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Review Article

Role of Neuroinflammation in Neurodegenerative Diseases: Therapeutic Perspectives

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ABSTRACT

Neuroinflammation has emerged as a major contributing factor in the progression of neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Multiple Sclerosis, and Amyotrophic Lateral Sclerosis. This review highlights the role of inflammatory pathways and immune-mediated mechanisms involved in neuronal degeneration. Activation of microglia and astrocytes leads to the release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, which contribute to neuronal damage and synaptic dysfunction. Key molecular pathways including NF-κB signaling, NLRP3 inflammasome activation, oxidative stress, mitochondrial dysfunction, and abnormal protein aggregation are critically involved in disease pathogenesis. Protein aggregates such as amyloid-β and α-synuclein further stimulate chronic inflammatory responses, accelerating neurodegeneration. Current therapeutic approaches mainly provide symptomatic relief and include cholinesterase inhibitors, dopamine agonists, immunomodulators, and antioxidant therapies. However, these treatments are limited by poor blood–brain barrier penetration and inability to halt disease progression. Emerging therapeutic strategies targeting neuroinflammation, including cytokine inhibitors, NLRP3 inflammasome blockers, monoclonal antibodies, stem cell therapy, gene therapy, and nanotechnology-based drug delivery systems, show promising potential as disease-modifying interventions. Understanding the molecular basis of neuroinflammation may facilitate the development of personalized and effective therapeutic approaches for neurodegenerative disorders in the future.

INTRODUCTION

Neurodegenerative illnesses comprise a diverse range of diseases that share as a common feature a progressive loss of the nervous system and its functional abilities, characterized by a general impairment of mental and physical functioning which eventually causes cognitive and motor disabilities. The most common of these are

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Alzheimer, Parkinson, multiple sclerosis and amyotrophic lateral sclerosis and they are known to pose a major health burden to the world. These disorders are widely prevalent and are closely linked with increasing populations of people of advanced age making them one of the major causes of concern to all healthcare systems globally[5]. Over the past few years, neuroinflammation has become one of the key mechanisms of pathogenesis of neurodegenerative diseases. Neuroinflammation is the stimulation of the brain's innate immunological response mainly conducted by microglia and astrocytes, to injury, infection, or the deposition of misfolded proteins[6]. Though acute inflammatory reactions can come into play in the early stages and have protective roles in the elimination of pathogen and cell debris, chronic and unregulated inflammation has an adverse effect on neurons and disease progression[7]. The activation of microglia is a central element in the process of the development and maintenance of neuroinflammatory reactions. Activated microglia secrete numerous pro-inflammatory mediators, such as tumor necrosis factor-alpha (TNF- 0), interleukin-1 beta (IL-1 -), interleukin-6 (IL-6) that worsen neuronal damage and synaptic dysfunction[8]. Also, the astrocytes aid in the inflammatory environment by producing chemokines and cytokines that improve immunological signaling[9]. In the central nervous system. One of the most fascinating aspects of neurodegenerative disease is the presence of abnormal protein, such as amyloid beta in Alzheimer's disease and □-synuclein protein in Parkinson's disease. Damage associated molecular patterns (DAMPs) are protein aggregates that cause immune response and result in persistent inflammation[10]. Furthermore, activation of intracellular signaling nuclear factor-kappa B(NF-KB)and the NLRP3inflammation form two essential pathways to control the expression of inflammatory genes and the release of cytokines[11]. Neurodegeneration is mostly caused by the intimate connections between oxidative stress, mitochondrial failure, and neuroinflammation. Reactive oxygen species (ROS) over production causes lipid peroxidation the death of the cells and DNA damage.

Objective[13]

- To investigate the pathophysiology of neurodegenerative diseases using neuroinflammation.
- To examine involved molecular mechanisms and signaling pathways.
- To assess the existing pharmacological interventions and approved medications.
- To determine the drawbacks and subsequent therapeutic views.

Major Diseases:

- Alzheimer disease (AD) memory loss and cognitive impairment[14]
- Parkinson disease (PD)- Shakiness and motor imparment[15]
- Demyelination and immunological damage in multiple sclerosis (MS)[16]
- Degeneration of motor neuron ALS, or amyotrophic lateral sclerosis[17]

Prevalence:

- In the world, the percentage of dementia caused by Alzheimer disease is 60-70%.
- Parkinson disease has a prevalence of more than 10 million individuals in the world.

- The prevalence of multiple sclerosis is rising particularly among the young adults.
- An aging population causes a huge burden of diseases.

Importance of study:

Knowledge of neuroinflammation yields

- The information on disease progression[18,19]
- Discovery of new drug targets [20,21]
- Possible disease modifying therapy as opposed to symptom management [22,23]

Mechanism of Disease: Molecular Pathways.

There are a number of interconnected molecular means of neuroinflammation:

1. Microglial Activation[24]

Initiated by trauma, toxins or protein aggregates.

Produces the pro-inflammatory cytokines TNF-a, IL-1b, and IL-6. The primary microglia are innate immune cells which live in the central nervous system to regulate inflammation in the brain. There are several different types of activated microglia, some of which are beneficial and some of which are detrimental. CNS microglial activation can be divided into two opposing phenotypes: the anti-inflammatory M2 phenotype and the pro-inflammatory M1phenotype (Figure1)

1. Microglia that express the nuclear factor-kB (NF-kB) and inducible nitric oxide synthase (iNOS)pathways produce TNF-□, interleukin-1 beta (IL-b), and other pro-inflammatory mediators, interleukin-6, superoxide, ROS, and nitric oxide (NO) all cause the normal activation type of microglia, referred to as M1 microglia[6]. Interleukin-4 (IL-4) interleukin-13 (IL-13) and interleukin-10 (IL-10)/transforming growth factor-beta (TGF-B) signalling, also referred to as alternative activation and acquired deactivation, respectively, trigger a variety of activation programs in M2 microglia. As long as the underlying clinical insult occurs in system circulation and peripheral organs, the question of how microglia alter phenotypes is crucial.

