European Journal of Neurodegenerative Diseases
ISSN 2279-5855 / 2020 vol. 9, ISSUE N. 2, July-December

ROLE OF INFLAMMATION IN ALZHEIMER'S DISEASE: AN EMPHASIS ON TREM2 AND CD33

Al. Caraffa*

School of Pharmacy, University of Camerino, Camerino, Italy.

Correspondence to:
Alessandro Caraffa,
School of Pharmacy,
University of Camerino,
Camerino, Italy.
e-mail: alecaraffa@libero.it

ABSTRACT

Alzheimer's disease (AD) is the leading cause of dementia globally. It is a progressive and irreversible neurologic disorder that results in personality changes, memory loss, cognitive decline, and death. Hallmarks of the disease include extracellular amyloid-β (Aβ) plaque deposition, the accumulation of neurofibrillary tangles (NFTs) of hyperphosphorylated tau, and neuroinflammation. Aβ plaque deposition is believed to be central to the pathogenesis of AD. Activation of microglia, innate immune cells of the central nervous system, can have both beneficial and harmful consequences, as they are able to aid in Aβ plaque clearance, but also release damaging pro-inflammatory cytokines. Microglial cells are involved with Aβ plaque formations and may play a central role in AD pathogenesis. Diverse gene networks implicating microglia and affecting immune function have been identified, including microglial receptors triggering receptors expressed on myeloid cells 2 (TREM2) and CD33. Both are considerable risk factors for the development of late-onset AD and in this paper, we summarize their role, and that of microglia, in the inflammation occurring in AD.

KEYWORDS: *Alzheimer's disease, inflammation, immunity, TREM2, CD33, microglia, neurology, neurodegenerative*

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurologic disorder and the leading cause of dementia worldwide (1). Most cases are late-onset, usually occurring after the age of 65 (2). It is characterized by extracellular amyloid-β (Aβ) plaque deposition and the accumulation of neurofibrillary tangles (NFTs) of hyperphosphorylated tau. Symptoms include memory loss, changes in personality and behavior, progressive cognitive decline, and eventually, death. Genetic changes can cause AD to an extent.

AD is complex, but different theories exist to explain the mechanisms involved. The most predominant is the Aβ cascade hypothesis, focusing on Aβ accumulation as the fundamental element in AD development (3). It theorizes that Aβ groups form plaques on the outside of brain neurons, followed by inflammation and NFTs of tau protein, eventually leading to neuronal death, which then results in neurodegeneration. Evidence has suggested that the inability to clear Aβ is central to AD pathogenesis, rather than the overproduction of Aβ (4).

Neuroinflammation is another hallmark of AD, with elevated expression of inflammatory mediators, and microglia and astrocytes showing changes in morphology, activation, and distribution (5, 6). Microglia are innate immune cells resident in the central nervous system (CNS), responsible for immune surveillance and mediation. They are important for

Received: 03 October, 2020
Accepted: 27 December, 2020

2279-5855 (2020)

tissue repair and damage control, but their response can also be detrimental to the release of pro-inflammatory substances. It is believed that inflammation mediated by microglia plays a central role in the progression of AD, but the process is complex and the exact mechanisms by which this occurs is still unclear.

CD33 and triggering receptor expressed on myeloid cells 2 (TREM2) are microglial receptors that regulate inflammation in AD and are associated risk factors. In this paper we summarize the pathogenesis of late onset AD with a focus on the role of microglia in inflammation and the involvement of CD33 and TREM2.

Microglial cells

In the brain, microglia have functions similar to macrophages, providing immune surveillance and tissue maintenance. Microglial cells and Aβ formation is linked. Microglia protect the CNS by helping to clear Aβ plaque formations, yet fibrillar Aβ can activate microglia, leading to the release of inflammatory mediators, such as pro-inflammatory cytokines, that can be damaging to the CNS (7).

Microglia are plastic, with the ability to change phenotype in response to stimuli and interact with neurons to mediate the immune environment (8). They show branching dynamics, the capability to expand and retract into neighboring tissue, which allows for continuous immune surveillance and rapid convergence to an injury site (9). This includes the response to Aβ plaque that occurs with AD.

Aβ plaque formation can activate microglia to an inflammatory phenotype, as seen in animal models (10,11). Microglia congregate to Aβ deposits, mostly converging at the sites of densely concentrated plaques, with fewer observed in unconcentrated surrounding areas (12,13). Microglia are attracted to plaque, congregating around formations, and increasing and growing over time (14-16).

