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The role of microglia in an Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is the most prevalent type of dementia, affecting an estimated 40 million individuals globally. The pathophysiology of AD also involves dysregulated microglia, intracellular Fibrillary neurons tangles, and extracellular amyloid plaques. Several investigations have shown that unchecked microglial activation disrupts microglia-associated mitosis, reasons tau pathology and amyloid buildup, and creates a chronic Inflammatory neurons milieu. Microglia play a crucial part in the pathophysiology of AD, according to recent research. The activation and buildup of microglial cells surrounding Beta-Amyloid plaques has long been shown in Alzheimer's disease (AD) in particular, and it is thought to cause persistent neuroinflammation, a term that is frequently used but lacks a clear meaning. Although new research indicates that microglia lose their natural protective role as AD progresses and may even eventually have a "toxic" nature, beta-amyloid may also not be a suitable trigger to cause microglia to Phagocytosis and degrade in vivo. One exciting option for analysing the function that microglia play in the initiation and growth of Alzheimer's disease is through employing induced pluripotent stem cell derived microglia. Developing novel therapeutic targets and expanding our knowledge of the pathogenic mechanisms behind Alzheimer's disease will depend on overcoming these obstacles.

Keywords **- Microglia, Alzheimer's disease, Beta-Amyloid.**

INTRODUCTION

Alzheimer's disease (AD) is the most common neurodegenerative illness, accounting for between 60 and 80 percent of dementia cases globally [1]. The goal of the early research was to determine whether the condition had a hereditary foundation. Less than 10% of all instances of AD occur before the age of 65, even if some cases are brought on by specific mutations in one of the three genes (APP, PSEN1, or PSEN2). Most occurrences occur at or after the mean age of 65, are sporadic, and lack a known cause. Evidence from large cohort studies that have identified genetic variations linked to and perhaps causing the late onset form of AD has advanced our understanding. Numerous genes and single nucleotide polymorphisms have been shown to contribute to the beginning, making it a multifactorial disease, according to these genome wide association studies (GWAS) [2]. Despite the high prevalence of the condition, little is known about the pathogenic mechanisms. Treatments that just address symptoms have been developed, but therapeutic and preventive remedies are still pending [3]. Reducing prevalence and morbidity worldwide requires a better understanding of AD biology and the identification of potential therapeutic targets that may be employed as preventative or curative strategies against the illness. The amyloid and tau hypothesis has been the main mechanism now thought to be involved in AD pathogenesis. The amyloid hypothesis is still the most widely recognized explanation for AD pathology due to the strong evidence that amyloid-beta is essential to the pathophysiology of the illness that has emerged in recent decades. The idea, however, is unable to offer a thorough explanation of the fundamental origins of the illness. The amyloid theory is further challenged by the failure of amyloid-beta targeted immunotherapies. No improvement in cognition was observed. [4]. Together with the idea of the amyloid cascade, studies conducted on animals or in clinical

trials have demonstrated that tau-dependent neurodegeneration is initiated by A while Amyloid buildup is increased by tau [5,6]. Even though the amyloid theory is believed to be the origin of AD, particularly early-onset AD, there has been recent conjecture that tau pathology could be the cause of late-onset AD; further research is need to confirm this [7]. A and Tau work in concert with other harmful components, such neuroinflammation, to cause neuronal death, synaptic malfunction, and cognitive decline, all of which are linked to the development of AD symptoms [8]. Since the effectiveness of amyloid targeted medications in clinical trials has not been correlated with the severity of cognitive dysfunction, there has been a surge in interest in recent years in the development of disease-modifying therapeutics that particularly target the tau pathology. Potential therapies for tauopathy include tau aggregation, tau post-translational modifications, and cytoskeletal stabilization [9]. Tau has a decreased affinity for microtubules and is more likely to aggregate under diseased situations, which affects neural plasticity. In fact, strategies for addressing tau include stabilizing microtubules, controlling Tau phosphatases and kinases, and preventing Tau buildup using Tau vaccines [10]. Neurodegeneration is a common characteristic of AD patients. It initially affects patients' short-term memory retention in the temporal lobe before progressing to the parietal lobe and affecting the development of long-term memory [8].