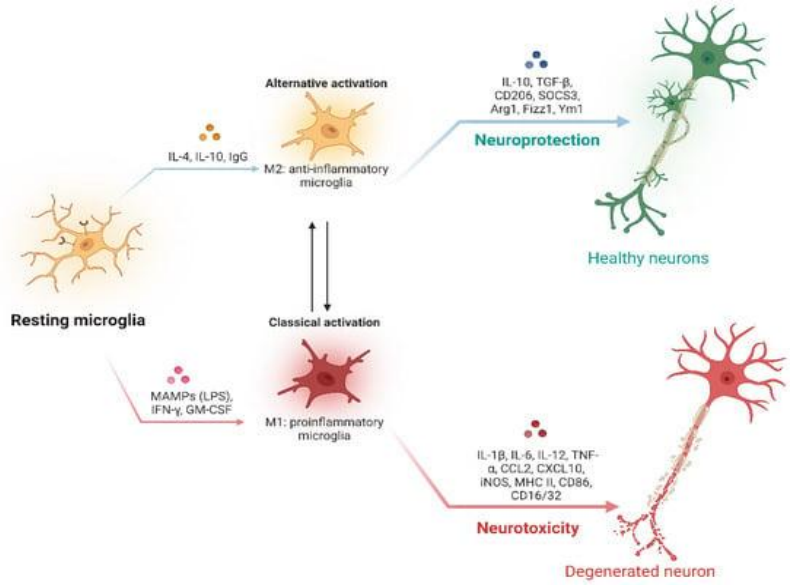

Figure 1: Microglial Activation

2. NF-κB Pathway[25]

Key controller of the inflammatory process.

Increases the inflammatory genes transcription[14]. A class of transcription factor protein complexes known as NF-kappa-light-chain-enhancer of activated B cells (NF-kappaB) controls DNA transcription, cytokine synthesis, and cell survival. NF-kB is recognised to be essential to the immune response to an infection and is expressed in almost all in animal cell types. Improper regulation of NF-kB has been linked to immunological development, viral infection, septic shock, cancer, and inflammatory/autoimmune diseases. It has also been discovered that NF-kb plays a role in memory and synaptic plasticity.

Structure:

NF-KB proteins the N-terminus of every protein in the NF-KB family has a Rel homology domain. The transactivation domain proteins of NF-kB are found in the C-termini of RelA, RelB, and c-Rel. On the other hand, the mature p50 and p52 proteins are formed by the regulation of the big progenitors of NF-kB1 and NF-kB2 proteins, which are around 105 and 100 nm in size, respectively. P105 and P100 are processed by the proteasome pathway. which is their C-terminal regions preference degradation which contains ankyrin repeats. In contrast to the tight regulation of the generation of p52 out of p100, p50 is generated out of constitutive processing of p105. The p50 protein has been suggested to be a transcriptional repressor when it binds to κB elements as a homodimer, and the process of p50 production is indeed confounding the interpretation of p105-knockout studies, where the genetic manipulation is removing an I 0 B (full-length p105) and a probable repressor.

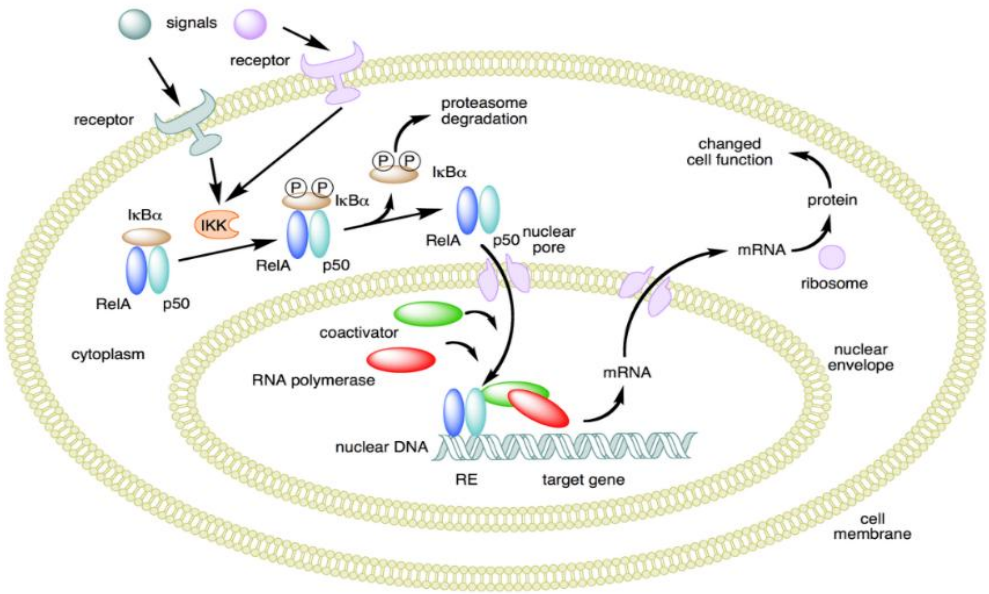

Figure 2: NF-κB Pathway

3. Activation of NLRP3 Inflammasome[26-29]

Causes IL-1β and IL-18 production.

Causes chronic inflammation.

1.Inflammasome NLRP3 (Signal 1) Priming:

In the case of macrophages, NLRP3 activators are not sufficient to trigger the activation of inflammasomes but also these need to be activated by a priming signal (signal 1). Priming stimuli, including the transcription factor NF-+ must be activated by ligands to toll-like receptor (TLRs), NLRs (NOD1, NOD2), or cytokine receptor ligands. NF- kB enhances the expression of pro-IL-1B, which resting macrophages do not generate, and NF-LRP3, which is thought to be present at insufficient levels to cause inflammasome activation in resting macrophages. Conversely, pro-caspase-1,pro-IL-18, and ASC expression levels appear to be unaffected by priming cues. Furthermore, in response to TLR ligands, NLRP3 and pro-IL-1B production is regulated by MyD88 and TRIF, two signaling molecules that orchestrate the NF-KB signalling pathway. According to recent research, caspase-8 and FADD, in addition to the NLRP3 signalling molecules, are also required for NLRP3 induction during priming phase, regardless of their apoptotic activity.

2. Activating the NLRP3 Inflammasome (Signal 2)

The possible variety of activating stimuli after this priming step is quite broad, which include K+ ionophores, heme, particulate particles, and ATP. pathogen-associated RNA as well as components and poisons produced by bacteria and fungi. Since none of these agonists have been shown to directly interact with NLRP3, it is hypothesised that they share a cellular signal due to their differences. The NLRP3 inflammasome is currently shown to be activated by a number of molecular and cellular signals in response to stimuli NLRP3, including mitochondrial, influx malfunction and lysosomal degradation and reactive oxygen species (ROS) generation.

