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Review Article

Alzheimer's Disease and Neuroinflammation: Exploring Cellular and Molecular Mechanisms

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ABSTRACT

Alzheimer's disease is a progressive neurodegenerative disorder characterized by cognitive decline, memory impairment, and behavioral changes. It is the most common cause of dementia, primarily affecting the elderly population. The pathological hallmarks of Alzheimer's disease include extracellular amyloid-beta plaques, intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein, neuroinflammation, and synaptic dysfunction. This review explores the cellular and molecular mediators involved in the progression of Alzheimer's disease, highlighting the role of amyloid-beta accumulation, tau pathology, neuroinflammatory responses mediated by microglia and astrocytes, oxidative stress, and inflammatory mediators. A deeper understanding of these cellular and molecular mechanisms is crucial for developing targeted therapeutic strategies to slow or halt disease progression.

INTRODUCTION

Alzheimer's disease (AD)is a neurodegenerative disorder that affects the elderly population worldwide, which is characterized by slowly progressive loss of memory and cognitive impairments. Dementia is one of the age-related mental problems and a characteristic symptom of Alzheimer's disease. It is a multifactorial syndrome that affects memory, thinking, language, behavior, and the ability to perform everyday activities. AD is thought to affect 4-8% of the population over 65 years of age, with the incidence continuing to increase with increasing age. The most predominant form of dementia is estimated that up to 2050 it will affect to more than 50 million people worldwide; so AD is categorized as a disease of public health priority by the WHO.[1] Clinically, AD is characterized by visuospatial dysgnosia and memory, language, emotional, personality, and complex cognition impairment. Two primary neuropathological hallmark signs are

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the presence of neurofibrillary tangles formed by unfolded protein aggregates (hyperphosphorylated tau protein) and extracellular aggregates of amyloid-beta peptide.[2] Aβ is produced by the sequential cleavage of amyloid β precursor protein by β and γ secretases. Formation Aβ plaques lead to neuronal loss in several brain regions, including the entorhinal cortex, hippocampus, neocortex, amygdala, and subcortical areas.[3]Neurofibrillary tangles (NFTs) are produced by the hyperphosphorylation of microtubule-associated proteins, which are known as tau. The excessive phosphorylation of tau proteins decreases their binding ability to microtubules, resulting in the formation of NFTs.[4] In the development of AD, moderate cognitive impairment (MCI) is inherently accompanied by oxidative stress. The receptor of advanced glycation end products (RAGE) is activated, which raises inflammatory mediators and oxidative stress, ultimately resulting in neurodegeneration. The activation of RAGE further triggers downstream regulatory pathways, including the NF-kB, STAT, and JNK pathways. However, chemokines and inflammatory cytokines are also associated with cognitive deficits.[5]

