[25] The results indicated that pretreatment with either Maresin 1 or Fer-1 significantly reversed the aberrant changes in these markers induced by seizures (P < 0.05). To gain deeper mechanistic insights, we performed RT-qPCR and Western blot analyses to evaluate the expression of crucial regulators of ferroptosis. As shown in Figure 7F–H, the KA-treated group exhibited marked reductions in the expression of nuclear factor erythroid 2–related factor 2 (Nrf2), SLC7A11/xCT, and glutathione peroxidase 4 (GPX4) compared to controls (P < 0.05). Importantly, these decreases were substantially attenuated following pretreatment with MaR1 or Fer-1 (P < 0.05). Consistent with these findings, Western blot analysis (Figure 7I) revealed elevated levels of 4-hydroxynonenal (4HNE), a lipid peroxidation marker of ferroptosis, alongside decreased expression of Nrf2, SLC7A11, ferritin heavy chain 1 (FTH1), and GPX4 in the KA group (P < 0.05). Administration of MaR1 or Fer-1 significantly mitigated these molecular alterations (P < 0.05).

Collectively, these results strongly suggest that MaR1 confers neuroprotection by modulating the crosstalk between neuroinflammation and ferroptosis. Specifically, MaR1 appears to suppress kainic acid-induced neuroinflammatory responses and ameliorate seizure-associated iron dysregulation, potentially through activation of the Nrf2-dependent ferroptosis regulatory pathway. These findings underscore the therapeutic potential of MaR1 in targeting ferroptosis to protect against epileptic brain injury.

Discussion

Maresin 1 (MaR1) is a highly specialized pro-resolving lipid mediator synthesized from docosahexaenoic acid (DHA) through specific enzymatic pathways in macrophages during the active resolution phase of inflammation. Recently, MaR1 has attracted significant attention in neurotherapeutic research due to its notable neuroprotective properties.[26] Increasing experimental evidence suggests that MaR1 can significantly slow disease progression in various chronic neurodegenerative conditions, including Alzheimer's disease, and reduce central nervous system lesion burden in experimental models of autoimmune encephalomyelitis by modulating neuroinflammatory signaling pathways.[26,27] In addition to its neuroprotective effects, recent studies have shown that MaR1 protects against ferroptosis-induced hepatic injury, indicating its potential therapeutic value across multiple organ systems.[19] Despite these promising findings, the

