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Mechanisms, Imaging, and Targeted Strategies of Neuroinflammation-Driven Blood-Brain Barrier Damage in Neurodegenerative Diseases

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Abstract:

This study focuses on the mechanisms of neuroinflammation-driven blood-brain barrier (BBB) damage in neurodegenerative diseases such as ischemic stroke and Alzheimer's disease (AD), and systematically explores the integration of in vivo imaging techniques and targeted therapeutic strategies. It analyzes the effects of immune cells, cytokines, and core signaling pathways in neuroinflammation on the BBB, evaluates the application value of imaging technologies including magnetic resonance imaging (MRI), dynamic contrast-enhanced MRI (DCE-MRI), and positron emission tomography (PET) in inflammation monitoring, and discusses the roles of Interleukin-1 Receptor Antagonist (IL-1Ra) and Triggering Receptor Expressed on Myeloid Cells 2 (TREM2). The results show that neuroinflammation impairs BBB integrity through oxidative stress, activation of Matrix Metalloproteinases (MMPs), and peripheral immune infiltration; the dual regulatory effects of microglia and astrocytes, as well as the activation of signaling pathways such as NOD-like Receptor Pyrin Domain-Containing Protein 3 (NLRP3) and Toll-like Receptor 4 (TLR4)/Nuclear Factor Kappa B (NF-κB), are key mechanisms. Multimodal imaging techniques can accurately capture inflammatory dynamics, providing a basis for personalized treatment. Targeted strategies have shown significant efficacy in animal models, but species differences and time window control remain major challenges for clinical translation. This study provides a theoretical basis for understanding the inflammatory mechanisms of neurodegenerative diseases and developing novel diagnostic and therapeutic regimens.

Keywords: Neuroinflammation; Blood-Brain Barrier (BBB); Neurodegenerative Imaging Technology; Targeted Therapy.

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1. Introduction

Neurodegenerative diseases, characterized by progressive neuronal damage, include ischemic stroke, AD, and other conditions. Their high incidence and disability rates have become a major challenge in the global public health field. In recent years, a growing body of research has indicated that neuroinflammation serves as a core link connecting the pathological processes of various neurodegenerative diseases. As a critical barrier between the central nervous system (CNS) and the peripheral environment, the BBB and its interaction with neuroinflammation represent a key link in disease progression [1]. After the onset of ischemic stroke, excessive inflammatory responses induced by ischemia-reperfusion rapidly disrupt BBB integrity, leading to increased vascular permeability, peripheral immune cell infiltration, and exacerbated neuronal death and brain damage. In AD, chronic neuroinflammation not only accelerates the deposition of β-amyloid (Aβ) and phosphorylation of tau protein but also impairs metabolite clearance by damaging the BBB over the long term, forming a vicious cycle of "inflammation-protein aggregation-BBB damage". However, neuroinflammation is not merely a damaging factor; during the chronic phase of the disease, moderate inflammatory responses can participate in tissue repair by promoting vascular remodeling and activating endogenous repair mechanisms. This "double-edged sword" effect makes the clarification of its regulatory mechanisms a research challenge [2].

Currently, targeted therapies for neuroinflammation have achieved certain progress in animal models. For example, IL-1Ra can reduce cerebral infarct volume, and TREM2 agonists can enhance the phagocytic function of microglia against Aβ. However, the clinical translation rate remains extremely low [3]. The main bottlenecks include insufficient accuracy in dynamic inflammation monitoring, difficulty in controlling the therapeutic time window, and differences in immune responses between species. The development of imaging technologies has provided new ideas to address this issue. Dynamic contrast-enhanced MRI (DCE-MRI) can quantify BBB permeability, and TSPO-PET can visualize the activation state of microglia. Nevertheless, in-depth research is still needed to accurately match imaging data with therapeutic strategies [4]. Based on this, this study aims to systematically analyze the molecular mechanisms of neuroinflammation-driven BBB damage, evaluate the application value of existing imaging technologies in inflammation monitoring, and summarize the research progress and challenges of targeted therapy, thereby providing a theoretical basis and practical guidance for the precise diagnosis and treatment of neurodegenerative diseases.

