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Review Article

The Role of Neuroinflammation in Alzheimer's Disease (AD)

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Abstract

Neuroinflammation is a critical process in Alzheimer's disease (AD) development in which different types of cells and cytokines are involved. Proinflammatory cytokine production and the disturbance of anti-inflammatory pathways play critical roles in AD. Neuroinflammation is affected by various factors such as metabolism (metabolic diseases such as obesity), genetics, and immune cells, especially resident immune cells in the brain. Moreover, the main pro-inflammatory cytokines and inflammatory pathways have different effects on neuroinflammation, neuronal biogenesis, and neuronal apoptosis in AD. Exploration of the relationship between neuroinflammation, risk factors of neuroinflammation, and pro-inflammatory cytokines in AD helps us to understand AD pathogenesis and select therapeutic targets more efficiently.

Keywords: Alzheimer's Disease (AD); Pro-Inflammatory Cytokine; Neuroinflammation; Metabolism

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Introduction

One of the world's most prevalent diseases and the most common cause of dementia is Alzheimer's disease (AD), which is responsible for 60-70% of dementia cases. It is estimated that the number of patients with AD will exceed 7 million in 2030 (1, 2). AD is characterized by a progressive decline in cognitive functions, usually initiated by decreased memory functions, and gradually leads to a total inability to do essential daily life tasks and, eventually, death (3). Based on recent epidemiological studies, the prevalence of AD would

double every 20 years, at least until 2040, due to the rapid aging of the nations (3). The etiology of this disease is complicated, and several factors, such as environmental and genetic factors, have been assumed to contribute to the multifactorial etiology of this disease. For instance, infections, diet, and metals (such as aluminum) are effective environmental factors (4). Regarding genetics, different genes have been attributed to the initiation and progression of AD, such as three well-studied genes: the *amyloid precursor protein* (*APP*), *presenilin 1* (*PSEN1*), and *presenilin 2* (*PSEN2*) genes (5-7). Studies show that one of the critical mechanisms in developing AD is inflammation, which is defined as the immune system's response to pathogens or organ damage (8). Inflammation occurs in almost all parts of the body, including the central nervous system (CNS), which leads to the activation of astrocytes and microglia, the accumulation of various chemokines and cytokines, and neurodegenerative processes (9). Microglia are the resident macrophages in the CNS, while astrocytes are the most frequent subtype of glial cells, which both are responsible for neuroinflammation by secreting different cytokines and chemokines (10). The most common hallmark of AD is the accumulation of beta-amyloid peptide (Aβ). Indeed, it could be the first trigger in the pathogenesis of this disease. Furthermore, tubulin-associated unit (tau) protein aggregation, the formation of different cellular and intercellular neuritic plaques, neurofibrillary tangles(NFTs), and neuropil threads are other hallmarks of AD (11).

Taken together, all these aggregations stimulate the activation of astrocytes and microglia, leading to the secretion of pro-inflammatory cytokines and chemokines from microglia and pro- and anti-inflammatory cytokines from astrocytes, which potentially cause synaptic damage, neuronal death, and finally AD development (12). Cytokines and chemokines, as important subcategories of immune mediators, are involved in the induction of inflammation; therefore, they play a prominent role in the development of AD through synaptic dysfunction, neuronal death, and inhibition of neurogenesis (13). However, the importance of microglia in brain functions such as neural plasticity, long-term potentiation (LTP), and brain homeostasis by producing pro-inflammatory cytokines at lower concentrations cannot be denied (14, 15). Inflammation is an important factor in various metabolic disorders, such as diabetes, and also in neurodegenerative diseases, such as AD (16). On the other hand, Metabolic disorders such as diabetes mellitus have a significant role in AD development and progression by induction of pathological changes in the body, including vascular changes, inflammation, and blood glucose increase (17, 18). Gut microbiota can also induce neuroinflammation and disturb metabolic homeostasis by either disrupting the blood-brain barrier (BBB) and delivering toxins in the brain or via various pro-inflammatory mediators (19). Considering the high prevalence and the potential heavy burden of AD, understanding the pathophysiology of this disease is of high value. In this review, the effects of inflammation and key factors involved in inducing neuroinflammation and neurodegeneration in the pathogenesis of AD and the possible target therapies are discussed.

Common Hallmarks of AD

Aβ

Beta-amyloid peptide (Aβ) is one of the most important hallmarks of AD, which plays a critical role in the pathogenesis and neuronal and synaptic dysfunction during the progression of AD (20). The *amyloid precursor protein* (*APP*) gene is located on chromosome 21, and its product, APP, is a precursor of the Aβ protein (21). Recent studies showed that *APP* has several essential roles for the brain's normal function, such as metal binding and protease inhibition, while it is also a component of the extracellular matrix (21, 22). APP can be cleaved by specific enzymes (secretases) and result in different substrates. Normally, it is cleaved by α-secretase, resulting in the formation of soluble APP (sAPPα) and transmembrane C-terminal fragment (α-CTF). Then, γ-secretase cleaves α-CTF to generate a 23-25 amino acid peptide called P3 and APP intracellular domain (AICD). This pathway is non-amyloidogenic and cannot lead to AD development. However, improper cleavage of APP resulted from β and γ secretase activity. In the first step of an amyloidogenic pathway, β-secretase cleaves APP to produce β-CTF and soluble APP-β. Then, γ-secretase

cleaves β-CTF and forms Aβ, composed of 38 to 43 amino acids with different solubility, stability, biological, and toxic properties (21, 23, 24). Accumulation of Aβ (Aβ1–42) leads to mast cell activation, which increases blood-brain barrier (BBB) permeability, and the release of inflammatory mediators such as cytokines, chemokines, and other neuroactive mediators, which cause glial cells and neuron activation (25-27). However, Aβ-activated astrocytes and microglia increase uptake of Aβ via microglia and protect neurons from Aβ toxicity by the secretion of transforming growth factor-β (TGF-β), which is a neurotrophic and anti-inflammatory cytokine (28)(Both pathways of APP proteolytic processing are presented in **Figure 1**). With regard to the pivotal role of Aβ in AD development, numerous therapies have been developed based on the inhibition of Aβ formation, aggregation, or degradation (29).

Tau Protein

The other major hallmark of AD is tau protein aggregations that form neuritic plaques (NP), neurofibrillary tangles, and neuropil threads. Tau is a soluble, microtubule-associated protein (MAPT), playing an essential role in supporting the neuronal cell's microarchitecture complex (30). Moreover, the tau protein is involved in synaptic modulation and neuronal growth (31). Several mechanisms lead to tau protein disturbances, such as the phosphorylation of tau by kinases and the formation of p-tau, which is insoluble in water. The aberrant hyperphosphorylation of tau leads to tau's dissociation from microtubules and the promotion of tau aggregation. Meanwhile, the aggregation of p-tau leads to neurofibrillary tangles and thread formation (32). In addition, inflammation is an important mechanism as well, since the increase in interleukin 1β (IL-1β), a pro-inflammatory cytokine, leads to the hyperphosphorylation of tau by kinases (33). Diabetes mellitus and genetic factors are also involved in tau protein alterations, with complex underlying mechanisms (34-36). The utilization of tau protein as a therapeutic target remains controversial, and several clinical trials are in process (36-38).

Role of Inflammation in AD

Since the 1980s, when Griffin *et al.* reported the increase in Interleukin-1 (IL-1) in AD patients, several studies have focused on the central role of inflammation in the development of AD (39, 40). Inflammation is a complex process that consists of several different pathways. Cytokines are important signaling molecules needed for proper homeostasis, which have inflammatory and/or anti-inflammatory functions depending on the target receptor, cell, and the phase of an immune response (41, 42). Neuroinflammation refers to the inflammation of the neurons, developed by various factors interfering with CNS homeostasis, consisting of external factors including infection, trauma, ischemia, and aging (43), while internal factors are composed of cytokines, chemokines, reactive oxygen species (ROS), microglia, epithelial cells (44). Epithelial cells in CNS can produce various substances such as IL-1b and TNF-α, as pro-inflammatory cytokines (45). Microglia, as another part of neuroinflammation, induce apoptosis in neurons and phagocytosis through pro-inflammatory cytokine secretion (46-49). Moreover, the role of T-cells and B-cells as parts of adaptive immunity in neuroinflammation is inevitable. T-cells can target neurons and induce apoptosis in them. Also, T-cells can interact with activated microglia, resulting in the inflammation of the CNS and demyelination (50).

T helper (Th)17 cells, as one of the subcategories of T-cells with inflammatory features, produce a wide spectrum of pro-inflammatory cytokines such as IL-6, Interleukin-17A (IL-17A), Interleukin-17F (IL-17F), interferon-γ (IFN-γ), and TNF-α, which exacerbate neuroinflammation (51, 52). It should be noted that inflammation is a critical response to trauma, infection, and the normal function of the CNS, leading to the induction of neurogenesis in different parts of the brain, such as the hippocampus, via activation of T lymphocytes (53). Additionally, studies showed that interleukin-4 (IL-4)-producing T cells are needed for cognitive performance (54). Neuroinflammation is required for the regulation of neurons and neurogenesis after an insult. Furthermore, the facilitation of axonal regeneration through M2-macrophages and Th1, but not Th2 or Th17 cells, provision of neurotrophic factors, and its critical role in remyelination of the neurons make this phenomenon an important part of the normal recovery of the CNS after an injury (55-59). However, inflammation plays a dou-

ble-edged sword in the prolonged form known as chronic neuroinflammation, which exacerbates neuronal damage and neurodegeneration. Neurodegeneration is a critical and central process for cognitive dysfunctions and the development of neurodegenerative diseases like AD (60, 61).

