The Role of TNF-α in Alzheimer's Disease

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder that represents the most common cause of dementia in the elderly. Tumor necrosis factor (TNF)-α, a proinflammatory cytokine, has attracted attention due to its multifaceted and still not fully characterized role in AD and the fact that it could potentially represent a future therapeutic target. Indeed, TNF-α has many roles, not only in inflammation, but also in cell death and proliferation, and is crucial in maintaining CNS homeostasis. TNF-α is primarily produced by microglia, astrocytes, and neurons in response to various stimuli. Although TNF-α has a fundamental role in modulating excitotoxicity, neuroinflammation, blood-brain barrier permeability, regulation of oligodendrocyte survival, myelin formation and repair, its excessive or dysregulated production can have detrimental effects on neuronal health, contributing to the development of neurodegeneration.

Alzheimer's disease dementia inflammation cognitive impairment TNF-α

1. Rationale for the TNF-α Involvement in Alzheimer's Disease

Increasing scientific evidence consistently confirms the significance of immunity in the pathogenesis of Alzheimer's disease (AD). These findings increasingly suggest a combined involvement of both innate and adaptive immunity. TNF exhibits a continual, low-level expression in the typical adult brain [1][2][3][4]. TNF-α is secreted by many cell types, albeit cells of the monocytic lineage, including microglia and are the primary synthesizers [5]. TNF-α modulates and influences many neuronal activities in the CNS, which include glutamatergic transmission [6][7][8] and gamma-aminobutyric acid (GABA) transmission [6][9][10], with an overall outcome of these alterations of an augmentation of excitatory synaptic transmission compared to inhibitory transmission in hippocampal slices [6] and potentially in other neuronal circuits [4]. The strengthening of excitatory transmission is further amplified by the release of glutamate from astrocytes influenced by TNF-α [4][11].

TNF-α is involved in a variety of activities within the CNS. It influences sleep [12] directly acting on neurons in key sleep regulatory areas of the brain, such as the hypothalamic preoptic area and basal forebrain, impacting sleep architecture [13]. Intracerebroventricular injection of TNF-α induces a significant increase in slow-wave sleep, as demonstrated by polysomnography, emphasizing its role in promoting specific sleep stages [14]. In mice, the administration of TNF-α to the peritoneum leads to significant elevations in non-rapid eye movement sleep duration while causing reductions in slow wave activity [15].

The roles of TNF-α receptors (TNFR) in CNS physiology are different. TNFR1 exhibits neuroprotective effects in the CNS by safeguarding cells against necrosis [16]. Despite the anti-apoptotic attributes of TNFR1 signaling, it only partially elucidates its neuroprotective role in acute CNS injuries. Notably, TNFR1 fails to shield neurons from insults like retinal ischemia–reperfusion injury and oligodendrocytes from immune-mediated damage in conditions such as multiple sclerosis (MS) and experimental autoimmune encephalomyelitis (EAE) [4]. Studies exploring caspase inhibition as a potential remedy for TNF toxicity yielded surprising results. Pan-caspase inhibition exacerbated TNF toxicity in mice, intensifying oxidative stress and mitochondrial damage [17]. TNFR1-mediated cell death involves a switch between caspase-induced apoptosis and necrosis, with key signaling molecules such as receptor-interacting protein 1 (RIP1) and RIP3 identified in TNF-induced programmed necrosis or necroptosis [18][19]. This reveals TNFR1 signaling and the Fas-associated death domain protein (FADD)/caspase 8 apoptotic platform as an additional protective layer, enabling cells to undergo apoptosis instead of inflammation-inducing necroptotic cell death. The neuroprotection mediated by TNFR1 in the CNS may operate on two levels: gene induction and de novo production of survival molecules and, in the absence of adequate survival signals, caspase 8-dependent apoptosis [4].