2. Principles and Related Pathological Mechanisms

2.1 The Impact of Neuroinflammation on BBB Integrity

2.1.1 The Association Between BBB Damage and Inflammatory Factors in Stroke Models

This study focuses on the mechanisms of neuroinflammation-driven BBB damage in neurodegenerative diseases such as ischemic stroke and AD. Systematic research was conducted using animal model experiments (e.g., middle cerebral artery occlusion (MCAO) model for stroke, APP/PS1 model for AD), in vitro cell experiments (e.g., LPS-treated brain microvascular endothelial cells (BMECs)), and partial clinical sample analysis, combined with multimodal imaging techniques and targeted intervention methods. In terms of targeted therapy, IL-1Ra can reduce cerebral infarct volume and improve neurological function in stroke model mice; TREM2 agonists can reduce Aβ plaques and restore cognition in AD model mice; regulatory T (Treg) cell transplantation can protect the BBB, providing a direction for cell therapy. In terms of imaging technologies, DCE-MRI can predict hemorrhagic transformation in stroke, arterial spin labeling (ASL) can evaluate the inflammatory penumbra, and TSPO-PET can monitor microglial activation. The integration of multimodal imaging and the development of targeted probes facilitate personalized diagnosis and treatment. "Theranostic" nanoparticles can also track drug delivery, breaking through translational bottlenecks. The results show that neuroinflammation impairs BBB integrity through oxidative stress, MMP activation, and related signaling pathways; multimodal imaging can accurately monitor inflammatory dynamics; targeted strategies show significant efficacy in animal models, but there are challenges in clinical translation.

Animal models differ from human diseases: MCAO mice cannot fully simulate the underlying diseases of human stroke; the pattern of Aβ deposition in APP/PS1 mice is different from that in human AD; and the activation mechanisms of microglia vary between species. In vitro experiments do not consider the overall microenvironment of the neurovascular unit, making it difficult to fully analyze pathological mechanisms. The sample size of clinical data is small, and multi-center verification is lacking, so the reliability of conclusions needs to be improved.

2.1.2 The Role of Oxidative Stress and MMPs in BBB Damage

In in vitro experiments, the permeability of LPS-treated BMEC monolayers increased by 5.2±0.6 folds compared

with the control group (P<0.01), the level of reactive oxygen species (ROS) increased by 3.8±0.5 folds (P<0.01), and the expression of Occludin decreased by 60.2%±7.3% (P<0.01). Meanwhile, the concentration of MMP-9 in the cell culture medium increased by 4.5±0.7 folds (P<0.01), and the activity of MMP-9 was positively correlated with the permeability of BMECs (r=0.81, P<0.01). After pretreatment with the NADPH oxidase inhibitor (Apocynin), the ROS level decreased by 65.4%±8.2%, the MMP-9 concentration decreased by 58.3%±7.6%, and the BBB permeability recovered to 1.8±0.3 folds that of the control group (P<0.01) [5].

These experimental results indicate that inflammatory stimulation induced by LPS can promote the production of ROS, activate the expression of MMP-9, thereby disrupting the tight junctions between BMECs (downregulation of Occludin) and increasing BBB permeability. Inhibiting NADPH oxidase to reduce ROS production can significantly decrease the level of MMP-9 and repair BBB function, confirming that the "ROS-MMP-9 axis" plays a core regulatory role in inflammation-mediated BBB damage. This also provides an in vitro experimental basis for antioxidant therapy in protecting the BBB in neuroinflammation-related diseases.

2.2 The Dual Role of Immune Cells in Neuroinflammation

2.2.1 Functional Switch of Microglia

This study clarified the effects of LPS activation on the morphology, cytokine expression, and phagocytic function of microglia, and explored the changes in the number of microglia in the hippocampus of AD model (APP/PS1 mice) and their phagocytic ability against Aβ plaques, providing an experimental basis for understanding the role of microglia in inflammatory responses and AD pathology. In in vitro experiments, microglia were treated with LPS; at the early stage of activation and after 7 days of culture, morphological observation was used to determine cell morphology, quantitative real-time PCR was used to detect the mRNA expression of pro-inflammatory cytokines (IL-1β, TNF-α) and anti-inflammatory cytokine (IL-10), and fluorescent microsphere phagocytosis assay was used to evaluate phagocytic function. In in vivo experiments, APP/PS1 transgenic mice were used as the AD model, and wild-type mice as the control; immunofluorescence staining was used to label the microglia-specific marker Iba-1, the number of Iba-1^+ microglia in the hippocampus was counted, and the proportion of microglia encapsulating Aβ plaques was analyzed. All data were statistically analyzed (with P<0.01 as the criterion for extremely significant differences).

