Neuroinflammation and Neurodegenerative Diseases

R. Gopinath[1], Dr.Lavanya Yaidikar[2]
[1,2]*Department of Pharmacology, Seven Hills College of Pharmacy (Autonomous), Tirupati-517561, Andhra Pradesh, India*

Abstract: Oxidative stress is associated with the onset and progression of various diseases, particularly neurodegenerative conditions. This study reviews the research linking oxidative stress to the pathogenesis of amyotrophic lateral sclerosis (ALS), Parkinson's disease, Alzheimer's disease, and Huntington's disease, focusing on the role of reactive oxygen species. It also examines how oxidative stress influences the inflammatory response. Although oxidative stress and neuroinflammation are distinct clinical phenomena, they are interconnected and impact each other. A thorough understanding of the pathways involved in the initiation and progression of neurodegenerative disorders is essential for developing effective treatments. This paper discusses common antioxidants, both enzymatic and non-enzymatic, as potential therapeutic options for these disorders due to their ability to modulate oxidative stress and mitigate symptoms of neurodegenerative diseases.

Keywords: Alzheimer's disease; chronic inflammation; interleukin-18; interleukin-1β; NLRP3 inflammasome; neuroinflammation; Parkinson's disease; type 2 diabetes mellitus.

INTRODUCTION

Increasing evidence indicates that neuroinflammation plays a crucial role in altering the physiology of neurodegenerative diseases (NDDs). Understanding the roles of neuroinflammation in NDDs can illuminate the molecular mechanisms underlying neurodegeneration and open new therapeutic avenues[1]. This chapter outlines the fundamental concepts of neuroinflammation in NDDs, the mechanisms by which inflammation leads to neurodegeneration, and the brain microenvironment's control over immune cell phenotypes, and summarizes preclinical and clinical studies on biomarkers and immunomodulatory therapies associated with neuroinflammation [2].

IMMUNOLOGY, INFLAMMATION, AND NEUROINFLAMMATION OVERVIEW

The immune system is divided into innate and adaptive immunity, both protecting the organism from pathogens. The innate immune system provides the first line of defense, constantly monitoring for a wide range of potential pathogens [3]. In contrast, the adaptive immune system retains immunological memory and mounts a specific, delayed response. Inflammation is the immune system's local response to infection, facilitating pathogen elimination, cellular debris clearance, and tissue repair and maintenance. Despite the central anxious framework (CNS) being considered immune-
privileged, broad investigation demonstrates that neuroinflammation is central to numerous CNS infections [4]. While neuroinflammatory responses protect the body from infections and cell damage, dysregulation, as seen in NDDs, can have detrimental effects. This section discusses the initiation of the inflammatory response in the periphery, signaling molecules involved, cellular migration to infection or damage sites, pathogen clearance mechanisms, and the resolution of the immune response, linking these processes to neuroinflammation and the relevant CNS immune cells in both healthy and diseased states[5].
Once thought to be a secondary reaction to neurological conditions, neuroinflammation is now understood to play a key role in the etiology of several neurodegenerative illnesses. This article sheds light on the underlying mechanisms of the complex link between neuroinflammation and neurodegenerative diseases [6].

NEUROINFLAMMATION: A DOUBLE-EDGED SWORD

"Neuroinflammation" refers to the inflammation of the nervous system due to illness, injury, or infection. While neuroinflammation is a critical defense mechanism aimed at eliminating infections and promoting tissue repair, chronic or dysregulated neuroinflammation can be detrimental to the brain [7]. A hallmark of neuroinflammation is the activation of astrocytes and microglia, the resident immune cells of the central nervous system (CNS). These cells can worsen brain damage

and brokenness by discharging pro-inflammatory cytokines, chemokines, and responsive oxygen species [8].