Surface cell receptor and toll-like receptor (TLR)-detection of intracellular proteins and damage-associated molecular patterns (DAMP) molecules initiate the innate immune response to injury. Interestingly, increased expression of CD14 (17), TLR2, and TLR4 (18) by microglia has been seen in the AD brain (19).

In the AD brain, deposition of fibrillar forms of Aβ occurs, activating microglia through a cell surface receptor complex that includes the B-class scavenger receptor CD36, the integrin-associated protein/CD47, and the α6β1-integrin (20). This leads to signaling cascades, and the defensive reaction of activated microglia includes the production of free radicals and the release of pro-inflammatory cytokines that can contribute to CNS injury. The inflammation that occurs is thought to be integral in the progression of the disease. In fact, microglial activation in AD brains has been associated with elevated levels of cytokines and chemokines, such as interferon γ (IFNγ), tumor necrosis factor (TNF), interleukin 1β (IL-1β), interleukin 6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1) (21-24).

In their role as principal immune effectors, microglia participate in phagocytosis, removing and clearing targets such as pathogens, apoptotic cells, and cellular debris. Microglia can internalize fibrillar forms of Aβ, but degradation and complete clearance is not always effective (25-27). Diverse studies have shown that inflammation may negatively interfere with the ability of microglial cells to clear Aβ plaques (28-30).

Additionally, microglia cell surface receptors are important for Aβ recognition and subsequent response (31). Microglia require the triggering receptor TREM2 for the phagocytosis of certain substrates, including Aβ (32). TREM2-deficient microglia were seen to remain inactivated and not congregate around Aβ plaques (33,34) (Fig.1).

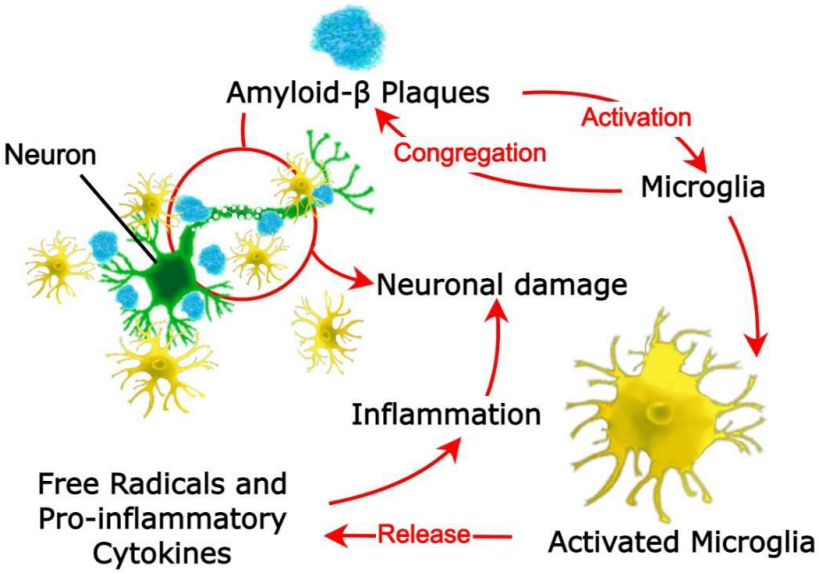

Fig. 1. *Amyloid-β (Aß) groups to form plaques on the outside of brain neurons, causing neuronal damage. Aß plaque deposition activates microglial cells, which congregate to sites of Aß plaque formation and release free radicals and pro-inflammatory cytokines, leading to inflammation and subsequent neuronal damage.*

Genetic risk factors

Heritability for late onset AD is high, does not differ by sex, and is estimated to be between 58-79% in twin studies (35). Apolipoprotein E ε4 (APOE ε4) was the first confirmed genetic risk factor (36), until recently when many different genes have been identified to be associated with the development of AD, numerous of which are also associated with inflammation and microglia (37). Some of these gene networks that are closely tied to the immune system, such as CR1, SPI1, the MS4As, TREM2, ABCA7, CD33, and INPP5D, are expressed by microglia (37). This supports the role that neuroinflammation plays in the development of AD.