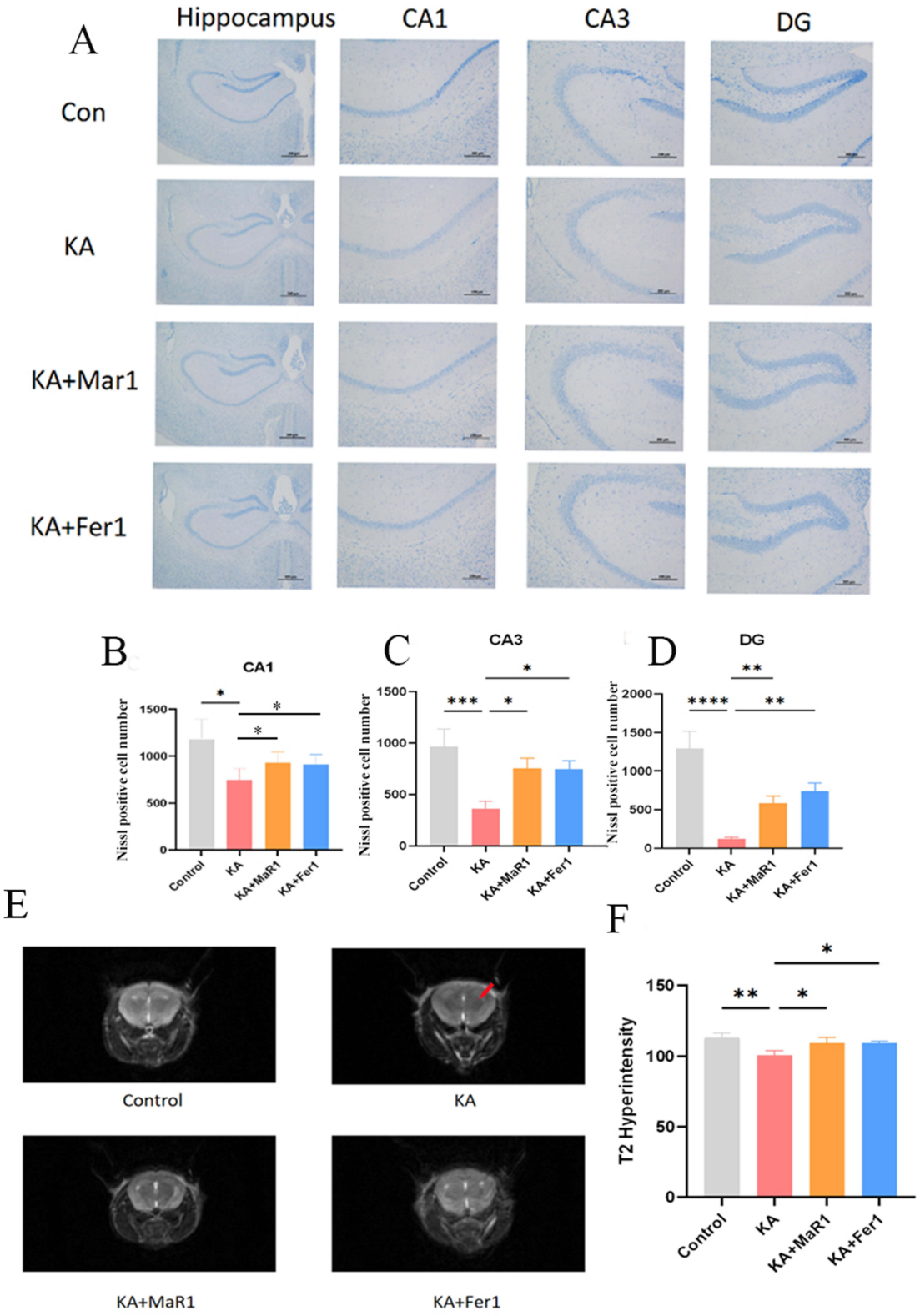

Figure 6 Maresin1-mediated neural preservation against hippocampal cell death and iron homeostasis disruption in seizure models.(**A**) Exemplary photomicrographs of Nissl-stained sections from distinct cerebral areas among experimental cohorts. (**B**–**D**) Statistical evaluation of viable neuronal populations within various hippocampal subfields. (**E**) T2-weighted magnetic resonance imaging findings among treatment groups, with hypointense regions denoting elevated iron deposition. Red arrowheads indicate markedly darker regions on the T2-weighted MRI of the mouse brain, which, compared to the control, suggest elevated iron levels. (**F**) Densitometric assessment of T2 MRI signal intensities among experimental conditions. Decreased T2 signal values reflect enhanced cerebral iron content. * P < 0.05, ** P < 0.01, *** P < 0.001, **** P < 0.0001.