NEURODEGENERATIVE DISEASES AND NEUROINFLAMMATION

Neurodegenerative diseases encompass a broad range of conditions characterized by the progressive loss of neurons, leading to movement disabilities, cognitive decline, and other neurological impairments [9]. Some of the most common neurodegenerative diseases include multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Parkinson's disease, Alzheimer's disease, and Huntington's disease. Recent studies highlight neuroinflammation as a crucial factor in the development and progression of these conditions [10].

AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Amyotrophic horizontal sclerosis (ALS), also known as Lou Gehrig's illness, is a dynamic neurodegenerative clutter characterized by the degeneration of engine neurons in the brain and spinal rope. This comprehensive survey covers the Etiology, pathophysiology, clinical introduction, determination, and treatment of ALS [11].

Etiology:

The correct cause of ALS remains to a great extent obscure, but both natural and hereditary variables are accepted to contribute to the disease's advancement. Familial ALS cases, which account for 5–10% of instances, are associated with mutations in genes such as C9orf72, SOD1, TARDBP, and FUS [12]. The majority of ALS cases are sporadic with no clear genetic predisposition, suggesting a complex etiology involving interactions between environmental triggers and genetic susceptibility.

Pathophysiology:

ALS involves the gradual degeneration of lower motor neurons (LMNs) in the brainstem and spinal cord and upper motor neurons (UMNs) in the motor cortex [13]. Protein aggregates, including misfolded superoxide dismutase 1 (SOD1), TAR DNA-binding protein 43 (TDP-43), and fused in sarcoma (FUS), accumulate within motor neurons affected by ALS, leading to cellular dysfunction and death [14]. These aggregates are pathological hallmarks of the disease. Molecular pathways implicated in ALS pathophysiology include glutamate excitotoxicity, mitochondrial dysfunction, oxidative stress, impaired axonal transport, and dysregulated RNA metabolism [15].

CLINICAL MANIFESTATIONS

Amyotrophic lateral sclerosis (ALS) typically presents with progressive muscle weakness, atrophy, stiffness, and hyperreflexia, resulting from the degeneration of both upper and lower motor neurons. Common early symptoms include: Initial Signs: Weakness or stiffness in one limb, difficulties with fine motor skills, muscle cramps, fasciculations (muscle twitching), and dysarthria (speech difficulties) [16]. Progression: As the disease advances, muscle atrophy and weakness spread to other regions, including the respiratory muscles, leading to respiratory failure, the primary cause of death in ALS patients.

DIAGNOSIS

Diagnosing ALS includes a combination of clinical assessment, electromyography (EMG), and avoidance of other potential causes of engine neuron dysfunction: Clinical Introduction: A careful appraisal of the patient's indications and history. Electromyography (EMG): Identifies characteristic signs of motor neuron degeneration, such as fibrillation potentials and positive sharp waves, indicating denervation and reinnervation. Neuroimaging: Nerve conduction studies and magnetic resonance imaging (MRI) help rule out other neurological conditions and identify structural abnormalities [17].

MANAGEMENT

The management of ALS aims to enhance the quality of life, maintain function, and alleviate symptoms through a multidisciplinary approach: Pharmacological Interventions: Medications like edaravone and riluzole can slightly slow disease progression and prolong survival. Symptomatic Treatment: Managing respiratory insufficiency, dysphagia, pain, spasticity, and muscle cramps to improve patient comfort [18]. Multidisciplinary Care: Teams comprising neurologists, physical therapists, occupational therapists, speech-language pathologists, respiratory therapists, and social

workers provide comprehensive support tailored to the diverse needs of ALS patients and their families [19]. Palliative Care and End-of-Life Planning: Focus on symptom management, advance care planning, and emotional support for both patients and caregivers.

ALZHEIMER'S DISEASE (AD)

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia, characterized by progressive neurodegeneration leading to memory loss, cognitive decline, and behavioral changes. Primarily affecting older adults, AD poses significant challenges for patients, caregivers, and healthcare systems worldwide [20].

