

Review Article**Neuroinflammation and its role in neurodegenerative diseases****N. Dinesh Siva*, P. Natarajan, H. Ganesh, R. Kannan, R. Indhuja***Sankaralingam Bhuvanewari College of Pharmacy, Sivakasi, Tamilnadu, India*

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Abstract

Neuroinflammation plays a central role in the pathophysiology of major neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. The objective of this review is to critically summarize the causes, cellular and molecular mechanisms, and emerging therapeutic strategies targeting neuroinflammation in neurodegenerative diseases. A comprehensive literature search was conducted using databases such as PubMed, Scopus, Web of Science, and Google Scholar, covering peer-reviewed articles published primarily between 2000 and 2024. The collected literature was systematically screened and analysed to identify experimental and clinical evidence related to inflammatory processes in neurodegeneration. Evidence indicates that chronic activation of glial cells, driven by environmental toxins, microbial infections, metabolic disorders, and genetic susceptibility, leads to sustained release of pro-inflammatory cytokines and neurotoxic mediators, thereby accelerating neuronal damage. Conventional anti-inflammatory therapies provide limited benefits, prompting increased interest in novel disease-modifying approaches. Emerging strategies such as stem cell-based interventions, metabolic hormone-based therapies, and RNA-based therapeutics are showing promise by modulating inflammatory pathways, reducing oxidative stress and enhancing neuroprotection. This review highlights recent advances in neuroinflammation research and discusses therapeutic approaches with the potential to alter disease progression in neurodegenerative disorders.

Keywords: Neuroinflammation, Neurodegenerative diseases microglial activation: GLP-1 receptor agonists: RNA-based therapeutics (microRNAs & Aptamers)

Introduction

Amyotrophic lateral sclerosis (ALS), Parkinson's disease, and Alzheimer's disease are all primarily brought on by the long-term activation of microglia and astrocytes, which generate pro-inflammatory cytokines like TNF- α , IL-1 β , and IL-6. Current therapeutic approaches, such as NSAIDs, glucocorticoids, and minocycline, have shown mixed efficacy, indicating the need for novel approaches. Emerging therapies, such as probiotics and fecal microbiota transplantation, as well as stem cell-based interventions like mesenchymal and neural stem cell therapies, represent promising avenues for mitigating neuroinflammation and slowing disease progression (Heneka et al., 2015). Neuroinflammation, while initially protective, becomes harmful when prolonged, contributing to diseases like

Alzheimer's and multiple sclerosis. Damage-causing inflammatory chemicals are released by activated microglia and astrocytes, neurons, impair synapses, and reduce neurogenesis. This leads to cognitive decline and worsens protein pathologies like amyloid- β and tau. Targeted anti-inflammatory therapies may help slow disease progression (Mukhara et al., 2020). Neuroinflammation is an immune response in the brain linked to diseases like Alzheimer's, Parkinson's, and depression. While initially protective, chronic inflammation damages neurons. It's influenced by factors like aging, infection, and sex hormones, and may be eased by exercise or anti-inflammatory treatments (Lyman et al., 2014).

Cause's for neuroinflammation

Air pollution: Shannon Levesque study investigates the impact of sub chronic exposure to diesel exhaust (DE) on the central nervous system. The researchers exposed male Fischer 344 rats to varying concentrations of DE over six months and assessed neuroinflammation and markers of early neuropathology. Results showed elevated levels of TNF- α in most brain regions except the cerebellum,

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626130**E-mail:** dineshsiva201@gmail.comDOI: <https://doi.org/10.31024/ajpp.2026.12.1.2>2455-2674/Copyright © 2026, N.S. Memorial Scientific Research and Education Society. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

indicating that prolonged DE exposure induces neuroinflammation. The findings contribute to growing evidence linking air pollution to neurodegenerative diseases, emphasizing the need for further investigation into long-term exposure effects (Levesque et al., 2011).

The study by Lilian Calderón-Garciduenas (2004) investigated the effects of severe air pollution on brain inflammation and Alzheimer's-like pathology in humans. The researchers compared autopsy brain tissues from lifelong residents of highly polluted cities (Mexico City and Monterrey) with those from less polluted areas. Findings revealed significantly higher levels of cyclooxygenase-2 (COX2), an inflammatory mediator, and increased accumulation of the neurotoxic protein β -amyloid (A β 42) in the frontal cortex, hippocampus, and olfactory bulb of individuals exposed to high pollution. These changes are associated with neuronal dysfunction and resemble early markers of Alzheimer's disease. The study suggests that chronic exposure to air pollution may accelerate neurodegenerative processes, highlighting a potential public health concern (Calderón-Garciduenas et al., 2004).