Consequently, in AD patients, neurodegeneration is linked to cognitive impairment, highlighting the importance of this correlation for understanding the clinical development of cognitive decline. The best way to treat AD would be to target neuronal deterioration in order to halt the progression of the illness. Our limited knowledge of the underlying mechanisms is mostly to blame for the dearth of clinically approved drugs to prevent or reverse neurodegeneration. A study on autosomal dominant AD found that pathophysiological alterations, including brain shrinkage, tau protein levels in the CSF, and amyloid plaques, begin at least 20 years before clinical symptoms appear [11]. The development of preventive and therapeutic strategies cantered on A and tau has accelerated due to numerous studies on the amyloid and tau alterations in AD; however, this focus may obscure the importance and potential of neuroinflammation, another promising target that has recently drawn attention [12–13].

The CNS's immune system being stimulated leads to a larger release of chemical mediators, which is how neuroinflammation is defined. Neuroinflammation was initially believed to be a subsequent reaction, which was followed by neurofibrillary tangles and the amyloid cascade. Recent research, however, indicates that immunological system modification takes place prior to the onset of AD symptoms, and neuroinflammation may also be a causative factor in the development of AD. It has been suggested that inflammation may both independently and in concert with the amyloid and tau pathways to contribute to the development of this illness, thus extending the vicious cycle [14].

The options for treating AD are incredibly limited. The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) presently only approve four drugs for the treatment of AD. These consist of three drugs from the class of acetylcholinesterase (AChE) inhibitors (donepezil, rivastigmine, and galantamine) and memantine, a selective and noncompetitive NMDA receptor antagonist [13,15-16]. AChE inhibitors increase the amount of ACh in the synaptic region, which helps patients' cognitive performance and quality of life [3]. By reducing calcium ion intracellular influx, memantine enhances NMDA receptor activation and provides neuroprotection [17,18]. Novel therapeutic and preventative approaches to AD are desperately needed, and neuroinflammation seems to be one of the most promising avenues to addressing this issue.

The first response to CNS injury is usually the migration of macrophages and microglia to the site of lesion [19,20]. Changes in microglia shape and increased expression are referred to as microgliosis [21]. Additionally, oligodendrocyte cells are sent to the damaged location to facilitate remyelination [22]. The last component is the elevated expression of astrocytes, the main glial response cells that also experience structural changes at the same time [22, 23]. These changes in astrocytes are known as astrogliosis. Thus, neuroinflammation influences memory loss and cognitive impairment in the pathogenesis of AD. One of the most important contributing factors to the development and course of AD may be a reactive gliosis. The notion that microglia-related pathways are crucial for the risk and pathophysiology of AD has been validated by recent transcriptome and genomic research. [10]. Interestingly, recent studies have demonstrated that microglia build up near amyloid-beta plaques in the AD brain and exacerbate the illness [24,25]. As such, providing an overview of microglia's role in neuroinflammation and AD pathophysiology is the focus of the article.

2. Physiology of Microglia

Microglia are mononuclear phagocytes that reside permanently in the central nervous system and are believed to be a component of the immune system [20, 26,27]. They serve a similar purpose as blood macrophages, which are phagocytic and inflammatory in nature. Microglial cells were described by Pio del Rio Hortega between 1919 and 1927 [28–29].

Numerous substances, such as pesticides (like paraquat), misfolded proteins (like A,-synuclein), air pollutants, and bacterial cell wall lipopolysaccharides (LPS), can cause microglia to become activated [30, 31]. The microglial response involves Toll-like receptors (TLRs), NOD-like receptors (NLRs), enhanced glycation end product (RAGE) receptors, scavenger receptors, formyl peptide receptors, complement receptors, and Fc receptors [32]. They are all immunological pattern recognition receptors (PRRs) that microglia express [32, 33]. PRRs can detect endogenous host-derived compounds known as damage-associated molecular patterns (DAMPs) or external pathogenic substances known as pathogen associated molecular patterns (PAMPs) [34,35]. PAMPs and DAMPs react to infections differently. While DAMPs activate surface receptors that detect signals emitted from injured cells in response to CNS traumas such trauma, hypoxia, and neurodegenerative diseases, PAMPs trigger inflammation and an antimicrobial response [36]. When PAMP/DAMPs

interact with microglial PRRs, a variety of intracellular cascades, kinases, and downstream transcription factors are activated, leading to the production of inflammatory mediators and other cellular responses [35,36].

