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From Cellular Stress to Neuroinflammation: The Vicious Cycle Mechanism in Alzheimer's Disease and Therapeutic Intervention Strategies

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Abstract. Traditional therapeutic strategies for Alzheimer's disease (AD) have primarily focused on the pathology of Aβ and tau proteins, but have repeatedly encountered setbacks due to the disease's pathogenesis being far more complex. In recent years, neuroinflammation and cellular stress (such as oxidative stress and mitochondrial dysfunction) have no longer been regarded as passive, secondary processes but are considered core forces driving disease progression. This review aims to systematically elaborate on the "stress-inflammation vicious cycle" present in AD: namely, cellular stress triggers microglia-mediated chronic neuroinflammation. Conversely, the persistent inflammatory state further exacerbates oxidative damage and energy crisis in neurons and glial cells. This self-reinforcing closed loop significantly accelerates Aβ deposition, tau protein hyperphosphorylation, and ultimately, neuronal loss. This research delves into the key molecular links within this cycle and critically reviews novel therapeutic strategies targeting these links. Finally, considering the future direction of early intervention integrated with the concept of precision medicine, the study provides a theoretical foundation and translation ideas for breaking through the bottlenecks in AD treatment.

Keywords: Alzheimer's disease, Neuroinflammation, Oxidative stress, Mitochondrial dysfunction, Microglia, Therapeutic targets

1. Introduction

Alzheimer's disease (AD), a major neurodegenerative disease, has a continuously rising global prevalence, posing an increasingly severe social and public health burden [1]. For a long time, the dominant "amyloid cascade hypothesis" has greatly promoted therapeutic exploration targeting Aβ. However, the repeated failures of numerous clinical trials targeting this pathway have prompted the academic community to profoundly reflect on the complete picture of AD's complex pathological mechanisms and to turn their attention to new perspectives beyond Aβ and Tau protein deposition, namely, the intrinsic immune dysregulation and cellular homeostasis imbalance in the brain [2].

Against this backdrop, this review systematically explores the mechanisms of interaction between the two core biological processes, cellular stress and neuroinflammation, which form a self-reinforcing vicious cycle and act as a key engine driving the onset and progression of AD. This

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article focuses on their dynamic interplay rather than treating them as independent pathological events: from oxidative stress and mitochondrial dysfunction triggering sustained microglial activation, to chronic neuroinflammation mediated by entities such as the NLRP3 inflammasome, to feedback mechanisms that exacerbate neuronal damage and protein aggregation. Based on this framework, this study outlines the causal chain from cellular mechanisms to degenerative pathology. The innovative therapeutic strategies aimed at breaking this vicious cycle include drug development targeting key signaling nodes such as TREM2 and NLRP3. The study will provide a theoretical basis and prospective guideline for developing more effective AD intervention strategies.

2. Composition of the vicious cycle

The pathological process of AD is not a simple cause-and-effect relationship but rather a vicious cycle driven and amplified by the interplay of various cellular and inflammatory factors. This cycle begins with oxidative stress and the integrated stress response, which activates innate immune cells to continuously release inflammatory signals, ultimately leading to neuronal functional loss and death. This chapter will delve into the molecular mechanisms of the key links within this vicious cycle.

2.1. Oxidative stress and mitochondrial dysregulation

Reactive oxygen species (ROS) are important signaling molecules at physiological levels. However, in the brains of AD patients, factors such as Aβ oligomers and metal ion imbalance lead to the production of excessive ROS beyond the cell's clearance capacity, thereby inducing oxidative stress. This includes lipid peroxidation, which damages the integrity of neuronal and organelle membranes and produces neurotoxic byproducts. These byproducts can further cross-link with proteins, affecting their normal physiological functions [3]. Protein oxidation leads to the inactivation of key enzymes (e.g., those related to energy metabolism and synaptic function) and significantly increases the aggregation propensity of Aβ and tau proteins, directly promoting the formation of pathological plaques and neurofibrillary tangles [4]. Nucleic acid oxidation, particularly of mitochondrial DNA, which lacks histone protection, is highly vulnerable and can induce mutations in the mitochondrial genome. These three types of stress cause direct and widespread damage to neurons.