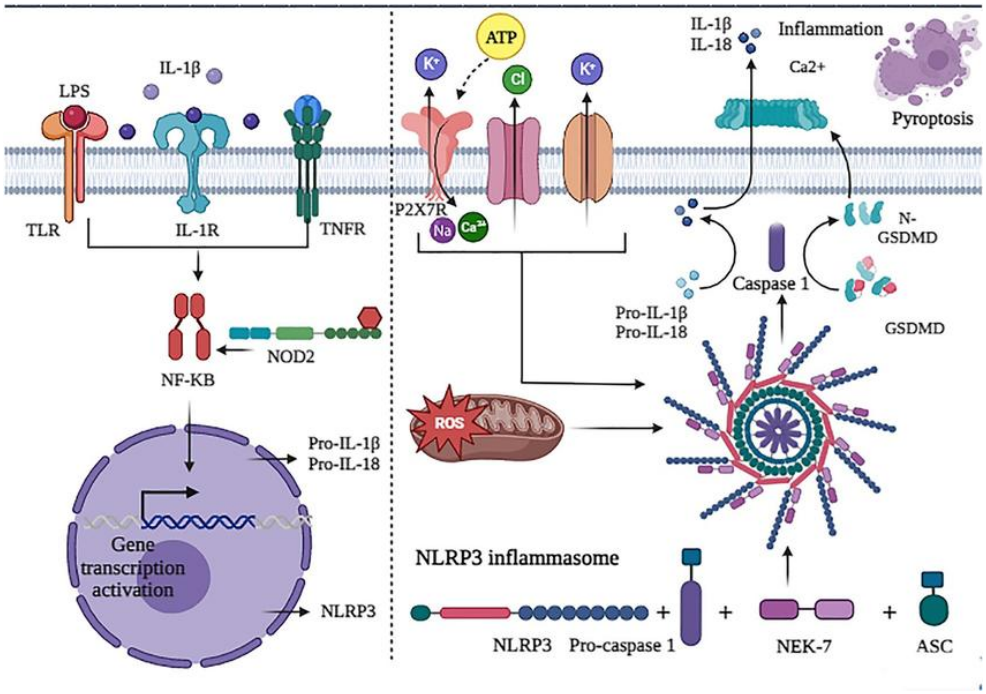

Figure 3: NLRP3 Inflammasome of activation.

4. Oxidative Stress [30, 31, 32, 33, 34, 35]

Too much ROS, or reactive oxygen species destroys neurons. The disparity between pro-oxidants and antioxidants in the body whereby the pro-oxidants activity is dominant as compared to antioxidants activity is referred to as oxidative stress The consequence of the reactive species is the oxidative damage of biomolecules in the event of oxidative stress. The cells are compartmentalized because of the complexity of the human body which enables oxidation micro environments which experience varying degrees of oxidative stress. The unique design and function of the organs within the human body also lead to opposing oxidative stress levels, which complicates the efforts to classify and treat the body's oxidative stress, along with the pathogenesis it leads to Oxidative stress is associated with many negative health disorders including neurodegenerative disorders, inflammatory disorders, cardiovascular disease, diabetes, allergies, immune dysfunction, aging and cancer (Fig. 4) The products of the mitochondrial metabolism in the human body are known as reactive species. The most common form of reactive species is the reactive oxygen species (ROS). Human body needs ROS to signal in the processes, including the one that entails the killing of viruses and bacteria, and then elimination of the reactive species eventually by the body occurs. Nevertheless, in cases where the ROS levels are too high in the body, it causes oxidative damage to RNA and DNA, lipids, and proteins. In particular, there are genetic mutations and cancer that can be induced by DNA damage. Moreover, cancer cells have high ROS requirements due to their augmented metabolic requirements.

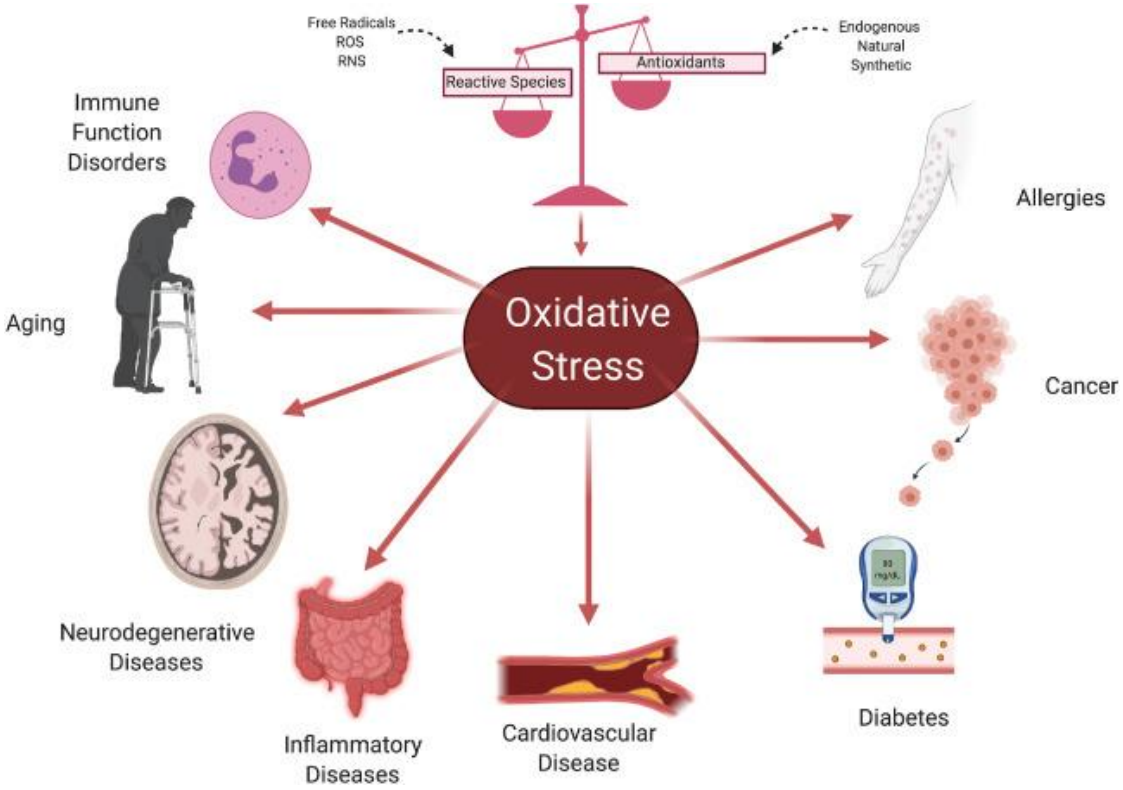

Figure 4: Oxidative Stress

5. Mitochondrial Dysfunction [36,37,38,39,40,41]

Defective energy generation and hyper apoptosis.