It was thought for a number of years that microglia activation was harmless; these cells were known as reactive microglia [37]. It is now known that microglia are essential for neuroprotection since their activation results in a variety of abnormalities [38]. The microglia are inactive (M0) and display ramified processes under physiological conditions [39]. However, research showed that microglia never rest and are always monitoring the brain for any changes in cerebral homeostasis, which revolutionized our knowledge of their function. More precisely, these investigations showed that microglia serve as protectors, assessing and scanning their immediate environment for potential alterations in brain homeostasis [40]. Any detrimental situation triggers cell activation, which can lead to different microglial phenotypes, similar to what happens in macrophages. M1 and M2 are the two primary activation phenotypes; M1 exhibits a proinflammatory phenotype, while M2 contributes to inflammation resolution [41] In vitro, both LPS and/or IFN stimulate the M1-like microglia phenotype. In particular, LPS triggered NF-kB, AP1, STAT5, and interferon regulatory factors (IRFs), among other pro-inflammatory transcription factors, by activating TLR4 through TIR domain-containing adapter inducing IFN (TRIF) and myeloid differentiation primary response protein 88 (MyD88)-dependent pathways [42,43]. IFN binds to IFN receptors 1 and 2 (IFNR1/2) and triggers the JAK/STAT cascade, allowing for the phosphorylation and translocation of STAT1 and other IRFs into the nucleus [44]. M1-like microglia induce transcription factors that lead to the upregulation of pro-inflammatory cell membrane indicators, such as MHCII and the cluster of differentiation marker 86 (CD86) [45,46]. Moreover, they boost the synthesis of several pro-inflammatory mediators, including cyclooxygenase-2 (COX-2), reactive oxygen and nitrogen species (ROS and RNS), inducible nitric oxide synthase (iNOS), and cytokines such as tumour necrosis factor (TNF) and interleukins IL-1, IL-6, IL-12, IL-17, IL-18, and IL-23, as well as CCL12 and CXCL10 chemokines [46–47]. In order to combat invasive pathogens, M1-like microglia are essential for triggering both the innate and adaptive immune responses [48]. However, neurotoxicity, oxidative stress, and neuroinflammation are associated with chronic activation under pathological conditions [48,49]. Tissue repair and immunological resolution are two processes that are commonly associated with M2 polarized microglia's release of neurotrophic and anti-inflammatory chemicals [49,50]. It is also possible for these microglia to become "alternatively activated" or "acquired deactivated." Endogenous defence mechanisms in the central nervous system promote tissue regeneration when brain homeostasis is upset due to brain injury or extended stress. Numerous growth factors, hormones, and anti-inflammatory cytokines, including glucocorticoids, are released by injured neurons, which promote the local microglia to adopt a protective phenotype akin to M2 [50,51]. Anti-inflammatory cytokines that can activate M2 microglia include TGF-, IL-4, IL-10, and IL-13. TNF, IL-6, and iNOS production are examples of M1 pro-inflammatory responses that are generally inhibited by IL-4 and IL-13, which also increase the alternate activation state [52,53]. When combined with IL-10, TGF-, a multifunctional cytokine that supports angiogenesis, immunoregulation, and tissue regeneration, causes the acquired deactivation state [55]. Three distinct M2 phenotypes—M2a, M2b, and M2c—have similar biochemical roles but differ in their method of action, activating stimulus, and marker expression [54]. As a result, microglia can dynamically transition between polarization states that resemble M1 and M2. Rather than employing two distinct states of activation, M1 and M2 represent a continuous spectrum of activation phenotypes, and a variety of phenotypic markers may coexist, indicating a large number of intermediate phenotypes [49]. In conclusion, the engagement mechanism, the duration of the injury, and the regulatory signalling molecules involved influence the function of microglia in the healthy and sick brain as well as the transition between different phenotypic states [56,57].

