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Neuroimmune interactions in Alzheimer's disease—New frontier with old challenges?

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Abstract

The perceived role of the immune system in neurodegenerative diseases has undergone drastic changes over time. Initially considered as a passive bystander, then condemned as a mediator of neurodegeneration and now established as an important player in the pathogenetic cascade, neuroimmune interactions have come a long way to arrive center stage in Alzheimer's disease research. Despite major breakthroughs in recent years, basic questions remain unanswered as conflicting data describe immune overactivation, inadequate response or exhaustion of the immune system in neurodegenerative diseases. Furthermore, difficulties in translating in vitro and in vivo studies in model systems to the complex human disease condition with multiple overlapping pathologies and the long disease duration in patients suffering from neurodegenerative diseases have hampered progress. Development of novel, advanced model systems, as well as new technologies to interrogate existing disease models and valuable collections of human tissue samples, including brain tissue in parallel with improved imaging and biomarker technologies are guiding the way to better understand the role of the immune system in Alzheimer's disease with hopes for more effective interventions in the future.

The identification of multiple risk associated variants in genes associated with the immune system has sparked an interest in neuroimmune interactions in neurodegenerative diseases, generated a flurry of new research, and made old challenges facing the field more obvious. For a long time, the immune system has been thought to be a passive bystander in the pathogenic cascade of neurodegenerative diseases, merely responding to damage inflicted by aggregates of pathological proteins. More recent research efforts in animal models and

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genetic association studies have painted a more diverse picture and assigned a more active role to immune responses in the process of neurodegeneration, ultimately coining the term “cellular phase” of Alzheimer’s disease (AD) pathogenesis, which accounts for the complex interactions between neurons, glial cells and vasculature in modulating the chronic process of neurodegeneration. Despite this significant progress, translational efforts are still hampered by many uncertainties, including: (a) when is the best time to intervene; (b) is inhibition or activation of the immune response the way to go; and (c) what are realistic goals to achieve by manipulating the immune system? Improvements in imaging and biomarker studies have helped elucidate the disease course and the association of inflammation with the emergence of pathological hallmarks, but do not discriminate with high certainty individual cellular immune players and signaling molecules involved. Uncertainty also exists with respect to which type of intervention holds the most promise for success—immunosuppression or immune activation? Given the mostly increased inflammatory activity in the diseased brain, anti-inflammatory intervention seems the obvious choice, but the fact that most of the genetic risk variants associated with AD are full or partial loss of function changes in molecules involved in key immune functions has cast doubt on the merits of anti-inflammatory treatment strategies. Instead, sophisticated intervention strategies may be required aimed at modulating the activity of key signaling pathways, like the Triggering receptor expressed in myeloid cells 2 (TREM2) and downstream molecules. A final area of uncertainty is what to expect from “immune-interventions” in AD, as more and more impressive success stories are published with respect to the use of checkpoint inhibitors or antigen-receptor chimeric T-cells in the cancer field. A big hope lies in the use of antibodies to prevent the accumulation of pathological proteins in neurodegenerative diseases, but there is also a role for manipulation of immune responses to ease the burdens of pathologies thereby improving cognitive decline as well activities of daily living. Progress in these translational efforts is hampered by the difficulty of adapting the findings in commonly used animal models and in vitro systems to the complex situation in the human brain, characterized by high order interactions between multiple cell types, regional differences in neuronal activity and neuro-glial interactions as well as the long period of disease development and clinical symptoms not easily modeled in small rodents and in vitro systems. Advances in experimental technology allow for better studies in human subjects, which will be an important pillar of understanding the complex interactions of the immune system and pathological protein aggregates in neurodegenerative diseases, thereby aiding in the translational efforts for this exciting new field of research.