PATHOPHYSIOLOGY

AD has a complex and multifactorial pathophysiology influenced by genetic, environmental, and age-related factors. The primary neuropathological features include:

1. Amyloid-Beta (Aβ) Plaques: Formation: Aβ peptides are derived from the amyloid precursor protein (APP) through the action of beta-secretase and gamma-secretase. Accumulation: Abnormal APP processing leads to the accumulation of insoluble Aβ aggregates forming plaques, particularly in brain regions associated with learning and memory, such as the neocortex and hippocampus [21]. Impact: Aβ plaques are believed to cause neurotoxicity, disrupt synaptic function, and initiate inflammatory responses.
2. Neurofibrillary Tangles (NFTs): Tau Protein: Ordinarily stabilizes neuronal microtubules. Pathology: In Advertisement, tau gets to be unusually phosphorylated, driving to the arrangement of NFTs. Effects: Hyperphosphorylated tau misfolds and aggregates into tangles, closely correlating with neuronal loss, synaptic dysfunction, and cognitive decline [22].
3. Neuronal Dysfunction and Loss: Damage: Aβ plaques and NFTs disrupt neuronal function and synaptic transmission, causing neuronal injury and cell death. Progression: Neurodegeneration initially impacts the entorhinal cortex and hippocampus, crucial for memory formation and consolidation, before affecting other cortical and subcortical structures [23]. In summary, ALS is characterized by progressive motor neuron degeneration, muscle weakness, and respiratory failure. Despite advances in understanding its pathophysiology and supportive therapies, ALS remains fatal and incurable, highlighting the urgent need for continued research into disease-modifying treatments. Alzheimer's disease, marked by cognitive decline and behavioural changes, presents significant challenges due to its complex pathophysiology and widespread impact.

CLNICAL PRESENTATION

Alzheimer's infection (Advertisement) regularly shows with an treacherous onset and progressive movement, in spite of the fact that the rate of cognitive decrease changes among people. Common clinical signs include:

1. Memory Impedance: Early indications regularly include troubles with verbose memory, such as inconvenience recollecting later occasions or discussions. Patients may over and over inquire the same questions or depend intensely on memory helps like notes and electronic reminders [24].
2. Cognitive Decrease: As the malady advances, cognitive disabilities amplify past memory to incorporate shortages in dialect, official work, visuospatial abilities, and consideration. Patients may battle with problem-solving, decision-making, and performing every day errands. Complex exercises like overseeing funds or taking after a formula gotten to be progressively challenging.
3. Behavioral and Mental Indications: Advertisement as often as possible includes behavioral changes that essentially affect the quality of life for both patients and caregivers. Common side effects incorporate disturbance, hostility, unresponsiveness, misery, and uneasiness. These indications can complicate care and compound caregiver stress. [24]
4. Utilitarian Disability: In the progressed stages of Advertisement, patients encounter extreme useful decrease, getting to be progressively subordinate on others for every day exercises such as eating, dressing, and toileting. This misfortune of freedom is a trademark of late-stage AD. Tau Protein: Ordinarily stabilizes neuronal microtubules.

PARKINSON'S Infection (PD)

Parkinson's infection (PD) is a dynamic neurodegenerative clutter characterized by the particular misfortune of dopaminergic neurons in the substantia nigra pars compacta of the brain. The trademark engine indications of PD, counting tremors, inflexibility, bradykinesia, and postural precariousness, result from this dopaminergic

neuron misfortune. Furthermore, PD is related with a extend of non-motor side effects that altogether affect patients' quality of life, counting temperament disarranges, autonomic brokenness, and cognitive impairment [25].