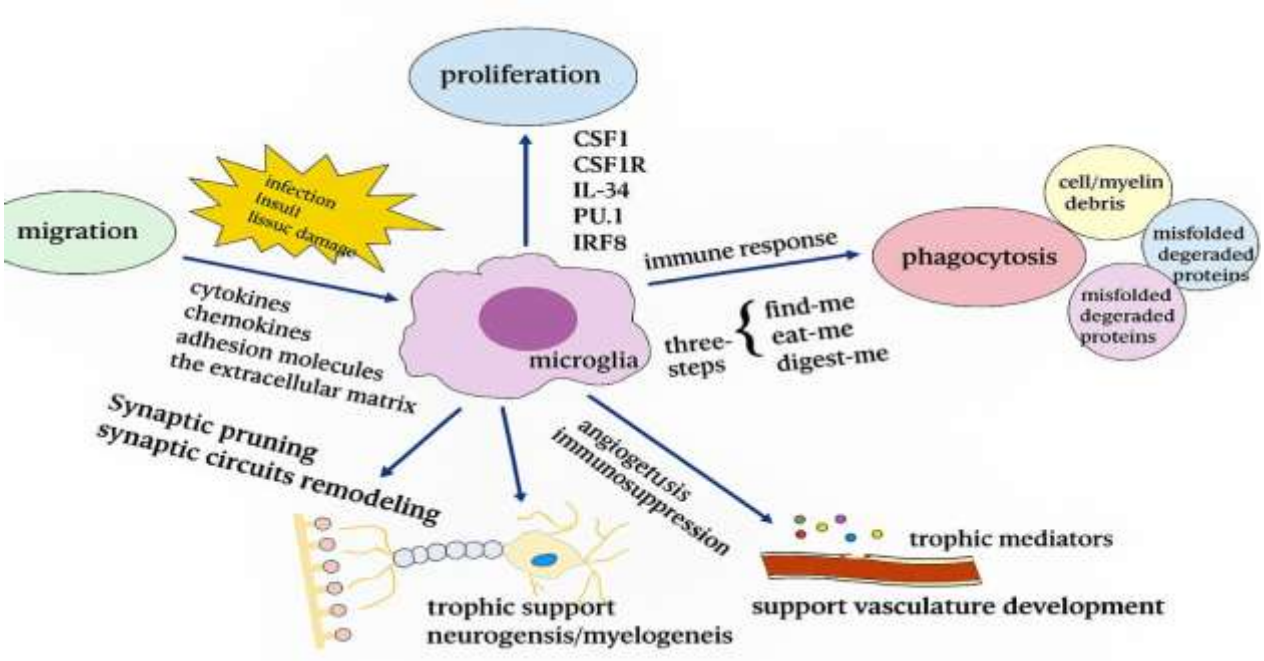

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Figure1: Physiology of Microglia

3. The immune system's innate response to Alzheimer's

The significance of microglia in the innate immune system's involvement in AD is becoming more and more interesting. The resident immune cells in the brain and spinal cord, known as microglia, are crucial for immunological surveillance, neurodevelopment, illness, and homeostasis [58]. Microglia are of hematopoietic lineage and emerge early in development, in contrast to neurons and other glial cell types [59]. and originate from the yolk sac's erythromyeloid progenitors (EMPs) [60]. According to their surroundings or the stimuli they receive, microglia can live in a variety of morphological and phenotypic states. The microglia undergo a transformation from a highly processed state to a more amoeboid state with more intracellular vesicles in order to be ready to absorb foreign particles. The terms "classical activation," "alternative activation," and "acquired deactivation" have been used appropriately to describe these distinct states [61]. According to earlier research, these states are distinct from one another, with an M1 or M2 phenotyping profiling index indicating a pro- or anti-inflammatory condition, respectively. It has lately become clearer that this stems from the notion that microglia are central macrophages and must therefore adhere to the same "kill or cure" switch that these cell types exhibit. Nevertheless, depending on the stimuli, microglia can live in several phases, with the same cell generating indicators of both pro- and anti-inflammatory components. The variability of microglia, which is essential to their local and global physiological responses, is not captured by the use of M1/M2 profile language [62]. IFN-γ stimulates classical activation, which is thought to be pro-inflammatory and linked to the synthesis of cytokines including TNF-α and IL-1β as well as nitric oxide [63,64]. Conversely, alternative activation is characterized by the production of arginase 2 and the anti-inflammatory cytokines IL-4 and IL-13. As a result, genes are expressed to support extracellular matrix rebuilding and tissue repair [61,65]. The development of scavenger receptors and the release of IL-10, TGF-β, IL-6, and CSF1 are hallmarks of acquired deactivation, which is primarily observed in the presence of apoptotic cells [61,66,67, 68]. To initiate the engulfment of hazardous particles, microglial phagocytosis depends on particular cell surface receptors and their downstream signalling cascades (Figure 2). Microglia have a role in the phagocytosis and removal of debris, infections, and poisons as well as mediating the brain's innate immune response. Not just AD patients with family APP mutations exhibit its malfunction and elevated Aβ buildup. This implies that inadequate clearance, rather than APP proteolysis, is the cause of Aβ accumulation. In neurodegenerative disorders, microglia will release pro- and anti-inflammatory chemicals, which may be advantageous or harmful. Numerous studies have demonstrated that inflammation plays a crucial role in the development of AD by promoting Aβ accumulation, neuronal death, and cognitive impairments. Pro-inflammatory cytokines and chemokines, such as TNFα, IFNγ, IL-1β, and IL-6, are consistently expressed in high levels in the brains of AD patients and those from mouse models of Aβ pathology [69]. By inhibiting long-term potentiation of synaptic transmission (LTP), IL-1β and TNFα can damage neuronal function [70]. In AD, a pro-inflammatory activation state is favoured by a number of interactions as well as increased expression of other cytokines/chemokines and innate immune receptors.