a) Bioenergetic Crisis (ATP Loss):

The impairment of the ETC components (Complexes I-V) decreases the ATP production, which leads to the lack of energy to perform cellular processes.

b) Oxidative Stress & ROS Production:

Overproduction of proteins reactive oxygen species (ROS), mitochondrial membranes, mtDNA, creating a vicious cycle of deterioration.

c) Dysregulated Calcium Homeostasis:

Mitochondria lose their ability to regulate calcium appropriately and accumulate it, resulting in calcium overload and activation of cell death (apoptosis).

d) **Low Quality Control (Mitophagy):**

The inability of the system to eliminate damaged mitochondria (mitophagy) leads to the accumulation of dysfunctional organelles into the cell.

e) mtDNA Instability:

Changes in mitochondrial DNA (mtDNA) mutations or deletions destroy the production of essential proteins required in the functioning of mitochondria.

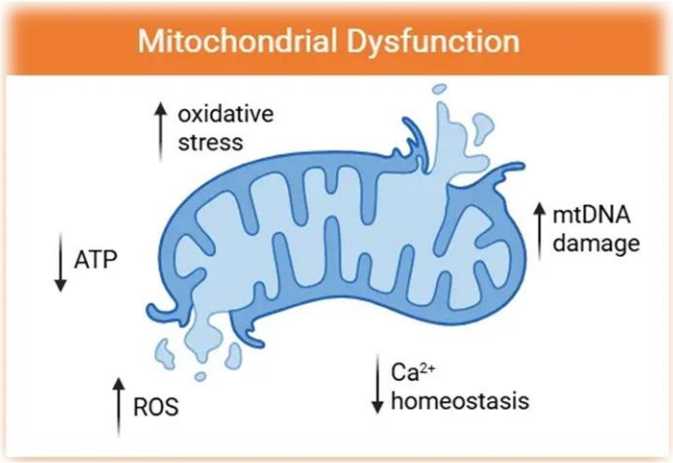

Figure 5: Mitochondrial Dysfunction

6. Protein Aggregation [42,43,44,45,46,47,48,49,50]

- ✓ Immunes are activated by Amyloid-2 (AD), and alpha-synuclein (PD).
- ✓ Present Pharmacological Intervention.
- ✓ One of the most prevalent pathways of protein destabilization is rote in aggregation, as well as in medicinal protein manufacturing may make the product is not ready for release.
- ✓ States of disease have the potential to undergo the aggregation of proteins, as amyloid fibrillogenic, which is associated with the neurodegeneration disease in relation to Parkinson and Alzheimer illnesses.

- ✓ Reversible or irreversible protein aggregation can result in soluble or insoluble, covalent or non-covalent, and native or non-native aggregates. The biopharmaceutical business typically deals with non-native protein aggregation, which shall be referred to as protein aggregation in this chapter.

- ✓ The numerous hypotheses and models that have be proposed to explain the phenomena that demonstrate protein aggregation is much different under different aggregation conditions and even the protein under investigation. With a multi domain protein like a monoclonal antibody, the individual domains can denature irreversibly and by various processes depending on the conditions of denaturing agent used.

- ✓ The denaturation method is thus able to influence the form of aggregates formed. A fab domain has been identified be more heat sensitive and Fc region to be more low pH sensitive.

- ✓ The process of aggregation must then be assessed on an individual basis on the new protein to reduce its likelihood.

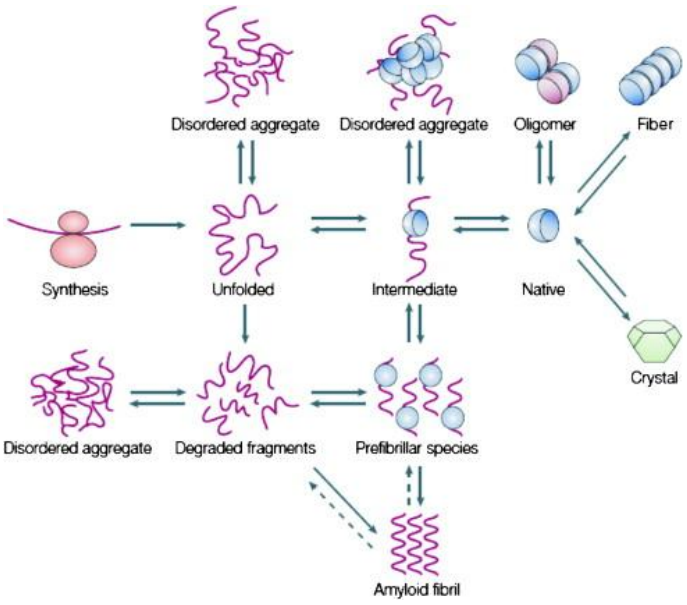

Figure 6: Protein Aggregation

Alzheimer's Disease[51]

- Cholinesterase inhibitors, such rivastigmine, donepezil.

- An NMDA receptor blocker, Memantine

- Alzheimer's disease (AD) is the most common type of dementia caused by neurodegenerative. condition, with approximately 60-70% of the cases with the most common initial symptom of the disease being the impairment in the ability to recall the recent events. In later the patients stage of the disease may experience difficulties in language, confusion, inability to find their way around, mood swings, lack of motivation, neglecting themselves, and behavioral difficulties. In a deteriorating state, an individual tends to isolate himself or herself within a family set up and society, in general. The functions of the body are gradually lost and it eventually results in death. Despite the rate of progression possibly range, the mean

prognosis of life after diagnosis is three to twelve years.

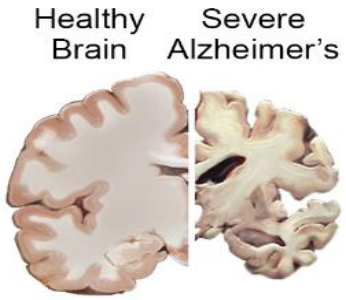

Figure 7: Alzheimer's disease

Parkinsons disease[52]

- Levodopa is the precursor to dopamine.
- Dopamine agonists

Parkinson disease is a progressive illness of the neurological system. It affects nerve cells (neurones) in certain brain regions to weaken, damage, and die resulting into symptoms such as movement problems, tremor, stiffness, and poor balance. Walking, talking, and other simple tasks can become challenging to people with the Parkinson disease (PD) as the symptoms progress.