Mitochondria are both the primary source of ROS and its primary target. Oxidative damage to electron transport chain proteins by ROS leads to decreased ATP synthesis efficiency and triggers more ROS leakage, forming the vicious cycle termed "ROS-induced ROS release" [5]. What's more, oxidative stress can induce defects in mitophagy, preventing damaged mitochondria from being effectively cleared. These dysfunctional mitochondria accumulate within the cell, becoming a persistent source of oxidative stress, and ultimately initiate neuronal apoptosis programs by releasing factors like cytochrome C. Thus, the overproduction of ROS not only directly damages neurons but also induces mitophagy defects and energy metabolism collapse, forming a positive feedback loop with Aβ deposition.

2.2. Aberrant activation of the integrated stress response

When cells face stresses like oxidative stress and endoplasmic reticulum stress, they initiate a conserved adaptive signaling pathway, the integrated stress response. In AD, the activation of this pathway shifts from a temporary adaptive response to a chronic, detrimental pathological process. Persistent phosphorylation of eIF2α leads to the sustained inhibition of protein synthesis. The

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concurrent upregulation of ATF4 further alters the downstream gene expression profile, which involves not only genes for coping with stress but also the suppression of genes related to synaptic plasticity and memory formation. Studies have shown that phosphorylated eIF2α levels are significantly elevated in neurons in AD model mice, and inhibiting its phosphorylation pharmacologically or genetically can effectively restore protein synthesis, improve synaptic function, and alleviate memory deficits [6]. This demonstrates that the aberrant integrated stress response is a key bridge connecting cellular stress to neuronal dysfunction.

2.3. The aggravating role of neuroinflammation

2.3.1. Functional polarization of microglia

Aberrantly activated microglia may polarize into a harmful phenotype, releasing large amounts of pro-inflammatory cytokines such as tumor necrosis factor and interleukins IL-1β and IL-18. These factors act directly on neurons through their receptors, inhibiting long-term potentiation, impairing synaptic function, and even inducing dendritic spine retraction and neuronal death [7]. Meanwhile, in the early stages of AD, the phagocytic clearance function of Aβ, which microglia should normally possess, becomes impaired, a dysfunction that is closely related to the impairment of their surface receptor TREM2.

2.3.2. Inflammasomes and cytokine storm

IIn AD, the NLRP3 inflammasome plays a pivotal role in neuroinflammation. Aβ fibrils can be phagocytosed by microglia and deposited in lysosomes, leading to lysosomal membrane permeabilization and activation of the NLRP3 inflammasome. Activated NLRP3 recruits and cleaves caspase-1, leading to the maturation and massive release of pro-IL-1β and IL-18 [8]. Importantly, NLRP3 activation also promotes the expression of β-secretase and drives Tau pathology, further amplifying both Aβ and Tau pathologies.

2.4. Formation of the vicious cycle

Initial Aβ deposition and cellular stress (oxidative stress, ISR) can trigger microglia-mediated neuroinflammation. The persistent inflammatory state (particularly driven by the NLRP3 inflammasome, releasing large amounts of factors like IL-1β) not only directly exerts toxic effects on neurons but also further exacerbates oxidative stress, impairs mitochondrial function, and promotes more Aβ production and Tau protein hyperphosphorylation. This vicious cycle continuously accelerates the pathological process, ultimately leading to large-scale neuronal loss and cognitive decline. Therefore, interventions aimed at breaking this cycle represent a promising therapeutic strategy for AD.

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3. Key signaling pathways and therapeutic targets

3.1. Comprehensive analysis of key signaling pathways

Table 1. Key signaling pathways and candidate therapeutic targets in the stress-inflammation vicious cycle of Alzheimer's Disease

Targeting Strategy	Key Molecule/Pathway	Role in AD	Representative Candidate	Targeted Pathological Stage
Stress Modulation	Nrf2/ARE pathway	Master regulator of antioxidant response, counteracts oxidative stress	Nrf2 activators	Early stress response
	Integrated Stress Response (ISR)	eIF2α phosphorylation inhibits protein translation	ISR inhibitors (e.g., ISRIB)	Cellular stress response
Immune Modulation	TREM2/DAP12 signaling	Regulates microglial phagocytic function and activation state	TREM2 agonists (e.g., AL002)	Microglial function
	NLRP3 inflammasome	Activates and releases pro-inflammatory factors like IL-1β	NLRP3 inhibitors (e.g., OLT1177)	Core inflammatory pathway
Intercellular Communication	Extracellular Vesicles (EVs)	Acts as pathological messengers and drug delivery vehicles	Engineered EVs delivering therapeutic molecules	Cross-cell propagation