In Mexico City (MC), Lilian Calderón-Garciduenas . (2007) investigated the neurological and systemic impacts of long-term exposure to air pollution in canines and children. The study focused on systemic inflammation, which includes increased proinflammatory cytokines, including COX2 and IL-1 β , respiratory tract inflammation, and the collapse of nasal and olfactory barriers. Notably, the study discovered signs of oxidative stress, inflammation, and β -amyloid (A β 42) buildup in the frontal cortex and olfactory bulb, which are similar to early indicators of Alzheimer's disease (AD). Cardiovascular consequences were also noted, including increased heart rate variability and endothelial dysfunction. According to the research, long-term exposure to air pollution, especially particulate matter, may increase the risk of cardiovascular disease and neurological diseases beginning in childhood (Calderón-Garciduenas et al., 2007).

Dheen (2007) Microglia, the brain's resident immune cells, play a key role in both protective and pathological responses in neurodegenerative diseases like Alzheimer's, Parkinson's, multiple sclerosis, and HIV-dementia. When activated by stimuli such as LPS, amyloid-beta, interferon- γ , thrombin, and pathogens, microglia release proinflammatory cytokines (e.g., TNF- α , IL-1 β), nitric oxide, and reactive oxygen species, contributing to neurotoxicity. Chronic activation, often referred to as "reactive microgliosis," maintains inflammation and neuronal injury.

The article highlights the potential benefits of neuroprotection by suppressing microglial activation through agents such as minocycline, dexamethasone, retinoic acid, endocannabinoids,

and TGF- β 1 as well as the need for further research into the physiology of resting microglia (Dheen et al., 2007).

Lull & Block, say that chronic microglial activation contributes to progressive neuron loss in neurodegenerative diseases. Triggered by injury or toxins, microglia release proinflammatory factors (e.g., TNF- α , ROS), with NADPH oxidase playing a central role in neurotoxicity. This sustained response termed reactive microgliosis—creates a self-perpetuating cycle of inflammation and damage, particularly affecting dopaminergic neurons in Parkinson's disease (Lull and Block, 2010).

In Mexico City (MC), Lilian Calderón-Garciduenas, looked at how long-term exposure to air pollution affected neuroinflammation and neurodegeneration. Lilian Calderón-Garciduenas et al. (2008) looked at children and young adults. The researchers found that high levels of air pollutants, including ultrafine particulate matter (UFP), were associated with significant neuroinflammation, disruption of the blood-brain barrier (BBB), and accumulation of amyloid β -42 (A β 42) and α -synuclein in key brain areas. These changes were seen in young, otherwise healthy individuals as well, suggesting that air pollution may increase the risk of Parkinson's and Alzheimer's disease. The study focused on how systemic inflammation, oxidative stress, and genetic vulnerability (such as the APOE ϵ 4 allele) together speed up neurodegenerative processes (Dabrowska et al., 2019).

Microbial Infection: The review paper by Van Thi Ai Tran et al. explores the relationship between persistent microbial infections and neurodegenerative diseases (Nds), including multiple sclerosis (MS), Parkinson's disease (PD), and Alzheimer's disease (AD). It defines the three primary pathways by which bacteria, viruses, and fungi can enter the central nervous system (CNS) and induce neurodegeneration and neuroinflammation: the gut-brain, lung-brain, and nose-brain. The authors explain how microbial elements (such as LPS and virus particles) stimulate microglia and astrocytes, causing chronic inflammation and neuronal injury. Additionally discussed are the potential use of antibiotics and a focus on neuropathogens as treatment strategies. The analysis highlights the need for additional research to clarify the role of certain illnesses and develop human models for studying these systems (Tran et al., 2022). Schematic representation of Causes for the neuro inflammation mentioned in Figure 1.