Microglial receptors TREM2 and CD33, which are involved in immune function activation and are associated with one another, are of particular interest in AD. CD33 is one of the top-ranked genes for risk of AD and is exclusively expressed in microglia. Rare variants of TREM2 are a considerable risk factor and can increase the risk of developing AD by 2-4 times (5).

CD33

CD33 is a transmembrane myeloid cell receptor that is expressed in microglia and macrophages in the brain, with the ability to inhibit immune cell functions. In genome-wide association studies, CD33 has been identified as one of the greatest risk factors for AD (38-40), with two variants posing the highest risk, rs3865444 and rs12459419 (41,42).

Studies have suggested that CD33 is involved in diverse immune functions, including cell adhesion processes, endocytosis, immune cell growth, TLR4 signaling, and can inhibit the release of cytokines (43-45).

It is believed that its expression regulates the activation of microglia and interferes with the clearance of Aβ by inhibition, with Aβ plaque formation resulting in turn (46). CD33 is increased in the brain with AD, correlated with disease severity as well as the extent of Aβ plaque formation (47). The T allele of single-nucleotide polymorphism (SNP) rs3865444 has been associated with decreased CD33 levels and Aβ plaque burden in the brain (45), and the C allele was associated with increased CD33 levels and Aβ plaque burden (48).

Evidence shows that CD33 may inhibit the production of pro-inflammatory cytokines such as IL-1β, TNF, IL-8, and furthermore, increased TNF secretion by immune cells was seen with the downregulation of CD33 (49). Animal studies have also revealed evidence, as mice without CD33 showed greatly reduced Aβ plaque levels (45).

Because CD33 inhibits Aβ clearance, subsequently generating the formation of Aβ plaques, targeting CD33 could be a therapeutic opportunity in AD.

TREM2

TREM2 is a triggering receptor expressed on myeloid cells, and microglia are responsible for TREM2 expression in the CNS, where it is associated with inflammation (5). It can suppress the production of pro-inflammatory cytokines and promote phagocytosis of Aβ plaque by microglia (50,51).

TREM2 expression is increased by the expression of anti-inflammatory molecules, while pro-inflammatory ones, such as TNF and IL-1β, decrease its expression (51,52). Microglial aggregation to Aβ plaques causes upregulation of TREM2, which has been reported in animal models and humans (53,54). TREM2 upregulation is also associated with aging (55).

TREM2 binds to Aβ, is involved in microglial activation and degradation of Aβ, and mediates the microglial expression of cytokines (56). TREM2 expression promotes phagocytosis by microglia, which has been seen in studies correlating increased expression with increased phagocytosis (50,57), and decreased phagocytosis with TREM2 loss (58,59). TREM2 moderates microglial functions and binds to Aβ, and mutations of TREM2 in AD reduce Aβ binding (56). TREM2 also modulates inflammation by signaling and has anti-inflammatory effects (50), although some studies seem to show an association with pro-inflammatory effects as well (60,61). Lastly, TREM2 affects the proliferation and survival of myeloid cells, including microglia (59).

TREM2 variants are a significant risk factor for late-onset AD. Rs75932628 is a common TREM2 gene variant risk factor. It has been identified in European and North American populations in diverse studies but cannot be confirmed in Chinese communities (62-65).

CONCLUSIONS

AD is a prevalent and highly complex neurodegenerative disorder. Increasing evidence suggests that inflammation plays a vital role in the development of the pathogenesis of the disease. Aβ plaque deposition is thought to be a fundamental characteristic of AD. The inability to effectively clear Aβ plaque formations is likely the key to disease progression, rather than Aβ overproduction. Microglia and Aβ are closely associated, with the formation of Aβ plaques activating microglia and causing microglial congregation. Microglia aid in phagocytosis and clearance of Aβ but can also release harmful pro-inflammatory cytokines.

Heritability is high and diverse genes have been identified that implicate microglia and immune function in the development of AD. Microglial receptors CD33 and TREM2 are involved in immune function and are two significant risk factors for AD development.

Conflict of interest

The author declares that they have no conflict of interest.