Aβ-induced microglial activation can happen before plaques even form, so it's not always a reaction to Aβ deposition. Maezawa and associates demonstrated that microglia were activated by nanomolar quantities of Aβ oligomers and that they needed the Ca2+-activated potassium channel KCa3.1 and another scavenger receptor, SR-A [71]. Another pathogenic feature of AD is the presence of intracellular neurofibrillary tangles of hyperphosphorylated tau. The precise processes that cause tau to become hyperphosphorylated are still unknown, though. Tau aggregation, hyperphosphorylation, and neurodegeneration have all been shown to positively correlate with neuro-inflammation in a number of models [72, 73,74,75, 76,77]. In the P301S tauopathy model, microglial activation also occurs before tau pathology [77]. Lipopolysaccharide treatment dramatically raised tau phosphorylation via toll-like receptor 4 signalling in the triple transgenic model of AD [78]. It's interesting to note that one study showed that microglia might contribute to the spread of tau disease in mammals through non-synaptic transmission [79]. demonstrated that microglia, which phagocytose tau-positive neurons or synapses and release tau protein in exosomes, effectively transmit tau to neurons using two distinct tau mouse models. Additionally, they showed that this propagation is susceptible to nSMase2 activity suppression and microglial depletion. However, in a mouse model of amyloid Pathy, a notable reduction in microglia showed that Aβ generation, maintenance, and Microglia did not depend on related neurotic dystrophy [80]. Remarkably, it has been suggested that Aβ may have a direct impact on microglial function. An substantial inverse relationship between Aβplaque burden and microglial phagocytic activity was found in this in vivo investigation. They discovered that early in AD, microglial dysfunction occurs in an Aβ-dependent manner and can be repaired by interventional anti-Aβ strategies, like Aβ immunization [81]. The abundance of voltage-gated ion channels found in microglia indicates that, despite not being excitable cells, they are important in both normal and pathological conditions. Brain inflammation is a characteristic of Microglia can directly interact with neurons to cause inflammation, as multiple studies have shown [82]. The investigation of microglial ion channels may offer insight on brain inflammation in neurodegenerative illnesses like AD as a result of this interaction [83].