TNFR2 also plays a crucial role in neuroprotection and repair processes in the CNS. TNFR2 is expressed in regulatory T cells, endothelial cells [20], oligodendrocyte lineage cells [21], and specific neuron populations [22] and is able to activate pro-survival signaling through TRAF2 recruitment [23] and PI3K/NF-κB pathway activation [24][25]. TNFR2 activation is associated with Akt/protein kinase B activation, crucial for neuroprotection against excitotoxicity and ischemia–reperfusion injury [4]. Actually, TNFR2 and TNFR1 cooperate to enhance neuroprotection, with additive effects on cell survival through NF-κB activation. Indeed, TNFR2 reinforces TNFR1-mediated cell survival and apoptotic signaling, maximizing neuroprotection [25][26]. Finally, TNFR2 may also promote oligodendrocyte precursor cell proliferation and remyelination, contributing to repair mechanisms [26][27].

However, TNF-α represents one of the pivotal pro-inflammatory cytokines and triggers the production of IL-1, IL-6, and IL-8, fostering chronic inflammation unless balanced by anti-inflammatory cytokines like IL-10 [28]. It induces APP and BACE1 expression in mouse astrocytes, activating γ-secretase in HEK cells, and releasing Aβ peptides [29][30][31]. Persistent brain inflammation forms a self-amplifying cycle, sustaining high TNF-α levels, potentially stimulating Aβ synthesis, causing neuronal loss, and hindering microglia Aβ phagocytosis [32]. The role of TNF-α in tau hyperphosphorylation is less understood, but few interesting data on mice suggest a possible connection [33][34].

Historically, microglia activation and gliosis were perceived as secondary to neurodegeneration in AD. However, recent genetic investigations in late-onset AD indicate the involvement of microglia- and astrocyte-related pathways together with the activation of multiple immune pathways in the very early stages of the disease [35][36][37][38][39][40][41][42][43]. Particularly, the innate immune receptor triggering receptor expressed on myeloid cells 2 (TREM2), expressed on microglia and myeloid cells, has garnered attention [44][45]. Rare TREM2 mutations linked to AD propose that TREM2 deficiency plays a role in AD susceptibility [46]. Functioning as a negative regulator, TREM2 modulates the release of TNF-α and other inflammatory cytokines via the Toll-receptor pathway [47]. Impairment of

TREM2 function in monocytes or macrophages may contribute to systemic TNF-α production, potentially serving as a treatable risk factor for AD [46][48].

The TNF-α gene promoter region contains multiple single nucleotide polymorphisms (SNPs), with the G308A mutation being of interest for AD [49]. This mutation elevates TNF-α mRNA and protein expression and a possible pathogenetic mechanism has been proposed. However, conflicting meta-analyses reveal regional variations, emphasizing the need for further investigation into the correlation between TNF-α G308A and AD risk [50].

Altogether, these insights underscore the intricate interplay of immune responses in AD pathogenesis and highlight the role of TNF-α. In the following paragraph, researchers will review the main evidence in human and animal studies and finally, researchers will discuss the possible future directions.

2. Evidence in Humans

2.1. Cerebrospinal Fluid and Blood Studies

The primary evidence for this association derives from an initial study performed on the CSF of mild cognitive impairment (MCI) patients which demonstrated higher TNFα and tau protein levels and lower TGFß and Aß levels in MCI patients compared to controls. Interestingly, MCI patients progressing to AD showed elevated CSF TNFα [51]. Elevated serum TNF-α concentrations in AD patients compared to healthy individuals and individuals with MCI were subsequently demonstrated [52][53][54]. A 6-month study exploring the association between TNF-α levels and cognitive performance in 300 subjects with varying AD severity, found that acute inflammation correlated with a twofold cognitive decline increase, and high-baseline TNF-α levels quadrupled the decline [55]. Kim and colleagues performed an analysis of serum cytokine levels in individuals affected by AD, in those with MCI, and in a cohort of healthy controls to ascertain the connections between these cytokine levels and the neuropsychological parameters. Noteworthy associations between the levels of TNF-α and interleukin-6 (IL-6) and the cognitive performance, assessed using the Mini-Mental State Examination (MMSE) score were described [56]. Another interesting study explored the correlation between CSF TNF-α and functional connectivity in 64 older adults and found that elevated TNF-α levels correlated with reduced connectivity in decision-making, inhibitory control, and memory regions, with APOE4 status moderating this effect [57]. The time courses of levels of multiple plasma and CSF cytokines in patients with AD and age-matched control subjects were assessed in a study by Llano and colleagues, by measuring cytokine levels 7 times over 24 h in plasma and CSF using a lumbar catheter. The authors found that CSF levels of IL-1β, IL-2, IL-10, IL-12p70, granulocyte-macrophage colony-stimulating factor, interferon-γ, and TNF-α diverged over time, with higher levels in AD subjects compared to controls, with no difference in cytokine trajectories observed in plasma [58]. Another noteworthy investigation revealed that TNFR displayed more robust connections with total tau and p-tau in comparison to Aβ1-42, spanning healthy controls, MCI, and AD subjects. Within the longitudinal cohort, individuals with MCI who exhibited heightened levels of CSF TNFR1 and diminished levels of TNFR2 had an increased susceptibility to advancing to AD [59].

