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MiR-25802: a potential target for treating Alzheimer's disease by regulating neuroinflammation

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1 Introduction

Alzheimer's disease (AD) holds global significance as a neurodegenerative disorder with a complex etiology still partly understood. Recent advancements in genetic and molecular research have underscored the intricate interplay of cellular pathways and gene networks, alongside feedforward and feedback regulatory mechanisms, which may differentially impact various pathogenic phenotypes and cellular stages of AD (1). Besides the strategies of neurotransmitter modulator interference and amyloid beta peptide (Aβ)-targeted plaque clearance, neuroinflammatory inhibitors have been widely explored as potential therapeutic approaches for AD, targeting toll-like receptors (TLRs), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome, among others (2–5). Notably, microglia play a pivotal role in clearing Aβ and damaged neuronal cells, crucial for maintaining the balance between pro- and anti-inflammatory processes during neuroinflammation. Their close association with tau phosphorylation, synapse loss, and cognitive decline makes these pathological processes central to AD research (6–11).

MicroRNA (miRNA) modulation of neuroinflammation emerges as a critical regulator in maintaining microglial homeostasis by altering immunoinflammatory-related gene and protein expression. Dysregulation of this process can induce a variety of AD-associated pathological processes, including Aβ metabolism (12, 13), tau phosphorylation (14, 15), neuronal damage (16, 17), and synapse dysfunction (18, 19). The full scope of miRNA mechanisms in regulating neuroinflammation and related disorders remains under exploration. Our research highlights the crucial influence of a newly identified miRNA, miR-25802, on pathological neuroinflammation in AD (20–23). This discussion delves into the role of miR-25802 in AD pathology and its potential as a biomarker and target for future miRNA-based AD therapies (Figure 1).

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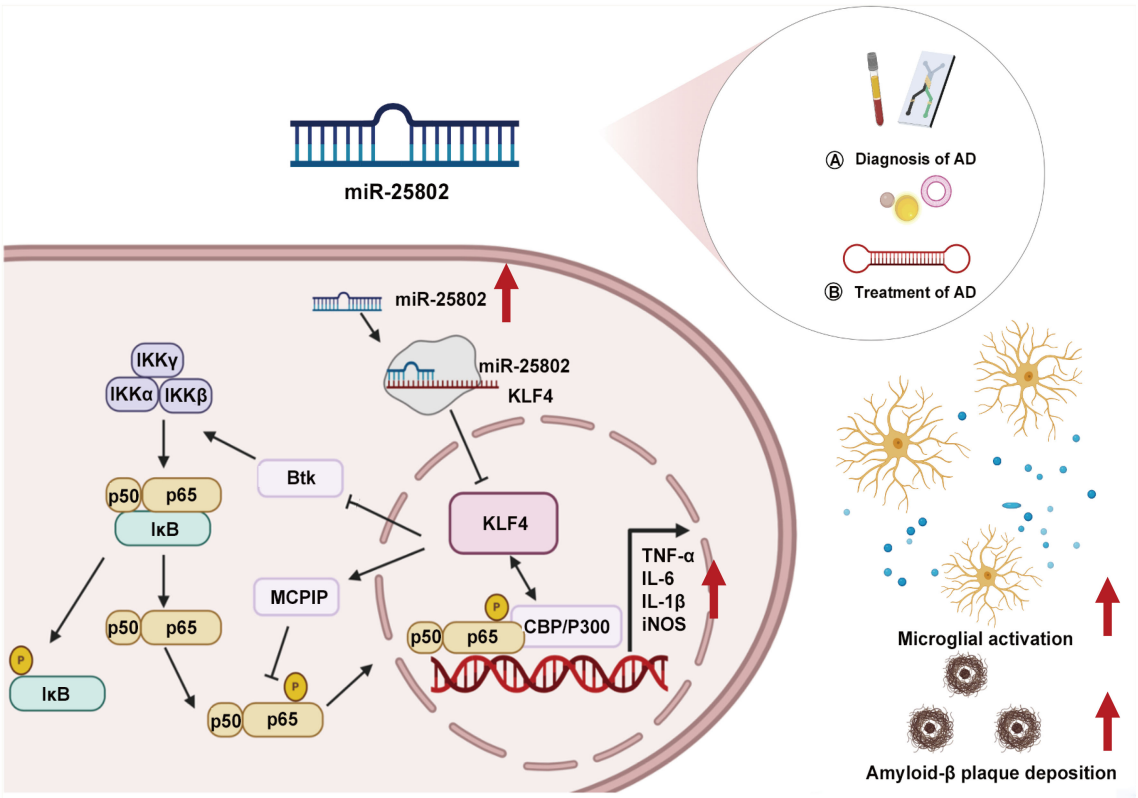