Diabetic: In rats with STZ-induced diabetes, *Borreria hispida* extract significantly reduces blood glucose and enhances glucose tolerance. Its phenolics and flavonoids

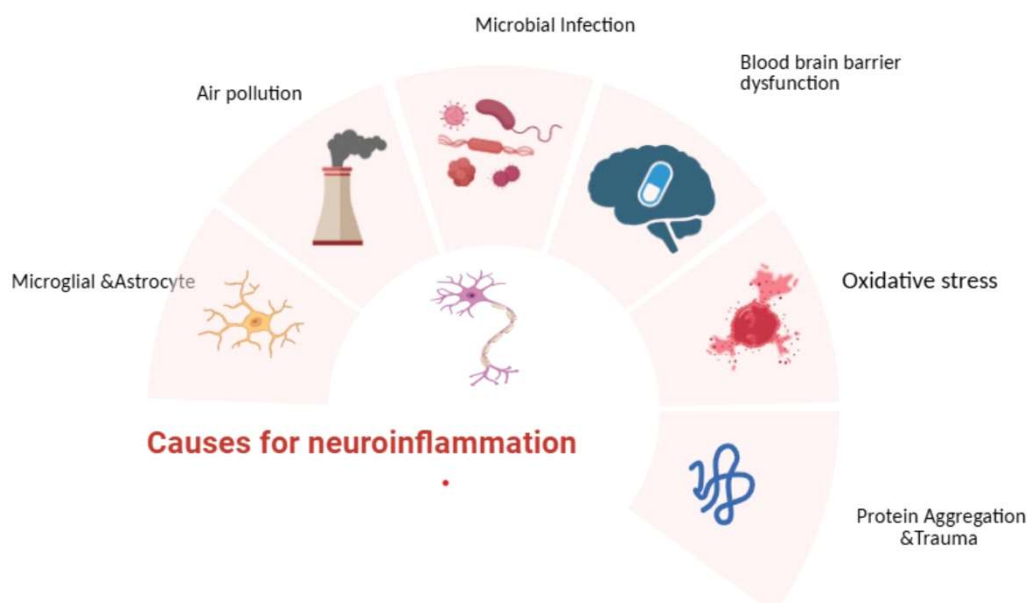


Figure 1. Causes for the neuro inflammation (Scientific Image and Illustration Software BioRender)

have anti-inflammatory and antioxidant properties that lower cytokines like IL-1 β and TNF- α . *Borreria hispida* may help reduce the risk of diabetes-associated neurodegeneration by regulating oxidative stress and hyperglycemia, two major causes of neuroinflammation (P et al., 2019).

The methanolic extract of *Pavetta indica* Linn significantly lowers blood glucose in STZ-induced diabetic rats. Its flavonoids and phenolics offer antioxidant and anti-inflammatory effects, which may help reduce hyperglycemia-driven neuroinflammation and the risk of diabetes-linked neurodegeneration.

The cardioprotective properties of a *Merremia emarginata* extract on isoproterenol-induced myocardial infarction in rats were examined and reported in the International Journal of Biological & Pharmaceutical Research. The study discovered that the extract prevented lipid peroxidation, maintained the normal histological structure of the heart, and dramatically decreased elevated cardiac enzyme markers (LDH, CPK, CRP, and SGOT). The study found that because of the plant's anti-ischemic and antioxidant qualities, it may have therapeutic relevance for ischemic heart conditions (Vaughan et al., 2006).

Emerging Therapeutics

Rahimi Darehbagh reported that stem cell therapies offer promising regenerative approaches in neurological disorders through mechanisms such as cell replacement, paracrine signalling, immunomodulation, and activation of endogenous repair. Various cell types—especially mesenchymal stem cells (MSCs) (Menaar et al., 2018), neural stem cells (NSCs), and induced pluripotent stem cells (iPSCs)—have shown potential

in preclinical and early clinical studies for conditions like Alzheimer's, Parkinson's, multiple sclerosis, and stroke. Despite challenges like tumorigenicity, immune rejection, and delivery limitations, ongoing research is advancing towards safer and more effective applications using gene editing, biomaterials, and patient-specific strategies (Rahimi Darehbagh et al., 2024).

Microbial Infection

The review paper by Van Thi Ai Tran, Luke P. Lee, and Hansang Cho explores the relationship between persistent microbial infections and neurodegenerative diseases (Nds), including multiple sclerosis (MS), Parkinson's disease (PD), and Alzheimer's disease (AD). It defines the three primary pathways by which bacteria, viruses, and fungi can enter the central nervous system (CNS) and induce neurodegeneration and neuroinflammation: the gut-brain, lung-brain, and nose-brain. The authors explain how microbial elements (such as LPS and virus particles) stimulate microglia and astrocytes, causing chronic inflammation and neuronal injury. Additionally discussed are the potential use of antibiotics and a focus on neuropathogens as treatment strategies. The analysis highlights the need for additional research to clarify the role of certain illnesses and develop human models for studying these (Bonsack et al., 2020).