Cellular and Molecular Pathways Involved in Alzheimer's Neuroinflammation

Microglia

Microglia are the resident macrophages of the CNS, which contribute to the homeostasis maintenance of the CNS. Microglia are classified into M1 (pro-inflammatory state) and M2 (repairing and protective state). However, it should be noted that several different subtypes of microglia have been identified in the brain, including KSPG-microglia, satellite microglia, Hox8b-microglia, and Disease-associated microglia (DAM)(62). Neurodegeneration-associated molecular patterns (NAMPs) are danger molecules present on myelin debris, apoptotic bodies of dying neural cells, and the accumulation of abnormal proteins such as Aβ, and are the triggers of the transition of resident microglia to DAM via TREM2, a main receptor of DAM (63). In the early stages of AD, activation of DAM could reduce the velocity of disease progression, but inappropriate activation of DAM leads to neuroinflammation and deterioration of AD (64). In a normal brain, microglia are in the M2 state. Studies showed that in the context of AD, microglia cells showed phenotypic alteration from M2 to M1 state (65, 66). M1 microglia have a prominent role in inflammation by secretion of various cytokines, especially pro-inflammatory cytokines such as IL-1B, IL-6, IL-18, IL-12, IL23, TNF-α, and neurotoxic substances, which are responsible for blocking neuronal differentiation, attenuating microglial phagocytosis, extracellular matrix damage through the activation of nuclear factor-kB and accumulation of Aβ and as well as calling other inflammatory cells to the inflammation site through cytokines (67-71). When the amyloid accumulation becomes overt, their phagocytic function is disturbed. Additionally, studies showed that Aβ can activate the molecular pathways of pro-inflammatory cytokine secretion in microglia, such as NF-κB and NLR family pyrin domain containing 3 (NLRP3) inflammasome secretion, mediated by cell surface receptors such as CD36, CD47, and a-6/b-1 integrin, leading to neuroinflammation and neurodegeneration (72-76). NF-κB is a protein family that controls DNA transcription and expression. It is important in inflammation as it increases the pro-inflammatory cytokine expression pathway. Additionally, NF-κB stimulates the β-secretase (BACE1) cleavage of APP and Aβ production by enhancing BACE1 expression (77, 78). NLRP3 is a part of the innate immune system and is found in macrophages and inflammasomes. These proteins can trigger immune responses (79, 80). Moreover, this inflammasome is an intracellular protein complex that regulates the maturation of IL-1β and IL-18 and also increases the cleavage and activity of caspase-1, which are significantly increased in AD brains and associated with the onset and progression of the disease (81, 82).

Astrocyte

Astrocytes are a group of glial cells that reside in the CNS. They have essential roles in the CNS, including repairing the CNS, protecting neurons from harmful agents and neurotoxic substances, modulating synapses (83). These cells are also important in neurodegenerative diseases like Parkinson's disease (PD) and AD (84, 85). Secretion of cytokines such as IL-1a and TNF-α from microglia, resulting in astrocyte activation and the formation of reactive astrocytes (86). There are two forms of reactive astrocytes: A1 and A2. Neuroinflammation gives rise to the A1 form. A proposed mechanism for this phenomenon is through Aβ and NF-κB. Aβ can activate the NF-κB pathway in astrocytes and induce A1. A1 is a neurotoxic astrocyte and upregulates the expression of the complement cascade gene, which leads to the release of the complement protein C3. This protein binds to the C3aR in microglia and neurons. Activation of the complement-3a receptor (C3aR) in microglia increases phagocytosis, and in neurons, it disrupts dendritic morphology and network function, both of which contribute to AD pathogenesis (28, 87, 88). A2 is a protective form of reactive astrocytes and is induced by ischemia. This form upregulates the expression of neurotrophic genes and promotes survival, growth, and repair of synapses (28). Astrocytes also contribute to glucose hypometabolism through the glu-

tamatergic excitotoxicity mechanism. Increasing glutamate production and decreasing the glutamate receptors of astrocytes, including GLT-1 and GLAST, causes an increase in the amounts of glutamate in the CNS. GLT-1 and GLAST are responsible for glutamate reuptake from CSF, and some studies have suggested that Aβ can suppress these receptors. Glucose hypometabolism increases stress oxidative production, which can cause neuroinflammation either directly or by producing pro-inflammatory cytokines (89-91).

Cytokines and Signaling Pathways

IL-1

IL-1 (also called "endogenous pyrogen") was the first cytokine that proved to affect the CNS(92). Both isoforms of IL-1 (IL-1α and IL-1β) are pro-inflammatory cytokines, have similar effects, and are produced in a variety of cells, like microglia and lymphocytes, as precursor proteins called pro-IL-1α and pro-IL-1β. Pro-IL-1α is an active form of IL-1α that can be cleaved to form IL-1α, a smaller active molecule, by a specific enzyme called CAPLAIN. IL-1α acts intracellularly, but it can also be released after neurodegeneration. Pro-IL-1β is a precursor of IL-1β, but unlike pro-IL-1α, it is an inactive form of IL-1β and should be broken down by the CASPASE-1 enzyme to form an active form, IL-1β (93, 94). IL-1α and IL-1β apply their intracellular signaling via membrane-bound type I IL-1 receptor (IL-1R1) (95). This complex is reinforced by IL-1-receptor accessory protein (IL-1RAcP), as this receptor is needed for the normal function of IL-1R1. Korher *et al.* showed that the response to IL-1 via IL-1RI internalization or IL-2 production in the absence of IL-1RAcP could not occur (96). Another receptor of IL-1 is IL-1R2, considered a decoy receptor, and no intracellular signaling pathway was identified for this receptor; however, recent studies suggested that it is mainly expressed on microglia and can diminish the cytokine-induced microglial activation (95, 97, 98). IL-1 receptors can also be shed from the neurons (99). An antagonist ligand of IL-1R is IL-1RA. Its secreted isoform (also called sIL-1RA) is produced by the IL-1-producing cells (100, 101). IL-1RA and IL-1R have polymorphic genes and are located on chromosome 2 (102, 103). These polymorphisms could explain the pathogenesis of some early-onset forms of AD (102, 104, 105). IL-1 is needed for normal brain functions. Mason *et al.* showed that the deficiency of IL-1β in mice leads to a delay in CNS repair and myelination. IL-1 is also required for normal sleep behavior and non-rapid eye movement (106). Another role of IL-1 is its stimulating effect on magnocellular neurons in the paraventricular nucleus and supraoptic nucleus of the Hypothalamus needed for vasopressin and oxytocin secretion (107). It also stimulates the corticotropin-releasing factor (CRF), which is secreted by neurons in the hypothalamus. In fact, this feature of IL-1 can affect Adrenocorticotropic hormone (ACTH) and cortisol secretion (108, 109).

IL-1 is involved in AD through several mechanisms: 1) It upregulates *APP* production. D. Goldgaber *et al.* showed that *APP* upregulation could occur through protein kinase C (PKC). The upstream binding site for *APP* promoter production is activator protein-1 (AP-1), which can be utilized by PKC to increase *APP* transcription(110). 2) The sustained release of IL-1 stimulates tau hyperphosphorylation in the neurons. Y.Li *et al.* showed the IL-1 effects on tau hyperphosphorylation, at least partly, via the p38-p38-Mitogen-activated protein kinase(MAPK) pathway, leading to neuronal structural changes, synaptic loss, and exacerbation of AD (33). 3) The overexpression and constant release of IL-1 and its engagement with IL-1R1 causes neuroinflammation mediated by nuclear factor kappa B (NF-κb). This pathway leads to an increase in the transcription of pro-inflammatory cytokines, including IL-6 and IL-1. 4) IL-1 can directly attach to the microglia cells, leading to the secretion of several neurotoxic substances, including pro-inflammatory cytokines (like TNF-α), chemokines (such as CC-chemokine ligand2 (CCL2)), eicosanoids (like PGE2), and reactive oxygen species (ROS)(111, 112). Shang *et al.* showed that IL-1β drives the cellular senescence of rat astrocytes when induced by oxidative stress and oligomerized Aβ peptide (113). 5) IL-1 changes the pattern of gene expression of astrocytes, resulting in astrocyte proliferation (known as astrogliosis), IL-6 secretion, an increase in the release of metalloproteinases(MMPs)(114). 6) IL-1 causes expression of E-selectin, intercellular adhesion mole-

cule 1 (ICAM-1), vascular cell adhesion protein 1 (VCAM-1), and CXC-chemokine family, such as chemokine ligand 1 (CXCL1) which increase leukocyte adhesion and invasion to the brain parenchyma (114-116). 7) IL-1 has positive effects on neuron function by inhibiting these cells through γ-aminobutyric acid (GABA), inhibiting glutamate release, and calcium entry. However, if this inhibition occurs in the inhibitory pathway, it could reinforce excitatory neurons and cause neuronal death (117). Additionally, IL-1 can cause neuronal death by increasing calcium entry through N-methyl-D-aspartate (NMDA) receptors. Calcium overload in the neurons causes mitochondrial dysfunction, which triggers the apoptotic pathways. Calcium accumulation in the mitochondria causes the opening of the permeability transition pore (PTP). Opening of PTP allows pro-apoptotic factors such as cytochrome C (CytC) and apoptosis-inducing factor (AIF) to be released in the cytoplasm and activate caspases (118). Besides, high calcium influx to the endoplasmic reticulum (ER) causes the C/EBP Homologous Protein (CHOP) overexpression, which induces endoplasmic reticulum stress-mediated apoptosis (119-123)**(Figure 2a)**.