ETIOLOGY AND PATHOPHYSIOLOGY

The correct cause of Parkinson's illness remains tricky, but a combination of hereditary helplessness, natural variables, and maturing are accepted to contribute to its advancement. Familial shapes of PD have been connected to changes in qualities such as SNCA, LRRK2, PARKIN, PINK1, and DJ-1, in spite of the fact that the larger part of cases are sporadic. Pathologically, Parkinson's infection is characterized by the nearness of Lewy bodies, intracellular protein totals essentially composed of misfolded alpha-synuclein protein. These totals disturb cellular work and contribute to neuronal brokenness and passing. Also, the pathophysiology of PD includes neuroinflammation, mitochondrial brokenness, oxidative push, and impeded protein clearance pathways [26]. Understanding the complex etiology and pathophysiology of Parkinson's infection is basic for the improvement of focused on treatments that can moderate infection movement and make strides results for influenced people. Continuous investigate endeavors proceed to investigate novel treatment approaches pointed at adjusting the fundamental malady components and giving symptomatic help for patients with PD.

CLINICAL MANIFESTATIONS

Motor Symptoms:

Parkinson's infection (PD) is characterized by a range of engine side effects that ordinarily start asymptomatically and dynamically compound over time. These include:

1. Tremor: One of the trademark indications of PD is tremor, regularly showing as a resting tremor that ordinarily begins in one appendage and may afterward spread to other parts of the body. This tremor is most recognizable when the influenced appendage is at rest and tends to reduce with deliberate movement [27].
2. Bradykinesia: Bradykinesia alludes to gradualness of development, decreased plentifulness of deliberate activities, and trouble starting developments. Patients may encounter delays in starting and executing developments, coming about in a common feeling of "gradualness" or "faltering" in their actions.
3. Unbending nature: Unbending nature is characterized by expanded resistance to detached development and solidness of the appendages. Patients may show muscle solidness and unbending nature, making it challenging for them to move openly or perform every day exercises. Inflexibility can contribute to a sensation of inconvenience or torment in influenced muscles.
4. Postural Precariousness: Postural precariousness regularly develops in the afterward stages of PD and is related with disabled adjust and an expanded hazard of falls. Patients may have trouble keeping up an upright pose and may encounter shakiness or a feeling of being "off-balance" when strolling or standing.

Non-Motor Symptoms:

In expansion to engine side effects, Parkinson's malady is moreover related with a assortment of non-motor indications that can altogether affect patients' quality of life. These include:

1. Temperament Disarranges: Patients with PD may encounter disposition unsettling influences such as uneasiness and discouragement, which can show as sentiments of pity, misery, or intemperate stress. These disposition clutters can antagonistically influence social working and generally well-being [28].
2. Autonomic Brokenness: Autonomic brokenness in PD can lead to different side effects such as stoppage and orthostatic hypotension. Clogging is a common gastrointestinal indication, whereas orthostatic hypotension alludes to a drop-in blood weight upon standing, causing tipsiness or light-headedness.
3. Cognitive Impedance: Cognitive disability is another common non-motor side effect of PD, characterized by shortages in official work, memory, and consideration. Patients may involvement challenges with arranging, problem-solving, and multitasking, which can affect their day by day functioning.
4. Rest Unsettling influences: PD frequently disturbs rest designs, driving to rest unsettling influences such as sleep deprivation, over the top daytime languor, and REM rest behavior clutter (RBD). Rest unsettling influences can encourage compound other side effects and contribute to by and large disability in quality of life [29].

DIAGNOSIS AND MANAGEMENT

Diagnosis:

Parkinson's infection is essentially analyzed clinically based on the nearness of characteristic engine side effects and the avoidance of other conceivable causes. Neuroimaging methods such as DaTscan or dopamine transporter (DAT) SPECT filters can help in affirming the determination by illustrating diminished striatal dopamine uptake[30].

Management:

The objectives of Parkinson's malady administration are to ease side effects, delay illness movement, and progress quality of life. Pharmacological mediations, counting dopamine substitution treatment with medicines like levodopa and dopamine agonists, are commonly utilized to oversee engine indications[31]. Non-pharmacological approaches such as profound brain incitement (DBS) surgery, word related treatment, discourse treatment, and physical treatment can moreover offer assistance address engine and non-motor side effects and improve utilitarian outcomes[32].