REFERENCES

1. Prince M, Wimo A, Ali GC, et al. *World Alzheimer Report 2015 the Global Impact of Dementia an analysis of prevalence, incidence, cost and trends Dr Maëlenn Guerchet Alzheimer's Disease International*.; 2015. Accessed September 29, 2019. http://www.alzheimer.it/report2015.pdf
2. Holtzman DM, Morris JC, Goate AM. Alzheimer's Disease: The Challenge of the Second Century. *Science Translational Medicine*. 2011;3(77):77sr1-77sr1. doi:10.1126/scitranslmed.3002369
3. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science (New York, NY)*. 2002;297(5580):353-356. doi:10.1126/science.1072994
4. Mawuenyega KG, Sigurdson W, Ovod V, et al. Decreased Clearance of CNS -Amyloid in Alzheimer's Disease. *Science*. 2010;330(6012):1774-1774. doi:10.1126/science.1197623
5. Gratuze M, Leyns CEG, Holtzman DM. New insights into the role of TREM2 in Alzheimer's disease. *Molecular Neurodegeneration*. 2018;13(1). doi:10.1186/s13024-018-0298-9
6. Itagaki S, McGreer P, Akiyama H, Zhu S, Selkoe D. Relationship of microglia and astrocytes to amyloid deposits of Alzheimer disease. *Journal of Neuroimmunology*. 1989;24(3):173-182. doi:10.1016/0165-5728(89)90115-x
7. Cameron B, Landreth GE. Inflammation, microglia, and alzheimer's disease. *Neurobiology of Disease*. 2010;37(3):503-509. doi:10.1016/j.nbd.2009.10.006

8. Colton CA. Heterogeneity of Microglial Activation in the Innate Immune Response in the Brain. *Journal of Neuroimmune Pharmacology*. 2009;4(4):399-418. doi:10.1007/s11481-009-9164-4
9. Davalos D, Grutzendler J, Yang G, et al. ATP mediates rapid microglial response to local brain injury in vivo. *Nature Neuroscience*. 2005;8(6):752-758. doi:10.1038/nn1472
10. Yan P, Bero AW, Cirrito JR, et al. Characterizing the Appearance and Growth of Amyloid Plaques in APP/PS1 Mice. *Journal of Neuroscience*. 2009;29(34):10706-10714. doi:10.1523/jneurosci.2637-09.2009
11. Bornemann KD, Wiederhold KH, Pauli C, et al. Aβ-Induced Inflammatory Processes in Microglia Cells of APP23Transgenic Mice. *The American Journal of Pathology*. 2001;158(1):63-73. doi:10.1016/s0002-9440(10)63945-4
12. Stalder M, Phinney A, Probst A, Sommer B, Staufenbiel M, Jucker M. Association of Microglia with Amyloid Plaques in Brains of APP23 Transgenic Mice. *The American Journal of Pathology*. 1999;154(6):1673-1684. doi:10.1016/s0002-9440(10)65423-5
13. Akiyama H, Mori H, Saido T, Kondo H, Ikeda K, McGeer PL. Occurrence of the diffuse amyloid beta-protein (Abeta) deposits with numerous Abeta-containing glial cells in the cerebral cortex of patients with Alzheimer's disease. *Glia*.1999;25(4):324–331.
14. Wegiel J. The role of microglial cells and astrocytes in fibrillar plaque evolution in transgenic APPSW mice. *Neurobiology of Aging*. 2001;22(1):49-61. doi:10.1016/s0197-4580(00)00181-0
15. Sasaki A, Shoji M, Harigaya Y, et al. Amyloid cored plaques in Tg2576 transgenic mice are characterized by giant plaques, slightly activated microglia, and the lack of paired helical filament-typed, dystrophic neurites. *Virchows Archiv*.2002;441(4):358-367. doi:10.1007/s00428-002-0643-8