IL-6

Another critical cytokine in AD development is IL-6. Its family has several cytokines, including IL-6, IL-11, LIF (leukemia inhibitory factor), OSM (oncostatin M), CNTF (ciliary neurotrophic factor), CT-1 (corticotrophin-1), and CLC (cardiotrophin-like cytokine)(124-126). IL-6 is a glycosylated protein composed of 4 α helixes, and its molecular weight is 21–28 kDa (127, 128). Its receptors are IL-6R and gp130. Gp130 is expressed in almost every cell in the body, and it is a crucial part of IL-6 signaling, but IL-6R is expressed in specific cells such as leukocytes, hepatocytes, T cells, etc. This selective expression helps IL-6 to act selectively in the body (129-131). IL-6 induces the proliferation and differentiation of B and T cells, increases the liver synthesis of acute-phase protein, regulates APP, increases serum amyloid A (SAA), a major acute-phase protein, induces megakaryocyte maturation and platelet release, increases collagen synthesis and collagen via an effect on fibroblast (132-137). These effects are applied through gp130 and its intracellular proteins: Janus kinase 1 (JAK1) and STAT3, two principal intracellular signaling pathways involved in IL-6 signaling (138). The activation of JAK via IL-6 activates the PI3/Akt pathway, which leads to NF-kb activation. NF-kb binds to the *APP* promoter and increases Aβ production (139). Additionally, Aβ can stimulate the release of IL-6 and exacerbate neuroinflammation (140), which activates microglia and astrocytes to produce pro-inflammatory cytokines like TNF-α (141). IL-6 can activate STAT proteins, especially signal transducers and activators of transcription 3 (STAT3), which is important for astrogliosis and astrocyte reactivity. These mechanisms are important in neuroinflammation and neurodegeneration in AD (142, 143). On the other hand, IL-6 is required for normal brain function. Gadient *et al.* showed that IL-6 and its receptor (IL-6R) increase during postnatal development, and they act as neurotrophic factors (144). IL-6 is involved in cognitive function, as D. Braida *et al.* showed that in IL-6-deficient mice, the cognitive function becomes disrupted (145). Although S. Toulmond *et al.* showed the preventive effect on the neurotoxicity of IL-6 after NMDA injection to the striatum (146). IL-6 also has a role in AD development, and its levels increase in the blood of AD patients. However, some studies have reported a decrease or normal level of IL-6 (147). M. Huberman *et al.* showed the correlation between IL-6 and AD severity. They observed a significant increase in IL-6 in both mild and moderately severe AD patients compared to the control group, but it did not significantly differ between mild and moderate patients (148).

As mentioned above, IL-6 is a strong stimulator for acute-phase protein release from the liver, like SAA, and it can be responsible for the high levels of acute-phase protein and hyperinflammation state in AD patients (149). SAA can interact with amyloid-beta and accumulate in the plaques, and facilitate memory decline (150, 151). IL-6 can increase tau hyperphosphorylation via dysregulation of the cyclin-dependent kinase 5 (cdk5)/p35 pathway and inactivation of phosphatases like protein phosphatase 1 (PP1)(152, 153). An increase in IL-6 induces Th-17 differentiation from naïve T cells. Th-17 cells exacerbate AD via two mechanisms: first, these cells activate astrocytes by IL-17 secretion and cause neurodegen-

eration. Second, it can cause neurodemyelination and neurodegeneration by secreting inflammatory cytokines, especially IL-23 (154-156). Despite the clear role of IL-6 in AD development, some studies reported its beneficial effect on the early phase of AD by facilitating plaque clearance (157) **(Figure 2b)**.

TNF-α

TNF-α is a TNF superfamily member and a powerful cytokine with cytotoxic properties that causes tumor necrosis. Its gene has been located on chromosome 6, and studies have shown that some polymorphisms of this gene can increase the AD risk (158, 159). All of the TNF members have a TNF homology domain (THD) and a trimer structure. TNF-α has two forms: soluble (sTNF-α) and membrane-bound (tmTNF-α) with 17 kDa and 26 kDa molecular weight, respectively (160, 161). The cleavage of tmTNF-α leads to sTNF-α formation. Both of them are active biologically and have different roles. sTNF-α has a high affinity for binding to TNFR1, a receptor that is important in apoptosis. Thus, inhibition of this form of TNF-α in the brain can inhibit neuronal apoptosis and reverse AD progression (162). tmTNF-α has a high affinity for TNFR2; this receptor is important for regulating genes involved in cell survival, myelination, and immunity against pathogens (163). TNF-α receptors (TNFR) are from the TNF receptor superfamily (TNFRSF) with a cysteine-rich domain (CRD), and the THD binds to this domain. Three types of TNFR have been discovered in recent years: 1) the receptors with the death domain (known as TNFR1), involved in TNF intracellular signaling and induction of apoptosis in the cell by using Fas-associated protein with death domain (FADD) (164). TNFR1 has mediated the major impact of TNF-α due to its expression at low levels on all nucleated cells of the body (165). 2) The receptors without the death domain (known as TNFR2) are expressed primarily on cells of hematopoietic origin, but neurons can also express them (166). 3- The decoy receptor binds to TNF-α with high affinity and specificity but cannot induce intracellular signaling (167).

TNF-α has numerous biological effects, including an increase in resistance to microbial infection (168), and cancer (169). Moreover, Shoham *et al.* showed the activity of TNF-α in normal sleep, as the reduced level of TNF-α correlates with a reduction in continuous sleep; the same effect has been seen in the knockout of the *TNFR1* gene in animal models by an increase in Aβ production. TNF-α and IFN-γ can increase the expression of β-secretase, which can lead to Aβ production and decrease its reuptake (170). Furthermore, TNF-α and IFN-γ synergistically can decrease soluble APP, which is a protective form of this protein compared to the insoluble form of APP, causing Aβ production (171). L. Osborn *et al.* showed the potency of TNF-α in NF-kB activation. This scenario can also occur in microglia and increase the release of TNF-α and other cytokines, and exacerbate the inflammation (172). TNF-α can also decrease Aβ clearance via an effect on microglia and cause synaptic dysfunction (173). N.Hovelmeyer *et al.* showed the involvement of TNF-α in the induction of apoptosis in oligodendrocytes. Numerous studies have shown the vulnerability of oligodendrocytes and the reduction of myelin in AD. This role of TNF-α can explain this vulnerability, even as a part of the mechanisms involved in the myelin breakdown in AD (174). The upregulation of *VCAM-1* on endothelium and astrocytes causes the crossing of lymphocytes and other immune cells through the BBB, and further inflammation (175). TNF-α can increase the expression of inducible nitric oxide (iNOS). The result of iNOS activity is NO, which is a neurotoxic substance and increases neuronal loss (176). TNF-α can increase the production of S100B as a zinc binder. Zinc is an important ion in normal synaptic function, and TNF-α can decrease it and induce synaptic dysfunction (177). TNF-α can decrease neurogenesis via NF-κB activation and caspase 3 and 9, two potent apoptotic factors, and related pathways (178, 179). One of the important aspects of AD is mitochondrial dysfunction. Excessive expression of TNF-α can disturb the mitochondrial function of the neurons directly. This disturbance can affect neuronal plasticity and synapses and can exacerbate AD(180)**(Figure 2c)**.

NF-κB

Nuclear factor-κB (NF-κB) is a regulator of various genes involved in the production of cytokines, chemokines, NO, and COX-2, which

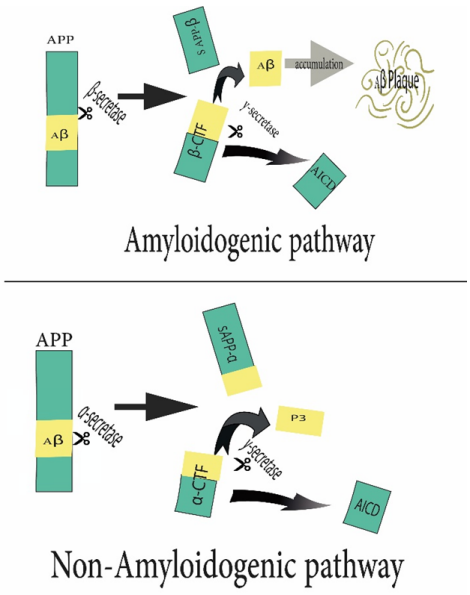

Figure 1. Summary of APP metabolism in two different ways: amyloidogenic and non-amyloidogenic pathway: 1-in the amyloidogenic pathway, β-secretase dissociates APP from its Aβ part from the long side of the APP. The product of this action is soluble APPβ and β-CTF, which consists of Aβ and AICD parts. Finally, γ-secretase cut the other end of Aβ connected to the AICD and separate them. Accumulation of Aβ causes Amyloid plaque and AD. 2- in the non-amyloidogenic pathway, first, α secretase dissociates APP to soluble APPα and α-CTF. This dissociation does not occur in the junction of sAPP and Aβ, but it occurs among Aβ. Then γ-secretase separates the small part of Aβ (also called p3), a part of α-CTF, from AICD. This pathway cannot lead to the formation or accumulation of amyloid plaques.