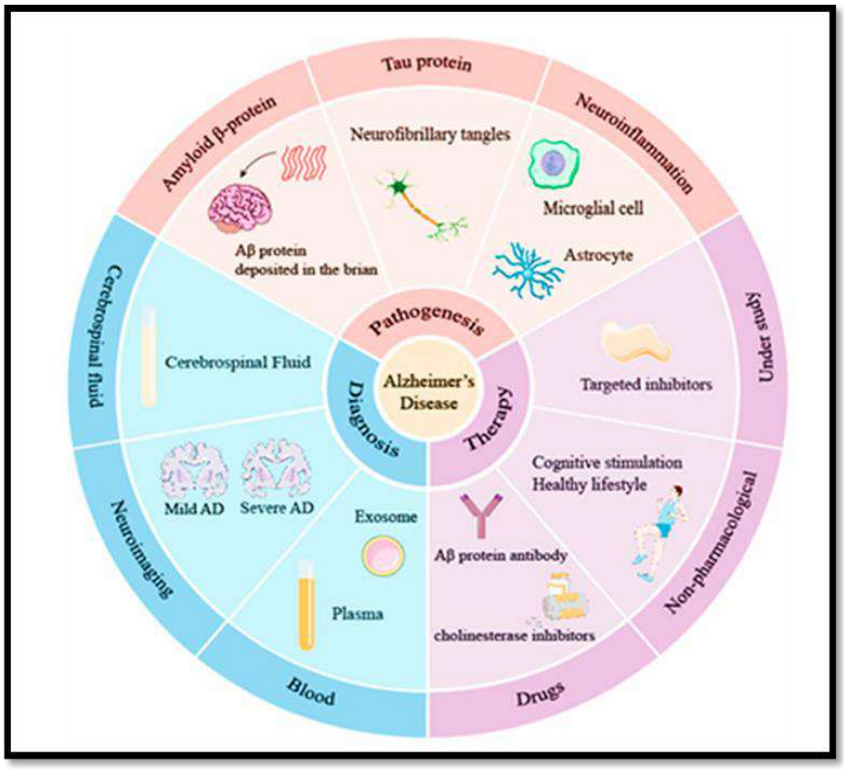


Fig.no.1 Pathogenesis of AD and treatment

It has been discovered that microglia-induced inflammation triggers the release of neurotoxic cytokines. Chronic microglial activation, followed by the production of proinflammatory cytokines, initiates a cascade of neurotoxic changes that contribute to the development and progression of Alzheimer's disease. Aβ plaques trigger astrocytes, leading to increased oxidative stress and the activation of cytokines such as IL-6 and IL-1β.[6] Several theories have been put forth to explain the pathophysiology of Alzheimer's disease, including oxidative stress, metal ions, inflammation, glutaminergic excitotoxicity, cholinergic, tau, and amyloid, as well as abnormal autophagy. In this review, we focused on the mechanisms underlying

inflammatory processes and their implications in Alzheimer's disease progression.

Inflammatory pathways involved in AD

Alzheimer's disease is a neurodegenerative disorder characterized by memory loss, cognitive decline, and behavioral changes. Neuroinflammation is a key component of Alzheimer's pathogenesis. The inflammatory pathways involved in Alzheimer's disease include the activation of microglia, the release of inflammatory cytokines, the complement system, and the role of astrocytes. These pathways contribute to the neuroinflammation observed in Alzheimer's disease which ultimately leads to neuronal damage and cognitive decline. The inflammatory response in Alzheimer's disease is primarily mediated by activation of microglia, which are the brain's resident immune cells and cytokines can exacerbate the inflammatory response, leading to further neuronal damage. Different immune system cells can migrate through the blood-brain barrier (BBB) to the brain, which is structurally different in people associated with AD rather than in healthy people. The amyloid beta plaques formed in the AD patient's brain are linked to activated microglial cells.[7] These cells are found to be responsible for the neuroinflammatory processes that occur in AD through the release of different mediators like cytokines, chemokines, neurotoxins, etc. Microglial cells can directly interact with infiltrating T lymphocytes which produces a variety of pro and anti-inflammatory cytokines.[8] The complement system, part of the innate immune response, is activated in Alzheimer's disease which is the major mediator of this inflammatory process. The complement system comprises three distinct activation pathways — the classical, lectin, and alternative pathways. It contributes to synaptic loss and neuronal death. Astrocytes, another type of glial cell are also involved in the inflammatory response by releasing cytokines and other inflammatory mediators.[9] Chronic activation of these pathways results in sustained inflammation, contributing to the accumulation of amyloid-beta plaques and tau tangles, hallmark features of Alzheimer's disease.

1. Complement system

In Alzheimer's Disease (AD), there are certain proteins called complements which are found in higher amounts in the AD patient's brain than in healthy people. These proteins are part of the immune system, and become more active in AD-affected brains, leading to the damaged brain cell. Amyloid plaques, which are harmful protein clumps, also trigger complement activation. This process damages neurons and increases tau proteins, forming neurofibrillary tangles (NFTs). These complement proteins help in maintaining brain health while uncontrolled activity can worsen AD. The complement system is part of the innate immune system and consists of over 30 proteins that aid in defending against pathogens, clearing damaged cells, and modulating inflammation. The classical complement pathway is primarily activated by the C1 complex, which includes C1q, C1r, and C1s. In Alzheimer's disease, C1q binds to amyloid-beta deposits, leading to the activation of C1r and C1s and the subsequent generation of the C3 convertase (C4bC2a). This enzyme cleaves C3 into C3b and C3a. C3b can opsonize amyloid-beta plaques and promote their clearance by microglial cells, the resident immune cells in the brain. However, in Alzheimer's disease, the efficiency of amyloid clearance by microglia is impaired, leading to chronic inflammation and neurodegeneration. C5a, derived from C5, is a potent inflammatory mediator that recruits immune cells to the site of complement activation and exacerbates

neuroinflammation. This chronic activation of the classical pathway leads to a sustained inflammatory environment that contributes to neuronal injury and synaptic loss.[10] C3a and C5a, derived from the cleavage of C3 and C5, are potent inflammatory mediators which are act as chemotactic factors, attracting more microglia and immune cells to the site of complement activation. C5a, in particular, binds to its receptor on microglia, exacerbating their activation and promoting the release of pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6[10]