1. Immune responses in neurodegenerative diseases early days

With the identification of disease causing proteins in major neurodegenerative diseases, including AD^{1–4} and Parkinson’s disease (PD),⁵ came the notion that these protein deposits, as well as the neuronal loss with which they are associated, are accompanied by an activation of intrinsic immune cells of the brain, namely microglia and astrocytes. Early studies of brain samples from AD and PD patients demonstrated microgliosis and astrogliosis in regions affected by pathological protein aggregates and neuronal death,^{6,7} and this activation of glial cells was suggested as an indicator of disease activity. However, early studies into the interaction of microglia and amyloid β -protein (A β) plaques in AD brought

a new notion to the table. Microglia processes were found to be in intimate proximity of amyloid fibrils^{8,9} and microglia in culture were reported to take up and not degrade, but rather release¹⁰ or even produce¹¹ A β , supporting the idea the microglia may be major players in plaque development.¹² Later findings of secretion of “neurotoxic” substances by microglia in contact with A β deposits, leading to the death of neurons in culture,^{13–15} fueled the concept of “bad” inflammation and suggested innate immune responses to be a driver of disease progression. Early epidemiological studies suggested a possible positive effect of non-steroidal anti-inflammatory drug (NSAID) use on the risk to develop AD,^{16–19} but this enthusiasm was dampened by disappointing results from several interventional studies.^{20–26} One caveat in interpreting the epidemiological studies is confounding effects of an often-present underlying inflammatory condition in patients taking NSAIDs, which raises an interesting notion, i.e., that possibly pro-inflammatory conditions may be protective.

Related to this idea are the facts that clustering of activated microglia cells around A β plaques has been observed (Fig. 1 and Ref.²⁷) but without obvious evidence of phagocytosis.^{28,29} Other studies described senescent or dystrophic microglia with higher frequency in aged and AD brains^{30–33} (see also figure 1C in Ref.³⁴), suggesting that impaired or “exhausted” immune responses are important in the pathogenesis of neurodegenerative diseases. These divergent concepts have made clarifying the proper role of microglia in neurodegenerative diseases difficult and increased uncertainty about the importance of immune responses for the pathogenesis and progression of AD and other neurodegenerative diseases, which has reduced the overall enthusiasm for further studies looking into interaction of neuroinflammation and disease processes.

2. Evidence for immune-overactivation in neurodegenerative diseases

Studies in animal models and in vitro systems, as well as biomarker studies, provide substantial evidence for increased pro-inflammatory immune responses correlating with the progression of pathological protein aggregation and neurodegeneration. A consistent finding is the upregulation of pro-inflammatory cytokines like IL-1,^{35,36} TNF-alpha^{37,38} and IL-12³⁹ in animal models of AD, as well as AD patient samples. Knockout or inhibitor studies in animal models consistently show that dampening these pathways is associated with reduced A β plaque burden and improved cognition,^{39–42} suggesting that microglia-associated pro-inflammatory pathways may be viable targets for therapeutic intervention. Studies validating the relevance of these findings demonstrated upregulation of these pathways in human brain tissue,^{41,43} CSF³⁹ and peripheral blood.^{44,45} Some of the identified pro-inflammatory pathways are also involved in autoimmune conditions, thus drugs already in clinical use that target these molecules could be repurposed for studies in AD patients.⁴⁶ However, very notably, studies demonstrating that over-expression of the pro-inflammatory cytokine IL-6 in the brain can also be beneficial for the clearance of protein pathology⁴⁷ and that over-expression of anti-inflammatory cytokines like IL-4⁴⁸ or IL-10⁴⁹ exacerbates pathology, while genetic knockout of IL-10 improved A β -pathology,⁵⁰ are exemplary notes of caution that manipulations of the immune system need to be carefully balanced to be beneficial for successful interventional purposes.

Another important function of microglia is the removal of synapses that are not needed or damaged in a process called synaptic pruning, or simply “pruning”. This process is obligatory for CNS development, but is active throughout life, where it is crucial for synaptic plasticity and removal of dead or damaged synapses in disease.⁵¹ Damaged synapses are tagged for removal by components of the complement system⁵² and multiple studies have demonstrated that this process is more active in brains of AD model mice^{53–55} as well as patients suffering from AD.^{56–58} Conversely, blocking these pathways has led to reduced pruning and improved cognition, providing another avenue of potential therapeutic interventions^{53–55} through dampening unwanted or overactive immune responses.