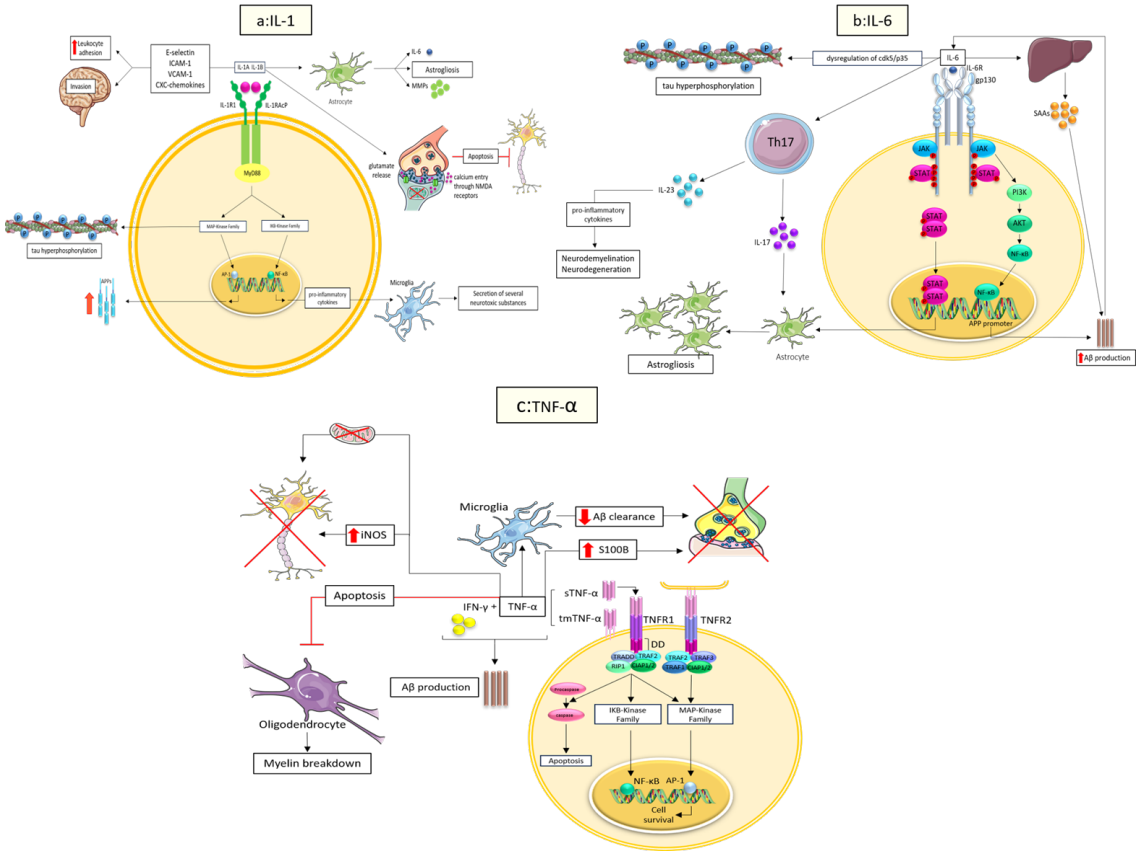

Figure 2. Summary of inflammatory cytokines in Alzheimer's Disease

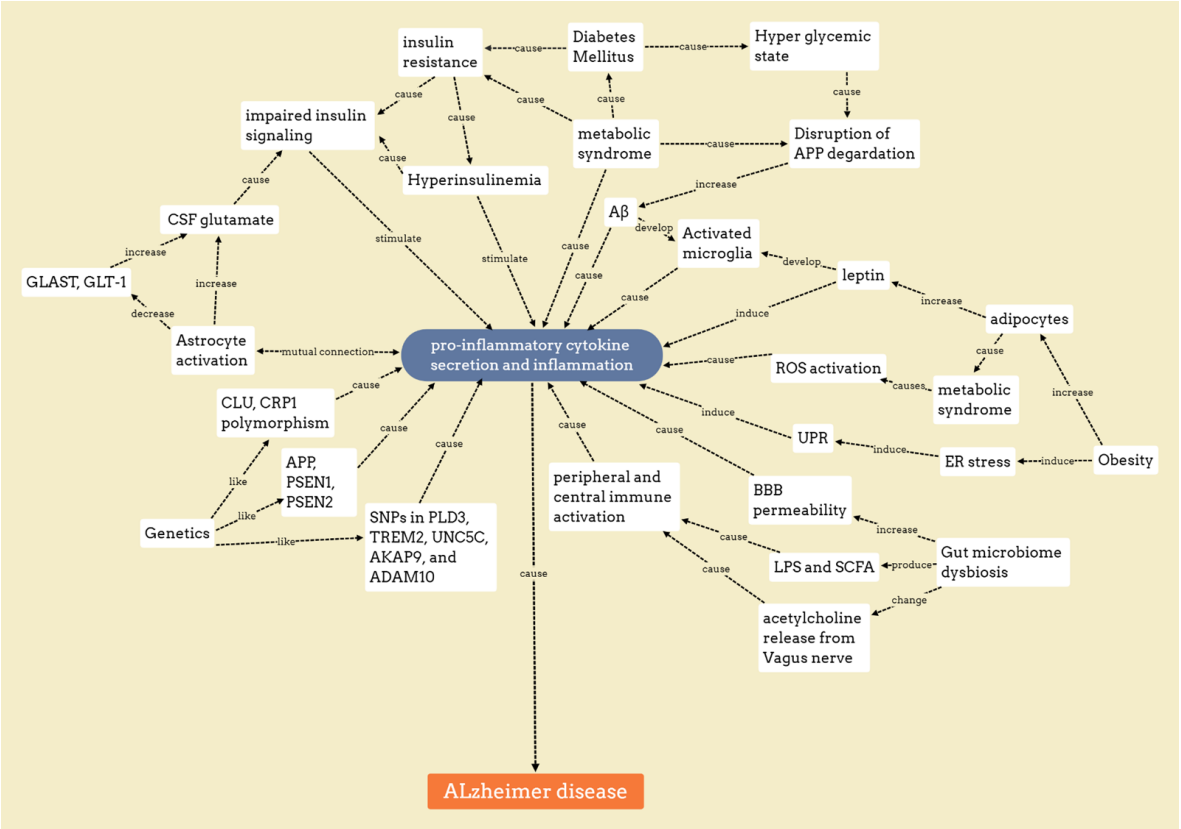

Figure 3. The interaction of significant etiologies the initiation of neuroinflammation through pro-inflammatory cytokine secretion.

mediate neuroinflammation and the activation of microglia and cause phagocytosis (181). It is a member of a family of inducible transcription factors and has five members: NF-κB1 (p50), NF-κB2 (p52), RelA (p65), RelB, and c-Rel (182). The NF-κB proteins are bound to IκB family proteins, which inhibit the activity of these proteins (183). The most important IκB protein is IκBα. Additionally, p105 and p100, the precursor proteins of NF-κB1 and NF-κB2, have a C-terminal portion with a similar structure to IκB and probably have NF-κB inhibitory functions (80, 184, 185).

Two major signaling pathways are responsible for the activation of NF-κB: Canonical and Non-canonical pathways (186, 187). The canonical pathway starts from the activation of the multi-subunit IκB kinase (IKK) complex. It has two catalytic subunits, including IKKα and IKKβ. Besides, a regulatory subunit called NF-κB essential modulator (NEMO) or IKKγ also gets involved in the IKK complex (181, 188, 189). Cytokines, microbial components, and stress are some of the most common triggers of the canonical pathway, which act via different receptors such as various cytokine receptors, pattern-recognition receptors (PRRs), T-cell receptor (TCR), B-cell receptors, and TNFR superfamily members (190, 191). Activation of IKK leads to the phosphorylation of IκBα, which triggers a ubiquitin-dependent IκBα degradation in the proteasomes. Finally, NF-κB is released in the cytosol, transferred to the nucleus, and regulates relevant genes (80, 192). Despite canonical pathways that respond to various types of stimuli, non-canonical pathways only respond to a specific group of stimuli, such as LTβR, BAFFR, CD40, and RANK, which are members of the TNFR superfamily (193-196). Additionally, activation of NF-κB via this pathway depends on p100, an NF-κB2 precursor protein (197, 198). NF-κB-inducing kinase (NIK), in cooperation with IKKα, phosphorylates p100, which further induces its ubiquitination and processing (199, 200). At the final step, degradation of p100 C-terminal IκB-like structure leads to the release of NF-κB2 p52 and activation of further signaling pathways (201-203). The canonical pathway is the main pathway for immune response, and the non-canonical pathway has a complementary

role and, in the adaptive system, cooperates with the canonical pathway (185, 204). T cells, particularly $CD4^+$ T-helper (Th) cells, are also involved in this cascade, which activates different proteins and genes, activating proinflammatory cytokines and releasing potentially toxic compounds that cause neurotoxicity, ultimately neuronal dysfunction, and cell death (205). Activation of naïve T cells occurred upon the stimulation of TCR by a specific antigen, which further activates the canonical pathway of NF-κB. RelA and c-Rel, two important members of NF-κB, have a central role in this process (206). Additionally, NF-κB promotes Th1 differentiation. Aronica *et al*. suggested that inhibition of NF-κB in T-cells leads to the Th1 response impairment (207).

A non-canonical pathway is required for proper differentiation and function (memory/effector) of T cells. Additionally, this pathway is required for Th17-mediated neuroinflammation (208-211). Some studies suggested that NF-κB activation increased *BACE1* and *APP* genes, as both *NF-κB* and *BACE1* are upregulated in the AD patients' brains (212, 213). Furthermore, aging, one of the most important risk factors for AD, leads to the perpetual activation of NF-κB, which further activates microglia, neuroinflammation, and the development of AD (214). Receptors for advanced glycation end products (RAGE) are receptors of advanced glycation end products (AGEs)(215). However, studies showed that Aβ is a ligand for this receptor (216). Interestingly, these receptors are overexpressed during neuroinflammation in microglia (216, 217). Binding of Aβ to RAGE activates which further induces NO and glutamate release, cytokine production, and BBB amplification (218, 219). NO combines with superoxides, which are associated with oxidative stress and BBB dysregulation (220, 221). Additionally, glutamate release leads to neuronal toxicity and degeneration (222, 223).