FIGURE 1
Role of miR-25802 in AD neuroinflammatory pathology. AD, Alzheimer's disease; Btk, Bruton tyrosine kinase; CBP/P300, CREB-binding protein/p300; IKKα, IκB kinase α; IKKβ, IκB kinase β; IKKγ, IκB kinase γ; IL-1β, Interleukin-1β; IL-6, Interleukin-6; iNOS, Inducible nitric oxide synthase; IκB, Inhibitor of nuclear factor kappa B; KLF4, Kruppel-like factor 4; MCPIP, Monocyte chemotactic protein-induced protein; TNFα, Tumor necrosis factor-alpha.

2 The role of miR-25802 in microglial phenotypic transformation in AD

The novel base sequences miR-25802 were identified in the AD mouse brain utilizing high-throughput sequencing (20–23). miR-25802 expression is conserved across species and relies on the canonical miRNA enzymes Dicer and Drosha for biogenesis. Notably, significant upregulation of miR-25802 in the plasma of AD patients hints at potential diagnostic utility, and its upregulation in brain regions associated with learning and memory across various AD mouse models suggests a crucial role in AD pathology. The peak upregulation of miR-25802 occurs in AD models from 5 to 7 months, which aligns with the early microglial activation in AD (24).

Subsequent study addresses the functional implications of miR-25802 in AD-related neuroinflammation. First, miR-25802 promotes the activation of pro-inflammatory microglial cells, leading to increased release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), inducible nitric oxide synthase (iNOS), and interleukin-1-beta (IL-1β), while the inhibition of miR-25802 shifts microglia toward an anti-inflammatory phenotype, characterized by M2 markers such as arginase 1 (Arg1), macrophage mannose receptor 1(CD206), interleukin 4 (IL-4), and transforming growth factor beta (TGF-β), ultimately alleviating the inflammatory response. Second, *in vivo* functional evidence underscored the significant impact of modulating miR-25802 expression on AD pathology. Overexpression of miR-25802 via adeno-associated virus type 9 (AAV9) in 5×familial AD (5×FAD) mice exacerbated spatial learning and memory abilities, Aβ deposition, and microglial activation. Conversely, inhibiting miR-25802 improved cognitive impairment, reduced Aβ deposition, and attenuated microglial activation in AD mice. These effects of miR-25802 depend on its regulation of Kruppel-like factor 4 (KLF4), a direct target of miR-25802 involved in microglial M1/M2 phenotype conversion and neuroinflammatory responses.

3 miR-25802-mediated inflammatory signaling pathways in AD

Using bioinformatics, a dual-luciferase reporter assay, gain- and loss-of-function experiments, quantitative real-time polymerase chain reaction (qRT-PCR), and Western blot analyses, KLF4 was

identified as a mediator of the effect of miR-25802 on microglia-mediated neuroinflammation in AD, both *in vitro* and *in vivo*. Overexpression or inhibition of miR-25802 post-transcriptionally regulated KLF4 expression. Consistently, KLF4 overexpression or silencing in 5×FAD mouse brain reversed the pathological characteristics associated with miR-25802 upregulation or inhibition, including cognitive impairment, Aβ deposition, microglial activation, and inflammatory reactions. KLF4 is a multifunctional transcription factor known to regulate inflammation in the peripheral tissue (25–27). Reports indicate that KLF4 suppresses the polarization of pro-inflammatory M1 macrophages while promoting anti-inflammatory M2 polarization (25, 28, 29). In line with these findings, silencing or overexpression of KLF4 had enhanced or inhibitory effects on the NF-κB cascades. By inhibiting KLF4 in microglia, miR-25802 encouraged microglial differentiation into the pro-inflammatory M1 phenotype, leading to excessive activation of the NF-κB signaling pathway and exacerbating the inflammatory response (20).