1.1 Activation of alternative pathway

In addition to the conventional complement pathway, it has been shown that β-pleated fibrillar Aβ can directly activate the alternative pathway without the need for antibodies. The activation of both the classical and alternative complement pathways by β-pleated fibrillar Aβ seems to be a specific occurrence, as other peptides of comparable size and charge to Aβ, such as the β-pleated fibrillar peptide amylin, do not activate either the classical or alternative pathways in their monomeric or aggregated forms. Moreover, earlier studies have indicated that the activation of both complement pathways results in the creation of covalent, ester-linked complexes of Aβ with fragments from the third complement component, C3, a characteristic feature of complement activation processes. The stability of covalent complexes against dissociation likely explains the observed presence of C3 alongside fibrillar Aβ in senile plaques. Furthermore, the activation of complement by fibrillar, β-pleated Aβ triggers the production of C5a, which is a potent cytokine-like cleavage product of C5 and leads to the formation of the pro-inflammatory C5b-9 MAC in vitro. [10,11]These processes appear to function in vivo, as numerous complement proteins—such as C1q, C4, C3, C5, C6, C7, C8, C9, activation fragments of C3 and C4, along with the C5b-9 MAC—are closely localized with Aβ deposits and neurofibrillary tangles in the brains of individuals with Alzheimer's disease.