2.2. Genetic Studies

Moreover, extensive research has suggested that specific TNF-α gene polymorphisms contribute to an increased risk of AD. In a meta-analysis aiming to define the association of common TNF-α gene polymorphisms with the risk of AD, Di Bona et al. selected 17 studies and evaluated them with a model-free method approach, to comprehensively analyze the results of these case-control genetic association studies. Notably, their research indicates a correlation between the −850 C > T polymorphism and the susceptibility to AD [60]. Additionally, Yang et al. performed a case-control study in the Southern Chinese population, involving the use of polymerase chain reaction-sequence specific primers (PCR-SSP) to assess TNF-α genotypes and alleles in 112 sporadic AD patients and 121 controls. Additionally, they quantified serum TNF-alpha levels through radioimmunoassay. They found significantly higher levels of serum TNF-α in sporadic AD patients and that both −308 A/G polymorphism and elevation of serum level of TNF-α were both associated with an increased risk of AD [61].

2.3. TNF-α Inhibitors

Observational investigations conducted on individuals with systemic inflammatory disorders treated with TNF-α inhibitors offer additional substantiation for the implication of TNF-α in the pathogenesis of AD. A large retrospective case-control analysis, encompassing 56 million adult patients afflicted with inflammatory conditions, revealed a diminished risk of AD development with the administration of TNF-α inhibitors [48]. A previous nested case-control study revealed a higher AD prevalence among RA patients compared to those without rheumatoid arthritis, with a further significant increase in risk in those who were affected by chronic conditions including coronary artery disease, diabetes, and peripheral vascular disease. Notably, exposure to anti-TNF agents, particularly etanercept, was associated with a reduced risk of AD in these patients [62]. Elderly rheumatoid arthritis patients showed improved cognitive performance with subcutaneous anti-TNF-α therapy using drugs like etanercept and adalimumab [63]. In contrast, a double-blind study in mild and moderate AD patients treated with subcutaneous etanercept did not show significant changes in cognitive function, behavior, and global functions though there was a positive trend in the anti-TNF-α treatment group [64]. The limited effectiveness of subcutaneous anti-TNF-α therapies in AD patients may be attributed to the large molecular weight of anti-TNF-α monoclonal antibodies because this makes the passage through the blood–brain barrier impossible under physiological conditions [34].

Interesting clinical studies collectively suggested that perispinal administration of etanercept may lead to significant and sustained improvements in AD and primary progressive aphasia, showcasing its potential as a therapeutic intervention. In a prospective, single-center, open-label, pilot study, involving 15 patients with AD and primary progressive aphasia, perispinal etanercept infusion (25–50 mg weekly for six months) demonstrated significant improvement in cognition [65]. The benefits of this treatment were sustained in patients who continued for over two years [66]. Furthermore, another case report describing an 81-year-old patient who was given 25 mg of perispinal etanercept by posterior cervical interspinous injection outlined swift cognitive enhancement, starting within minutes. The rapid cognitive improvement observed in this patient has been hypothesized to be linked to the mitigation of the effects of excess TNF-α on gliotransmission or other synaptic mechanisms in AD [67][68]. Due to the limitations of large molecules like etanercept in crossing the blood–brain barrier with traditional systemic administration, the perispinal direct drug delivery system likely played a role in the treatment's efficacy [68].