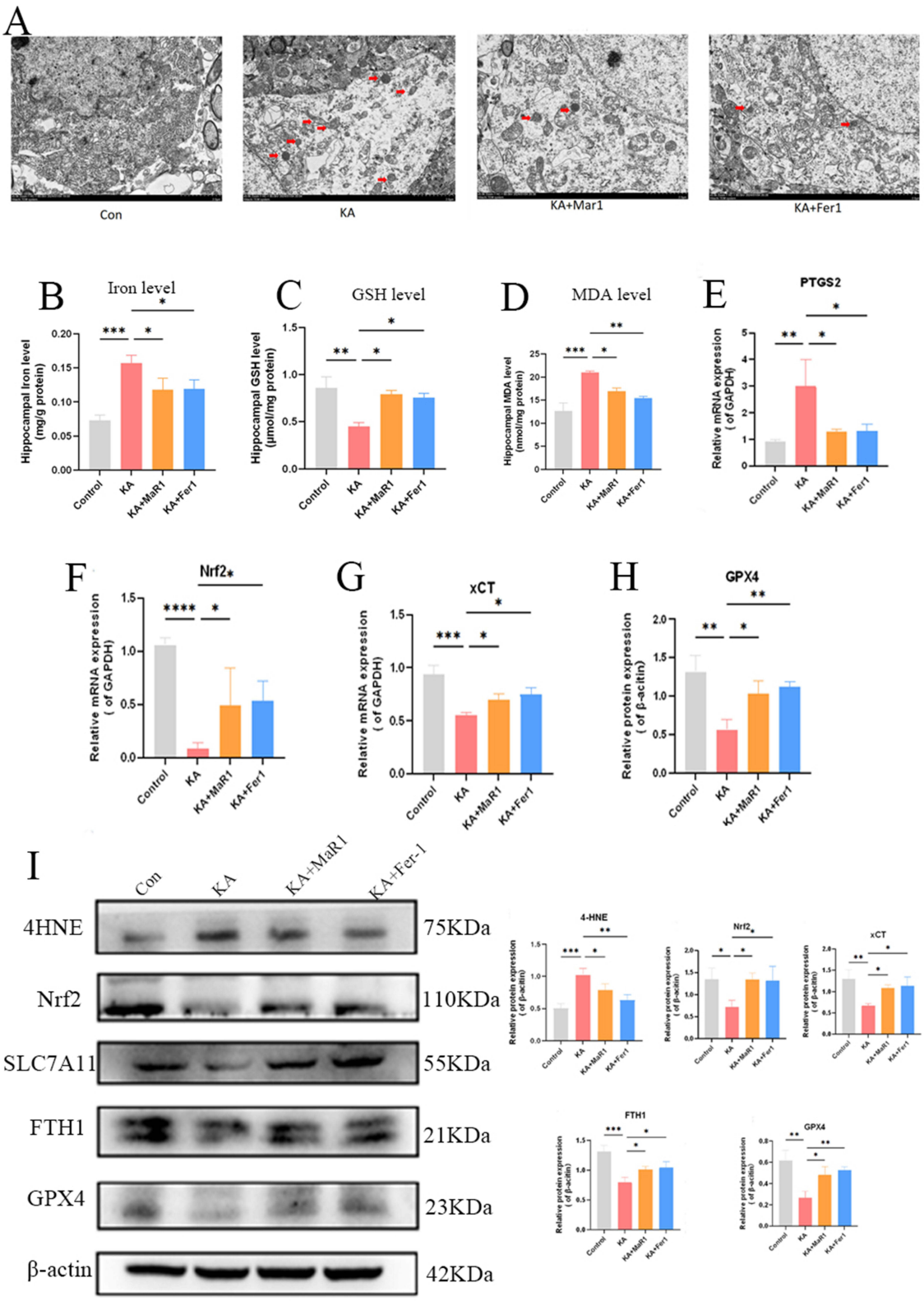

Figure 7 Maresin1 intervention on hippocampal neuronal ferroptotic cell death in seizure-induced mouse models. (**A**) Exemplary transmission electron microscopy (TEM) micrographs demonstrating mitochondrial condensation with diminished volume and enhanced membrane electron density, serving as hallmark morphological signatures of ferroptosis, documented among experimental cohorts. (Red arrowheads denote specific ultrastructural alterations; Scale bar = 1 μm). (**B**–**E**) Biochemical quantification of Fe2+, glutathione (GSH), malondialdehyde (MDA), and prostaglandin-endoperoxide synthase 2 (PTGS2) concentrations among treatment groups utilizing enzyme-linked immunosorbent assays. (**F**–**H**) Gene expression levels of key protective proteins. MaR1 increased the expression of Nrf2, SLC7A11/xCT, and GPX4, which are all crucial for defending against ferroptosis. (**I**) Immunoblot analysis of 4-hydroxynonenal (4HNE), Nrf2, SLC7A11/xCT, ferritin heavy chain 1 (FTH1), and GPX4 protein expression profiles among experimental conditions. * P < 0.05, ** P < 0.01, *** P < 0.001,**** P < 0.0001.