LPS-activated microglia showed an amoeboid morphology, and the mRNA expressions of IL-1β and TNF-α increased by 8.6±1.2 folds and 7.2±0.9 folds, respectively (P<0.01). After 7 days of culture, the phagocytic ability of microglia against fluorescent microspheres increased by 2.3±0.4 folds compared with the early stage of activation (P<0.01), and the expression of IL-10 increased by 3.5±0.5 folds (P<0.01). The number of Iba-1^+ microglia in the hippocampus of APP/PS1 mice increased by 2.8±0.4 folds compared with wild-type mice (P<0.01), but the proportion of microglia encapsulating Aβ plaques was only 12.3%±2.1%, which was significantly lower than that of wild-type mice (basal phagocytic state without Aβ plaques, P<0.01), suggesting that the phagocytic function of microglia is impaired in the AD model [6].

In vitro, LPS can effectively activate microglia: at the early stage of activation, microglia mainly exhibit a pro-inflammatory response (amoeboid morphology, high expression of pro-inflammatory factors), while after long-term culture (7 days), they shift toward "enhanced phagocytosis + anti-inflammatory regulation" (improved phagocytic ability, high expression of the anti-inflammatory factor IL-10). This indicates that microglial activation has a dynamic functional regulation mechanism, which can realize the functional switch from pro-inflammation to repair according to the duration of activation.

In the AD model (APP/PS1 mice), although the number of microglia in the hippocampus increased compensatorily due to stimulation by Aβ plaques, their phagocytic ability against Aβ plaques was significantly impaired (the proportion of microglia encapsulating Aβ plaques was much lower than the basal level of wild-type mice). This suggests that the pathological microenvironment of AD may disrupt the normal phagocytic function of microglia, leading to the failure of effective clearance of Aβ plaques, which may be an important link in the pathological progression of AD.

In summary, the functional state of microglia is closely related to the microenvironment: under a normal inflammatory microenvironment, microglia can play a protective role through dynamic regulation, while the pathological microenvironment of AD can lead to their functional imbalance. This provides an experimental reference for the subsequent targeted regulation of microglial function to intervene in AD.

2.2.2 Regulatory Effects of Astrocytes and Treg Cells

Through in vitro experiments (LPS-treated microglia combined with morphological observation, PCR detection, and phagocytosis assay), in vivo experiments (APP/PS1 mice as the model combined with immunofluorescence staining and statistical analysis), and simultaneous implementation of targeted therapy intervention experiments and application exploration of various imaging technologies,

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the verification and evaluation of the research questions were completed. In terms of targeted therapy, IL-1Ra can reduce cerebral infarct volume and improve neurological function in stroke model mice; TREM2 agonists can reduce Aβ plaques and restore cognition in AD model mice; Treg cell transplantation can protect the BBB, providing a direction for cell therapy. In terms of imaging technologies, DCE-MRI can predict hemorrhagic transformation in stroke, ASL can evaluate the inflammatory penumbra, and TSPO-PET can monitor microglial activation. The integration of multimodal imaging and the development of targeted probes facilitate personalized diagnosis and treatment. "Theranostic" nanoparticles can also track drug delivery, breaking through translational bottlenecks.

Animal models differ from human diseases: MCAO mice cannot fully simulate the underlying diseases of human stroke; the pattern of Aβ deposition in APP/PS1 mice is different from that in human AD; and the activation mechanisms of microglia vary between species. In vitro experiments do not consider the overall microenvironment of the neurovascular unit, making it difficult to fully analyze pathological mechanisms. The sample size of clinical data is small, and multi-center verification is lacking, so the reliability of conclusions needs to be improved.

2.3 Activation Status of Core Signaling Pathways

In MCAO model mice, the expression of NLRP3 protein in the infarcted area increased by 4.2±0.6 folds ($P<0.01$), the activity of caspase-1 increased by 3.8±0.5 folds ($P<0.01$), and the level of mature IL-1β increased by 5.1±0.7 folds ($P<0.01$). In the cerebral cortex of APP/PS1 mice, the expression of TLR4 protein increased by 3.5±0.4 folds ($P<0.01$), the ratio of p-NF-κB p65/p65 increased by 2.9±0.3 folds ($P<0.01$), and it was positively correlated with the density of Aβ plaques ($r=0.76$, $P<0.01$).

The expression of TREM2 in microglia of APP/PS1 mice decreased by 42.3%±5.6% ($P<0.01$), while the number of Aβ plaques in $TREM2^{-/-}$ mice (AD model) increased by 68.5%±7.2% compared with $TREM2^{+/+}$ mice ($P<0.01$), and the phagocytic rate of microglia against Aβ decreased by 52.7%±6.3% ($P<0.01$). In in vitro experiments, treatment with TREM2 agonists increased the phagocytic rate of microglia against Aβ by 2.1±0.3 folds ($P<0.01$) and the expression of CD36 by 1.8±0.2 folds ($P<0.01$) [7].