NLRP3 Inflammasome

Inflammasomes are large multiprotein complexes assembled by different receptors such as TLRs and NOD-like receptors (NLRs). Inflammasomes induce pyroptosis, characterized by the activation of caspase-1-mediated inflammatory response (224, 225). Several inflammasomes have been discovered, such as NLRP1, NLRP2, NLRP3, AIM2, and NLRC4 (226). Among these inflammasomes, the most well-studied one is NLRP3. NLRP3, a 118 kDa PRR protein, is a cytosolic protein expressed by different cells such as neurons, microglia, neutrophils, and macrophages. It has a C-terminal leucine-rich repeat (LRR) domain and a central ATPase-containing NACHT domain required for oligomerization. Besides, its N-terminal pyrin (PYD) domain recruits proteins for the formation of the inflammasome complex. NLRP3 inflammasome is composed of a sensor (NLRP3 protein), an adaptor (apoptosis-associated speck-like protein, ASC), and an effector (caspase-1) (224, 225, 227, 228). Activation of NLRP3 and its inflammasome formation could be triggered by a plethora of stimuli such as pathogens, uric acid crystals, silica, asbestos, extracellular ATP, and toxins (229, 230). Some studies hypothesized that NLRP3 activation is due to the common cellular events caused by this wide range of stimuli instead of directly binding to them (231, 232). Disruption of the trans-Golgi network (TGN) by multiple NLRP3 stimuli resulted in binding of NIMA-related kinase 7 (NEK7), an important NLRP3 inflammasome modulator, to NLRP3, which further disrupts the NLRP3 double-ring structure, inactive structure, and causes structural rearrangement. Structural rearrangement of NLRP3 exposes its PYD domain, which further associates with NACHT domain oligomerization. After the activation of the NACHT domain, the PYD domain recruits ASC and forms the ASC pyroptosome via PYD-PYD domain interaction (233-236). At the next step, the caspase recruitment domain (CARD) of ASC interacts with the pro-caspase-1 ASC domain, which further converts pro-caspase-1 to its active form, caspase-1. Caspase-1 not only converts pro-IL-1β and pro-IL-18 into their active forms, IL-1β and IL-18, respectively, but also activates the membrane pore-forming gasdermin D (GSDMD), a critical protein for pyroptosis (227, 237, 238).

NLRP3 inflammasomes are involved in the pathogenesis of autoinflammatory diseases, including diabetes, obesity, and AD (227). Similar to the NF-κB pathway, NLRP3 has also been activated via canonical and non-canonical pathways. Two signals are required to activate the canonical pathway. Priming signal (first signal) includes TLR ligands and cytokines such as TNF-α and

IL-1β, leading to the activation of NF-κB and further upregulation of NLRP3 and pro-IL-1β expression. The second signal (an activating signal) activates NLRP3 activation, followed by NLRP3 inflammasome, caspase-1-mediated secretion of IL-1β and IL-18, and pyroptosis. There are different activating signals, such as mitochondrial dysfunction, ion flux, including K^+ efflux, Cl^- efflux, Na^+ influx, ROS, and lysosomal disruption (227, 238). Caspase 4 and caspase 5 are involved in the NLRP3 non-canonical pathway in humans. These caspases bind to LPS directly, which leads to their autoproteolysis and activation. Finally, caspase four and caspase 5 induce pyroptosis by activation of GSDMD or triggering of K^+ efflux (239).

NLRP3 inflammasomes are expressed abundantly in microglia and astrocytes. Interestingly, the NLRP3 inflammasomes expressed in astrocytes are non-functional, and stimuli could not induce IL-1β and IL-18 secretion in them (240). Halle *et al.* found that NLRP3 inflammasomes could be activated by Aβ, which leads to IL-1β and IL-18 production and further inflammation (241). Some studies suggested that NLRP1 inflammasomes are expressed in neurons, and Aβ could activate them, but the expression of NLRP3 remains controversial (242). Besides, chronic expression of NLRP3 inflammasomes in microglia disturbs their clearance capacity for Aβ and NFTs, which further exacerbate AD (243). These findings are consistent with Heneka and colleagues' study, which found that $NLRP3^-$ or caspase-1-deficient APP/PS1 mice were resistant to neuroinflammation, AD, and amyloid plaque (244).

TREM2

TREM2 (the triggering receptors expressed on myeloid cells 2) is a cell surface transmembrane glycoprotein with a cytoplasmic tail (245), which is expressed in some subgroups of myeloid cells, such as granulocytes and dendritic cells (246-248). TREM2 is expressed by microglia, and it has higher expression in the hippocampus and spinal cord, which suggests its CNS region-dependent expression (249). Inflammation and its related cytokines, such as TNFα and IL1β, decrease, and anti-inflammatory molecules increase TREM2 expression (250-252). TREM2 acts via an intracellular adaptor called DAP12 (DNAX-activation protein 12, also known as TYROBP) through the TREM2 cytoplasmic short tail. The interaction between a positively-charged lysine in TREM2 and a negatively-charged aspartic acid in DAP12 regulates further intracellular events. TREM2 ligation to DAP12 activates Src family kinases, which generate tyrosine phosphorylation of DAP12 within its immunoreceptor tyrosine-based activation motifs (ITAMS). ITAMS phosphorylation makes a docking site for SH2 domains of different molecules, which is associated with immune response via a cascade of signaling molecules. TREM2 signaling components such as PI3K, Akt, and MAPK are activated via Syk, a principal kinase recruited by ITAM (253-259). TREM2 ligands have not been identified well, but their functions have been studied. It increases phagocytosis rate, Aβ uptake, and myeloid cell number and survival. Furthermore, it decreases inflammation via modulation of TNFα and NO synthase-2 transcription (NOS2)(253, 260-263). However, studies suggested a dual role of this signaling pathway, with some considering an inflammatory role for TREM2 (264, 265). PD, amyotrophic lateral sclerosis (ALS), stroke, traumatic brain injury, and AD are some of the pathological conditions in which TREM2 expression is upregulated. It seems that TREM2 overexpression in AD recruits microglia to amyloid plaques (227, 266, 267). Interestingly, some studies suggested that Aβ could directly bind and activate TREM2 (268). On the other hand, lack of TREM2 expression is associated with a reduction of late-stage amyloid plaque accumulation(269). However, reduction of TREM2 expression is associated with Tau spreading around amyloid plaque (266, 270). Studies showed the involvement of TREM2 in different inflammatory pathways, such as NF-κB. Cosker *et al.* found that TREM2 inhibits neuroinflammation by inhibition of NF-κB (271). Another similar study found the downregulation of PI3K/AKT by TREM2 for inhibition of neuroinflammation (272). Taken all together, TREM2 has a dual role in AD and could enhance some pathological features and relieve others.

cGas-STING

Detection of foreign DNAs is a crucial part of the immune system. In mammals, cyclic GMP–AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway is responsible for this de-

tection and induces a powerful immune system response against these foreign DNAs (273). cGAS, part of this pathway, is an innate immune system receptor, and its functional part is STING. Activation of cGAS by DNAs leads to the conversion of ATP and GTP to a cyclic dinucleotide 2030-cyclic GMP-AMP (cGAMP). This activation occurs via the C-terminal part of this molecule. This part has a nucleotidyltransferase domain (the catalytic part) with a positively charged DNA-binding site. Binding of DNA to this part leads to the cGAS conformational changes and rearranges its catalytic part, which allows it to convert ATP and GTP (274-277). At the next step, cGMP activates STING, which is located on the ER (278, 279). Conformational changes of STING lead to the binding of this molecule to TBK1, which further phosphorylates the transcription factor interferon regulatory factor 3 (IRF3). IRF3 is transferred to the nucleus, which results in the production of Type-I IFNs and some inflammatory cytokines (273). Studies showed that STING could mediate a non-canonical pathway of autophagy, which requires limited types of molecules such as PI3P effector WIPI2 and the ATG5-12-16L1 complex (280-282). The advantage of this pathway is the restriction of viral propagation (283). Interestingly, some studies suggested that this pathway could prevent tumor growth by induction of autophagy in the cell during proliferation (284). STING upregulates p21 and other cell-cycle inhibitors along with proapoptotic proteins (285, 286). Additionally, phosphorylated IRF3 could induce apoptosis by interaction with BAK and BAX (287-290). Even under conditions in which apoptosis is restricted, activation of STING leads to the RIPK3-dependent necroptosis development, which occurs via type I interferon and TNF signaling pathways (291-293).

One of the critical signaling pathways in neuroinflammation is cGAS/STING/IFNs. Several studies showed the abundance of cGAS/STING in different neuroinflammation-related disorders. One of the main elevated types of interferons during neuroinflammation is IFN-I, a main product of the cGAS/STING pathway. It has receptors on microglia, astrocytes, and neurons (227, 294). Activation of microglia by IFN-I leads to the pro-inflammatory cytokine production and neuroinflammation (295, 296). Wang *et al.*, showed that STING could regulate the activation of NLRP3 (297). Another study held by Jin and colleagues showed that polyglutamine binding protein 1 (PQBP1), an important protein for splicing, transcription, and cognitive functions of the brain, interacts with tau 3R/4R proteins, resulting in cGAS/STING activation and further immune response (298).