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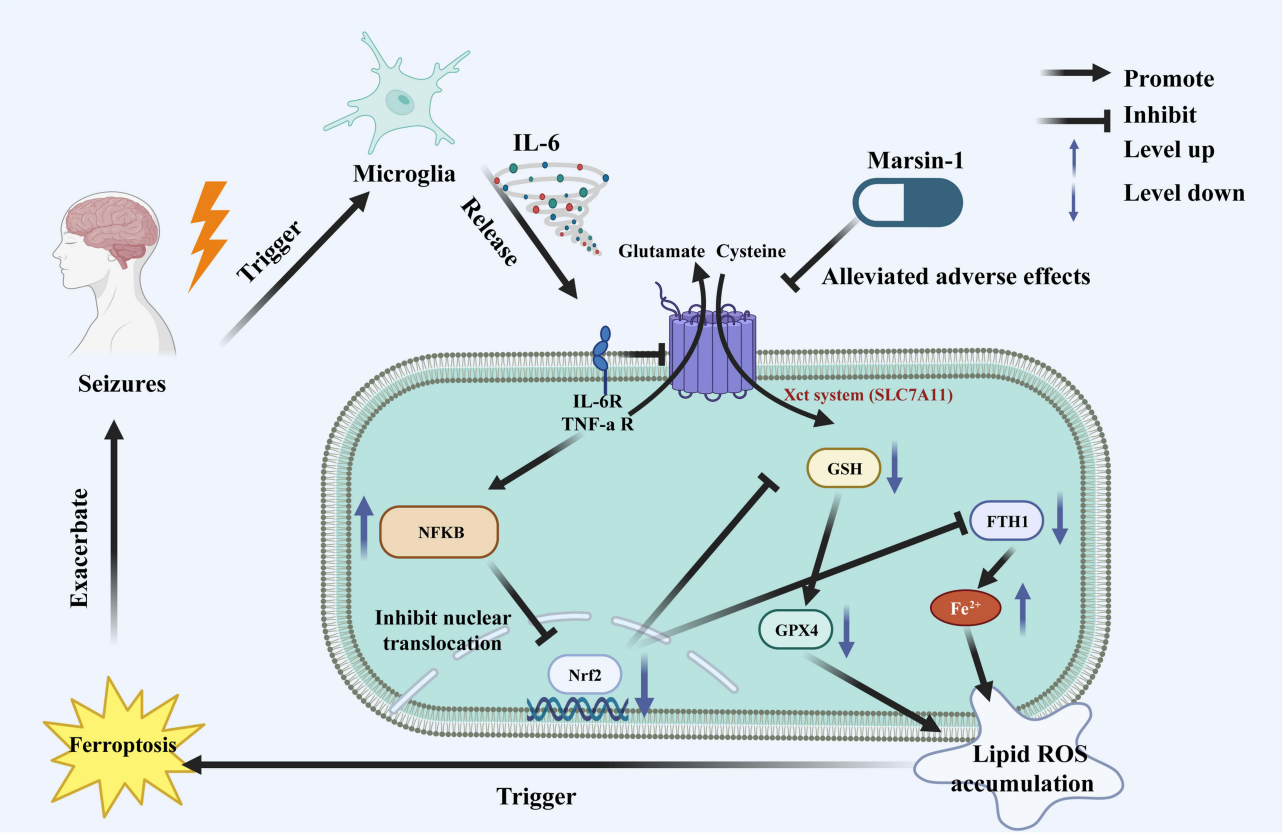