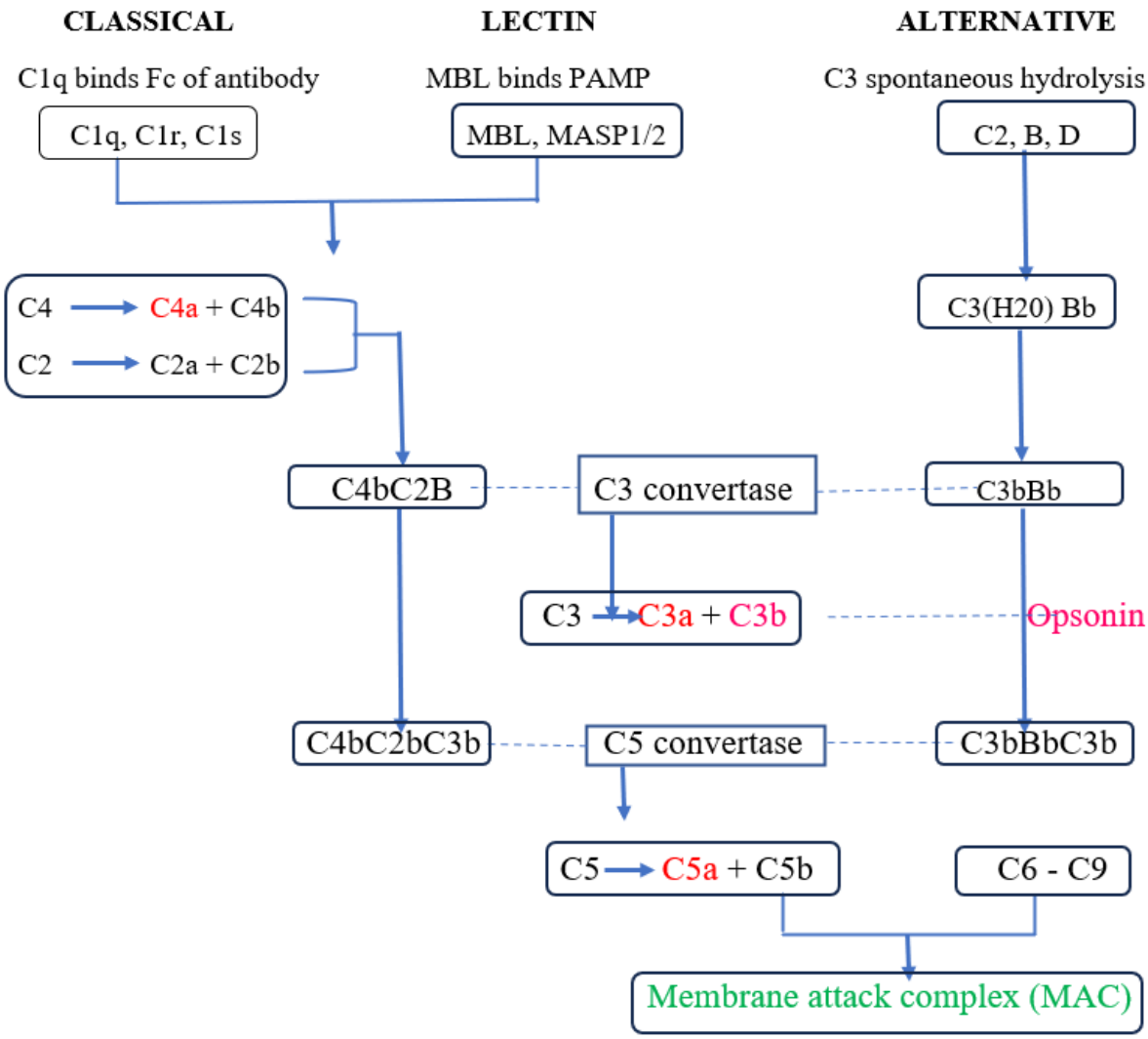
1.2 The Lectin Pathway

Mannose-binding lectin (MBL) or ficolin binds to specific carbohydrate patterns on the pathogen or damaged cell surfaces, activating the lectin pathway. Amyloid-beta plaques in Alzheimer's disease can activate the lectin pathway by binding to MBL. MBL-associated serine proteases (MASPs) are activated, cleaving C4 and C2 to form C3 convertase (C4bC2a) and producing C3b.[12] The presence of C3b on amyloid-beta plaques activates microglia and promotes plaque phagocytosis. However, like the traditional pathway, this activation does not always remove amyloid, resulting in a chronic inflammatory state. The lectin pathway exacerbates neuroinflammation by producing C3a and C5a, which recruit additional inflammatory cells such as neutrophils and monocytes, exacerbating the inflammation and causing additional neuronal damage.

1.3 Membrane attack complex

Activation of the classical and alternative complement pathways leads to the formation of the C5b-9 MAC complex. It makes sense that high levels of the MAC would be present near these pathological hallmarks due to complement activation by Aβ or tangles, but as its name suggests, to bind the MAC needs a membrane or other lipid bilayer structure. An ultrastructural examination of the area around Aβ aggregates reveals dystrophic neurites decorated with MAC adhered to their membranes.[10] These neurites display the blebbing and endocytosis of the membrane segment where complement is fixed,

which are typical reactions of living cells under active complement attack.



Cellular mediators involved in AD

Microglial cells

The brain's resident immune cells microglia, are critical to its growth and maintenance. They control neuronal death via CD11b, TREM2, and DAP12, produce neurotrophic factors such as brain-derived neurotrophic factor (BDNF), and stimulate blood vessel development. Microglia in the adult central nervous system (CNS) improve neuronal health by generating CX3CR1, which aids in neural network formation and homeostasis.[13] Microglia are particularly vulnerable to pathogenic triggers such as oxidative stress and misfolded proteins. When triggered, they travel to sites of damage or sickness to recognize pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs). Amyloid beta (Aβ) aggregation causes Alzheimer's disease by interacting with immunological receptors such as CD36, CD14, and toll-like receptors (TLR2, TLR4, TLR6, TLR9). [14,15] This results in the release of pro-inflammatory cytokines and