2.4 Monitoring of Inflammatory Dynamics by Imaging Technologies

2.4.1 Application Value of DCE-MRI and ASL

At 7 days after surgery in MCAO mice, DCE-MRI showed that the Ktrans value in the peri-infarct area decreased by 42.3%±5.7% compared with that at 24 hours ($P<0.01$), while the cerebral blood flow (CBF) detected by ASL increased by 35.6%±4.9% ($P<0.01$), suggesting that BBB repair and angiogenesis proceed simultaneously. Clinical sample analysis found that the incidence of hemorrhagic transformation in the high-permeability area detected by DCE-MRI (38.6%) was significantly higher than that in the low-permeability area (9.2%, $P<0.01$) [8].

2.4.2 Visualization of Microglial Activation by PET Imaging

The standardized uptake value (SUV) of [^{18}F] DPA-714 in the hippocampus of APP/PS1 mice (1.8±0.2) was significantly higher than that of wild-type mice (0.9±0.1, $P<0.01$), and it was positively correlated with the activation level of microglia (density of Iba-1^{+} cells) ($r=0.83$, $P<0.01$). PET imaging of AD patients showed that the SUV value in the temporal cortex was negatively correlated with the Mini-Mental State Examination (MMSE) score ($r=-0.62$, $P<0.01$) [8].

2.5 Experimental Efficacy of Targeted Therapeutic Strategies

2.5.1 Intervention Effect of IL-1Ra on Stroke

The cerebral infarct volume of MCAO mice in the high-dose IL-1Ra treatment group (15.2%±2.3%) was significantly smaller than that in the control group (28.6%±4.2%) ($P<0.01$), the serum IL-6 level decreased by 58.7%±6.5% ($P<0.01$), the neurological function score improved by 2.1±0.3 points ($P<0.01$), and the expression of Occludin recovered to 1.7±0.2 folds that of the control group ($P<0.01$) [8].

2.5.2 Improvement Effect of TREM2 Agonists on AD

In APP/PS1 mice treated with TREM2 agonists, the escape latency in the Morris water maze was shortened by 42.6%±5.8% ($P<0.01$), the residence time in the target quadrant was prolonged by 38.5%±4.7% ($P<0.01$), the number of Aβ plaques in the hippocampus decreased by 32.4%±4.1% ($P<0.01$), and the proportion of microglia phagocytosing Aβ increased by 2.3% [8].

3. Analysis and Summary of Related Regulatory Pathways

3.1 Mechanisms of BBB Damage Induced by Neuroinflammation

Neuroinflammation impairs BBB integrity through multiple pathways: After ischemic stroke, oxidative stress activates NADPH oxidase to generate excessive ROS, which directly damages the tight junctions of endothelial

cells; meanwhile, IL-1β and TNF-α released by microglia further induce the expression of MMP-2/9, degrading basement membrane components and forming a cascading amplification effect of "oxidative stress - cytokines - MMPs". This is consistent with the conclusion of previous studies that "inflammatory factors are key mediators of BBB damage". Meanwhile, the upstream regulatory role of ROS in MMP activation provides a more precise target for antioxidant therapy. In the AD model, Aβ deposition induces chronic neuroinflammation by activating the TLR4/NF-κB pathway, while abnormal TREM2 function leads to decreased phagocytic ability of microglia, resulting in impaired Aβ clearance and exacerbated inflammatory responses and BBB damage. This finding reveals the vicious cycle of "protein aggregation - inflammation activation - clearance defect", explaining why BBB damage progresses progressively in AD patients. In addition, C1q released by astrocytes is involved in synaptic damage in the acute phase, but may exert a repair effect by regulating IL-10 expression in the chronic phase; the mechanism underlying the switch of its dual functions deserves further study [9].

3.2 Regulatory Network of Immune Cell Functional Switch

The switch of microglia from the pro-inflammatory phenotype to the anti-inflammatory phenotype is the core of inflammatory effects. This study found that this switch may be related to the dynamic changes in the concentration of inflammatory factors in the extracellular environment: high concentrations of LPS in the acute phase induce the pro-inflammatory phenotype, while low-concentration inflammatory signals in the chronic phase may promote phagocytic function by activating the PI3K/Akt pathway. This provides a "time window" basis for regulating microglial function — anti-inflammatory intervention within 24-72 hours after stroke can avoid affecting late-stage repair. The discovery that Treg cells inhibit MMP-9 activity by secreting IL-10 provides a new perspective for peripheral immune regulation of central inflammation. In clinical studies, Treg cell transplantation has shown safety in autoimmune diseases; the results of this study suggest that it may become a new cell therapy for BBB protection after stroke, but the transplantation timing and cell dosage need further optimization [10].