Studies exploring the efficacy of anti-TNF-α drugs on the progression of AD are summarized in **Table 1**. To the best of our knowledge, there is currently no ongoing study that can adequately elucidate the potential role of these drugs in AD. Further research and larger-scale studies are warranted to establish the efficacy of TNF-α inhibition in AD conclusively.

Table 1. Clinical trials exploring the efficacy of anti-TNF-α drugs on the progression of Alzheimer's disease.

Reference	Type of Study	Intervention	Main Findings
Tobinick et al., 2006 [65]	prospective, single-center, open-label, pilot study	25–50 mg of etanercept was administered once weekly by perispinal administration for 6 months	significant improvement in cognition in treated patients
Tobinick et al., 2008 [67]	prospective, single-center, open-label, pilot study	weekly administration of etanercept, 25–50 mg, perispinally for six months in 12 patients with mild to severe AD for 6 months	Significant improvement in cognition in treated patients and rapid improvement in verbal fluency and aphasia in two dementia patients, starting minutes after administration of perispinal etanercept.
Butchart et al., 2015 [64]	randomized, placebo-controlled, double-blind, phase 2 trial registered with EudraCT (2009-013400-31) and ClinicalTrials.gov (NCT01068353)	peripheral subcutaneous administration of etanercept 50 mg once weekly for 24 weeks; 41 participants with mild to moderate Alzheimer disease	Treatment well tolerated but no significant change in cognition, behavior, or global function.
Chen et al., 2010 [63]	pilot study	15 elderly patients with rheumatoid arthritis: 8 received etanercept 25 mg twice weekly and 7 received adalimumab 40 mg twice monthly	Cognitive improvement in 11 of 15 participants; no improvement in depression.

References

1. Breder, C.D.; Tsujimoto, M.; Terano, Y.; Scott, D.W.; Saper, C.B. Distribution and Characterization of Tumor Necrosis Factor-α-like Immunoreactivity in the Murine Central Nervous System. J. Comp. Neurol. 1993, 337, 543–567.
2. Vitkovic, L.; Bockaert, J.; Jacque, C. "Inflammatory" Cytokines' Neuromodulators in Normal Brain? J. Neurochem. 2000, 74, 457–471.
3. Boulanger, L.M. Immune Proteins in Brain Development and Synaptic Plasticity. Neuron 2009, 64, 93–109.

4. Probert, L. TNF and Its Receptors in the CNS: The Essential, the Desirable and the Deleterious Effects. Neuroscience 2015, 302, 2–22.
5. Raffaele, S.; Lombardi, M.; Verderio, C.; Fumagalli, M. TNF Production and Release from Microglia via Extracellular Vesicles: Impact on Brain Functions. Cells 2020, 9, 2145.
6. Stellwagen, D.; Beattie, E.C.; Seo, J.Y.; Malenka, R.C. Differential Regulation of AMPA Receptor and GABA Receptor Trafficking by Tumor Necrosis Factor-α. J. Neurosci. 2005, 25, 3219–3228.
7. He, P.; Liu, Q.; Wu, J.; Shen, Y. Genetic Deletion of TNF Receptor Suppresses Excitatory Synaptic Transmission via Reducing AMPA Receptor Synaptic Localization in Cortical Neurons. FASEB J. 2012, 26, 334–345.
8. Ogoshi, F.; Yin, H.Z.; Kuppumbatti, Y.; Song, B.; Amindari, S.; Weiss, J.H. Tumor Necrosis-Factor-Alpha (TNF-α) Induces Rapid Insertion of Ca2+-Permeable α-Amino-3-Hydroxyl-5-Methyl-4-Isoxazole- Propionate (AMPA)/Kainate (Ca-A/K) Channels in a Subset of Hippocampal Pyramidal Neurons. Exp. Neurol. 2005, 193, 384–393.
9. Pribiag, H.; Stellwagen, D. Tnf-α Downregulates Inhibitory Neurotransmission through Protein Phosphatase 1-Dependent Trafficking of GABAA Receptors. J. Neurosci. 2013, 33, 15879–15893.
10. Leonoudakis, D.; Zhao, P.; Beattie, E.C. Rapid Tumor Necrosis Factor α-Induced Exocytosis of Glutamate Receptor 2-Lacking AMPA Receptors to Extrasynaptic Plasma Membrane Potentiates Excitotoxicity. J. Neurosci. 2008, 28, 2119–2130.
11. Santello, M.; Bezzi, P.; Volterra, A. TNFα Controls Glutamatergic Gliotransmission in the Hippocampal Dentate Gyrus. Neuron 2011, 69, 988–1001.
12. Zielinski, M.R.; Gibbons, A.J. Neuroinflammation, Sleep, and Circadian Rhythms. Front. Cell. Infect. Microbiol. 2022, 12, 853096.
13. Kaushal, N.; Ramesh, V.; Gozal, D. TNF-α and Temporal Changes in Sleep Architecture in Mice Exposed to Sleep Fragmentation. PLoS ONE 2012, 7, e45610.
14. Dickstein, J.B.; Moldofsky, H.; Lue, F.A.; Hay, J.B. Intracerebroventricular Injection of TNF-α Promotes Sleep and Is Recovered in Cervical Lymph. Am. J. Physiol. Regul. Integr. Comp. Physiol. 1999, 276, R1018–R1022.
15. Zielinski, M.R.; Dunbrasky, D.L.; Taishi, P.; Souza, G.; Krueger, J.M. Vagotomy Attenuates Brain Cytokines and Sleep Induced by Peripherally Administered Tumor Necrosis Factor-α and Lipopolysaccharide in Mice. Sleep 2013, 36, 1227–1238.
16. Papazian, I.; Tsoukala, E.; Boutou, A.; Karamita, M.; Kambas, K.; Iliopoulou, L.; Fischer, R.; Kontermann, R.E.; Denis, M.C.; Kollias, G.; et al. Fundamentally Different Roles of Neuronal TNF Receptors in CNS Pathology: TNFR1 and IKKβ Promote Microglial Responses and Tissue Injury