As shown in Table 1, current targeted therapeutic strategies form a clear intervention framework. For stress modulation, the targets are to enhance cellular antioxidant defense capacity by activating the Nrf2 pathway, or restoring normal protein translation by inhibiting the ISR. These approach aim to block the early cascade amplification of oxidative stress and the integrated stress response, thereby containing the initiation of the vicious cycle at its source. Immune modulation targets focus on regulating the core functions of microglia: on one hand, using TREM2 agonists to enhance their protective phagocytic capacity; on the other hand, using NLRP3 inhibitors to directly block the activation of key inflammasomes via NLRP3 inhibitors, thereby alleviating neuroinflammatory damage. Particularly important is that extracellular vesicles (EVs), as an emerging technological platform, not only participate in pathological propagation themselves but can also be engineered into a highly promising delivery system. This technology potentially enables the precise delivery of the aforementioned therapeutic molecules to brain lesions, overcoming the blood-brain barrier limitations of traditional drugs.

3.2. Case analysis of target molecules

3.2.1. TREM2

Triggering Receptor Expressed on Myeloid cells 2 (TREM2) is an immune receptor primarily expressed on the microglial membrane, which, upon binding with the adaptor protein DAP12, transmits activation signals (as described in Table 1). TREM2 signaling is crucial for microglial metabolic reprogramming, chemotaxis, phagocytosis, and the transition from a pro-inflammatory to a neuroprotective state. Loss-of-function mutations in TREM2 are strong risk factors for AD, leading to a blunted microglial response to pathological proteins. Therefore, using TREM2 agonistic

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antibodies to enhance its signaling represents a strategy that aims to restore the protective functions of microglia, promote Aβ clearance, and suppress harmful inflammation. Administering TREM2 agonistic antibodies (e.g., AL002a) to AD model mice can enhance microglial clustering and phagocytic activity, reduce amyloid plaque burden, and improve cognitive performance [9].

3.2.2. NLRP3 inflammasome

The NLRP3 inflammasome is the core molecular platform connecting Aβ pathology to the release of mature inflammatory factors. By specifically inhibiting the assembly or activation of NLRP3, the maturation and release of IL-1β and IL-18 can be effectively blocked, alleviating the intense inflammatory response at its source and potentially indirectly reducing inflammation-driven pathology. The well-characterized NLRP3 inhibitor OLT1177 has shown therapeutic efficacy in various AD mouse models: it not only reduced brain IL-1β levels but also decreased Aβ deposition and tau protein hyperphosphorylation, and rescued memory deficits.

3.2.3. Extracellular vesicles

Extracellular Vesicles (EVs) possess natural blood-brain barrier penetration capability and good biocompatibility. They can act as disease messengers participating in AD pathological propagation and can also be engineered into intelligent drug delivery systems. Research indicates that engineered EVs loaded with antioxidant enzymes can effectively deliver their cargo to the brain, alleviating oxidative stress in AD mouse models [10]. This makes it feasible to load therapeutic substances (e.g., Nrf2 activators, NLRP3 inhibitors) into EVs and achieve cell-specific targeted delivery through surface modifications.

4. Emerging therapeutic strategies and cutting-edge technologies

4.1. Novel therapeutic concepts

4.1.1. Combination therapy: synergistic treatment strategies

Given that stress responses and neuroinflammation often interact in the pathological process of AD, interventions targeting a single node often struggle to break the entire pathological cycle. Therefore, ideal combination regimens should cover multiple aspects such as stress and inflammation. For example, experiments have shown that combining the mitochondria-targeted antioxidant SS-31 with the NLRP3 inhibitor OLT1177 in AD models resulted in more significant improvement in cognitive performance compared to single-drug treatments [11]. This synergistic effect arises because the two drugs blocking different, interconnected links in the cycle: SS-31 reduces the initial trigger signal (ROS) for inflammation, while OLT1177 blocks the downstream inflammatory amplification signal triggered by ROS and Aβ.