A chronic neurological condition is multiple sclerosis (MS). It MS is an autoimmune disease, which damages the immune system, which should protect us against viruses, bacteria and other harmful things, attacks healthy cells. MS symptoms normally occur among young adults, ages 20-40.

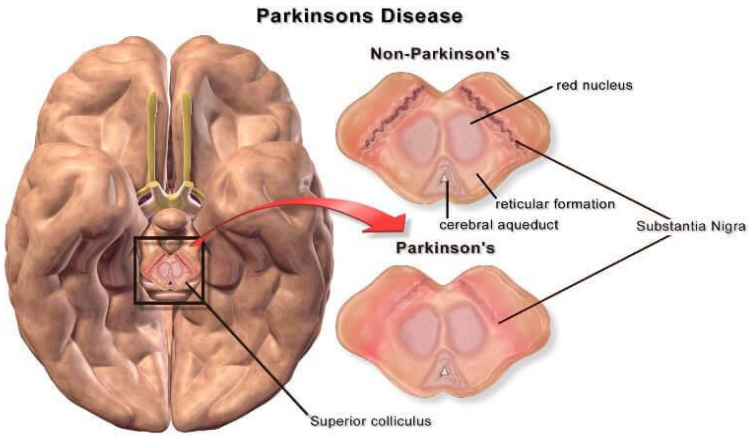

Figure 8: Parkinson's Disease

Multiple Sclerosis [53]

- Interferon-beta
- Glatiramer acetate
- MS does not have identical effects on people. Only few individuals with MS will

experience mild symptoms with minimal disability, but others will experience deteriorating symptoms which will cause greater disability in the long run.

- Individuals with MS experience most of their symptoms in short durations and which are resolved completely or partially once they manifest. Such intervals are succeeded by extended periods of time without any evident symptoms.
- The life expectancy of most individuals with MS is normal.

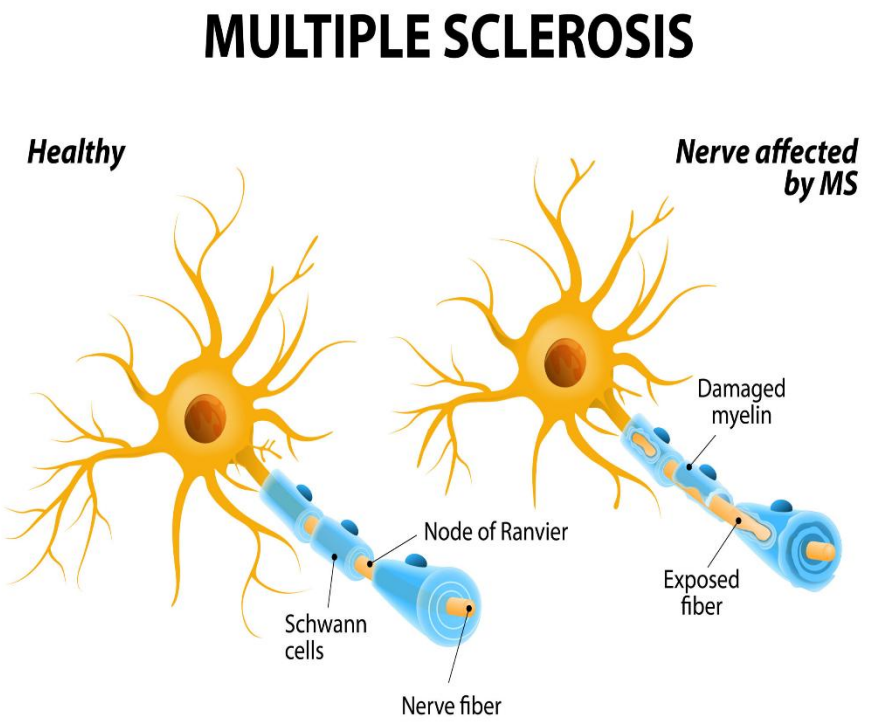

Figure 9: Multiple Sclerosis

ALS [54]

- Riluzole
- Edaravone

Clinically approved Drugs and Mechanism of Action [55,56,57,58]

Drug	Disease	Mechanism
Donepezil	AD	Inhibits acetylcholinesterase.
Memantine	AD	NMDA receptor antagonist.
Levodopa	PD	Dopamine replacement.
Interferon-2	MS	Immunomodulation

Shortcomings of Existing Therapy

- In the majority of cases, symptomatic, not curative.
- Restricted capacity of penetrating blood-brain barrier.
- Long-term adverse effects.
- Lack of full knowledge od disease processes.
- Drug resistance and variation of patient response.

Therapeutic Perspectives:

- The activation of microglia.
- NSAIDs (anti-inflammatory agents), cytokine inhibitors.
- Antioxidants
- Gene therapy
- Stem cell therapy
- Drug delivery based on nanotechnology.

New Therapeutic Targets and Clinical Perspectives:

Novel Therapeutic Targets: Neuroinflammation has emerged as a useful disease-modifying therapy in neurodegenerative diseases. Microglial activation pathways, cytokine signaling, and inflammasome parts are the major molecular targets. Specifically, NLRP3 inflammasome inhibition has demonstrated a lot of promise in lessening neuroinflammatory reaction and neuronal harm[59]. On the same note, Additionally, NF-0 B, or nuclear factor-kappa B, signaling has been adjust to dampen the pro-inflammatory gene transcription[60]. The other target of interest is the TREM2, a triggering receptor produced on myeloid cells that regulates microglial activation and phagocytosis. Enhanced TREM2 can be useful in the disease like Alzheimer to ameliorate clearance of pathological protein aggregates[61]. Also, the use of chemokine receptors CCR2 and CX3CR1 has also been promising in controlling the recruitment of immune cells and neuroinflammation[62].

New Drug Candidates and Molecules:

A number of new molecules are being investigated as anti-neuroinflammatory. NLRP3 small-molecule inhibitors, including MCC950, have shown intensive neuroprotective efficacy in preclinical models in terms of cytokine generation and inflammasome activation[63]. Aducanumab monoclonal antibodies that target amyloid-beta have been created to inhibit protein aggregation and other related inflammatory reactions in Alzheimer disease[64]. Moreover, alpha-synuclein-targeting agents are under development as a Parkinson's disease treatment to inhibit aggregation and microglial stimulation[65]. Natural substances like resveratrol and curcumin have also demonstrated antioxidant and anti-inflammatory qualities by modification of various signaling pathways, one of which is the transforming the NF-KB and MAPK[66].