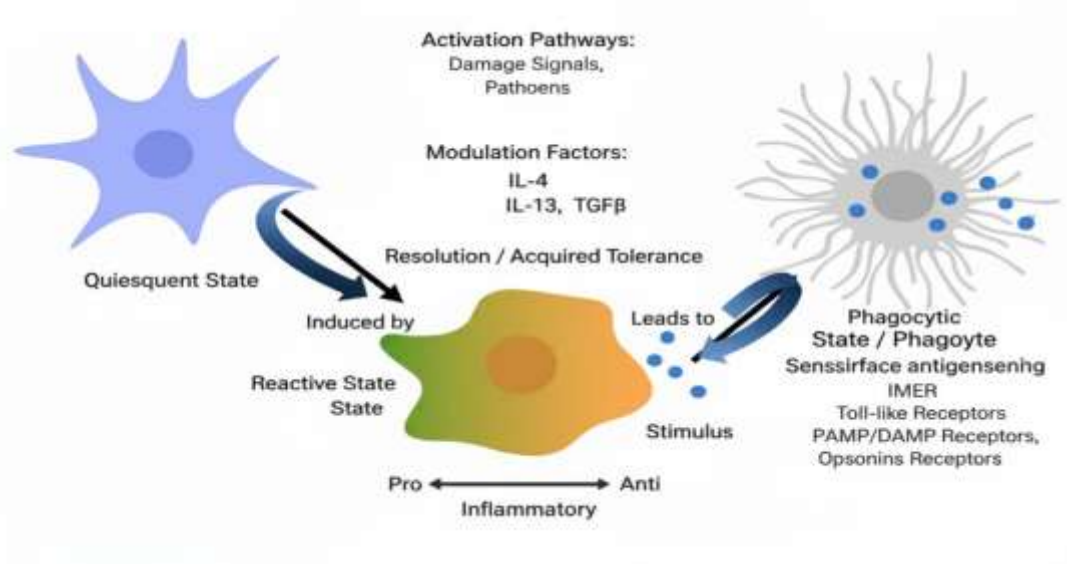

Figure 2: Immune system's innate response to Alzheimer's

4. Microglia analysis in Alzheimer's disease

In an effort to demonstrate context-dependent microglia activation, the idea of categorizing peripheral macrophages based on the kind of T-cell mediated stimulation in "M1" ("classically activated") and "M2" ("alternately activated") activation states [84] has recently been applied to microglia [85]. There appears to be agreement that, similar to normal aging, microglia undergo a transition from a neuroprotective to a more classically activated phenotype at later stages of the disease [86,87], even though microglia express markers for both classical and alternative activation in AD [23]. These results are frequently interpreted as proof that microglia, particularly in later stages of the disease, are releasing neurotoxic chemicals that aid in the course of the disease [87]. On the other hand, this shift in microglia's cytokine release and gene expression may potentially indicate a state of growing malfunction that keeps these cells from becoming actively harmful rather than helpful [89]. The interventional potential of the control of microglia activation is demonstrated by findings where the deletion of CD14 reduced plaque pathology by modifying the inflammatory reaction of microglia in neurons [90]. The NALP3 inflammatory system appeared to be a key factor influencing the immune system's natural reaction to Ab and the cytokine ambiance in neurons [91,92]. This encourages the pro-inflammatory reaction indicated by IL-1b release. In an AD animal model, deletion of the NALP3 inflammasome or the crucial effector enzyme caspase 1 reduced the amount of Ab plaque, which was linked to a more "M2" biased activation profile of microglia [92]. M1 and M2 phenotyping is not a truly functional measure and may therefore be of limited assistance in characterizing the activation status of microglia because, in the end, it is just another method of characterizing a pattern of molecular markers on microglia (limited by the distinction of measurable molecules).

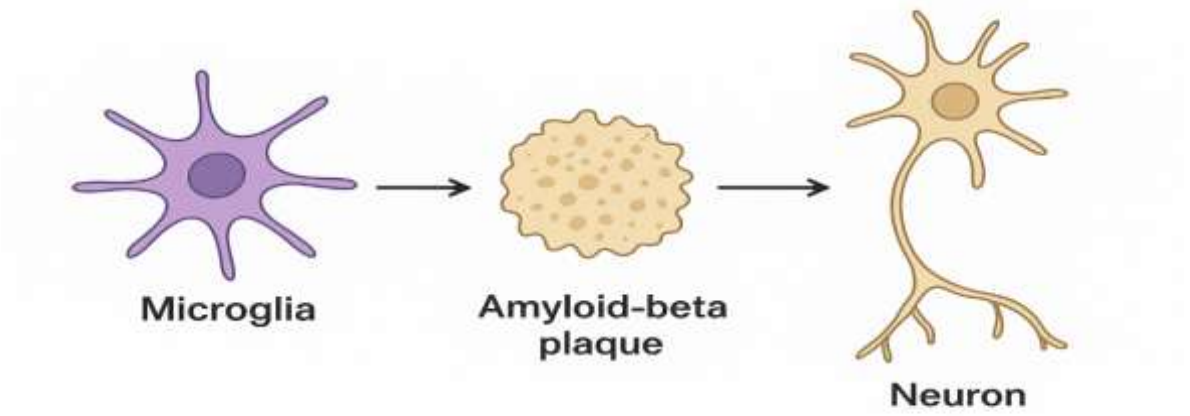

Figure3: Microglia analysis in Alzheimer's disease

5. Neuronal Activity, apoptotic and the Microglia function in AD

It's critical to take into account how microglia interact with other glial and neuron cells in order to comprehend how AD develops. It is important to note that neurons and glia are known to cooperate to modulate cognitive activities by controlling synaptic plasticity and neurotransmission [93].