NF-κB plays a central role in microglial activation and inflammatory factor release in the brain of AD patients, mediating the downstream neuroinflammatory response triggered by Aβ deposition (30–32). Interestingly, miR-25802 has a genetic affinity with let-7a-2-3p, a member of the let-7 family identified with protective effects in immunoinflammatory disorders like stroke, AD, and multiple sclerosis. Upregulation of let-7 in macrophages promotes an anti-inflammatory phenotype by reducing expression of the transcription factor CCAAT/enhancer binding protein delta (C/ebp-δ) (33). Other inflammation-related targets of let-7 include *IL6* and toll-like receptor 4 (*Tlr4)* (34, 35). NF-κB inhibits let-7-mediated anti-inflammatory actions via inflammatory feedforward loops involving RNA-binding protein Lin28 or IL-6 signaling (36, 37). Combining gene sequence potential analysis with experimental evidence, the involvement of miR-25802/KLF4/NF-κB signaling in microglia-mediated neuroinflammation in AD has been established.

4 Clinical transformation prospects and strategies based on miR-25802 modulation

Recent studies have substantiated significant dysregulation of miRNA expression in the body fluids of AD patients (38, 39), which can be predictive of mild cognitive impairment (40), indicating its potential as a promising biomarker for early AD diagnosis. Notably, the emergence of biological miRNA sensing platforms has opened a new avenue for early AD detection, enabling real-time, sensitive detection of miRNAs in body fluids through electrochemical, fluorescence, and surface plasmon resonance biosensing technologies (41, 42). Our previous studies have revealed remarkable downregulations of miR-200a-3p (43) and miR-148a-3p (17) in the blood of AD patients, both playing protective roles in AD. As potential biomarkers, miR-200a-3p and miR-148a-3p have been successfully incorporated into biosensors to facilitate early detection of AD (44–46). *In vivo* models hypothesize the abnormal upregulation of miR-25802 contributes to neuroinflammation and cognitive deficits in the early stages of AD (20–23). Receiver operation curve analysis in the plasma of AD patients shows that miR-25802 expression levels have high diagnostic efficacy for cognitive dysfunction, suggesting its potential as an AD biomarker. Given the strong correlation between miR-25802 and AD progression, the early development of miR-25802-based diagnostic devices for AD is desirable.

Regarding miRNA-based treatment, preclinical studies have achieved precise gene expression regulation and cognitive improvement through the introduction of exogenous miRNAs using various miRNA delivery approaches, including viral vectors (12), liposomes (47), nanoparticles (48, 49), and exosomes (50). Among these, viral delivery systems, particularly due to their high efficiency in facilitating cellular RNA uptake, have attracted significant attention (51). For example, adeno-associated virus (AAV) type 5 serves as a delivery vector for AMT-130, a miRNA-based therapy currently in phase 2 clinical trials targeting Huntington's disease (52, 53). Additionally, recombinant AAV9, a highly effective platform for central nervous system delivery, has been approved by the FDA for gene therapy in spinal muscular atrophy (54).

Importantly, our findings demonstrate that lateral ventricular injection of AAV9-encapsulated miR-25802 sponges in 5×FAD mice improved learning and memory abilities (20–23). Conversely, AAV9-coated KLF4 shRNA functioned to suppress the enhancement of learning and memory induced by miR-25802 sponges. This suggests that regulating miR-25802 expression or targeting its associated signaling pathways through AAV9 delivery might offer novel therapeutic approaches for AD, potentially counteracting disease progression and ameliorating cognitive deficits. Besides, the primary challenge in AD treatment remains the development of ncRNA-based therapies capable of effectively crossing the blood-brain barrier (55). Non-viral vectors have been investigated for miRNA-based treatment, particularly by packaging negatively charged miRNAs into liposome nanoparticles. This approach not only protects miRNAs from degradation by endogenous nucleases but also enables cell type-specific targeted delivery (56–58), presenting new opportunities for the development of suitable brain delivery systems for miR-25802.