Clinical Trials:

The recent clinical trials have been on immunotherapy and anti-inflammatory measures. Anti-amyloid drugs such as monoclonal antibodies have advanced to late clinical trials in the management of Alzheimer's disease with mild effects on the disease's progression Inflammatory cytokines targeting drugs, including TNF-alpha-inhibitors, are also under consideration to reduce neuroinflammation and improve neurological outcomes[67]. In addition, cell therapies using stem

cells are being clinically tested to have the capability of regulating the immune system and neuronal regeneration[68].

Experimental Studies:

Preclinical investigations in animal models have given solid evidence in attacking neuroinflammation. Blockage of microglial stimulation has been reported to prevent neuronal death and enhance cognitive capabilities of the experimental models of Alzheimer and Parkinson diseases. There are efforts in the area of gene-editing to control inflammatory genes expression and correct disease-related mutations including CRISPR/Cas9[69]. Drug delivery systems based on nanotechnology are also under development to increase the penetration of blood-brain barriers and targeted delivery of the anti-inflammatory agents[70].

Future Perspectives:

The future therapeutic approaches must employ the use of early intervention and personalized medicine. The multiple pathway combination therapies such as inflammation, oxidative stress and protein aggregation can be offered with a better chance to manage the disease[71]. Discoveries in the field of biomarkers e.g. inflammatory cytokines and image will help in early diagnosis and monitoring of progress in treatment[72]. More advanced methods of artificial intelligence and precision medicine are also likely to transform the procedure of drug discovery and treatment interventions in the neurodegenerative diseases.

Clinical Relevance[73,74,75,76,77]

Targeting neuroinflammation has clinical advantages, such as reduction of the disease progression and patients' quality of life. Anti-inflammatory medication can be utilized to supplement the existing symptomatic therapies and has disease-modifying effects. Knowing patient-specific inflammatory profiles can provide individual treatment plans, reduce adverse effects and increase the therapeutic benefit.

Discussion[78,79]

Neuroinflammation is a two-sided sword that has benefits as well as adverse outcomes. General chronic activity causes neural injury and pathology. Even though there are therapies in place that are symptomatic, they do not prevent the progression of the disease. Inhibiting individual inflammatory pathways like NF- -B and NLRP3 inflammasome is a potential strategy. Incoming research must be conducted on the topics of early diagnosis, personal medicine, and combination therapy.

CONCLUSION[80,81,82,83]

One important aspect of the pathophysiology of neurodegenerative diseases is neuroinflammation. Knowing the molecular pathways provides new prospects of therapeutic intervention. Regardless of the progress in the use of the drug therapies, disease-modifying therapies are still needed. The inflammatory pathways are potential targets that can offer effective mechanisms to delay or inhibit neurodegeneration.

REFERENCES

1. Heneka MT, Kummer MP, Latz E. Innate immune activation in neurodegenerative disease. Nat Rev Immunol. July 2014;14(7):463–477.doi: 10.1038/nri3705
2. Ransohoff RM. How neuroinflammation contributes to neurodegeneration. Science.Aug2016;353(6301):777–783. doi: 10.1126/science. aag2590

3. Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH. Mechanisms underlying inflammation in neurodegeneration. Cell. March 2010;140(6):918–934. doi: 10.1016/j.cell.2010.02.016
4. Stephenson J, Nutma E, van der Valk P, Amor S. Inflammation in CNS diseases. Trends Immunol. July 2018;39(7):503–517. doi: 10.1016/j.it.2018.03.008
5. Prince M, Wimo A, Guerchet M, Ali GC, Wu YT, Prina M. The global impact of dementia. Alzheimers Dement. August 2015;11(8):891–900. doi: 10.1016/j.jalz.2015.04.007
6. Ransohoff RM, Brown MA. Innate immunity in the central nervous system. J Clin Invest. April 2012;122(4):1164–1171. doi: 10.1172/JCI58644
7. Heneka MT, Carson MJ, El Khoury J, et al. Neuroinflammation in Alzheimer's disease. Lancet Neurol. April 2015;14(4):388–405. doi: 10.1016/S1474-4422(15)70016-5
8. Block ML, Zecca L, Hong JS. Microglia-mediated neurotoxicity. Nat Rev Neurosci. January 2007;8(1):57–69. doi: 10.1038/nrn2035
9. Sofroniew MV. Astrocyte reactivity and neuroinflammation. Trends Immunol. October 2015;36(10):637–647. doi: 10.1016/j.it.2015.07.006
10. Heppner FL, Ransohoff RM, Becher B. Immune attack in the CNS. Nat Rev Neurosci. June 2015;16(6):358–372. doi:10.1038/nrn3880
11. Swanson KV, Deng M, Ting JP. The NLRP3 inflammasome. Nat Rev Immunol. August 2019;19(8):477–489. doi:10.1038/s41577-019-0165-0
12. Wang X, Wang W, Li L, Perry G, Lee HG, Zhu X. Oxidative stress and mitochondrial dysfunction. Biochim Biophys Acta. August 2014;1842(8):1240–1247. doi: 10.1016/j.bbadis.2013.10.015
13. Adamu A, Li S, Gao F, Xue G. Neuroinflammation and therapeutic targets. Front Aging Neurosci. 2024; 16:1283456. doi:10.3389/fnagi.2024.1283456
14. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease: progress and problems. Cold Spring Harb Perspect Med. July 2016;6(7): a024588. doi:10.1101/cshperspect.a024588
15. Schapira AHV, Lang AE. Parkinson's disease. Lancet. February 2017;389(10080):896–912. doi:10.1016/S0140-6736(16)30330-8
16. Hauser SL, Baranzini SE. Multiple sclerosis: prospects and promise. Ann Neurol. March 2018;74(3):317–327. doi:10.1002/ana.25270
17. van den Berg LH, Al-Chalabi A. Amyotrophic lateral sclerosis. Lancet. November 2017;390(10107):2084–2098. doi:10.1016/S0140-6736(17)31287-4
18. Heneka MT, et al. Neuroinflammation in Alzheimer's disease. Lancet Neurol. April 2015;14(4):388–405. doi:10.1016/S1474-4422(15)70016-5
19. Glass CK, et al. Mechanisms underlying inflammation in neurodegeneration. Cell. March 2010;140(6):918–934. doi: 10.1016/j.cell.2010.02.016
20. Amor S, Puentes F, Baker D, van der Valk P. Inflammation in neurodegenerative diseases. Immunology. February 2010;129(2):154–169.doi:10.1111/j.1365-2567.2009.03225.x
21. Ransohoff RM. How neuroinflammation contributes to neurodegeneration. Science. August 2016;353(6301):777–783. doi: 10.1126/science.aag2590
22. Calsolaro V, Edison P. Neuroinflammation in Alzheimer's disease: current evidence and future directions. Alzheimers Dement. June 2016;12(6):719–732. doi: 10.1016/j.jalz.2016.02.010
23. Leng F, Edison P. Neuroinflammation and microglial activation in Alzheimer disease:

where do we go from here? Nat Rev Neurol. March 2021; 17:157–172. doi: 10.1038/s41582-020-00435-y