RESEARCH AND FUTURE DIRECTIONS

Current inquire about in Parkinson's malady centers on illustrating the fundamental components of neurodegeneration, recognizing biomarkers for early determination and illness movement, and creating disease-modifying medicines[33]. Developing areas of intrigued incorporate alpha-synuclein-targeted treatments, quality treatment methodologies, and stem cell-based treatments pointed at neuroprotection and neuronal substitution. The advancement of viable disease-modifying treatments is significant to abating or ending illness movement and progressing the quality of life for people living with Parkinson's disease [34].

THERAPEUTIC SUGGESTIONS OF NEUROINFLAMMATION IN NEURODEGENERATIVE DISEASES

Neuroinflammation, characterized by glial cell actuation and the discharge of pro-inflammatory go betweens inside the central anxious framework (CNS), plays a significant part in the pathogenesis of different neurodegenerative maladies, counting Alzheimer's malady (Advertisement), Parkinson's illness (PD), Huntington's malady (HD), amyotrophic horizontal sclerosis (ALS), and different sclerosis (MS) [35]. Understanding the restorative suggestions of neuroinflammation is fundamental for creating compelling treatment procedures [36]. Here's a comprehensive overview:

1. Targeting Incendiary Pathways:

Pro-inflammatory cytokines, enacted microglia, and dysregulated resistant reactions contribute to neuroinflammation. Focusing on these pathways with anti-inflammatory solutions like corticosteroids, minocycline, and NSAIDs appears guarantee for lessening neuroinflammation and minimizing neuronal damage.

2. Immunomodulatory Agents:

Immunomodulatory drugs point to control fiery reactions and re-establish resistant homeostasis in the CNS [37]. Biologics focusing on resistant cells or cytokines, such as sphingosine-1-phosphate receptor modulators or anti-TNF-α antibodies, are being assessed in clinical trials for their neuroprotective effects.

3. Microglial Modulation:

Microglia, the inhabitant safe cells of the CNS, play a central part in neuroinflammation and neurodegeneration [38]. Restorative approaches focusing on microglial enactment and polarization point to move microglia from a pro-inflammatory (M1) to an anti-inflammatory (M2) phenotype, possibly decreasing neuroinflammation and neuronal damage [39].

4. Neuroprotective Compounds:

Anti-inflammatory and antioxidant compounds like curcumin, resveratrol, and EGCG appear neuroprotective impacts by diminishing oxidative stretch and neuroinflammation [40]. Omega-3 greasy acids, especially DHA and EPA, tweak incendiary signaling pathways and offer neuroprotection in preclinical models.

5. Tweaking Blood-Brain Obstruction Integrity:

Keeping up the judgment of the blood-brain boundary (BBB) is pivotal for avoiding the penetration of provocative arbiters and fringe safe cells into the CNS [41]. Helpful intercessions focusing on pericytes, endothelial cells, and tight intersection proteins point to stabilize the BBB and anticipate brokenness, in this manner lessening neuroinflammation and neuronal damage.

6. Combination Therapies:

Given the multifaceted nature of neuroinflammation, combination treatments

focusing on a few fiery pathways may have synergistic impacts and increment helpful viability. Combining immunomodulatory operators, neuroprotective compounds, and anti-inflammatory solutions offers a comprehensive approach to tending to neuroinflammation and giving neuroprotection. [42] In conclusion, focusing on neuroinflammation holds guarantee as a potential treatment technique for neurodegenerative illnesses. By balancing provocative pathways, directing resistant reactions, and keeping up neuronal judgment, helpful intercessions pointed at constricting neuroinflammation may moderate malady movement and move forward clinical results [43]. In any case, assist investigate is required to way better get it the fundamental components of neuroinflammation and create more successful treatment approaches for neurodegenerative diseases.

IN SUMMARY

Neuroinflammation, complicatedly connected to the etiology of neurodegenerative maladies, remains a complex and essential marvel. A comprehensive understanding of its components and recognizable proof of reasonable restorative targets hold the guarantee of inventive treatment approaches for these weakening conditions. In any case, accomplishing this objective requires advance broad investigate.