It's interesting to note that glial cell dysregulation may be a major factor in the neurodegenerative processes and cognitive impairments associated with AD, according to recent study. Astrocyte-microglia interaction has been observed to stimulate microglial motility, astrocyte and microglia proliferation, and maybe both of their phagocytic activities [94,95]. Astrocytes have also been found to be in a disease-associated state, similar to microglia, with higher levels of glial fibrillary acidic protein (GFAP) and genes linked to inflammatory responses and hazardous chemical reactivity. [96]. This harmful-reactive astrocytes, referred to as A1, have been shown to be more common in the prefrontal cortex of AD patients and are created by activated microglia via pro-inflammatory cytokines [97]. It's interesting to note that activated microglia and reactive astrocytes are often seen near the senile plaques of AD patients, suggesting their crucial role in the disease's aetiology [98]. Furthermore, it has been observed that the development of astrocytes into A1 requires TNF, which has been shown to be produced by neutrophils, macrophages, and microglia [97,99]. Following neuronal myelination loss, an increase in GFAP activity was observed in AD cells [100]. The TgF344 rat model of AD has a rise in astrocytes, which may lead to excitability and neuronal death by generating a co-agonist that activates the N-methyl-D-aspartate receptor (NMDAR) on neuronal [101]. Crucially, astrocytes and microglia produce a variety of signalling molecules (including growth factors, neurotransmitters, cytokines, and chemokines) upon CNS insult or damage, creating a bidirectional relationship for tight reciprocal regulation [102,103]. In reaction to disease or injury, damaged neurons preferentially create self-antigens or modified proteins, which awaken latent microglia. As the main immunological effector, these latter travel to injured sites to collect dead cells and debris [104]. To completely comprehend how microglia and astrocytes potentially collaborate with neurons in the AD setting, more research is needed.

6. Conclusions

Amyloid-beta, tau pathology, and neuroinflammation interact intricately in Alzheimer's disease (AD), which is still a multifactorial neurodegenerative illness. The exact mechanisms underlying its development and progression remain unclear despite a great deal of research. Although the tau and amyloid theories explain important clinical characteristics, they are unable to fully explain the diversity and course of the disease. Neuroinflammation, including microglial activation and reactive gliosis, is increasingly shown to be a key factor in neuronal injury and cognitive impairment. Amyloid and tau toxicity are amplified by microglia-mediated inflammatory responses, creating a vicious pathogenic loop. Only symptomatic alleviation is provided by current treatments; the course of the disease is not altered. Thus, a possible therapeutic approach is to target neuroinflammatory pathways. Novel approaches to disease modification may result from an understanding of the interactions between glial activation, cytokine signalling, and neuronal damage. To create effective preventive and curative treatments for AD, future research must incorporate immunological, genetic, and molecular viewpoints. Microglia are dynamic immune cells found in the central nervous system that have two functions: they mediate neuroinflammation and preserve brain homeostasis. Whether they aid in neuronal injury or healing depends on whether they are activated into M1 (pro-inflammatory) or M2 (anti-inflammatory) phenotypes. While M2 polarization encourages tissue regeneration and neuroprotection, persistent M1 activation causes oxidative stress and neurotoxicity. For the health of the brain, these states must be in balance. Comprehending the regulation of microglial polarization has significant therapeutic opportunities for neurodegenerative illnesses such as Alzheimer's. Microglia play a pivotal role in Alzheimer’s disease by regulating neuroinflammation, amyloid-beta clearance, and tau pathology. Their dysregulation contributes to neuronal damage, synaptic dysfunction, and disease progression. Understanding microglial activation mechanisms and modulation offers promising therapeutic avenues for preventing or slowing AD pathology. Microglial activation in Alzheimer’s disease reflects a dynamic, context-dependent process rather than a fixed M1/M2 state. Shifting from neuroprotective to pro-inflammatory phenotypes contributes to disease progression and neuronal damage. Targeting pathways that modulate microglial activation, such as inflammasome signalling, may offer novel therapeutic strategies for AD management. Microglia and astrocytes closely interact with neurons, forming a complex cellular network that influences Alzheimer’s disease progression. Dysregulation of these glial interactions leads to neuroinflammation, excitotoxicity, and neuronal death. Understanding the bidirectional signalling between microglia, astrocytes, and neurons may uncover new therapeutic targets for mitigating AD-related neurodegeneration.

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