chemokines, which contribute to neuroinflammation

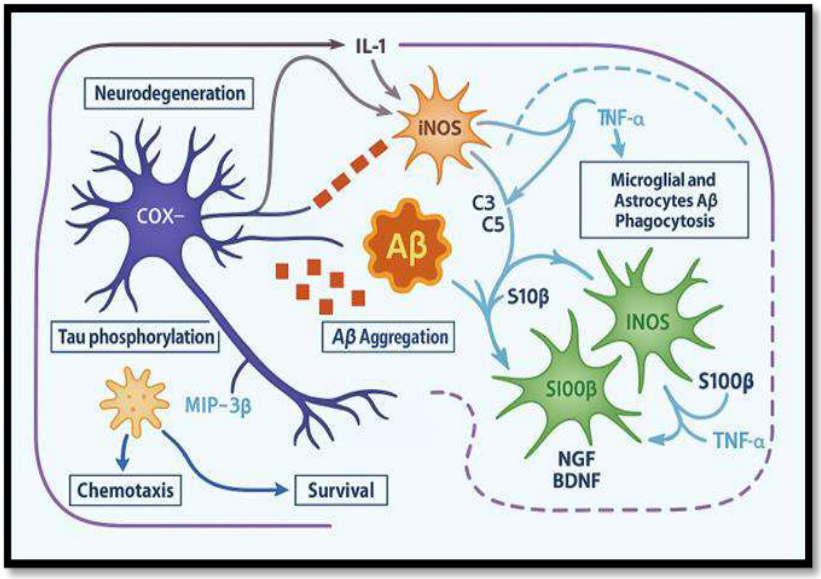


Fig.No.2. Aβ clearance is mediated by the acute synthesis of complement system molecules (C1q, C3, and C5), pro-inflammatory cytokines (IL-1, IL-6, TNF-α), and chemokines. Chronic exposure to these chemicals may result in altered APP processing, Aβ deposition, Tau phosphorylation, and neurodegeneration. In addition, glial cells produce NO, which enhances oxidative stress. The inflammatory environment promotes the development of COX-2 in neurons, which causes apoptosis.

Removing the immune receptor gene CD36 has been demonstrated to decrease the generation of pro-inflammatory cytokines triggered by Aβ and to stop intracellular Aβ accumulation. Microglia clear Aβ by phagocytosis, but inadequate clearance leads to accumulation and worsens Alzheimer's pathology.[16] This indicates their dual role: initially protective, but ultimately contributing to chronic inflammation and neurodegeneration. Their tendency to change functions highlights their complexity in neurodegenerative diseases like Alzheimer's.

Astrocytes

Astrocytes, the most common glial cell type in the CNS, play important functions in neuroprotection, structure, and brain function. They contribute to neurotransmitter metabolism, synaptic remodeling, stress control, and neuronal signaling. In early Alzheimer's disease (AD), activated astrocytes, such as microglia, are found around amyloid beta (Aβ) plaques and play a role in phagocytosis and Aβ elimination. This indicates a role in Aβ removal in AD-affected brain tissue. When astrocytes encounter fibrillar Aβ aggregates, they activate and release inflammatory mediators such as brain cytokines and nitric oxide, which can be detrimental. This contributes to the central nervous system's inflammatory reaction.[17] Experiments show that injecting Aβ oligomers in the left retrosplenial cortex directly activates astrocytes via the nuclear factor kappa B (NFκB) pathway. Activation triggers the production of inflammatory mediators such as TNFα, IL1β, S100, and COX2. Astrocytes through NFκB signaling govern cytokine and chemokine production, which leads to inflammation and neurodegeneration. [16,18] Astrocytes perform a dual role in Alzheimer's disease, initially helping to remove Aβ and later contributing to inflammation and neuronal damage.

2. Cytokine and chemokine pathways

Cytokines and chemokines serve similar signaling processes in microglia and astrocytes as they do in the

periphery. However, mechanisms specific to the central nervous system have also been proposed. Mediators like tumor necrosis factor (TNF)-α, interleukin (IL)-6, IFN-γ, inducible protein-10, monocyte chemoattractant protein (MCP)-1, and C-X-C motif ligand (CXCL) 8, etc. which can increase in the prodromal stage of AD. [19]. Understanding the distinct roles of cytokines in Alzheimer's disease is key to differentiating protective from harmful immune responses, enabling the development of targeted therapies like TNF inhibitors and IL-1 blockers. It allows for safer modulation of neuroinflammation without disrupting beneficial immune functions and helps clarify cytokine-specific effects on amyloid-beta and Tau pathology.[22] For clarity and ease of reference, the mechanisms and roles of the major inflammatory mediators have been outlined in the following table.

Pro-Inflammatory Chemokines in Cognitive Impairment

1. CCL2

The pro-inflammatory chemokine CCL2 also referred to as monocyte chemotactic protein-1 (MCP-1), interacts with CCR2 to control immunological responses. It is produced by CNS cells such as oligodendrocytes, astrocytes, and microglia, and it is essential for attracting monocytes to areas of inflammation. CCL2 plays a dual role in AD, contributing to both neurodegeneration and neuroprotection.[23]. AD pathology is characterized by amyloid plaques and neurofibrillary tangles (NFTs). Amyloid precursor protein (APP) cleavage leads to Aβ accumulation, triggering CCL2 release. This activates microglia and astrocytes, amplifying neuroinflammation while the CCL2-CCR2 pathway facilitates Aβ clearance by promoting microglial phagocytosis, excessive CCL2 overexpression paradoxically increases Aβ oligomer formation, which is neurotoxic. Aβ oligomers impair synaptic plasticity, induce oxidative stress, and interfere with intracellular signaling. Their binding to AMPAR reduces long-term potentiation (LTP), impairing cognitive function. They also activate NMDAR, increasing intracellular Ca2+ levels, and leading to oxidative stress, dendritic spine loss, and neuronal death.[24] CCL2 overexpression also elevates IL-6, which enhances APP synthesis, further accelerating Aβ formation. Additionally, CCL2 dysregulates glutamate (Glu) metabolism by upregulating glutaminase (GLS) while suppressing glutamate transporters (GLAST, GLT-1). This leads to excessive synaptic Glu levels, over-activating AMPAR and NMDAR. Elevated intracellular Ca2+ levels cause mitochondrial calcium overload, triggering oxidative stress, ROS production, and mitochondrial dysfunction, ultimately leading to neuronal death.[25] Thus, while CCL2 has neuroprotective roles in clearing Aβ, its excessive expression exacerbates neuroinflammation, synaptic dysfunction, and oxidative stress, contributing to AD progression.