Joshi Study explored about stem cell therapy for Neuropathic Pain. The use of neural stem cells (NSCs) and mesenchymal stem cells (MSCs) in stem cell treatment has demonstrated encouraging promise in reducing neuropathic pain (NP) and regulating neuroinflammation. By

preventing glial activation, producing anti-inflammatory cytokines, secreting neurotrophic substances, and suppressing excitotoxic pathways including NMDA receptor signaling, these cells reduce central sensitization and produce therapeutic effects. MSC-derived extracellular vesicles aid in brain healing even more. Even with encouraging preclinical results, there are still issues with dose, administration, and long-term safety optimization (Joshi et al., 2021).

By reducing neuroinflammation, mesenchymal stem cells (MSCs) and their extracellular vesicles (EVs) have the potential to treat stroke, according to Dabrowska. Inflammatory reactions after ischemia injury worsen neuronal damage by disrupting the blood-brain barrier, activating microglia, and releasing cytokines. By reducing inflammation and encouraging neurogenesis and angiogenesis, MSCs have neuroprotective and regenerative benefits. MSC-derived EVs are a safer, cell-free substitute that can penetrate the blood-brain barrier and has a lower immunogenicity. Although, MSCs have demonstrated safety and certain functional advantages in clinical trials, EVs are still undergoing preclinical research, with preliminary findings suggesting great therapeutic potential (Dabrowska et al., 2019).

GLP-1:

GLP-1 receptor agonists, initially developed to treat type 2 diabetes, have shown promise in the treatment of Alzheimer's disease (AD) because of their neuroprotective, anti-inflammatory, and antioxidant properties (Du et al., 2022). These compounds improve cognitive function by promoting synaptic plasticity and neuronal survival while reducing amyloid-beta aggregation, tau hyperphosphorylation, and neuroinflammation. Examples of substances that cross the blood-brain barrier and trigger protective signalling pathways like cAMP/PKA and PI3K/Akt include ligarglutide, exenatide, and semaglutide. Our findings imply that GLP-1R agonists are appealing choices for AD disease-modifying therapy, pending additional clinical validation (Du et al., 2022).

Exenatide, a GLP-1 receptor agonist, dramatically lowers neuroinflammation and anxiety-like behaviour in mice with diet-induced obesity, according to Lin. Exenatide decreased the expression of proinflammatory cytokines (TNF- α , IL-1 β), decreased astrocyte and microglial activation, and increased anti-inflammatory microglial M2 polarization. Additionally, it inhibited the expression of SR-A4, a scavenger receptor linked to neuroinflammation that was elevated in obese mice. AKT was not connected to these effects, whereas ERK signalling activity was. The study emphasizes that, in addition to their ability to decrease blood sugar, GLP-1R agonists may be used to treat neurodegenerative symptoms associated with metabolic inflammation (Lin et al., 2023).

Song J, Kim YK, and Yoon G study examines the

neuroprotective benefits of glucagon-like peptide-1 (GLP-1), a hormone with antidiabetic qualities in the setting of neuroinflammation. The authors demonstrate that GLP-1 lowers pro-inflammatory cytokine production, reduces microglial and astrocyte activation, and improves brain structure in experimental models. These effects are connected to GLP-1's regulation of signalling pathways (including NF- κ B) relevant to inflammation and oxidative stress. The results imply that GLP-1 or its analogs could be used as therapeutic agents to treat neurodegenerative disorders and neuroinflammatory condition (Yoon et al., 2020).

According to Chen, non-coding RNAs (ncRNAs), namely microRNAs (miRNAs), are increasingly playing a significant role in controlling neuroinflammation in neurological conditions. via focusing on inflammatory mediators such as TLRs, cytokines, and NF- κ B, miRNAs alter immune responses via influencing neuronal signalling and microglial polarization. The pathophysiology of conditions like epilepsy, Alzheimer's, Parkinson's, and ALS has been connected to the dysregulation of miRNAs such as miR-155, miR-124, and miR-146a. These miRNAs are intriguing therapeutic targets because they influence oxidative stress, cytokine production, and inflammasome activation (Chen et al., 2024).

Aptamers and microRNAs (miRNAs) are novel RNA-based therapeutic agents that may be utilized to treat neurodegenerative disorders like Alzheimer's, Parkinson's, and ALS by lowering neuroinflammation, claim Khan. miRNAs post-transcriptionally affect gene expression and regulate key inflammatory pathways by altering the activity of microglia and astrocytes. For instance, miR-155 promotes inflammation while miR-124, miR-146a, and miR-21 have anti-inflammatory effects. By attaching themselves to specific molecular targets, such as misfolded proteins (like tau, α -synuclein, and A β), aptamers, often known as "chemical antibodies," can both diagnose and treat illnesses. Both strategies present promising avenues for focused, non-immunogenic therapies in the pathophysiology of neurodegenerative disorders (Khan et al., 2022a).