REFERENCE

[1] Ransohoff, R. M. (2016). "How neuroinflammation contributes to neurodegeneration." *Science, 353*(6301), 777-783.

[2] Amor, S., Peferoen, L. A., Vogel, D. Y., et al. (2014). "Inflammation in neurodegenerative diseases—an update." *Immunology, 142*(2), 151-166.

[3] Colonna, M., &Butovsky, O. (2017). "Microglia function in the central nervous system during health and neurodegeneration." *Annual review of immunology, 35*, 441-468.

[4] Hardy, J., &Selkoe, D. J. (2002). "The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics." *Science, 297*(5580), 353-356.

[5] Heneka, M. T., Carson, M. J., El Khoury, J., et al. (2015). "Neuroinflammation in Alzheimer's disease." *The Lancet Neurology, 14*(4), 388-405.

[6] Itzhaki, R. F., Lathe, R., Balin, B. J., et al. (2016). "Microbes and Alzheimer's disease." *Journal of Alzheimer's Disease, 51*(4), 979-984.

[7] Dorsey, E. R., Elbaz, A., Nichols, E., et al. (2018). "Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016." *The Lancet Neurology, 17*(11), 939-953.

[8] Hirsch, E. C., &Hunot, S. (2009). "Neuroinflammation in Parkinson's disease: a target for neuroprotection?." *The Lancet Neurology, 8*(4), 382-397.

[9] Tansey, M. G., & Goldberg, M. S. (2010). "Neuroinflammation in Parkinson's disease: its role in neuronal death and implications for therapeutic intervention." *Neurobiology of disease, 37*(3), 510-518.s

[10] Compston, A., & Coles, A. (2008). "Multiple sclerosis." *The Lancet, 372*(9648), 1502-1517.

[11] Frohman, E. M., Racke, M. K., & Raine, C. S. (2006). "Multiple sclerosis—the plaque and its pathogenesis." *New England Journal of Medicine, 354*(9), 942-955.

[12] Lassmann, H. (2014). "Mechanisms of white matter damage in multiple sclerosis." *Glia, 62*(11), 1816-1830.

[13] Brown, R. H., & Al-Chalabi, A. (2017). "Amyotrophic lateral sclerosis." *New England Journal of Medicine, 377*(2), 162-172.

[14] Philips, T., &Robberecht, W. (2011). "Neuroinflammation in amyotrophic lateral sclerosis: role of glial activation in motor neuron disease." *The Lancet Neurology, 10*(3), 253-263.

[15] Rentzos, M., Evangelopoulos, E., Sereti, E., et al. (2012). "Alterations of T cell subsets in ALS: a systemic immune activation?." *Acta NeurologicaScandinavica, 125*(4), 260-264.

[16] Heneka, M. T., et al. (2015). Neuroinflammation in Alzheimer's disease. *The Lancet Neurology*, 14(4), 388-405.

[17] Heppner, F. L., et al. (2015). Immune attack: the role of inflammation in Alzheimer disease. *Nature Reviews Neuroscience*, 16(6), 358-372.

[18] Amor, S., et al. (2010). Inflammation in neurodegenerative diseases. *Immunology*, 129(2), 154-169.