2. CCL3

CCL3 belongs to the CC subfamily of pro-inflammatory chemokines known as macrophage inflammatory proteins 1-alpha. It is produced by monocytes/macrophages, lymphocytes, and neutrophils, as well as immune cells like basophils, mast cells, fibroblasts, and dendritic cells, according to multiple studies. CCL3 binds to multiple cell surface receptors (CCR1, CCR3, CCR5, and CCR4), leading to various biological effects. CCL3 binds to CCR1, CCR4, and CCR5 receptors which promote the secretion of pro-inflammatory cytokines. It also interacts with CCR1 and CCR5 to recruit immune cells to sites of inflammation, promoting an inflammatory response.[26]

3. CCL4

CCL4 belongs to the CC subfamily of pro-inflammatory chemokines, specifically macrophage inflammatory protein 1b. On a smaller scale, CCL4 has a molecular weight of 7.8 kDa, its gene is located on chromosome 17, and 92 amino acid precursors constitute a normal CCL4 protein. On a larger scale, CCL4 exists in the form of an asymmetric homodimer an elongated cylinder. CCL4 is primarily secreted by immune, fibroblast, endothelial, and epithelial cells. The main immune cells are monocytes, B lymphocytes, and T lymphocytes. CCL4 activates acute centrophilic inflammation and releases inflammatory cytokines like IL-1, IL-6, and TNF-a from fibroblasts and macrophages. CCL4 also plays a crucial role in AD. Inflammation plays a significant role in the progression of Alzheimer's disease, and Aβ deposition contributes to neuroinflammation and CCL4 plays a critical role in the inflammatory response. Alzheimer's disease primarily affects elderly individuals. CCL4 expression is regulated by miR-125b, and decreasing miR-125b leads to a significant increase in CCL4.[27] Increased CCL4 reduces astrocytes' ability to remove Aβ, leading to deposition, neuroinflammation, and AD.

4. CCL 5

CCL5, also known as RANTES, plays a critical role in neurodegenerative diseases like Alzheimer's disease (AD). Elevated RANTES levels are found in the microcirculatory system of AD-affected brains, with astrocytes and endothelial cells upregulating its expression in response to oxidative stress and cytokine activation. Increased RANTES levels in brain injury models lead to immune cell recruitment and neuronal death. Produced primarily by T cells and macrophages, CCL5 regulates the migration of memory B cells, monocytes, and eosinophils to the CNS, contributing to neuroinflammation. Its receptors, CCR1 and CCR5, play significant roles in neurological diseases. CCL5 binding to CCR1 damages the blood-brain barrier (BBB), while the CCL5/CCR5 axis promotes AD progression. In early AD, Aβ deposition mobilizes microglia and astrocytes for clearance, but CCL5 disrupts this process by increasing NO secretion, reducing IL-10 and IGF-1 production, and impairing Aβ clearance. It also inhibits the MAPK/CREB signaling pathway, exacerbating synaptic defects.[29] Knockdown of CCL5 in rats showed partial protection against synaptic degeneration. Overall, CCL5 plays a dual role in neuroinflammation, contributing to AD pathology by enhancing immune cell recruitment, BBB disruption, and impairing Aβ clearance, making it a potential therapeutic target.