Schematic representation of Moa of GLP-1 agonist plays the role in neuroinflammation and how miRNA supports (Figure 2)

Aptamers:

The CD200R1-targeting aptamer (M52) was assessed in glial cultures in this study by Burgada. Only lower quantities (25–50 nM) of PAGE-purified M52 somewhat decreased nitric oxide generation, but high doses resulted in

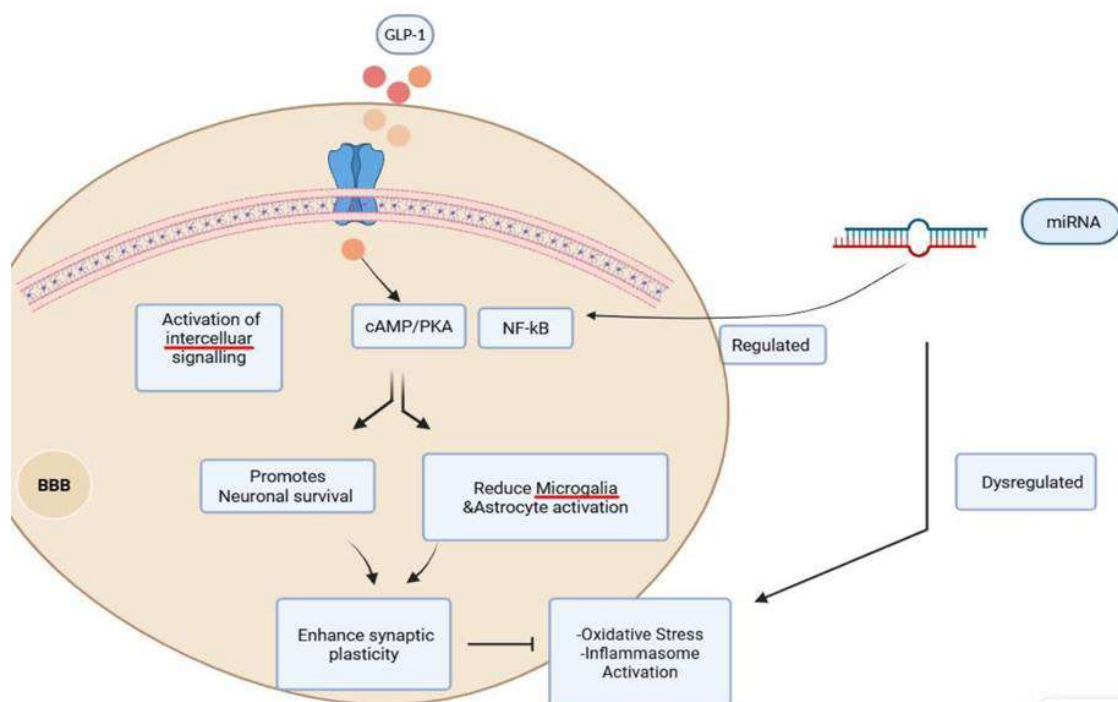


Figure 2. Moa of GLP-1 agonist Plays the role in neuroinflammation and how miRNA supports (Scientific Image and Illustration Software, BioRender, n.d.)

morphological alterations. There were few effects on the expression of inflammatory genes, and no distinct CD200R1-mediated signalling was verified (Ferigle Burgada, 2018).

Short, single-stranded nucleic acids called aptamers are being reviewed by Kong as potentially useful diagnostic and treatment tools for neuroinflammation and neurodegenerative diseases (NDDs) such as Parkinson's and Alzheimer's. Aptamers have the ability to target misfolded proteins (such as tau, α -synuclein, and A β), modify inflammatory mediators, and penetrate the blood–brain barrier (BBB) through delivery vehicles such as exosomes and nanoparticles. They have several benefits over antibodies, including as high specificity, chemical stability, and minimal immunogenicity. But there are still issues with distribution, uniformity, and stability. The review highlights the promise of aptamers for real-time biomarker detection in NDDs and targeted brain therapy (Kong et al., 2023).