16. Meyer-Luehmann M, Spires-Jones TL, Prada C, et al. Rapid appearance and local toxicity of amyloid-beta plaques in a mouse model of Alzheimer's disease. *Nature*. 2008;451(7179):720-724. doi:10.1038/nature06616
17. Liu Y, Walter S, Stagi M, et al. LPS receptor (CD14): a receptor for phagocytosis of Alzheimer's amyloid peptide. *Brain*. 2005;128(8):1778-1789. doi:10.1093/brain/awh531
18. Walter S, Letiembre M, Liu Y, et al. Role of the Toll-Like Receptor 4 in Neuroinflammation in Alzheimer's Disease. *Cellular Physiology and Biochemistry*. 2007;20(6):947-956. doi:10.1159/000110455
19. Letiembre M, Liu Y, Walter S, et al. Screening of innate immune receptors in neurodegenerative diseases: A similar pattern. *Neurobiology of Aging*. 2009;30(5):759-768. doi:10.1016/j.neurobiolaging.2007.08.018
20. Bamberger ME, Harris ME, McDonald DR, Husemann J, Landreth GE. A Cell Surface Receptor Complex for Fibrillarβ-Amyloid Mediates Microglial Activation. *The Journal of Neuroscience*. 2003;23(7):2665-2674. doi:10.1523/jneurosci.23-07-02665.2003
21. T. Griffin WS, Sheng JG, Roberts GW, Mrak RE. Interleukin-1 Expression in Different Plaque Types in Alzheimer's Disease. *Journal of Neuropathology and Experimental Neurology*. 1995;54(2):276-281. doi:10.1097/00005072-199503000-00014
22. Dickson DW, Lee SC, Mattiace LA, Yen SHC, Brosnan C. Microglia and cytokines in neurological disease, with special reference to AIDS and Alzheimer's disease. *Glia*. 1993;7(1):75-83. doi:10.1002/glia.440070113
23. Akiyama H, Barger S, Barnum S, et al. Inflammation and Alzheimer's disease. *Neurobiology of aging*. 2000;21(3):383-421. doi:10.1016/s0197-4580(00)00124-x
24. Ishizuka K, Kimura T, Igata-yi R, Katsuragi S, Takamatsu J, Miyakawa T. Identification of monocyte chemoattractant protein-1 in senile plaques and reactive microglia of Alzheimer's disease. *Psychiatry and Clinical Neurosciences*. 1997;51(3):135-138. doi:10.1111/j.1440-1819.1997.tb02375.x
25. Paresce DM, Chung H, Maxfield FR. Slow Degradation of Aggregates of the Alzheimer's Disease Amyloid β-Protein by Microglial Cells. *Journal of Biological Chemistry*. 1997;272(46):29390-29397. doi:10.1074/jbc.272.46.29390
26. Chung H, Brazil MI, Soe TT, Maxfield FR. Uptake, Degradation, and Release of Fibrillar and Soluble Forms of Alzheimer's Amyloid β-Peptide by Microglial Cells. *Journal of Biological Chemistry*. 1999;274(45):32301-32308. doi:10.1074/jbc.274.45.32301
27. Grathwohl S, Kälin RE, Bolmont T, et al. Formation and maintenance of Alzheimer's disease beta-amyloid plaques in the absence of microglia. *e-Neuroforum*. 2010;16(1):164-167. doi:10.1515/nf-2010-0107
28. Zelcer N, Khanlou N, Clare R, et al. Attenuation of neuroinflammation and Alzheimer's disease pathology by liver x receptors. *Proceedings of the National Academy of Sciences*. 2007;104(25):10601-10606. doi:10.1073/pnas.0701096104