[19] Glass, C. K., et al. (2010). Mechanisms underlying inflammation in neurodegeneration. *Cell*, 140(6), 918-934.
[20] Perry, V. H., et al. (2010). The role of central and peripheral inflammation in neurodegeneration. *Journal of Neurochemistry*, 114(4), 871-878.
[21] Lull, M. E., & Block, M. L. (2010). Microglial activation and chronic neurodegeneration. *Neurotherapeutics*, 7(4), 354-365.
[22] Cunningham, C., et al. (2009). Systemic inflammation induces acute behavioral and cognitive changes and accelerates neurodegenerative disease. *Biological Psychiatry*, 65(4), 304-312.
[23] McGeer, P. L., &McGeer, E. G. (2007). NSAIDs and Alzheimer disease: epidemiological, animal model and clinical studies. *Neurobiology of Aging*, 28(5), 639-647.
[24] Streit, W. J., et al. (2004). Microglia and neuroinflammation: a pathological perspective. *Journal of Neuroinflammation*, 1(1), 14.
[25] McGeer, P. L., &McGeer, E. G. (2001). Inflammation, autotoxicity and Alzheimer disease. *Neurobiology of Aging*, 22(6), 799-809.
[26] Wyss-Coray, T., & Rogers, J. (2012). Inflammation in Alzheimer disease—a brief review of the basic science and clinical literature. *Cold Spring Harbor Perspectives in Medicine*, 2(1), a006346.
[27] Heneka, M. T., &O'Banion, M. K. (2007). Inflammatory processes in Alzheimer's disease. *Journal of Neuroimmunology*, 184(1-2), 69-91.
[28] Holmes, C., et al. (2009). Systemic inflammation and disease progression in Alzheimer disease. *Neurology*, 73(10), 768-774.
[29] Perry, V. H. (2004). The influence of systemic inflammation on inflammation in the brain: implications for chronic neurodegenerative disease. *Brain, Behavior, and Immunity*, 18(5), 407-413.
[30] Witoelar, A., et al. (2017). Genome-wide Pleiotropy between Parkinson Disease and Autoimmune Diseases. *JAMA Neurology*, 74(7), 780-792.
[31] Perry, V. H., & Holmes, C. (2014). Microglial priming in neurodegenerative disease. *Nature Reviews Neurology*, 10(4), 217-224.
[32] Gao, H. M., & Hong, J. S. (2008). Why neurodegenerative diseases are progressive: uncontrolled inflammation drives disease progression. *Trends in Immunology*, 29(8), 357-365.
[33] Ransohoff, R. M., & Perry, V. H. (2009). Microglial physiology: unique stimuli, specialized responses. *Annual Review of Immunology*, 27, 119-145.
[34] Heneka, M. T., et al. (2014). Neuroinflammation in Alzheimer's disease. *The Lancet Neurology*, 14(4), 388-405.
[35] Chitnis, T., & Weiner, H. L. (2017). CNS inflammation and neurodegeneration. *Journal of Clinical Investigation*, 127(10), 3577-3587.
[36] Kettenmann, H., et al. (2011). Physiology of microglia. *Physiological Reviews*, 91(2), 461-553.
[37] Ransohoff, R. M. (2016). How neuroinflammation contributes to neurodegeneration. *Science*, 353(6301), 777-783.
[38] Sarlus, H., &Heneka, M. T. (2017). Microglia in Alzheimer's disease. *Journal of Clinical Investigation*, 127(9), 3240-3249.
[39] Subramaniam, S. R., & Federoff, H. J. (2017). Targeting microglial activation states as a therapeutic avenue in Parkinson's disease. *Frontiers in Aging Neuroscience*, 9, 176.
[40] Stephenson, J., et al. (2018). Inflammation in CNS neurodegenerative diseases. *Immunology*, 154(2), 204-219.
[41] Voet, S., et al. (2019). Microglia in central nervous system inflammation and multiple sclerosis pathology. *Trends in Molecular Medicine*, 25(2), 112-123.
[42] Singh, S., et al. (2016). A promising therapeutic target for neurodegenerative diseases: Involvement of TNF-α signaling pathway. *Current Drug Targets*, 17(5), 564-576.
[43] Heneka, M. T., et al. (2010). Nitric oxide metabolites in Alzheimer's disease. *Journal of Alzheimer's Disease*, 19(2), 587-607.
[44] Wyss-Coray, T. (2006). Inflammation in Alzheimer's disease: driving force, bystander or beneficial response? *Nature Medicine*, 12(9), 1005-1015.
[45] Macedo, A. C., & Ferreira, I. L. (2013). NLRP3 inflammasome: a novel target for Alzheimer's disease. *Trends in Molecular Medicine*, 19(9), 513-518.