5. CCL11

CCL11, or eotaxin-1, is an eosinophil chemokine involved in innate immunity, produced in response to cytokines like IL-13, IL-10, and IL-4. Various cells, including eosinophils, T and B cells, fibroblasts, epithelial and endothelial cells, macrophages, chondrocytes, and microglia, produce CCL11. It crosses the blood-brain barrier and primarily binds to CCR3, with a higher affinity than CCR2 and CCR5. CCL11 is a key marker of aging and cognitive decline, earning names like accelerated brain aging chemokine (ABAC) and endogenous cognitive deterioration chemokine (ECDC). Elevated CCL11 levels are linked to neuroinflammatory diseases like multiple sclerosis (MS), psychiatric disorders such as schizophrenia, and neurodegenerative diseases like Parkinson’s (PD) and Alzheimer’s (AD). It contributes to cognitive dysfunction by inhibiting neurogenesis, reducing synaptic density, and causing neuronal toxicity. Neuroglial activation releases CCL11, which binds to microglia-expressed CCR3, upregulating NOX-1 and

promoting reactive oxygen species (ROS) production. This triggers inflammation and neuronal cell death. Activated astrocytes and blood-brain barrier crossover sources also contribute to CCL11 release, worsening neuroinflammation. Ultimately, CCL11 plays a significant role in brain aging and cognitive decline, making it a potential therapeutic target for neurodegenerative and inflammatory conditions.[30]

6. CCL20

CCL20, also known as macrophage inflammatory protein-3a (MIP-3a), liver activation-regulated chemokine (LARC), and Exodus-1, is a small protein (~8 kDa) primarily released by neurons, astrocytes, and microglial cells in the central nervous system (CNS). It is encoded by the **SCYA20** gene on chromosome 2 and specifically binds to its unique receptor, **CCR6**, which is highly expressed on **Th17 cells**. Functionally, CCL20 is chemotactic for dendritic cells (DCs), T cells, and B cells and plays a key role in tissue inflammation, infectious diseases, and cancer. In the CNS, CCL20 is implicated in brain nerve damage and neuroinflammation. Studies in rodents have demonstrated its involvement in neurodegenerative changes following trauma, spinal cord injury, and cerebral ischemia**.** Neutralizing CCL20 or knocking down CCR6 leads to reduced microglial activation and neuroinflammation, highlighting its role in neurodegeneration. CCL20 is also involved in Treg cell recruitment, which inhibits astrocyte proliferation and neurotoxicity. This recruitment is regulated by FOXO1/CEBPB/NF-kappaB signaling.[32] Given its strong connection to immune-mediated inflammation, CCL20 plays a crucial role in CNS immune responses. However, its impact on cognitive disorders remains unclear**,** indicating a potential area for further research.

7. CXCL8

CXCL8, also known as interleukin-8 (IL-8), is a pro-inflammatory chemokine encoded on chromosome 4q13-q21. It is produced by various cells, including endothelial cells, macrophages, and epithelial cells, especially in response to inflammatory cytokines like TNF-α and IL-1β. CXCL8 primarily functions through CXCR1 and CXCR2 receptors, activating signaling pathways such as PKB, MAPK, and PKC. Its main roles include recruiting and activating neutrophils, promoting monocyte and macrophage proliferation, stimulating angiogenesis, and enhancing oxidative metabolism, leading to oxidative stress.[33] In Alzheimer's disease (AD), CXCL8 levels are elevated in blood and cerebrospinal fluid (CSF), potentially facilitating microglial recruitment to amyloid-beta (Aβ)-affected brain regions. This amplifies neuroinflammation and contributes to neuronal damage through dystrophic synapses and pro-apoptotic protein expression. Additionally, CXCL8 influences matrix metalloproteinases (MMP-2, MMP-9), which mediate neuronal death, correlating with AD severity and suggesting its role as a biomarker for disease progression. However, CXCL8 may also exert neuroprotective effects.[30] It inhibits Aβ-induced neuronal apoptosis and promotes brain-derived neurotrophic factor (BDNF) production, supporting neuron survival. While its overall impact on AD remains complex, CXCL8 appears to contribute to both neuroinflammation and neuroprotection, making it a potential therapeutic target for disease modulation.