24. Kim S, Sharma C, Jung UJ, Kim SR. Pathophysiological role of microglial activation induced by blood-borne proteins in Alzheimer's disease. Biomedicines. May 2023;11(5):1383. doi: 10.3390/biomedicines11051383
25. Schroder K, Tschopp J. The inflammasomes. Cell. March 2010;140(6):821–832. doi: 10.1016/j.cell.2010.01.040
26. Bauernfeind FG, Horvath G, Stutz A, Alnemri ES, MacDonald K, Speert D, et al. Cutting edge: NF-κB activating pattern recognition and cytokine receptors license NLRP3 inflammasome activation by regulating NLRP3 expression. J Immunol. July 2009;183(2):787–791. doi: 10.4049/jimmunol.0901363
27. Guo H, Callaway JB, Ting JP. Inflammasomes: mechanism of action, role in disease, and therapeutics. Nat Med. July 2015;21(7):677–687. doi: 10.1038/nm.3893
28. Kawai T, Akira S. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. Nat Immunol. May 2010;11(5):373–384. doi: 10.1038/ni.1863
29. Sies H. Oxidative stress: a concept in redox biology and medicine. Redox Biol. April 2015; 4:180–183. doi: 10.1016/j.redox.2015.01.002
30. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol. January 2007;39(1):44–84. doi: 10.1016/j.biocel.2006.07.001
31. Betteridge DJ. What is oxidative stress? Metabolism. February 2000;49(2 Suppl 1):3–8. doi : 10.1016/S0026-0495(00)80077-3
32. Pham-Huy LA, He H, Pham-Huy C. Free radicals, antioxidants in disease and health. Int J Biomed Sci. June 2008;4(2):89–96.
33. Schieber M, Chandel NS. ROS function in redox signaling and oxidative stress. Curr Biol. May 2014;24(10): R453–R462.doi: 10.1016/j.cub.2014.03.034
34. Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer. Free Radic Biol Med. December 2010;49(11):1603–1616. doi: 10.1016/j.freeradbiomed.2010.09.006
35. Lin MT, Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature. 2006 Oct;443(7113):787–795. doi:10.1038/nature05292.
36. Nunnari J, Suomalainen A. Mitochondria: in sickness and in health. Cell. 2012 Mar;148(6):1145–1159. doi: 10.1016/j.cell.2012.02.035.
37. Chen H, Chan DC. Mitochondrial dynamics in regulating the unique phenotypes of cancer and stem cells. Cell Metab. 2009 Aug;10(2):97–108. doi:10.1016/j.cmet.2009.07.003.
38. Youle RJ, Narendra DP. Mechanisms of mitophagy. Nat Rev Mol Cell Biol. 2011 Jan;12(1):9–14. doi:10.1038/nrm3028.
39. Wallace DC. Mitochondrial genetic medicine. Nat Genet. 2018 Dec;50(12):1642–1649. doi:10.1038/s41588-018-0264-1.
40. Giorgi C, Baldassari F, Bononi A, Bonora M, De Marchi E, Marchi S, et al. Mitochondrial Ca^{2+} and apoptosis. Cell Calcium. 2012 Jul;52(1):36–43. doi:10.1016/j.ceca.2012.02.005.
41. Chiti F, Dobson CM. Protein misfolding, functional amyloid, and human disease. Annu Rev Biochem. 2006 Jul;75:333–366. doi:10.1146/annurev.biochem.75.101304.123901.
42. Knowles TPJ, Vendruscolo M, Dobson CM. The amyloid state and its association with

protein misfolding diseases. Nat Rev Mol Cell Biol. 2014 Jun;15(6):384–396. doi:10.1038/nrm3810.

43. Ross CA, Poirier MA. Protein aggregation and neurodegenerative disease. Nat Med. 2004 Jul;10 Suppl:S10–S17. doi:10.1038/nm1066.
44. Selkoe DJ. Alzheimer's disease is a synaptic failure. Science. 2002 Oct;298(5594):789–791. doi:10.1126/science.1074069.
45. Spillantini MG, Schmidt ML, Lee VMY, Trojanowski JQ, Jakes R, Goedert M. α-Synuclein in Lewy bodies. Nature. 1997 Aug;388(6645):839–840. doi:10.1038/42166.
46. Wang W. Protein aggregation and its inhibition in biopharmaceutics. Int J Pharm. 2005 Feb;289(1–2):1–30. doi:10.1016/j.ijpharm.2004.11.014.
47. Roberts CJ. Non-native protein aggregation kinetics. Biotechnol Bioeng. 2007 Dec;98(5):927–938. doi:10.1002/bit.21527.
48. Jiskoot W, Randolph TW, Volkin DB, Middaugh CR, Schöneich C, Winter G, et al. Protein instability and immunogenicity: roadblocks to clinical application of injectable protein delivery systems. Pharm Res. 2012 Apr;29(4):1013–1026. doi:10.1007/s11095-011-0602-8.
49. Giri PM, Banerjee A, Ghosal A, Layek B. Neuroinflammation and therapeutic implications. Int J Mol Sci. 2024 Feb;25(5):2567. doi:10.3390/ijms25052567.
50. Hickman S, Izzy S, Sen P, Morsett L, El Khoury J. Microglia in neurodegeneration. Nat Neurosci. 2018 Oct;21(10):1359–1369. doi:10.1038/s41593-018-0242-x.
51. Lane RM, Potkin SG, Enz A. Targeting acetylcholinesterase and NMDA receptors in AD. J Neural Transm. 2006 Nov;113(11):1717–1731. doi:10.1007/s00702-006-0575-2.
52. Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, et al. Parkinson disease. Nat Rev Dis Primers. 2017 Mar;3:17013. doi:10.1038/nrdp.2017.13.
53. Hauser SL, Cree BAC. Treatment of multiple sclerosis. Ann Neurol. 2020 Feb;87(2):191–205. doi:10.1002/ana.25651.
54. Hardiman O, Al-Chalabi A, Chio A, Corr EM, Logroscino G, Robberecht W, et al. Amyotrophic lateral sclerosis. Nat Rev Dis Primers. 2017 Oct;3:17071. doi:10.1038/nrdp.2017.71.
55. Coll RC, Robertson AA, Chae JJ, Higgins SC, Muñoz-Planillo R, Inserra MC, et al. A small-molecule inhibitor of the NLRP3 inflammasome. Nat Med. 2015 Mar;21(3):248–255. doi:10.1038/nm.3806.
56. Liu T, Zhang L, Joo D, Sun SC. NF-κB signaling in inflammation. Signal Transduct Target Ther. 2017 Jul;2:17023. doi:10.1038/sigtrans.2017.23.
57. Ulland TK, Colonna M. TREM2—a key player in microglial biology. Nat Rev Neurol. 2018 Nov;14(11):667–675. doi:10.1038/s41582-018-0072-1.
58. Ransohoff RM. Chemokines and neuroinflammation. Nat Rev Immunol. 2009 Jul;9(7):429–439. doi:10.1038/nri2583.
59. Sevigny J, Chiao P, Bussière T, Weinreb PH, Williams L, Maier M, et al. Aducanumab reduces amyloid plaques in Alzheimer's disease. Nature. 2016 Sep;537(7618):50–56. doi:10.1038/nature19323.
60. Fields CR, Bengoa-Vergniory N, Wade-Martins R. Targeting alpha-synuclein. Front Mol Neurosci. 2019 Nov;12:299. doi:10.3389/fnmol.2019.00299.
61. Zhang L, Fiala M, Cashman J, Sayre J, Espinosa A, Mahanian M, et al. Curcumin analogs reduce inflammation. J Neuroinflammation. 2006 Apr;3:10.doi:10.1186/1742-2094-3-10.
62. McCoy MK, Tansey MG. TNF signaling inhibition in neurodegenerative diseases. J