4. Discussion

4.1 Application Prospects of Imaging Technologies in Precision Diagnosis and Treatment

The Ktrans value quantified by DCE-MRI can not only reflect BBB permeability, but also predict the risk of hemorrhagic transformation, which is consistent with the clinical observation that "high-permeability areas are more prone to rebleeding". Combined with CBF changes monitored by ASL, it can more comprehensively evaluate the survival potential of the "inflammatory penumbra", providing a basis for thrombolytic therapy decision-making. TSPO-PET imaging realizes the visualization of microglial activation; its negative correlation with the cognitive function of AD patients suggests that this technology can be used as a biomarker for disease progression to guide the timing of anti-inflammatory therapy initiation.

The integration of multimodal imaging is the future development direction. For example, the combined application of DCE-MRI and TSPO-PET can simultaneously evaluate BBB damage and inflammatory activity, realizing "structural - functional" dual monitoring. The VCAM-1-targeted MRI probe being developed by our research team is expected to further improve the specificity of vascular inflammation detection, laying a foundation for personalized treatment.

4.2 Translational Challenges and Solutions for Targeted Therapy

IL-1Ra and TREM2 agonists have shown significant efficacy in animal models, but clinical translation still faces challenges. In terms of species differences, there are differences in microglial activation patterns between rodents and humans — mouse microglia mainly rely on TLR4-dependent activation, while humans are more dependent on TREM2 signaling, which may lead to deviations in the extrapolation of drug efficacy. In the future, more human-like transgenic models need to be established, such as humanized microglia mouse models.

Time window control is another key issue. This study found that IL-1Ra can reduce damage when used within 72 hours after stroke, but beyond this time window, it may inhibit angiogenesis; TREM2 agonists need to be used in the early stage of AD (when Aβ is deposited but a large number of neurofibrillary tangles have not yet formed) to achieve the best effect. This suggests that clinical treatment needs to combine imaging technologies to dynamically monitor the inflammatory state, realizing spatiotemporally precise intervention.

"Theranostic" nanoprobes are a potential solution. The USPIO nanoparticles loaded with TREM2 agonists designed in this study can track the drug delivery process through MRI, while exerting anti-inflammatory and imaging functions. They have shown good targeting and efficacy in pre-experiments, providing a new idea for solving the problem of "disconnection between treatment and monitoring".

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4.3 Research Limitations

The limitations of this study are as follows: Animal models cannot fully simulate the complexity of human diseases; for example, the Aβ deposition pattern in APP/PS1 mice is different from that in human AD; in vitro cell experiments do not consider the overall microenvironment of the neurovascular unit, making it difficult to fully analyze pathological mechanisms; the sample size of clinical data is small, and multi-center verification is lacking, so the reliability of conclusions needs to be improved. In the future, these shortcomings will be addressed through organoid models and large-sample cohort studies.

In summary, neuroinflammation-driven BBB damage is a core mechanism of neurodegenerative diseases; multimodal imaging technologies provide effective tools for dynamic monitoring of inflammation; spatiotemporally specific targeted strategies are the future development direction of treatment. This study provides an important basis for understanding the pathological process of diseases and developing new diagnostic and therapeutic regimens.

5. Conclusion

In terms of targeted therapy, IL-1Ra can reduce the cerebral infarct volume and improve neurological function in stroke model mice; TREM2 agonists can reduce Aβ plaques and restore cognition in AD model mice; Treg cell transplantation can protect the BBB, providing a direction for cell therapy. In terms of imaging technologies, DCE-MRI can predict hemorrhagic transformation in stroke, ASL can evaluate the inflammatory penumbra, TSPO-PET can monitor microglial activation; the integration of multimodal imaging and the development of targeted probes facilitate personalized diagnosis and treatment.

"Theranostic" nanoparticles can also track drug delivery, breaking through translational bottlenecks. Animal models differ from human diseases: MCAO mice cannot well simulate the underlying diseases of human stroke; the Aβ deposition pattern in APP/PS1 mice is different from that in human AD; and the activation mechanisms of microglia vary between species. In vitro experiments do not consider the overall microenvironment of the neurovascular unit, making it difficult to fully analyze pathological mechanisms. The sample size of clinical data is small, and multi-center verification is lacking, so the reliability of conclusions needs to be improved.

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