4.1.2. Precision medicine: targeted therapy and early intervention

Due to the significant individual differences in the pathological mechanisms of AD patients, precise subtyping is needed for targeted treatment. The high heterogeneity of AD means that the dominant pathological pathways may differ among patients. Current research utilizes biomarkers such as APOE genotyping and cerebrospinal fluid (CSF) analysis for patient risk assessment and population stratification. This strategy not only helps reduce misdiagnosis and missed diagnosis but also

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improves drug response rates, providing timely and precise treatment and intervention for patients. Targeted therapy aims to stratify patients through biomarkers (e.g., APOE genotyping, CSF) to select the most effective treatment plan for specific populations.

4.2. Technology-driven approaches

4.2.1. Organ-on-a-chip technology

In recent years, brain microfluidic chips and human induced pluripotent stem cell-derived three-dimensional brain organoids have provided new avenues for highly simulating the complex cellular composition and microenvironment of the human brain in vitro. These platforms can recapitulate the pathological changes of various cells, including neurons, in vitro, providing a powerful platform for the rapid, high-throughput testing of drug efficacy and toxicity in human-derived systems, thereby reducing over-reliance on animal models [12].

4.2.2. Single-cell sequencing

The heterogeneity of AD is evident not only among patients but also among different brain cell types and their states. Single-cell sequencing technology can reveal specific gene expression changes across different cell types in the AD brain, including various microglial morphologies and astrocytes. This technology can not only discover cell-type-specific new drug targets but, more importantly, it can parse the cellular basis for patients' differential responses to treatment at the molecular level, providing guidance for understanding disease heterogeneity and developing precision therapies [13].

4.2.3. Artificial intelligence

Artificial intelligence (AI) algorithms can integrate massive datasets from genomics, transcriptomics, proteomics, and clinical imaging to identify new disease subtypes, predict disease progression, and discover novel network pharmacology targets. Meanwhile, AI can also help simulate the AD pathological microenvironment in silico, analyze cellular heterogeneity, and accelerate drug design, providing new avenues for future AD cures.

5. Discussion

5.1. Limitations

Current medical approaches face limitations in subject models. Although AD animal models can compensate for the shortage of human subjects, they still cannot fully simulate the complexity of the human immune system, leading to the poor performance of many preclinically effective therapies (such as NLRP3 inhibitors) in human trials[14]. Furthermore, the precise role of neuroinflammation remains unclear. Research shows its role changes dynamically with disease stage, making the timing of intervention difficult to determine. Finally, treatment risks still require full assessment. Immune modulation may impair the brain's normal defense functions, while combination therapies face complex drug interactions and potential additive toxicity. Considering that AD patients are generally elderly, with poor drug tolerance and long treatment durations, drug safety and compliance will become major obstacles in therapeutic strategy design.

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5.2. Future directions

In future research and clinical exploration, progress can be made in the following aspects. Develop human model systems such as brain organoids and organ-on-a-chip models. Combine single-cell sequencing and AI analysis to validate targets in human systems. Develop precision regulation tools, including cell-specific gene therapies and novel biomarkers, to achieve spatiotemporally precise intervention in the disease process. Shift the intervention window earlier, conducting trials in the preclinical stage, and defining optimal strategies for combination therapy. Expand the systemic perspective to study the impact of peripheral factors on brain inflammation, opening up new therapeutic pathways.

6. Conclusion

The cellular stress-neuroinflammation vicious cycle is a core driving mechanism in AD. Compared to the traditional amyloid hypothesis, it provides a more integrated model for understanding the complex pathophysiology of AD. The study elucidates a number of promising new therapeutic targets, such as the NLRP3 inflammasome and TREM2.

This review also has certain limitations. It is primarily based on the integration and analysis of existing secondary literature, lacking support from primary experimental data. The process of literature selection and argumentation may have overlooked contradictory or negative results. Subsequent research could utilize cell or animal models to directly intervene in key nodes of this cycle, providing primary evidence in support of this theoretical framework through experimentation. Simultaneously, attempts could be made to construct quantitative or computational models to simulate the dynamic process of this vicious cycle, thereby more accurately predicting the effects of interventions. Furthermore, promoting interdisciplinary collaboration, integrating methods from neuroscience, immunology, and systems biology, and combining multi-omics data are expected to break through the limitations of secondary data.

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