in Demyelination While TNFR2 Protects against Excitotoxicity in Mice. J. Neuroinflamm. 2021, 18, 222.

17. Cauwels, A.; Janssen, B.; Waeytens, A.; Cuvelier, C.; Brouckaert, P. Caspase Inhibition Causes Hyperacute Tumor Necrosis Factor-Induced Shock via Oxidative Stress and Phospholipase A2. Nat. Immunol. 2003, 4, 387–393.
18. Vandenabeele, P.; Declercq, W.; Van Herreweghe, F.; Berghe, T. Vanden The Role of the Kinases RIP1 and RIP3 in TNF-Induced Necrosis. Sci. Signal 2010, 3, re4.
19. Zhang, D.W.; Shao, J.; Lin, J.; Zhang, N.; Lu, B.J.; Lin, S.C.; Dong, M.Q.; Han, J. RIP3, an Energy Metabolism Regulator That Switches TNF-Induced Cell Death from Apoptosis to Necrosis. Science 2009, 325, 332–336.
20. Chen, X.; Subleski, J.J.; Kopf, H.; Howard, O.M.Z.; Männel, D.N.; Oppenheim, J.J. Cutting Edge: Expression of TNFR2 Defines a Maximally Suppressive Subset of Mouse CD4+CD25+FoxP3+ T Regulatory Cells: Applicability to Tumor-Infiltrating T Regulatory Cells. J. Immunol. 2008, 180, 6467–6471.
21. Tchélingérian, J.-L.; Monge, M.; Le Saux, F.; Zalc, B.; Jacque, C. Differential Oligodendroglial Expression of the Tumor Necrosis Factor Receptors In Vivo and In Vitro. J. Neurochem. 1995, 65, 2377–2380.
22. Naudé, P.J.W.; Den Boer, J.A.; Luiten, P.G.M.; Eisel, U.L.M. Tumor Necrosis Factor Receptor Cross-Talk. FEBS J. 2011, 278, 888–898.
23. Rothe, M.; Sarma, V.; Dixit, V.; Goeddel, D. TRAF-2-Mediated Activation of NF-KappaB by TNF Receptor 2 and CD40. Science 1995, 269, 1424–1427.
24. Rao, P.; Hsu, K.C.; Chao, M.V. Upregulation of NF-KB-Dependent Gene Expression Mediated by the P75 Tumor Necrosis Factor Receptor. J. Interferon Cytokine Res. 1995, 15, 171–177.
25. Medvedev, A.E.; Sundan, A.; Espevik, T. Involvement of the Tumor Necrosis Factor Receptor P75 in Mediating Cytotoxicity and Gene Regulating Activities. Eur. J. Immunol. 1994, 24, 2842–2849.
26. Weiss, T.; Grell, M.; Hessabi, B.; Bourteele, S.; Müller, G.; Scheurich, P.; Wajant, H. Enhancement of TNF Receptor P60-Mediated Cytotoxicity by TNF Receptor P80: Requirement of the TNF Receptor-Associated Factor-2 Binding Site. J. Immunol. 1997, 158, 2398–2404.
27. Maier, O.; Fischer, R.; Agresti, C.; Pfizenmaier, K. TNF Receptor 2 Protects Oligodendrocyte Progenitor Cells against Oxidative Stress. Biochem. Biophys. Res. Commun. 2013, 440, 336–341.
28. Neta, R.; Sayers, T.J.; Oppenheim, J.J. Relationship of TNF to Interleukins. Immunol. Ser. 1992, 56, 499–566.