Figure 8 Hypothetical molecular cascade mediating Maresin 1-induced neural protection against hippocampal ferroptotic cell death in seizure-induced mouse models: Maresin 1 protects neurons from seizure-induced damage by regulating the interaction between inflammation and ferroptosis. It suppresses microglial activation, reducing the release of pro-inflammatory cytokines such as TNF-α and IL-6. This, in turn, inhibits the activation of the NF-κB pathway in neurons. Meanwhile, Maresin 1 activates the Nrf2 antioxidant pathway, boosting the production of GSH and GPX4—key molecules that detoxify lipid peroxides and prevent ferroptotic cell death. Created in BioRender. Zhao Hong. (2025) https://BioRender.com/us0ggg7.

specific neuroprotective mechanisms of MaR1, particularly its regulatory role in the complex interplay between inflammatory processes and ferroptotic cell death in seizure disorders—remain poorly understood and warrant further investigation. Importantly, emerging evidence has identified MaR1 as a potent inhibitor of ferroptosis, an iron-dependent form of regulated cell death that plays a crucial role in various neurological and inflammatory conditions. MaR1 exerts its anti-ferroptotic effects by upregulating key cytoprotective pathways, such as enhancing GPX4 expression and modulating iron homeostasis. By preventing ferroptotic cell death, MaR1 not only reduces neuronal injury but also attenuates associated inflammatory responses, thereby promoting neural tissue preservation and functional recovery.[28] This combined anti-ferroptotic and anti-inflammatory action positions MaR1 as a promising therapeutic candidate for disorders in which both cell death and inflammation contribute to disease progression, such as epilepsy and seizure-related neuronal damage.

Seizures are among the most common neurological disorders in children. The relationship between seizures, inflammation, and ferroptosis is becoming increasingly important in neuroscience, especially for understanding epilepsy and seizure-related brain injury. These processes are connected in a cycle that leads to neuronal damage, the development of epilepsy, and cognitive decline. When seizures occur, they quickly trigger a strong neuroinflammatory response, activating microglia and astrocytes in the brain. These glial cells release pro-inflammatory cytokines like TNF-α and IL-6, which increase inflammation and worsen neuronal injury. At the same time, ferroptosis, a newly recognized, iron-dependent form of cell death marked by excessive lipid peroxidation, has emerged as a key cause of neuronal damage in pediatric seizures. This process is especially harmful in the developing brain.[29] Previous studies indicated that seizures, especially if they are prolonged or happen repeatedly, can cause iron to build up in areas like the hippocampus, which is important for generating seizures.[30] Excess iron produces reactive oxygen species (ROS) and promotes lipid

peroxidation, both key features of ferroptosis. Studies have found increased iron levels in the brains of children with epilepsy and have linked iron overload to the development of epilepsy.[31] Our previous research in children with epilepsy has shown that the GSH/GPX4 pathway—the main defense against lipid peroxidation—is disrupted during seizures, making neurons more vulnerable to ferroptotic cell deaths.[6–8,17,19] Recent preclinical data also demonstrate that a high seizure burden increases hippocampal concentrations of maresin 1 in the Scn1a± mouse model of Dravet syndrome, a severe genetic epilepsy. This finding suggests that seizures may trigger endogenous upregulation of maresin 1 as part of the brain's adaptive response to neuroinflammatory stress, potentially facilitating resolution and repair mechanisms.[32] Despite these findings, research on MaR1 potential to protect against seizure-induced ferroptosis is still limited. Therefore, this study aims to explore how MaR1 affects seizure severity and cognitive impairment, focusing on its role in regulating the ferroptosis pathway.