29. Yamamoto M, Kiyota T, Walsh SM, Liu J, Kipnis J, Ikezu T. Cytokine-Mediated Inhibition of Fibrillar Amyloid-βPeptide Degradation by Human Mononuclear Phagocytes. *The Journal of Immunology*. 2008;181(6):3877-3886. doi:10.4049/jimmunol.181.6.3877
30. Koenigsknecht-Talboo J. Microglial Phagocytosis Induced by Fibrillar -Amyloid and IgGs Are Differentially Regulated by Proinflammatory Cytokines. *Journal of Neuroscience*. 2005;25(36):8240-8249. doi:10.1523/jneurosci.1808-05.2005
31. Mandrekar-Colucci S, Landreth GE. Microglia and Inflammation in Alzheimers Disease. *CNS & Neurological Disorders - Drug Targets*. 2010;9(2):156-167. doi:10.2174/187152710791012071
32. Kleinberger G, Yamanishi Y, Suárez-Calvet M, et al. TREM2 mutations implicated in neurodegeneration impair cell surface transport and phagocytosis. *Science Translational Medicine*. 2014;6(243). doi:10.1126/scitranslmed.3009093
33. Jay TR, Miller CM, Cheng PJ, et al. TREM2 deficiency eliminates TREM2+ inflammatory macrophages and ameliorates pathology in Alzheimer's disease mouse models. *Journal of Experimental Medicine*. 2015;212(3):287-295. doi:10.1084/jem.20142322
34. Mazaheri F, Snaidero N, Kleinberger G, et al. TREM2 deficiency impairs chemotaxis and microglial responses to neuronal injury. *EMBO Reports*. 2017;18(7):1186-1198. doi:10.15252/embr.201743922
35. Gatz M, Reynolds CA, Fratiglioni L, et al. Role of Genes and Environments for Explaining Alzheimer Disease. *Archives of General Psychiatry*. 2006;63(2):168. doi:10.1001/archpsyc.63.2.168
36. Schmechel DE, Saunders AM, Strittmatter WJ, et al. Increased amyloid beta-peptide deposition in cerebral cortex as a consequence of apolipoprotein E genotype in late-onset Alzheimer disease. *Proceedings of the National Academy of Sciences*. 1993;90(20):9649-9653. doi:10.1073/pnas.90.20.9649
37. Efthymiou AG, Goate AM. Late onset Alzheimer's disease genetics implicates microglial pathways in disease risk. *Molecular Neurodegeneration*. 2017;12(1). doi:10.1186/s13024-017-0184-x
38. Lambert JC, Ibrahim-Verbaas CA, Harold D, et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nature Genetics*. 2013;45(12):1452-1458. doi:10.1038/ng.2802
39. Naj AC, Jun G, Beecham GW, et al. Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. *Nature Genetics*. 2011;43(5):436-441. doi:10.1038/ng.801
40. Cukier HN, Kunkle BK, Hamilton KL, et al. Exome Sequencing of Extended Families with Alzheimer's Disease Identifies Novel Genes Implicated in Cell Immunity and Neuronal Function. *Journal of Alzheimer's Disease & Parkinsonism*. 2017;07(04). doi:10.4172/2161-0460.1000355
41. Malik M, Simpson JF, Parikh I, et al. CD33 Alzheimer's Risk-Altering Polymorphism, CD33 Expression, and Exon 2 Splicing. *Journal of Neuroscience*. 2013;33(33):13320-13325. doi:10.1523/jneurosci.1224-13.2013
42. Bertram L, Lange C, Mullin K, et al. Genome-wide Association Analysis Reveals Putative Alzheimer's Disease Susceptibility Loci in Addition to APOE. *The American Journal of Human Genetics*. 2008;83(5):623-632. doi:10.1016/j.ajhg.2008.10.008
43. Crocker PR, Paulson JC, Varki A. Siglecs and their roles in the immune system. *Nature Reviews Immunology*. 2007;7(4):255-266. doi:10.1038/nri2056
44. Ishida A, Akita K, Mori Y, et al. Negative Regulation of Toll-like Receptor-4 Signaling through the Binding of Glycosylphosphatidylinositol-anchored Glycoprotein, CD14, with the Sialic Acid-binding Lectin, CD33. *Journal of Biological Chemistry*. 2014;289(36):25341-25350. doi:10.1074/jbc.m113.523480
45. Griciuc A, Serrano-Pozo A, Parrado Antonio R, et al. Alzheimer's Disease Risk Gene CD33 Inhibits Microglial Uptake of Amyloid Beta. *Neuron*. 2013;78(4):631-643. doi:10.1016/j.neuron.2013.04.014
46. Karch CM, Jeng AT, Nowotny P, Cady J, Cruchaga C, Goate AM. Expression of Novel Alzheimer's Disease Risk Genes in Control and Alzheimer's Disease Brains. Ginsberg SD, ed. *PLoS ONE*. 2012;7(11):e50976. doi:10.1371/journal.pone.0050976
47. Jiang T, Yu JT, Hu N, Tan MS, Zhu XC, Tan L. CD33 in Alzheimer's Disease. *Molecular Neurobiology*. 2013;49(1):529-535. doi:10.1007/s12035-013-8536-1
48. Bradshaw EM, Chibnik LB, Keenan BT, et al. CD33 Alzheimer's disease locus: altered monocyte function and amyloid biology. *Nature Neuroscience*. 2013;16(7):848-850. doi:10.1038/nn.3435
49. Gonzalez Y, Herrera MT, Soldevila G, et al. High glucose concentrations induce TNF-α production through the down-regulation of CD33 in primary human monocytes. *BMC Immunology*. 2012;13(1):19. doi:10.1186/1471-2172-13-19