29. Zhao, J.; O’Connor, T.; Vassar, R. The Contribution of Activated Astrocytes to Aβ Production: Implications for Alzheimer’s Disease Pathogenesis. J. Neuroinflamm. 2011, 8, 150.
30. Blasko, I.; Marx, F.; Steiner, E.; Hartmann, T.; Grubeck-Loebenstein, B. TNFalpha plus IFNgamma Induce the Production of Alzheimer Beta-Amyloid Peptides and Decrease the Secretion of APPs. FASEB J. 1999, 13, 63–68.
31. Liaoi, Y.F.; Wang, B.J.; Cheng, H.T.; Kuo, L.H.; Wolfe, M.S. Tumor Necrosis Factor-α, Interleukin-1β, and Interferon-γ Stimulate γ-Secretase-Mediated Cleavage of Amyloid Precursor Protein through a JNK-Dependent MAPK Pathway. J. Biol. Chem. 2004, 279, 49523–49532.
32. Koenigsknecht-Talboo, J.; Landreth, G.E. Microglial Phagocytosis Induced by Fibrillar β-Amyloid and IgGs Are Differentially Regulated by Proinflammatory Cytokines. J. Neurosci. 2005, 25, 8240–8249.
33. Montgomery, S.L.; Narrow, W.C.; Mastrangelo, M.A.; Olschowka, J.A.; O’Banion, M.K.; Bowers, W.J. Chronic Neuron- and Age-Selective down-Regulation of TNF Receptor Expression in Triple-Transgenic Alzheimer Disease Mice Leads to Significant Modulation of Amyloid- and Tau-Related Pathologies. Am. J. Pathol. 2013, 182, 2285–2297.
34. Ou, W.; Yang, J.; Simanauskaite, J.; Choi, M.; Castellanos, D.M.; Chang, R.; Sun, J.; Jagadeesan, N.; Parfitt, K.D.; Cribbs, D.H.; et al. Biologic TNF-α Inhibitors Reduce Microgliosis, Neuronal Loss, and Tau Phosphorylation in a Transgenic Mouse Model of Tauopathy. J. Neuroinflamm. 2021, 18, 312.
35. Halliday, G.; Robinson, S.R.; Shepherd, C.; Kril, J. Alzheimer’s Disease and Inflammation: A Review of Cellular and Therapeutic Mechanisms. Clin. Exp. Pharmacol. Physiol. 2000, 27, 1–8.
36. McGeer, E.G.; McGeer, P.L. Brain Inflammation in Alzheimer Disease and the Therapeutic Implications. Curr. Pharm. Des. 2023, 5, 821–836.
37. Heppner, F.L.; Ransohoff, R.M.; Becher, B. Immune Attack: The Role of Inflammation in Alzheimer Disease. Nat. Rev. Neurosci. 2015, 16, 358–372.
38. Guzman-Martinez, L.; Maccioni, R.B.; Andrade, V.; Navarrete, L.P.; Pastor, M.G.; Ramos-Escobar, N. Neuroinflammation as a Common Feature of Neurodegenerative Disorders. Front. Pharmacol. 2019, 10, 1008.
39. Wang, S.; Colonna, M. Microglia in Alzheimer’s Disease: A Target for Immunotherapy. J. Leukoc. Biol. 2019, 106, 219–227.
40. Gao, C.; Jiang, J.; Tan, Y.; Chen, S. Microglia in Neurodegenerative Diseases: Mechanism and Potential Therapeutic Targets. Signal Transduct. Target. Ther. 2023, 8, 359.
41. Hansen, D.V.; Hanson, J.E.; Sheng, M. Microglia in Alzheimer’s Disease. J. Cell Biol. 2018, 217, 459–472.