Genetics

The trace of genetics can be found in almost every disease, and it is also important in neuroinflammation and neurodegeneration. Several genes have been identified for early onset AD, PD, neuroprotection against inflammation, induction, and early resolution of inflammation in the CNS(299, 300). Four well-studied genes involved in AD are *PSEN1*, *PSEN2*, *APP*, and *APOE4*.

PSEN1

PSEN1 is located on chromosome 14q24.3 and encodes PS1, a multi-spanning transmembrane protein with a hydrophilic loop (301, 302). Its N-terminal and hydrophilic loop are available for interaction with other proteins. Besides, PS1 is a highly conserved 50 kDa protein found in different brain regions such as the dentate gyrus, neocortex (especially in layers II and IV), the CA1-CA3 layers, and the subiculum of the hippocampus. The intracellular location of PS1 is in intracellular membranous organelles such as the ER, nuclear envelope, and Golgi apparatus. Mutations of *PSEN1* are the first cause of familial Alzheimer's disease (FAD)(303). PS1 is a catalytic subunit of γ-secretase, and as mentioned above, this enzyme plays a crucial role in the production of Aβ and the development of AD (304, 305). However, the exact role of PS1 in the development of AD remains debatable. Two main hypotheses have been developed to explain the role of PS1 in FAD: the amyloid and presenilin hypotheses. The former one proposed that mutations of *PSEN1* lead to the overproduction of Aβ and further development of AD (306, 307). This hypothesis has been evolved and proposed that *PSEN1* mutations increase the Aβ42/Aβ40 ratio. (308). Presenilin hypothesis provides an alternative view and proposes that mutations of *PSEN1* cause loss of function of its protein, which is associated with dementia and neuroinflammation

(309). This hypothesis is supported by several studies, which showed that *PSEN1* is important in the survival of neurons during aging, as well as learning and memory (310-312). Besides, *PSEN1* loss of function disturbs γ-secretase activity. As Xi *et al*. showed, despite decreased production of both Aβ42 and Aβ40 after γ-secretase loss of function, Aβ42/Aβ40 increases, which is further associated with AD development (313).

PSEN2

PSEN2 was first reported as a causative gene for AD development in 1995 (314). It is located on chromosome 1q42.13 and encodes the PSEN2 protein (315). PS1 and PSEN2 are homologous proteins with 67% similarity (316). Their hydrophobic region is highly conserved, and their difference is in their N-terminal and hydrophilic loop (315). PSEN2 has two isoforms: Isoform 1 is found in different tissues such as the placenta, liver, and kidney, and Isoform 2 is found in the brain, placenta, and skeletal muscles (315). Like PS1, this protein is also a subunit of γ-secretase, and *PSEN2* mutations could change the activity of this enzyme and further AD development. PSEN2 like PS1 resides in ER and Golgi appartus (317). Studies showed that some mutations of *PSEN2* increase Aβ production, while others change the intracellular calcium signaling (318-320).

APP

APP or amyloid beta precursor protein is the substrate of enzymes for the production of Aβ and further development of AD. It is a highly conserved protein encoded by the *APP* gene (321-323). APP is an integral membrane protein with a large extracellular and small intracellular region. Its extracellular region has two subdomains: E1 and E2, which are linked to each other by an acidic domain (324). APP is expressed in different tissues such as skin, adipose tissue, muscles, and CNS, but its main functions are in the CNS, which are the regulation of synapse formation, enhancing synapse adhesion, increasing neuronal viability, and axon pruning (325-327). *APP* mutations could increase the Aβ42/Aβ40 ratio and increase Aβ generation. Additionally, mutations could impair α-secretase action on the APP and increase the hydrophobicity of Aβ, which is further associated with amyloid plaque formation (328-330). Several mutations have been identified, including: 1) Mutations in the N-Terminal of Aβ Domain: *K670N/M671L* is an example of this type of mutation, which leads to the lysine-to-asparagine substitution at codon 670 and a methionine-to-leucine substitution at codon 671, are within the extracellular part of APP at the β-secretase cleavage site and increase both Aβ40 and Aβ42 (331, 332). 2) mutations in the *Aβ* Domain: For instance, E693G increases Aβ protofibril formation (333, 334). 3) Mutations in the C-Terminal of *Aβ* Domain: These mutations disturb their respective secretases and lead to the production of longer Aβ (Aβ42), which aggregates easily (330, 335). 4) *A673V* mutation (substitution of alanine to valine at codon 673) increases production of Aβ(336). 5) A673T (alanine-to-threonine substitution) decreases Aβ formation and has a protective role against AD, probably via impairment of BACE1 cleavage of APP (337, 338).

APOE4

Apolipoprotein E (*APOE*) is located on the chromosome 19q13.32 and is a primary apolipoprotein lipid and cholesterol transporter in the CNS (339, 340). It also enhances the transportation of lipids via different cells by acting as a ligand of low-density lipoprotein receptor (LDLR) and lipoprotein receptor-related protein (LRP)(341). *APOE* is composed of N-terminal and C-terminal domains linked by a hinge, and its isoforms are mainly different in the N-terminal of this protein (339).

APOE has 3 isoforms: E2, E3, and E4. APOE4 is the strongest risk factor for AD development, as it influences different aspects of AD (342). APOE4 is associated with more Aβ accumulation and aggregation in the brain (343-345). Additionally, some studies reported that APOE4 could change the clearance of Aβ (346). It also influences tau pathology via induction of neuroinflammation, increase of neuronal accumulation, and redistribution of this protein (347-349). Furthermore, induction of a more damaging related reactive astroglia signature in APOE4 harboring mice indicates its effect on astrocytes (347, 350, 351). Prasad *et al*. showed that APOE4 could restrict the ability of astrocytes in amyloid clearance (351). APOE4 could also promote disease-associated microglia

(DAM) in the brain. These microglia are involved in the induction of neuroinflammation and tau pathology (352-354).

Non-coding RNAs

Regulation of gene transcription depends on several factors, and non-coding RNAs (ncRNAs) are one of the crucial parts of gene transcription regulation. Long non-coding RNAs (LncRNAs), microRNAs (miRNAs), and circular RNAs (Currans) are three important members of this family. LncRNAs are RNAs with more than 200 nucleotides that interfere with mRNA and/or miRNAs. miRNAs have 18-24 nucleotides. miRNAs bind to mRNA and lead to the degradation of mRNA. CircRNAs are closed LncRNAs that have similar roles to LncRNAs. Some of the ncRNAs and their targets are shown in **Table 1**.

miR-155 is a highly conserved miRNA and is important for the immune system and T-helpers. Studies showed that this miRNA could lead to neuroinflammation. miR-155 decreases the endogenous anti-inflammatory cell response, which is further associated with neuroinflammation and brain damage. It is also involved in the inflammatory response after CNS ischemia, Parkinson's disease, MS, ALS, and traumatic brain injury (355-360). Guedes *et al*. investigated the functional role of miR-155 in AD using the 3xTg AD animal model. They showed a strong upregulation of miR-155 levels in the brain of 3xTg AD animals. Simultaneously, the rise of microglia and astrocytes activation rate suggests neuroinflammation. Furthermore, they investigated whether miR-155 and c-Jun are involved in the Aβ-mediated activation of glial cells. Results showed the upregulation of these two molecules in mouse models and Aβ-activated microglia and astrocytes. Taken all together, miR-155 could be a promising therapeutic factor for the reduction of neuroinflammation in AD (361).

Neuroblastoma differentiation marker 29 (NDM29) is an LncRNA, and its transcription is mediated by RNA pol III (362). Its expression could be influenced by the expression of pro-inflammatory cytokines such as TNF-α and IL-1α (363). Interestingly, this LncRNA could induce differentiation of neuroblastoma (NB) cells to a non-malignant neuron-like phenotype (364, 365). Massone *et al*. investigated the role of NDM-29 on APP synthesis. Results showed an increase in Aβ secretion and Aβ42/Aβ40 ratio. Furthermore, expression of this LncRNA and further Aβ formation could be influenced by inflammation (increase of NDM29 and Aβ formation). The expression of NDM29 is increased in the brain of neurodegenerative disease patients, indicating that NDM29 provides a situation in which Aβ could be formed in the extracellular space (366).

ciRS-7, a 1500 nt circular RNA located on chromosome Xq27.1, was first identified in 2011 (367, 368). It is an antisense of cerebellar degeneration-related protein 1 (CDR1AS) without a 3' poly-A tail and a 5' cap, indicating its circular structure. It has more than 70 seed regions for miRNAs, and most of them are for miR-7 (368, 369). Short interspersed nuclear elements upstream and downstream of the *ciRS-7* gene induce its transcription (369). Zhao *et al*. investigated the *ciRS-7* role in AD development. They found a disruption of the ciRS-7-miRNA-7-UBE2A axis in the hippocampal CA1 and Broadmann A22 of the AD patients' brains. ciRS-7 acts as a sponge in the brain, and its deficit leads to higher levels of miR-7, which are further associated with downregulation of this miRNA targets. One of the miR-7 targets is the ubiquitin conjugating enzyme E2A (UBE2A), which is required for the ubiquitin-26S proteasome system, a critical complex for amyloid peptides clearance. Taken all together, the results indicated that dysfunction of the aforementioned axis leads to the formation of amyloid plaque and AD development (370).

Possible Etiologies of Neuroinflammation

Pathogen Aspects of Neuroinflammation and AD

Studies showed that bacterial and viral infections are important in the progression and development of cognitive decline in AD patients. Furthermore, AD itself increases the vulnerability to the effects of peripheral infection with bacteria or viruses (371).