Neuroinflammation. 2008 Jan;5:10. doi:10.1186/1742-2094-5-10.
63. Trounson A, McDonald C. Stem cell therapies in clinical trials. Cell Stem Cell. 2015 Jul;17(1):11–22. doi:10.1016/j.stem.2015.06.007.
64. Hsu PD, Lander ES, Zhang F. CRISPR-Cas9 genome editing. Cell. 2014 Jun;157(6):1262–1278. doi:10.1016/j.cell.2014.05.010.
65. Saraiva C, Praça C, Ferreira R, et al. Nanoparticle-mediated brain drug delivery. J Control Release. 2016 Sep;235:34–47. doi:10.1016/j.jconrel.2016.05.044.
66. Cummings J, Lee G, Zhong K, et al. Alzheimer's disease drug development pipeline. Alzheimers Dement (N Y). 2021 Jan;7(1):e12179. doi:10.1002/trc2.12179.
67. Hampel H, O'Bryant SE, Durrleman S, et al. Biomarkers for Alzheimer's disease. Nat Rev Neurol. 2017 Sep;13(9):553–565. doi:10.1038/nrneurol.2017.100.
68. Dantas JM, et al. Efficacy of anti-amyloid-β monoclonal antibody therapy in early Alzheimer's disease: a systematic review and meta-analysis. Neurol Sci. 2024. doi:10.1007/s10072-024-07345-2.
69. Yang HM. Recent advances in antibody therapy for Alzheimer's disease: focus on bispecific antibodies. Int J Mol Sci. 2025. doi:10.3390/ijms26010234.
70. Elamin SA, et al. Anti-amyloid monoclonal antibody therapies in Alzheimer's disease: a scoping review. Neuroscience. 2025. doi: 10.1016/j.neuroscience.2025.01.015.
71. Saraiva C, Praça C, Ferreira R, Santos T, Ferreira L, Bernardino L. Nanoparticle-mediated brain drug delivery: overcoming blood–brain barrier to treat neurodegenerative diseases. J Control Release. 2016 Sep;235:34–47. doi:10.1016/j.jconrel.2016.05.044.
72. Cummings J, Lee G, Zhong K, Fonseca J, Taghva K. Alzheimer's disease drug development pipeline: 2021. Alzheimers Dement (N Y). 2021 Jan;7(1):e12179. doi:10.1002/trc2.12179.
73. Hampel H, O'Bryant SE, Durrleman S, et al. A precision medicine initiative for Alzheimer's disease: the road ahead to biomarker-guided integrative disease modeling. NPJ Digit Med. 2018 Jan;1:2. doi:10.1038/s41746-017-0006-5.
74. Ransohoff RM. How neuroinflammation contributes to neurodegeneration. Science. 2016 Aug;353(6301):777–783. doi:10.1126/science.aag2590.
75. Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH. Mechanisms underlying inflammation in neurodegeneration. Cell. 2010 Mar;140(6):918–934. doi: 10.1016/j.cell.2010.02.016.
76. Calsolaro V, Edison P. Neuroinflammation in Alzheimer's disease: current evidence and future directions. Alzheimers Dement. 2016 Jun;12(6):719–732. doi: 10.1016/j.jalz.2016.02.010.
77. Heppner FL, Ransohoff RM, Becher B. Immune attack: the role of inflammation in Alzheimer disease. Nat Rev Neurosci. 2015 Jun;16(6):358–372. doi:10.1038/nrn3880.
78. Heneka MT, Kummer MP, Latz E. Innate immune activation in neurodegenerative disease. Nat Rev Immunol. 2014 Jul;14(7):463–477. doi:10.1038/nri3705.
79. Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH. Mechanisms underlying inflammation in neurodegeneration. Cell. 2010 Mar;140(6):918–934. doi:10.1016/j.cell.2010.02.016.
80. Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, et al. Neuroinflammation in Alzheimer's disease. Lancet Neurol. 2015 Apr;14(4):388–405. doi:10.1016/S1474-4422(15)70016-5.

81. Ransohoff RM. How neuroinflammation contributes to neurodegeneration. Science. 2016 Aug;353(6301):777–783. doi:10.1126/science.aag2590.
82. Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH. Mechanisms underlying inflammation in neurodegeneration. Cell. 2010 Mar;140(6):918–934. doi:10.1016/j.cell.2010.02.016.
83. Stephenson J, Nutma E, van der Valk P, Amor S. Inflammation in CNS neurodegenerative diseases. Immunology. 2018 Jun;154(2):204–219. doi:10.1111/imm.12922.

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