42. Mandrekar-Colucci, S.; Landreth, G.E. Microglia and Inflammation in Alzheimer’s Disease. CNS Neurol. Disord. Drug Targets 2012, 9, 156–167.
43. Mrak, R.E. Microglia in Alzheimer’s Brain: A Neuropathological Perspective. Int. J. Alzheimers Dis. 2012, 2012, 165021.
44. Mazaheri, F.; Snaidero, N.; Kleinberger, G.; Madore, C.; Daria, A.; Werner, G.; Krasemann, S.; Capell, A.; Trümbach, D.; Wurst, W.; et al. TREM 2 Deficiency Impairs Chemotaxis and Microglial Responses to Neuronal Injury. EMBO Rep. 2017, 18, 1186–1198.
45. Jay, T.R.; Von Saucken, V.E.; Landreth, G.E. TREM2 in Neurodegenerative Diseases. Mol. Neurodegener. 2017, 12, 56.
46. Gratuze, M.; Leyns, C.E.G.; Holtzman, D.M. New Insights into the Role of TREM2 in Alzheimer’s Disease. Mol. Neurodegener. 2018, 13, 66.
47. Li, R.; Zhang, J.; Wang, Q.; Cheng, M.; Lin, B. TPM1 Mediates Inflammation Downstream of TREM2 via the PKA/CREB Signaling Pathway. J. Neuroinflamm. 2022, 19, 257.
48. Zhou, M.; Xu, R.; Kaelber, D.C.; Gurney, M.E. Tumor Necrosis Factor (TNF) Blocking Agents Are Associated with Lower Risk for Alzheimer’s Disease in Patients with Rheumatoid Arthritis and Psoriasis. PLoS ONE 2020, 15, e0229819.
49. Alvarez, V.; Mata, I.F.; González, P.; Lahoz, C.H.; Martínez, C.; Peña, J.; Guisasola, L.M.; Coto, E. Association between the TNFα-308 A/G Polymorphism and the Onset-Age of Alzheimer Disease. Am. J. Med. Genet. 2002, 114, 574–577.
50. Wang, T. TNF-Alpha G308A Polymorphism and the Susceptibility to Alzheimer’s Disease: An Updated Meta-Analysis. Arch. Med. Res. 2015, 46, 24–30.
51. Tarkowski, E.; Andreasen, N.; Tarkowski, A.; Blennow, K. Intrathecal Inflammation Precedes Development of Alzheimer’s Disease. J. Neurol. Neurosurg. Psychiatry 2003, 74, 1200–1205.
52. Khemka, V.K.; Ganguly, A.; Bagchi, D.; Ghosh, A.; Bir, A.; Biswas, A.; Chattopadhyay, S.; Chakrabarti, S. Raised Serum Proinflammatory Cytokines in Alzheimer’s Disease with Depression. Aging Dis. 2014, 5, 170–176.
53. Brosseron, F.; Krauthausen, M.; Kummer, M.; Heneka, M.T. Body Fluid Cytokine Levels in Mild Cognitive Impairment and Alzheimer’s Disease: A Comparative Overview. Mol. Neurobiol. 2014, 50, 534–544.
54. Culjak, M.; Perkovic, M.N.; Uzun, S.; Strac, D.S.; Erjavec, G.N.; Leko, M.B.; Simic, G.; Tudor, L.; Konjevod, M.; Kozumplik, O.; et al. The Association between TNF-Alpha, IL-1 Alpha and IL-10 with Alzheimer’s Disease. Curr. Alzheimer Res. 2020, 17, 972–984.
55. Holmes, C.; Cunningham, C.; Zotova, E.; Woolford, J.; Dean, C.; Kerr, S.; Culliford, D.; Perry, V.H. Systemic Inflammation and Disease Progression in Alzheimer Disease. Neurology 2009, 73, 768–

774.