Herpes simplex virus-1 (also called HSV-1) is one of these pathogens involved in AD development. It is a latent infection of the CNS, and studies confirmed the presence of HSV-1 DNA in brain regions that are also involved in AD, such

Table 1. The connection of Non-coding RNAs (ncRNAs) with neuroinflammation and Alzheimer's disease

Name	Target	Expression	Function	Reference
miRNAs				
miR-206	BDNF	Up	Decrease BDNF, a neuroprotective protein against cell death	(1)
miR-613	BDNF	Up	Decrease BDNF, a neuroprotective protein against cell death	(2)
miR-155	SOCS-1	Up	Increase production of pro-inflammatory cytokines such as IL-6 and IFN-β	(3)
miR-339-5p	BACE-1	Down	Regulation of BACE-1 expression	(4)
miR-144	ADAM10	Up	Negatively regulates ADAM10, an important Aβ inhibitor	(5)
miR-1908	APOE	Up	Inhibition of APOE expression	(6)
miR-33	ABCA1	Up	-Impairment of cellular cholesterol efflux -increase Aβ secretion and its clearance inhibition	(7)
miR-219	Tau	Down	Decrease Tau expression	(8)
miR-146a	ROCK1	Up	ROCK1/PTEN pathway is involved in Tau hyperphosphorylation in early neurofibrillary tangles	(9)
miR-200b/c	S6K1	Down	Decrease insulin resistance by reduction of IRS-1pSer and further Aβ clearance improvement.	(10)
miR-125b	DUSP6, PPP1CA and Bcl-W	Up	Tau hyperphosphorylation due to downregulation of DUSP6, PPP1CA, and Bcl-W	(11)
miR-137	CACNA1C	Down	miR-137 and CACNA1C decrease Tau hyperphosphorylation	(12)
miR-124	PTPN1	Up	Memory deficit and synaptic failure via miR-124/PTPN1	(13)
miR-134-5p	CREB-1 and BDNF	Up	long-term potentiation (LTP) and synaptic tagging and capture (STC) were disturbed	(14)
miR-342-5p	AnkG	Up	AnkG is important in the axon initial segment, and its downregulation leads to the axonopathy	(15)
miR-188-5p	Nrp-2	Down	Reduction of dendritic spine density and mEPSCs, and further cognitive dysfunction	(16)
miR-34c	SYT1	Up	The ROS-JNK-p53 pathway is important in miR-34c upregulation and further SYT1 downregulation, which are associated with synaptic and cognitive dysfunction	(17)
miR-214-3p	Atg12	Down	Upregulation of miR-214-3p decreased neuronal apoptosis and autophagy	(18)
miR-98	HEY-2	Down	miR-98 suppresses apoptosis by inhibition of the Notch signaling pathway via HEY-2 suppression	(19)
Lnc RNAs				
NDM29	APP	Up	Increase in APP synthesis and further Aβ secretion	(20)
51A	SORL1	Up	Decreased SORL1 expression leads to impaired APP processing and increased Aβ formation.	(21)
BACE1-AS	BACE1	Up	BACE1-AS increased BACE1	(22)

Table 1. Continued

BDNF-AS	BDNF	Up	Decreased viability and induction of apoptosis due to BDNF-AS upregulation	(23)
SNHG1	miR-137	Up	SNHG1/miR-137/ KREMEN1 axis is involved in neuronal viability and apoptosis	(24)
NAT-RAD18	RAD18	Up	-	(25)
NEAT1	CAV2, TGFB2 and TGFBR1	Down	Endocytosis-related genes, which are important in Aβ clearance, and also H3K27Ac and H3K27Cro, which are important for several gene expressions, are affected by NEAT1	(26)
MALAT1	miR-125b	Down	MALAT1/miR-125b axis regulated neuronal apoptosis and inflammation	(27)
BC200	BACE1	Up	BC200 decreased cell viability and induced apoptosis and BACE-1 expression	(28)
			CircRNAs	
CircHDAC9	miR-138	Down	circHDAC9/miR-138/Sirt1 axis regulates synaptic function and APP processing	(29)
Circ-0000950	miR-103	Up	Circ-0000950/miR-103 pathway is involved in neuroinflammation, neurite outgrowth, and neuron apoptosis	(30)
ciRS-7	miR-7	Down	ciRS-7/miRNA-7/UBE2A axis is involved in the Aβ process and clearance	(31)

as the hippocampus (372). Additionally, this virus increases amyloid-β production, and it is a prominent risk factor in patients with Apolipoprotein E4 (APOE4) for further AD development (373-375). Another lifelong infection is cytomegalovirus (CMV), which is linked with accelerated cognitive decline and AD development (376, 377). Human Immunodeficiency Virus (HIV) is another chronic lifelong infection that can penetrate the BBB and proliferate in the CNS and cerebrospinal fluid (CSF). This virus could induce chronic neuroinflammation through its gp120 and TAT protein, which exacerbates neurodegeneration. Besides, it increases amyloid deposition in the brain, which could be a risk factor for further AD development (378, 379). Several cohort studies confirmed the increased rate of Human Herpes-Virus (HHV)-6A and HHV-7 infection in AD patients. Like other viruses mentioned above, these viruses cause persistent infection, chronic inflammation, and further glia activation, which could accelerate AD development and progression (380, 381). Some studies confirmed that Epstein-Barr Virus (EBV) is a risk factor for AD development and progression, especially in APOEε4 carriers. Besides, serologic EBV positivity in patients with AD and EBV IgG plasma levels is correlated with cognitive decline and AD progression (376, 382).

Several bacterial pathogens have also been associated with AD. *Chlamydia pneumoniae*, an obligate intracellular, Gram-negative bacterium, increases the AD development risk up to fivefold (383). It passes through the BBB, infects microglia, astrocytes, and neurons, and causes chronic inflammation. Additionally, it increases Aβ deposition in the brain and tends to aggregate in the hippocampus more than in other parts of the brain (384, 385). *Heliobacter pylori* (*H. pylori*), another Gram-negative bacterium, is also significantly associated with AD and dementia in the elderly. *H. pylori* increases the severity of cognitive decline, pro-inflammatory cytokines, and tau protein in the brain (386, 387). An interesting risk factor for AD is periodontitis. Studies showed that healthy elderly individuals with periodontitis have higher levels of amyloid in the CNS (388). *Treponema* species are involved in periodontitis, and some studies showed an increased sus-

ceptibility to infection with *Treponema* species in AD patients, but there is no cause-and-effect relationship between these pathogens and AD (389). *Borrelia burgdorferi* is also involved in periodontitis. It could induce Aβ accumulation in the brain through neurons and glia (390). Studies suggest a tenfold increase in the AD development in the context of spirochetes such as *B. burgdorferi* infection (383). *P. gingivalis*, a Gram-negative bacterium involved in chronic periodontitis, is a strong risk factor for AD, which could reproduce hallmarks of AD in wild-type mouse models due to the ability of *P. gingivalis* to induce Aβ and tau production in the brain (384, 391). Dominy *et al.* found a positive correlation between the level of some toxic proteases of *P. gingivalis* called gingipains in the AD patients' brains and tau and ubiquitin pathology (392). Besides infections, various etiologies can contribute to the initiation of neuroinflammation and the subsequent neurodegeneration.

Metabolic Aspects of Neuroinflammation and AD

Another important aspect of AD is metabolic dysfunction. Metabolic syndrome (MetS), which is a consequence of modern lifestyle, is a risk factor for a wide range of chronic diseases. MetS is characterized by overweight, insulin resistance, high glucose levels, and hypertension, and studies showed that it has a critical role in AD development and progression, especially in LOAD (393). The exact mechanisms are currently unknown, but some studies have suggested that MetS induces neuroinflammation and also increases amyloid plaque production (394, 395). The interaction of MetS and neuroinflammation in the development of AD is mentioned in **Figure 3**.

Diabetes Mellitus (DM)

Diabetes mellitus can potentially induce inflammation in the CNS (396) by two main mechanisms. Firstly, insulin resistance can occur in the CNS, causing an increase in insulin in the blood and the impairment of insulin signaling. An excess amount of insulin induces the secretion of different cytokines and causes inflammation in the CNS. Insulin resistance is a risk factor for cognitive impairment and seems essential for the conversion of these impairments to AD. Molecular mechanisms need to be elucidated, but it seems that insulin resistance causes Ser-phosphorylation of the insulin receptor substrate 1 (IRS1) instead of normal Tyr-phosphorylation. Furthermore, insulin resistance results in decreased phosphorylation of Akt, affecting several downstream components of the insulin pathway, including Glycogen synthase kinase-3 (GSK-3). The increase of unphosphorylated GSK-3 (active form) is correlated with Tau hyperphosphorylation and NFTs formation (397-399). It can also suppress the BBB insulin transporters (400, 401), which are essential for glucose transportation and metabolism across the neurons; therefore, the neurons' available insulin would be decreased (401). Impaired insulin signaling and a decrease in insulin amounts cause neuroinflammation and neurodegeneration. Another important mechanism is amyloidogenesis. In the hyperglycemic state, which can be expected in DM, the APP degradation has been disturbed (402, 403). Thus, the increment of Aβ can be associated with neuroinflammation and neurodegeneration. These observations have been seen in both streptozotocin (STZ) induced type 1 diabetes mellitus (DMT1) and high-fat diet-induced type 2 diabetes mellitus (DMT2) rodents (404, 405). Cao *et al.* investigated the role of sugar in AD in a transgenic AD mouse fed with sucrose-sweetened water and reported that, in comparison with the control group, sugar could accelerate the amyloidogenesis and exacerbate AD (405). In another study, Insub *et al.* found a relationship between AD and DMT2 through Aβ autoantibodies, as the level of Aβ autoantibodies was dramatically elevated in the patient serum of T2DM (406). Further studies revealed that diabetes mellitus is a potent risk factor for the development and exacerbation of AD by the acceleration of not only Aβ but also tau protein production and aggregation (407-409).