The functions of aptamers and microRNAs as RNA-based treatments for neurodegenerative diseases (NDDs) are reviewed by Khan in (2022). MicroRNAs like miR-124, miR-146a, and miR-155 control neuroinflammation via altering signalling pathways like TLR and NF- κ B, microglial activation, and cytokine production. Short nucleic acid ligands called aptamers function as "chemical antibodies" and can attach to proteins linked to disease, including tau, α -synuclein, and A β , to help in diagnosis and treatment. While pointing out delivery and specificity issues, the article emphasizes their potential in treating NDDs such as Parkinson's, Alzheimer's, and others (Khan et al., 2022b).

The increasing therapeutic promise of aptamers—short, synthetic DNA/RNA molecules in addressing neuroinflammation and neurodegenerative illnesses is highlighted by Hernández-Jimenez. The article centres on ApTOLL, a TLR4-binding aptamer that has been demonstrated to enhance outcomes in multiple sclerosis models and decrease inflammation, infarct volume, and disability in stroke patients. Compared to antibodies, aptamers have minimal immunogenicity, excellent specificity, and ease of chemical modification. Nonetheless, there are still issues with clinical translation, regulatory classification, and pharmacokinetics (Hernández-Jiménez and de Castro, 2025).

A thorough review of aptamers short, single-stranded nucleic acids chosen using SELEX—as potentially useful instruments in neurology, diagnosis, and the treatment of neurodegenerative diseases is given by Wang et al. (2024). Potential treatments for Alzheimer's, Parkinson's, and ALS are made possible by aptamers' high specificity and affinity for targets like tau, α -synuclein, amyloid- β , and TDP-43. Low immunogenicity, chemical stability, and transferrin receptor targeting for blood–brain barrier (BBB) penetration are among the benefits. For better distribution and therapeutic efficacy, the review also describes novel modifications (such as SOMAmers and LNA) and aptamer-conjugated nanoparticles. Aptamers present a viable substitute for antibodies in neuromedicine, notwithstanding issues like as

off-target effects and in vivo degradation (Wang et al., 2024).

Qu, examine the expanding use of aptamers, which are short, single-stranded nucleic acids or peptides, as diagnostic and therapeutic agents for neurodegenerative disorders (NDDs), including multiple sclerosis, Alzheimer's, Parkinson's, Huntington's, and prion diseases. Pathological proteins such as A β , α -synuclein, and mutant huntingtin are bound by aptamers with excellent selectivity, which stops them from aggregating and becoming toxic. Aptamers are perfect for addressing misfolded proteins in the central nervous system because they are smaller, non-immunogenic, and chemically stable than antibodies. Additionally covered in the study are chemical changes for increased stability, aptamer synthesis via SELEX, and new delivery techniques such nanoparticle conjugate (Qu et al., 2017).

Rhinehardt designed and analysed aptamers that target important indicators of traumatic brain damage (TBI), including GFAP, S100 β , and IL6, using molecular dynamics simulations. The work used surface plasmon resonance imaging (SPRi) to validate interactions, forecast structures, and evaluate aptamer-protein binding. The specificity and binding stability of peptide and nucleic acid aptamers were assessed. The study shows how computational modeling may be used to pre-screen aptamers for the construction of biosensors, providing an economical method for designing diagnostic tools for neuroinflammation (*Computational Modeling of Nucleic and Peptide Aptamer Interactions – IL6, S100 β and GFAP Protein Biomarkers for Traumatic Brain Injury - ProQuest, n.d.*).

A 3D neurovascular unit-on-a-chip created by Choi, more precisely simulates inflammation in the human brain than in animal systems. In order to replicate the blood-brain barrier, the chip combines neurons, astrocytes, and endothelial cells. LPS causes neuroinflammation, which results in the production of cytokines, disruption of the blood-brain barrier, and a decrease in TEER. Crucially, the device detects TNF- α and IL-6 in real-time using graphene oxide-linked fluorescent aptamers, allowing for non-invasive monitoring. In a regulated, human-relevant setting, this technology offers a promising tool for drug testing and comprehending neuroinflammatory networks (*In Situ Detection of Neuroinflammation Using Multicellular 3D Neurovascular-Unit-on-a-Chip - Choi - 2023 - Advanced Functional Materials - Wiley Online Library, n.d.*).

The author Fan showed that TNF- α causes necroptosis in bone microvascular endothelial cells (BMECs) through the RIP1/RIP3/MLKL pathway, which in turn increases osteonecrosis of the femoral head (ONFH). Their research shown that TNF- α can be efficiently blocked by a DNA aptamer (ApTNF- α), increasing BMEC survival and decreasing necroptosis. These results demonstrate the possibility of the

aptamer as a targeted treatment for ONFH (Fan et al., 2022).