In this study, we initially investigated whether the crosstalk between inflammation and ferroptosis plays a key role in the pathophysiology of epilepsy by analyzing human brain gene expression profiles from the GEO database. Our results highlight that the interaction between these two pathways is pivotal in the development and progression of epilepsy. Based on these findings, we hypothesized that MaR1, a specialized pro-resolving mediator, may attenuate seizure severity by modulating the interplay between inflammation and ferroptosis. To test this hypothesis, we conducted in vivo behavioral experiments, combining video recording with Racine scale analysis. Our results suggest that MaR1 administration alleviates seizure severity, potentially through inhibition of both inflammatory responses and the ferroptosis pathway. Furthermore, using the MWM and NOR tests, we demonstrated that MaR1 exerts neuroprotective effects, mitigating cognitive dysfunction in epileptic mice. These benefits are likely attributable to the suppression of kainic acid-induced inflammatory responses, as evidenced by RNA-seq analyses and changes in mRNA and protein levels of NF-κB, TNF-α, and IL-6. The relationship between ferroptosis and neuroinflammation in seizures and epilepsy forms a complex, bidirectional, and self-perpetuating cycle that significantly contributes to neuronal damage. Previous research has established a strong correlation between elevated levels of inflammatory mediators and increased seizure frequency.[33] On one hand, ferroptotic neuronal death leads to membrane rupture and the release of damage-associated molecular patterns (DAMPs), which activate resident glial cells—primarily microglia and astrocytes—in the brain. These activated glia subsequently release pro-inflammatory cytokines, such as TNF-α and IL-6, further intensifying neuroinflammation. On the other hand, these cytokines can disrupt iron metabolism by enhancing iron uptake or reducing iron efflux, resulting in intracellular iron overload. Additionally, inflammatory mediators may directly or indirectly inhibit key antioxidant enzymes like GPX4 or deplete GSH, further weakening cellular defenses against lipid peroxidation and aggravating ferroptosis.[34] Moreover, cytokines such as TNF-α and IL-6, which are implicated in epilepsy and neural injury, can activate the NF-κB pathway via inducible IκB degradation.[35,36] This activation allows NF-κB to translocate into the nucleus and regulate gene expression, including that of Nrf2, a critical modulator in the ferroptosis pathway (Figure 8). Therefore, interventions targeting either ferroptosis or neuroinflammation could interrupt this vicious cycle, providing neuroprotective and anti-epileptic effects. Our findings indicate that kainic acid-induced epilepsy upregulates TNF-α and IL-6 expression, thereby activating NF-κB signaling. This activation, together with the direct effects of these cytokines, enhances oxidative stress and iron dysregulation, creating a permissive environment for ferroptosis. The resultant ferroptotic cell death further releases DAMPs, perpetuating inflammation and NF-κB activation, and reinforcing the cycle. This detrimental interplay among inflammation, NF-κB signaling, and ferroptosis contributes to pronounced neuronal loss, synaptic dysfunction, and cognitive decline.[37,38] Importantly, MaR1 appears to simultaneously modulate both inflammatory and ferroptotic pathways, offering a potentially more effective approach for the management of seizures and associated neurological impairments.

Nrf2 is a key transcription factor orchestrating cellular defense against oxidative stress. Upon exposure to oxidative insults or inflammation, Nrf2 translocates to the nucleus, where it binds to Antioxidant Response Elements (AREs) in the promoters of target genes.[39] Among its most vital downstream effectors is GPX4, a selenoenzyme that serves as the primary cellular safeguard against lipid peroxidation-mediated membrane damage. GPX4 catalyzes the reduction of lipid hydroperoxides, including those embedded in phospholipid membranes, using glutathione as a cofactor. This activity is indispensable for preventing the accumulation of oxidized phospholipids, which are the molecular triggers for ferroptotic cell death, positioning GPX4 as a central gatekeeper of ferroptosis. Nrf2 also upregulates FTH1, a core component of the

ferritin complex responsible for iron storage and sequestration. FTH1's ferroxidase activity converts reactive ferrous iron (Fe^{2+}) to the less reactive ferric form (Fe^{3+}), thus reducing the labile iron pool available for Fenton chemistry.[40] Furthermore, Nrf2 enhances the expression of the cystine/glutamate antiporter system Xc^-, which is composed of SLC7A11/xCT. This transporter mediates cystine uptake in exchange for glutamate, supplying the substrate necessary for glutathione biosynthesis. Intracellular cystine is rapidly reduced to cysteine, the rate-limiting precursor for glutathione synthesis. Elevated glutathione levels bolster the cell's capacity to detoxify lipid hydroperoxides and prevent formation of toxic aldehydes such as 4-hydroxynonenal (4-HNE), thereby providing broad protection against ferroptosis via multiple complementary mechanisms.[41]