Obesity

Obesity induces a hyperinflammatory state, a situation in which inflammatory cytokines increase and immune cells become activated (410, 411). Although the mechanism of how obesity leads to a hyperinflammation state has not been completely understood, some studies suggested the role of leptin as an essential hormone for conducting inflammation in obese patients (412-

414). Leptin has a similar structure to cytokines (415) and has receptors on immune cells such as macrophages, T cells, and microglia. The activated microglia by leptin can cause IL-6 and IL-1B production (416, 417). Another important mechanism is the contribution of obesity to metabolic syndrome. Increased body fat, accompanied by adipocyte hypertrophy and hyperplasia, excessive cholesterol and glucose in blood, induces stress in adipocytes, causing the secretion of TNF-α and IL-6 alongside the ROS activation, causing a hyperinflammatory state in the body and increasing the risk of neuroinflammation and degeneration (67, 418-421). Additionally, ROS disrupts the BBB as detected by the serum increase of calcium-binding protein B (S100B), a glial-specific protein expressed primarily in astrocytes, and neuron-specific enolase (NSE)(422, 423). Therefore, BBB dysfunction could result in altered permeability and cerebrovascular integrity loss in the human hippocampus, a region involved in learning and memory that is early damaged in AD (423-425). Brain cholesterol levels directly influence Aβ formation through stimulation of the amyloidogenic pathway, since different experiments strongly suggest that cholesterol has an elevated affinity for APP and Aβ (423, 426, 427). Another possible mechanism for the hyperinflammatory state in obesity is the endoplasmic reticulum stress. ER is an important site for protein synthesis and folding, and the stress resulting from fat deposition and compression of adipocytes increases the need for protein and protein synthesis, triggering unfolded protein response (UPR) in it. UPR is the accumulation of unfolded proteins in the ER, which causes the pro-inflammatory cytokine release from adipocytes and inflammation (428-430). Obesity has a strong correlation with DMT2 and insulin resistance. ROS, hyperinflammation state, adiponectin secretion dysfunction, Excess lipid substrates and lipotoxicity, and changes in the gut microbiome are the main causes of insulin resistance in obesity. As mentioned above, insulin resistance could exacerbate amyloidogenesis and AD (431-433).

Gut Microbiome

The microbiota-gut-brain axis is a mutual communication system that is connected via neural, immune, endocrine, and metabolic pathways. Alteration in gut microbiome is associated not only with gastrointestinal disorders but also with some neurodegenerative disorders, such as AD (434). Gut microbiome dysbiosis can increase the permeability of both the intestine and the blood-brain-barrier and expose the CNS to some microbiome products, such as lipopolysaccharides (LPS) and small-chain fatty acids (SCFAs). These products could induce inflammation, increase the production of pro-inflammatory cytokines, and facilitate neuronal apoptosis (435, 436). Besides, dysbiosis could induce an unresolved inflammation in the gut and activate immune system cells such as $CD4^+$ T cells. These cells could further pass through the BBB and induce neuroinflammation (437). Microglia activation can also occur in this context and not only exacerbate the neuroinflammation but also impact astrocytes indirectly via microglia-astrocyte communication (438). Studies showed that Bacteroidetes, Rikenellaceae, and Tenericutes were increased, and Firmicutes, Verrucomicrobia, Proteobacteria, Akkermansia, Allobacilum, and Actinobacteria were decreased in the gut in animal models of AD. These changes could enhance amyloid production and plaque-localized inflammation in the brain by a change in the activation of glia in the brain (439-442). Germ-free mice studies revealed a reduction in brain-derived neurotrophic factor in germ-free mice. This factor is essential for synaptic plasticity and cognitive function, besides studies confirmed its reduced expression in AD (443, 444). Probiotics are living microorganisms ingested for some gastrointestinal disorders as they can modulate the gut microbiome. Several studies confirmed that certain probiotics, such as *Lactobacillus helveticus NS8*, could ameliorate cognitive impairments and restore brain-derived neurotrophic factor (BDNF) content in the brain in the context of chronic stress (445). However, further studies are needed to determine the best combination of different probiotics for the maximum effect. The gut microbiome could also act directly through the vagus nerve. The acetylcholine neurotransmitter is released in response to vagus nerve stimulation and modulates the inflammation of the CNS by controlling the activity of immune cells. Thus, gut microbiome could alter the secretion of acetylcholine, and further changes in immune system function (446, 447).

Treatments for AD

Development of new drugs and therapeutic targets is an urgent need for AD due to its severe cognitive and neuropsychiatric symptoms. More than 100 agents in more than 150 clinical trials are in progress for the treatment of this disease, and disease-modifying therapies (DMTs) are the most common agents. More than 20 agents are in phase 3 of clinical trials (448). Treatment for the AD is classified into different types based on their mechanisms of action and several other variables. Two main types based on their mechanisms of the action are DMTs such as Aducanumab, Atuzaginstat (COR388), Azeliragon, and Blarcamesine (ANAVEX2-73), which act via different mechanisms including monoclonal antibody against Aβ plaques, reduction of neurodegeneration and neuroinflammation by inhibition of P. gingivalis protease inhibitor, reduction of inflammation by antagonizing RAGE and inhibition of Aβ transport to the brain, reduction of oxidative stress, protein misfolding, mitochondrial dysfunction, and inflammation by targeting M2 and Sigma-1 receptors respectively. These are some of the common mechanisms of the DMT drugs for the reduction of AD development and symptoms (449-452). Another group is neuropsychiatric and cognitive symptoms relievers such as AVP-786, Brexpiprazole, Ginkgo biloba, Guanfacine, and Nabilone. These drugs act via different mechanisms, including inhibition of acetylcholinesterase, inactivating NMDA receptors, and activation of Sigma1 receptors (453-457). These two types of AD treatments (DMT and neuropsychiatric/cognitive symptoms reliever) account for about 86% and 13% of all treatments, respectively (448). Additionally, there is a one-vaccine trial in the phase 3 (CAD106)(448). CAD106 is composed of different copies of Aβ1–6 with a carrier that is composed of 180 copies of bacteriophage Qβ coat protein. This vaccine induces Aβ antibodies without involvement of Aβ-specific T-cell response (458-460). Collectively, there are numerous treatments under investigation for AD treatment, and each of them acts via specific mechanisms. These drugs make new hopes for AD treatment soon. Targeting signaling pathways, especially inflammatory pathways and pro-inflammatory cytokines, to reduce neuronal damage and AD progression is another strategy. Anakinra and rilonacept are developed against IL-1, and canakinumab is against IL-1β (461-463). Several drugs are also developed based on the NLRP3 pathway. JC124, a NLRP3 inflammasome and caspase-1 inhibitor, CY-09, which binds to the NACHT domain to inhibit NLRP3 ATPase activity, and several similar drugs are among this group (464, 465). Use of curcumin, phytochemicals such as Resveratrol, MW01-2-069A-SRM, a p38α MAPK inhibitor, are the strategies to inhibit NF-κB signaling pathway (466-468). Nicotinamide riboside (NR) is a promising therapeutic target for normalizing cGAS-STING in preclinical studies (469). Targeting macrophages could also be a successful strategy. Increase in microglial phagocytosis and switch from M1 to M2 are two main strategies. PPARα is a nuclear receptor that promotes microglia recruitment and phagocytosis and further increases Aβ clearance. Gemfibrozil and Wy14643 are two PPARα agonists used to increase autophagy of microglia and structural neuroplasticity (469, 470). Another member of the PPAR family is PPARy with opposite effects. PPARy antagonist T0070907 could enhance microglial autophagy via Liver kinase B1 (LKB1)-AMPK pathway (470). LC3 is an important part of autophagy and phagosome formation. Anti-inflammatory drugs and cytokines such as dimethyl fumarate (DMF) and IL-4 could be used for upregulation of LC3 and increased microglial autophagy (471-474). Switching from M1 to M2 macrophages due to their beneficial effects against AD progression could be used as another strategy for AD treatment. L-cysteine-derived hydrogen sulfide (H2S), CaMKK inhibitor (STO-609), and T0070907 are used for this strategy (475-478).

Conclusion

AD is a multifactorial disease, and different mechanisms are involved in its pathogenesis. Inflammation can be considered a principal mechanism in AD initiation and progression. Various studies have been done over the years to examine different parts of inflammation in the brain. Pro-inflammatory cytokines and inflammatory pathways are vital parts of inflammation. They are double-edged, either having a preventive and protective role against diseases or being harmful and damaging to the cells. Overall, in acute immune response, activation of inflammatory pathways

and production of pro-inflammatory cytokines are essential for proper immune system function, but if the immune system's stimulator remained, the inflammation could be chronic, and in this situation, the cytokines can be harmful to the body the same as what occurs in Alzheimer's disease. This article summarizes and discusses different aspects of AD, from its molecular pathways to gut microbiome and current treatments and clinical trials, and provides a new insight into AD development and its promising therapeutic targets. Further studies would be needed to investigate the hidden aspects of this disease.

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Conflict of Interest

Authors approve that they have no conflict of interest.

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