The development and validation of aptamer-based biosensors for the detection of blood biomarkers in neurodegenerative diseases (NDDs) were investigated by Chowdhury et al. in 2023. The thesis focuses on the detection of brain-derived neurotrophic factor (BDNF) through the use of an aptamer-linked assay (ALISA) and a unique DNA aptamer. In a tauopathy mouse model (rTg4510), it also examined biomarkers such as NfL, p-tau181, neurogranin, and NSE to evaluate their association with brain pathology and responsiveness to treatment. The results encourage aptamers as viable substitutes for antibodies in diagnostics and support the use of blood biomarkers for early identification and monitoring of NDDs (Chowdhury, 2024).

Minocycline:

In a Dicer conditional knockout (cKO) mice model, Cheng et al. (2015) demonstrated that minocycline, a tetracycline antibiotic, efficiently decreased neuroinflammation by reducing indicators such as GFAP, Iba1, and IL-6. Minocycline did not stop tau hyperphosphorylation, apoptosis, synaptic injury, or neuron death, even though it inhibited microglial and astrocyte activation. This implies that even while minocycline has anti-inflammatory properties, it might not be enough to stop neurodegeneration on its own (Cheng et al., 2015).

In a mouse model of a brain abscess induced by *Staphylococcus aureus*, Kielian, showed that minocycline, regardless of its antibacterial efficacy, decreases neuroinflammation. They demonstrated that, without altering the bacterial burden, minocycline decreased proinflammatory mediators (such as IL-1 β , TNF- α , and CCL2), decreased the size of brain abscesses, and preserved tissue viability using a bacterial strain that was resistant to the drug. Even when minocycline was given after the commencement of the infection, these anti-inflammatory benefits were seen. Additionally, the medication decreased glial TLR2 expression and inhibited astrocyte and microglia activation, indicating that it may be used as an adjuvant immunotherapy for CNS infections accompanied by severe inflammation (Kielian et al., 2007).

This study demonstrates that minocycline, a tetracycline-derived antibiotic with anti-inflammatory properties, significantly attenuates lipopolysaccharide (LPS)-induced neuroinflammation, sickness behaviour, and anhedonia. Using BV-2 microglial cultures and BALB/c mouse models, the authors show that minocycline inhibits inflammatory cytokine secretion, reduces TLR2 expression, and lowers mRNA levels of IL-1 β , IL-6, and

IDO in the cortex and hippocampus. Behaviourally, minocycline facilitated recovery from anorexia, weight loss, social withdrawal, and prevented anhedonia in LPS-challenged mice. Importantly, its effects extended to aged mice, where it suppressed exaggerated neuroinflammatory responses. Collectively, these findings highlight minocycline's potential to mitigate microglia-driven cytokine production and associated behavioural disturbances, supporting its exploration as a therapeutic strategy in conditions characterized by excessive neuroinflammation and mood/cognitive impairments (*Minocycline Attenuates Lipopolysaccharide (LPS)-Induced Neuroinflammation, Sickness Behavior, and Anhedonia | Journal of Neuroinflammation, n.d.*).

In mice exposed to chronic mild stress (CUMS), Yang in (2020) showed that long-term minocycline therapy reduces depressive-like behaviours. The medication restored gut microbiota balance, including metabolite profiles and intestinal barrier integrity, and prevented hippocampus neuroinflammation by lowering proinflammatory cytokines (IL-1 β , IL-6, and TNF- α). Acute therapy did not produce these effects. The study emphasizes that rather than minocycline's antibacterial action, its antidepressant benefits might be mediated by a combination regulation of neuroinflammation and gut flora (Yang et al., 2020).

Cai, (2010) showed that in a rat model of vascular cognitive impairment caused by chronic cerebral hypoperfusion, minocycline therapy dramatically lowers astrocytic activation and neuroinflammation. Minocycline suppressed astroglia reactivity and inflammatory cytokine release by lowering the expression of GFAP, COX-2, NF- κ B, IL-1 β , and TNF- α . The potential of minocycline as a neuroprotective drug through astrocyte-mediated inflammatory control is supported by these findings (*Minocycline Corrects Early, Pre-Plaque Neuroinflammation and Inhibits BACE-1 in a Transgenic Model of Alzheimer's Disease-like Amyloid Pathology | Journal of Neuroinflammation, n.d.*).