56. Kim, Y.S.; Lee, K.J.; Kim, H. Serum Tumour Necrosis Factor-α and Interleukin-6 Levels in Alzheimer’s Disease and Mild Cognitive Impairment. Psychogeriatrics 2017, 17, 224–230.
57. Contreras, J.A.; Aslanyan, V.; Sweeney, M.D.; Sanders, L.M.J.; Sagare, A.P.; Zlokovic, B.V.; Toga, A.W.; Han, S.D.; Morris, J.C.; Fagan, A.; et al. Functional Connectivity among Brain Regions Affected in Alzheimer’s Disease Is Associated with CSF TNF-α in APOE4 Carriers. Neurobiol. Aging 2020, 86, 112–122.
58. Llano, D.A.; Li, J.; Waring, J.F.; Ellis, T.; Devanarayan, V.; Witte, D.G.; Lenz, R.A. Cerebrospinal Fluid Cytokine Dynamics Differ between Alzheimer Disease Patients and Elderly Controls. Alzheimer Dis. Assoc. Disord. 2012, 26, 322–328.
59. Zhao, A.; Li, Y.; Deng, Y. TNF Receptors Are Associated with Tau Pathology and Conversion to Alzheimer’s Dementia in Subjects with Mild Cognitive Impairment. Neurosci. Lett. 2020, 738, 135392.
60. Di Bona, D.; Candore, G.; Franceschi, C.; Licastro, F.; Colonna-Romano, G.; Cammà, C.; Lio, D.; Caruso, C. Systematic Review by Meta-Analyses on the Possible Role of TNF-α Polymorphisms in Association with Alzheimer’s Disease. Brain Res. Rev. 2009, 61, 60–68.
61. Yang, L.; Lu, R.; Jiang, L.; Liu, Z.; Peng, Y. Expression and Genetic Analysis of Tumor Necrosis Factor-α (TNF-α) G-308A Polymorphism in Sporadic Alzheimer’s Disease in a Southern China Population. Brain Res. 2009, 1247, 178–181.
62. Chou, R.C.; Kane, M.; Ghimire, S.; Gautam, S.; Gui, J. Treatment for Rheumatoid Arthritis and Risk of Alzheimer’s Disease: A Nested Case-Control Analysis. CNS Drugs 2016, 30, 1111–1120.
63. Chen, Y.M.; Chen, H.H.; Lan, J.L.; Chen, D.Y. Improvement of Cognition, a Potential Benefit of Anti-TNF Therapy in Elderly Patients with Rheumatoid Arthritis. Jt. Bone Spine 2010, 77, 366–367.
64. Butchart, J.; Brook, L.; Hopkins, V.; Teeling, J.; Puntener, U.; Culliford, D.; Sharples, R.; Sharif, S.; McFarlane, B.; Raybould, R.; et al. Etanercept in Alzheimer Disease: A Randomized, Placebo-Controlled, Double-Blind, Phase 2 Trial. Neurology 2015, 84, 2161–2168.
65. Tobinick, E.; Gross, H.; Weinberger, A.; Cohen, H. TNF-Alpha Modulation for Treatment of Alzheimer’s Disease: A 6-Month Pilot Study. MedGenMed 2006, 8, 25.
66. Tobinick, E. Perispinal Etanercept for Treatment of Alzheimers Disease. Curr. Alzheimer Res. 2007, 4, 550–552.
67. Tobinick, E.L.; Gross, H. Rapid Cognitive Improvement in Alzheimer’s Disease Following Perispinal Etanercept Administration. J. Neuroinflamm. 2008, 5, 2.

68. Griffin, W.S.T. Perispinal Etanercept: Potential as an Alzheimer Therapeutic. J. Neuroinflamm. 2008, 5, 3.