CXCL12

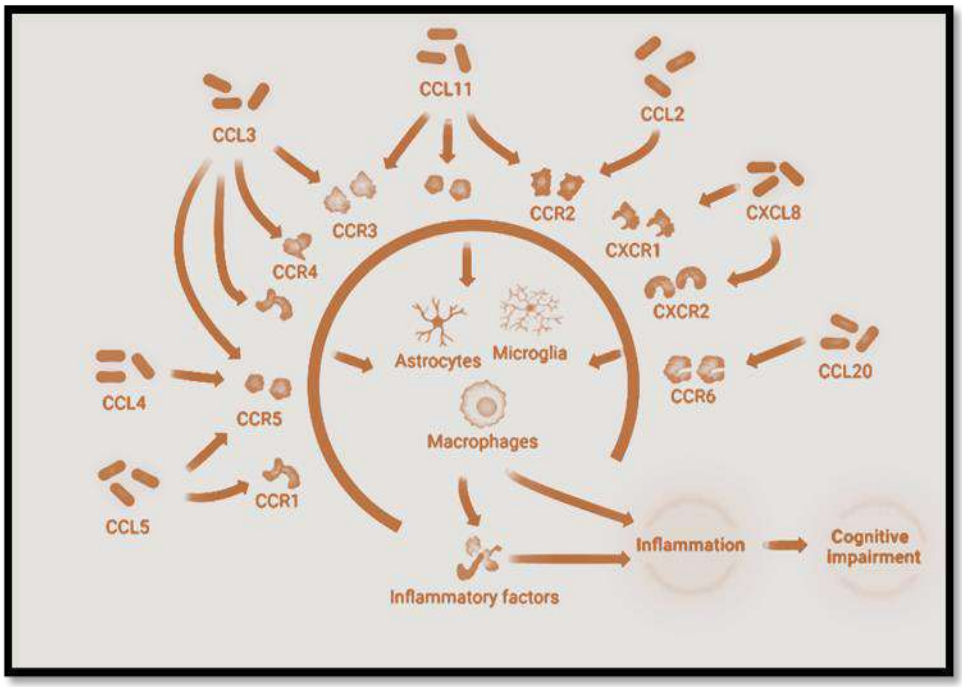


Fig.No.3 Pro-inflammatory chemokines (CCL2, CCL3, CCL4, CCL5, CCL11, CCL20, and CXCL8) stimulate immune cells to process pathogens by attaching to receptors, resulting in an inflammatory response. The inflammation that results damages neurons and leads to cognitive impairment.

An in vitro study provided further evidence of CXCL12's neuroprotective role. Neurons pre-treated with CXCL12 were significantly shielded from antibody-induced dendritic regression and apoptosis. This protective effect was mediated by the activation of protein kinase B (PKB/Akt) and extracellular signal-regulated kinases 1/2 (ERK1/2), both of which are involved in cell survival and neuroprotection. Additionally, CXCL12 maintained the expression of a disintegrin and metalloproteinase 17 (ADAM17), an enzyme associated with neuronal health and synaptic stability. These findings suggest that CXCL12 may play a crucial role in protecting neurons from degeneration and could have therapeutic potential in AD by reducing inflammation, supporting neuronal survival, and preserving cognitive function.

8. CX3CL1

C-X3-C motif ligand 1 (CX3CL1), also known as fractalkine, is a chemokine primarily produced and constitutively expressed by neurons. It plays a crucial role in neuroprotection by suppressing microglial activation through its interaction with the C-X3-C motif receptor 1 (CX3CR1). The CX3CL1/CX3CR1 complex helps regulate microglial activity and prevent excessive neurotoxicity.[33] Studies have shown that plasma-soluble CX3CL1 levels are significantly higher in patients with mild to moderate Alzheimer's disease (AD) compared to those with severe AD. This suggests that CX3CL1 may play a protective role in AD progression and could serve as a potential biomarker for disease severity. Additionally, CX3CL1 has been implicated in other neurodegenerative diseases, such as Parkinson's disease, where inflammation is a key contributing factor. Research by Cho et al. highlights the CX3CL1/CX3CR1 signaling pathway as a crucial mechanism for protecting against AD-related neurodegeneration. [36] This

pathway is linked to the suppression of aberrant microglial activation and the reduction of inflammatory cytokine levels, both of which are critical for mitigating neuroinflammation in AD. Given its neuroprotective properties, CX3CL1 may offer therapeutic potential for treating neurodegenerative diseases by modulating inflammation and preserving neuronal function.

CONCLUSION

Alzheimer's disease is a multifactorial disorder driven by complex cellular and molecular interactions, including amyloid-beta accumulation, tau pathology, neuroinflammation, oxidative stress, and synaptic dysfunction. Among these, neuroinflammatory responses mediated by microglia and astrocytes, along with inflammatory mediators, play a significant role in disease progression. Understanding these pathological mechanisms is essential for identifying potential therapeutic targets. Future research should focus on developing strategies that modulate neuroinflammation, reduce oxidative stress, and restore synaptic integrity to slow or prevent disease progression. Advancing targeted interventions based on these molecular insights holds promise for improving treatment outcomes and enhancing the quality of life for affected individuals.

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