50. Takahashi K, Prinz M, Stagi M, Chechneva O, Neumann H. TREM2-Transduced Myeloid Precursors Mediate Nervous Tissue Debris Clearance and Facilitate Recovery in an Animal Model of Multiple Sclerosis. Graeber M, ed. *PLoS Medicine*. 2007;4(4):e124. doi:10.1371/journal.pmed.0040124
51. Turnbull IR, Gilfillan S, Cella M, et al. Cutting Edge: TREM-2 Attenuates Macrophage Activation. *The Journal of Immunology*. 2006;177(6):3520-3524. doi:10.4049/jimmunol.177.6.3520
52. Zheng H, Liu CC, Atagi Y, et al. Opposing roles of the triggering receptor expressed on myeloid cells 2 and triggering receptor expressed on myeloid cells-like transcript 2 in microglia activation. *Neurobiology of Aging*. 2016;42:132-141. doi:10.1016/j.neurobiolaging.2016.03.004
53. Celarain N, Sánchez-Ruiz de Gordoa J, Zelaya MV, et al. TREM2 upregulation correlates with 5-hydroxymethycytosine enrichment in Alzheimer's disease hippocampus. *Clinical Epigenetics*. 2016;8:37. doi:10.1186/s13148-016-0202-9
54. Matarin M, Salih Dervis A, Yasvoina M, et al. A Genome-wide Gene-Expression Analysis and Database in Transgenic Mice during Development of Amyloid or Tau Pathology. *Cell Reports*. 2015;10(4):633-644. doi:10.1016/j.celrep.2014.12.041
55. Forabosco P, Ramasamy A, Trabzuni D, et al. Insights into TREM2 biology by network analysis of human brain gene expression data. *Neurobiology of Aging*. 2013;34(12):2699-2714. doi:10.1016/j.neurobiolaging.2013.05.001
56. Zhao Y, Wu X, Li X, et al. TREM2 Is a Receptor for β-Amyloid that Mediates Microglial Function. *Neuron*. 2018;97(5):1023-1031.e7. doi:10.1016/j.neuron.2018.01.031
57. N'Diaye EN, Branda CS, Branda SS, et al. TREM-2 (triggering receptor expressed on myeloid cells 2) is a phagocytic receptor for bacteria. *Journal of Cell Biology*. 2009;184(2):215-223. doi:10.1083/jcb.200808080
58. Hsieh CL, Koike M, Spusta SC, et al. A role for TREM2 ligands in the phagocytosis of apoptotic neuronal cells by microglia. *Journal of Neurochemistry*. 2009;109(4):1144-1156. doi:10.1111/j.1471-4159.2009.06042.x
59. Kawabori M, Kacimi R, Kauppinen T, et al. Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) Deficiency Attenuates Phagocytic Activities of Microglia and Exacerbates Ischemic Damage in Experimental Stroke. *Journal of Neuroscience*. 2015;35(8):3384-3396. doi:10.1523/jneurosci.2620-14.2015
60. Kobayashi M, Konishi H, Sayo A, Takai T, Kiyama H. TREM2/DAP12 Signal Elicits Proinflammatory Response in Microglia and Exacerbates Neuropathic Pain. *Journal of Neuroscience*. 2016;36(43):11138-11150. doi:10.1523/jneurosci.1238-16.2016
61. Bouchon A, Hernández-Munain C, Cella M, Colonna M. A DAP12-mediated pathway regulates expression of C Cchemokine receptor 7 and maturation of human dendritic cells. *The Journal of Experimental Medicine*. 2001;194(8):1111-1122. doi:10.1084/jem.194.8.1111
62. Guerreiro R, Wojtas A, Bras J, et al. TREM2 Variants in Alzheimer's Disease. *New England Journal of Medicine*. 2013;368(2):117-127. doi:10.1056/nejmoa1211851
63. Jonsson T, Stefansson H, Steinberg S, et al. Variant of TREM2 associated with the risk of Alzheimer's disease. *The New England journal of medicine*. 2013;368(2):107-116. doi:10.1056/NEJMoa1211103
64. Sims R, van der Lee SJ, Naj AC, et al. Rare coding variants in PLCG2, ABI3, and TREM2 implicate microglial-mediated innate immunity in Alzheimer's disease. *Nature Genetics*. 2017;49(9):1373-1384. doi:10.1038/ng.3916
65. Wang P, Guo Q, Zhou Y, et al. Lack of association between triggering receptor expressed on myeloid cells 2 polymorphism rs75932628 and late-onset Alzheimer's disease in a Chinese Han population. *Psychiatric Genetics*. 2018;28(1):16-18. doi:10.1097/ypg.0000000000000188