Minocycline's neuroprotective properties were assessed by Hiskens, using a mouse model of repetitive mild traumatic brain injury (mTBI). At chronic time points, minocycline therapy reduced neurodegeneration (MAPT, TARDBP, NEFL), neuroinflammation (e.g., TNF, AIF1, GFAP), and glutamate excitotoxicity (GRIA1). It also enhanced cognitive function in the Morris Water Maze. The medication alleviated tau and TDP-43 pathology and decreased long-term microglial and astrocytic activation. According to these results, minocycline may be able to stop long-term neurotoxicity after repeated sub concussive traumas (Hiskens et al., 2021).

A randomized, placebo-controlled study was carried out by Petrakis to determine whether minocycline could lessen the neuroinflammation caused by ethanol in heavy drinkers. After

ten days of receiving a placebo, 100 mg, or 200 mg of minocycline, the subjects got an intravenous ethanol infusion. Although minocycline was well tolerated, it had no discernible impact on serum cytokine levels, desire, ethanol-induced subjective reaction, or cognitive function. Nonetheless, the sedative effects of ethanol did correlate with baseline cytokine levels. Alternative neuroimmune-targeted treatments for alcohol use disorder are necessary, as the study finds that short-term minocycline treatment does not reduce alcohol-related inflammation in people (Ferretti et al., 2012).

Future Directions:

They have two roles in disease, according to Gao, they are initially protective by clearing protein clumps like tau and A β , but they later contribute to neuroinflammation and neurodegeneration. We found that detrimental microglial states are driven by persistent activation, which is impacted by age, TREM2 or APOE4 polymorphisms, and peripheral immunological signals. Our results lend support to treatment approaches that improve phagocytosis, modulate inflammation (e.g., NLRP3, NF- κ B), or foster protective phenotypes such as disease-associated microglia in order to restore microglial homeostasis (Gao et al., 2023).

Neurological conditions like ALS, Parkinson's, and Alzheimer's. Protein aggregation and other stresses cause microglia and astrocytes to become chronically activated, which results in persistent inflammation and exacerbates neuronal damage. This reaction is heightened by environmental stimuli (e.g., infections, age, TBI) and genetic risk factors (e.g., APOE4, TREM2). TLRs and NLRP3 are examples of inflammatory signalling pathways that are essential to the development of illness. There is encouraging therapeutic potential in addressing neuroinflammation, particularly if done early (*Role of Neuroinflammation in Neurodegeneration Development | Signal Transduction and Targeted Therapy, n.d.*).

The research trends on neuroinflammation-induced moderate cognitive impairment (MCI) throughout the previous 11 years are examined in this bibliometric analysis. The authors evaluated research hotspots, notable authors, institutions, and publication patterns using CiteSpace and VOSviewer. Since 2018, the number of publications has increased dramatically, with the United States topping the world in both productivity and impact. Key findings highlight how inflammation drives microglial and astrocyte activation, which is influenced by genetic and metabolic variables (e.g., APOE4, TREM2). The gut-brain axis, neuroimmune interactions, and biomarkers (such as tau and TREM2) have all been the subject of research. Targeting

microglial phenotypes, altering the microbiome, and using anti-inflammatory drugs like IFN- β 1a, IL-33, and tanshinone IIA are examples of recent treatment approaches. The study notes the necessity of inter-institutional cooperation, a better comprehension of glial phenotypes, and exploration of gender differences and metabolic influences in future research (*Frontiers; The Past, Present, and Future of Research on Neuroinflammation-Induced Mild Cognitive Impairment: A Bibliometric Analysis, n.d.*).

Conclusion

A key pathological characteristic of many neurodegenerative illnesses, such as ALS, Parkinson's, and Alzheimer's, is neuroinflammation. One important mechanism impacting the course of disease is the regulation of inflammatory pathways by non-coding RNAs, especially microRNAs. As important modulators of neuroimmune homeostasis, microRNAs such as miR-124, miR-146a, and miR-155 alter microglial activation and cytokine production. At the same time, aptamers, which are short, single-stranded nucleic acid ligands, have a high specificity for binding pathogenic proteins such as tau, α -synuclein, and A β , making them useful for both diagnostic and therapeutic purposes. When combined, these RNA-based compounds offer a new and exciting family of instruments for addressing neurodegeneration and neuroinflammation. Preclinical results are promising, but before clinical translation can be achieved, more research is required to address issues with stability, delivery, and off-target effects.

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Author contribution

All author are equally contributed

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Conflict of interest

NO

Ethics approval

None to declare

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