5 Discussion

Microglia-driven neuroinflammation is implicated in both the initiation and progression of AD. Microglia activation serves as a defense mechanism for the brain against detrimental pathogens. However, this activation also incites inflammatory reactions that exacerbate the brain injury. Intriguingly, studies have predicted that more than 50% of mRNAs host miRNAs, allowing them to regulate an array of biological processes, encompassing oxidative stress, inflammation, and apoptosis (59). Specific miRNAs have emerged as potential mediators of neuroinflammation. For instance, miR-155 and miR-223 bind to TLRs to modulate the inflammatory response and influence the production of inflammatory mediators

by sponging off suppressors of cytokine signaling in transgenic AD mouse models (60–62). Additionally, miRNAs like miR-146a, miR-873, and miR-34a are involved in neuropathology and neuroinflammation, regulated by NF-κB-associated signaling (63–65). Our research indicates that miR-25802, highly expressed in the brain and microglia across various AD models, is a functional RNA molecule devoid of coding capabilities but capable of regulating KLF4 expression and function through NF-κB signaling in neuroinflammation. The let-7 family, consisting of 8–12 members, has been reported to be dysregulated in AD compared to normal controls (66). miR-25802 exhibits high sequence similarity to the let-7 family, whose meta-analysis as biomarkers for early AD detection aligns with our identification of miR-25802 as an inflamma-miRNA based on microglial regulation in AD pathology.

miRNAs may emerge as therapeutic interventions for AD in the future. Currently, ncRNA-based therapies have been developed for complex, intractable diseases such as cardiovascular diseases and cancers (67, 68). In our prior studies, miR-25802 mimics, inhibitors, and sponges were designed based on functional modifications or complementary sequences. miR-25802 mimics, derived from exogenous synthesis and composed of small double-stranded RNA molecules, exacerbated microglial activation via aberrant regulation of the KLF4/NF-κB pathways both *in vitro* and *in vivo*. Conversely, miR-25802 inhibitors and sponges shielded anti-inflammatory microglial conversion by restoring KLF4/NF-κB inflammatory signaling *in vitro* and *in vivo*, respectively. Furthermore, intracranial injection of these mimics of miR-25802 into wild-type or 5×FAD mice resulted in no significant systemic discomfort or exercise capacity alterations during the one-month observation period. These findings suggest the miR-25802/KLF4/NF-κB pathway as a viable therapeutic target for AD.

6 Conclusions

Our opinion delves into the biological function, underlying mechanisms, and potential clinical application of miR-25802, an innovative non-coding RNA sequence, within the context of AD. miR-25802 orchestrates the KLF4/NF-κB pathway in microglia-mediated neuroinflammation, facilitating cognitive impairments and Aβ toxicity, highlighting the potential of targeting miR-25802 and its regulatory network as an emerging frontier in AD treatment. Future research on miR-25802 will be further advanced through potential interdisciplinary collaborations, including neuroscience, bioengineering, and clinical medicine. Initially, identifying the drivers of miR-25802 upregulation in AD and other specific mRNA targets using tissue-specific knockout technologies will be crucial. Additionally, clinical research necessitates exploring the diagnostic and differential diagnostic implications of the miR-25802/KLF4 axis across a broader patient cohort. Furthermore, most miRNA-centric diagnostic tools and therapeutic interventions for AD are still in their initial stage. Regarding miR-25802, biological macromolecular inhibitors, employing oligonucleotide analogues as scaffolds, may afford benefits such as high selectivity and efficiency; however, they also pose challenges like immunogenicity and multiple conformations. Alternatively, the development of small molecule inhibitors targeting miR-25802 and its signaling pathway boasts its own strengths, including robust cell membrane penetration, resistance to intracellular enzymatic degradation, and reduced synthesis costs. In summary, achieving a profound understanding of the mechanism of miR-25802 in AD, coupled with the creation of more effective delivery systems or targeted small molecule drugs, will pave the way for translating miR-25802 research from the laboratory to clinical practice.

Author contributions

KZ: Writing – original draft. ZL: Writing – original draft. LZ: Visualization, Writing – original draft. ZC: Visualization, Writing – original draft. RL: Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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