In this study, we systematically explored the multifaceted effects of MaR1 on both Nrf2-dependent anti-ferroptotic signaling and the neuroinflammatory responses underlying seizure-induced hippocampal injury. The TEM was employed as the gold standard for identifying and characterizing ferroptotic cell death in hippocampal neurons. This high-resolution technique allows direct visualization of the distinctive subcellular alterations of ferroptosis, particularly the mitochondrial changes that are pathognomonic for this form of regulated cell death. Our TEM analyses provided strong ultrastructural evidence that MaR1 administration effectively mitigates seizure-induced ferroptotic neuronal death in the hippocampus. Morphologically, ferroptosis is distinguished from apoptosis or necrosis by unique mitochondrial features: pronounced shrinkage, increased electron density of mitochondrial membranes, and severe disruption or loss of cristae.[42] These alterations reflect the central role of iron-catalyzed lipid peroxidation in compromising mitochondrial integrity, ultimately leading to bioenergetic failure and cell death. Complementing our ultrastructural data, T2-MRI offered additional support by demonstrating that MaR1 reverses seizure-induced cerebral iron accumulation. MRI provides a non-invasive means to detect and quantify tissue iron, as iron deposition shortens T2 relaxation times, resulting in hypointense signals on T2-weighted MRI images. The observed MRI improvements following MaR1 treatment suggest it effectively modulates iron homeostasis and prevents pathological iron buildup, thereby limiting oxidative injury and neuronal dysfunction.

Seizures induce profound disturbances in neural network activity, triggering cascades of pathological responses, among which iron dysregulation and oxidative stress are particularly critical. Iron overload is a key factor in seizure-induced brain injury, as excess Fe^{2+} catalyzes the Fenton reaction, generating highly reactive hydroxyl radicals (•OH) from hydrogen peroxide.[30] These radicals initiate lipid peroxidation chain reactions in cellular membranes, leading to toxic lipid peroxidation products and activation of ferroptotic death pathways. Malondialdehyde (MDA), a stable end-product of polyunsaturated fatty acid peroxidation, is widely used as a biomarker for oxidative stress and ferroptotic activity. Elevated MDA levels indicate increased membrane lipid peroxidation and correlate with seizure frequency and severity, underscoring the pivotal role of lipid peroxidation-driven ferroptosis in seizure-related neuronal loss. PTGS2 (also known as COX-2) is a crucial enzyme linking inflammation and ferroptosis. Under normal conditions, COX-2 expression is minimal in the brain, but seizures rapidly induce its upregulation in neurons, astrocytes, and microglia, especially in the hippocampus. Beyond its role in prostanoid synthesis, COX-2 directly promotes lipid peroxidation by oxygenating polyunsaturated fatty acids, generating lipid hydroperoxides that propagate oxidative damage.[43] Its peroxidase activity under oxidative stress further amplifies this process, creating a cycle of oxidative and inflammatory injury. Upregulation of PTGS2 mRNA serves as a sensitive marker of ferroptotic activity and a cellular response to oxidative stress, making it a valuable tool for monitoring ferroptosis and evaluating anti-ferroptotic therapies.

Our experimental results demonstrate that MaR1 treatment confers significant neuroprotection by reversing key biochemical and molecular indicators of seizure-induced ferroptosis. Specifically, MaR1 markedly reduced brain levels of ferrous iron, MDA, and PTGS2 expression, collectively indicating effective inhibition of the ferroptotic cascade. To elucidate the underlying mechanisms, we combined RT-qPCR and Western blotting to assess transcript and protein levels of ferroptosis-related targets. The integration of ultrastructural, neuroimaging, biochemical, and molecular data provides a comprehensive mechanistic framework, revealing that MaR1 exerts neuroprotection by modulating both Nrf2-driven anti-ferroptotic pathways and neuroinflammatory networks. This dual-action mechanism highlights the complex interplay between ferroptosis and neuroinflammation in seizure-induced brain injury and identifies their cross-talk as a promising target for neuroprotective interventions. The capacity of MaR1 to simultaneously attenuate both ferroptosis and neuroinflammation represents a substantial advance in our understanding of seizure pathophysiology and suggests new avenues for therapeutic development in epilepsy and related neurological disorders.

Limitations

There are several methodological and conceptual limitations in our study that should be acknowledged. First, some experiments were conducted with only three biological replicates per group, which may not be sufficient to fully capture the complex relationship between Maresin 1 and seizure-related ferroptosis. Increasing the sample size in future studies would enhance the statistical power and reliability of our findings, as well as facilitate the detection of subtle but potentially significant effects. Secondly, our research primarily focused on the direct effects of Maresin 1 on kainic acid-induced ferroptosis in a specific mouse model of epilepsy. While this approach provided valuable mechanistic insights, it may have overlooked other relevant pathways and mechanisms, such as autophagy, mitochondrial dysfunction, or alterations in synaptic plasticity, which could also contribute to the neuroprotective effects of Maresin 1 during seizures. The intricate networks connecting inflammation, oxidative stress, iron metabolism, and ferroptosis in epilepsy remain incompletely understood. Further research is needed to elucidate how these interactions evolve over time, differ across brain regions or tissues, and vary by sex, which may help to identify additional therapeutic targets beyond those investigated in the current study. Moreover, the interplay between NF-κB and Nrf2 signaling is highly complex and may differ depending on brain region, developmental stage, or pathological context. Comprehensive studies are required to delineate the dynamic crosstalk between these pathways during epilepsy and neuroprotection, including potential compensatory mechanisms and feedback loops. It is also important to note that our findings are based solely on animal models, which may not fully recapitulate the heterogeneity and complexity of human epilepsy. Therefore, future clinical studies in human populations are necessary to validate the efficacy and safety of Maresin 1 in reducing seizure severity, frequency, and duration, as well as in preventing cognitive and behavioral impairments across different ages and epilepsy subtypes. Such studies will be essential to establish the clinical potential of Maresin 1, including optimal dosing regimens, administration routes, and treatment durations. Additionally, it will be important to investigate potential drug interactions, long-term safety, and the feasibility of personalized treatment strategies based on genetic or biomarker profiles to ensure the successful translation of Maresin 1 into clinical practice.

Conclusion

Recent research has underscored MaR1's robust capacity to inhibit ferroptosis, primarily through activation of the Nrf2 pathway, which enhances antioxidant defenses and regulates iron homeostasis, while also attenuating the inflammatory milieu that promotes ferroptosis. This multifaceted mechanism renders MaR1 an attractive candidate for further investigation and therapeutic development in neurological diseases. Notably, studies have shown that MaR1 mitigates lipid peroxidation-driven ferroptosis following radiation-induced brain injury in mice by engaging the Nrf2/SLC7A11/GPX4 axis, thereby improving neurological outcomes. Similar protective effects have been reported in models of liver injury and diabetic osteoporosis, where MaR1 suppresses ferroptosis via activation of the same pathway. The dual ability of MaR1 to activate the Nrf2/SLC7A11/GPX4 pathway and modulate inflammation highlights its promise as a therapeutic agent for neurological disorders characterized by ferroptosis, including epilepsy and acute brain injury. To our knowledge, this is the first study to explore the neuroprotective effects of MaR1 through the ferroptosis pathway in a seizure model. Compared with conventional antiepileptic drugs, MaR1 may offer a safer alternative for ameliorating epilepsy-related cognitive deficits, presenting new opportunities for clinical intervention. Our findings lay the groundwork for future research to further assess the translational potential of MaR1 and to clarify the molecular mechanisms underlying its neuroprotective actions in epilepsy and other neurological conditions.

Data Sharing Statement

The datasets generated during this study can be obtained from the corresponding author upon request.

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Disclosure

All contributing authors declare no competing financial or personal interests.

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