3. Immune exhaustion or inadequate immune responses in AD?

While studies implicating pro-inflammatory mechanisms in neurodegenerative diseases are prominent, a vast amount of data exists demonstrating inadequate or exhausted immune responses in AD and calling for strategies to activate, rather than to inhibit the immune system to intervene with the pathogenic cascade. Microglia surrounding A β plaques do not appear to be engaged in phagocytosis and studies demonstrate that certain microglia functions, including phagocytosis or microglial process movement, are inhibited in the A β rich environment.^{59–62} In line with that, depletion of microglia from the murine CNS did not have a major impact on plaque deposition and maintenance,^{63–65} although more recent studies suggest that longer term microglial depletion improves cognitive functions and prevents neuronal loss without major effects on A β burden, likely due to blockage of overly active synaptic pruning and pro-inflammatory signaling.^{63,65} Evidence for microglia exhaustion also exists in brain tissue from patients suffering from AD. Researchers noticed that a subset of microglia in brain regions affected by pathological protein deposition show a peculiar morphologic phenotype characterized by broken up and vacuolated cellular processes and shrunken cytoplasmic bodies, termed senescent or dystrophic microglia.^{30,32,34,66–68} These forms of microglia are typically observed in chronic, long standing human disease conditions and are difficult to study in animal models.³³ It has been speculated that these exhausted forms of innate immune cells are limited in their ability to respond to pathologic insults and show unregulated secretion of various pro- and anti-inflammatory molecules.⁶⁹ The concept of cellular senescence is well known in the cancer field but recent studies have suggested a role for senescent cells in overall lifespan and brain aging.^{70,71} In addition, it has been suggested that removal of senescent cells, including, but not limited to, microglia cells from the CNS environment in a mouse model of tau-pathology prevented tau phosphorylation and neuron loss as well as improving cognitive function.⁷² Better understanding of the process of cellular senescence and the pathways involved in development of senescent microglia may aide our understanding of this unique state of innate immune cells and help to tailor possible therapeutics.

4. Innate or adaptive immunity or both?

Given the clustering of genetic risk variants for sporadic AD in microglia associated genes,⁷³ these main players of the brain’s innate immune system have taken center stage in recent research efforts to understand immune contributions in AD. Mutations in receptors and signaling molecules associated with basic microglial functions are among the prominent

genetic variants associated with sporadic AD.^{74–76} In fact, the demonstration of mutations in colony stimulating factor receptor 1 (CSF1R) in patients suffering from a white matter dominant neurodegenerative disease termed hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS)⁷⁷ was the first direct link between a microglia-associated gene and causality of a neurodegenerative process. In addition, mutations in key players of other microglial pathways, including TREM2 and downstream signaling molecule DAP12, were associated with familial forms of dementia.^{78–81} Variants in TREM2 and “TYRO protein tyrosine kinase binding protein” (TYROBP, also known as DAP12) highlight the close relationship between microglia and peripheral myeloid cells, including monocytes, macrophages and tissue resident histiocyte populations. TYROBP loss of function mutations are associated with Nasu-Hakola disease,⁸² which is characterized by a white matter dominant neurodegenerative phenotype through changes in microglia function as well as bone cysts ascribed to changes in macrophage activation patterns. This close relationship of microglia and peripheral monocytes has muddled the waters for recent research efforts on inflammation. While Microglia are derived from a unique monocyte population residing in the yolk sac,⁸³ which populates the brain during early embryonic development and are sustained by local self-renewal,^{84,85} peripheral monocytes are a very mobile population of cells with a relatively short half-life, renewed from bone marrow precursors.⁸⁶ Some of the mutations and genetic variants associated with increased risk of AD affect microglia, as well as monocyte functions, making it hard to ascribe definitive roles for each of the two cell populations. While the contribution of peripheral myeloid cells to the pool of macrophages/microglia cells in the brain appears to be limited,^{87,88} several studies suggest that reduced recruitment of peripheral myeloid cells enhances A β pathology.^{89–91} While an increased influx of (manipulated) peripheral macrophages into the brain was linked to beneficial effects on containing protein pathology,⁹² the mere exchange of myeloid cell populations did not significantly alter AD associated pathology.⁹³ Single cell RNA sequencing technologies reveal a complicated system comprising multiple diverse microglia/myeloid cell populations during development and in the adult CNS in association with specific local functions and implications in disease processes.^{94–97}

Microglia are highly connected in the complex architecture of the brain and their processes are constantly monitoring the surrounding CNS environment.⁹⁸ Changes in microglial functions and activity are therefore expected to affect other cell types in the CNS. In addition, there is evidence of regional differences in microglia populations,^{99–101} which may in return reflect differences in regional vulnerability of certain brain regions for neurodegenerative processes.^{99–101} The interaction of microglia and astrocytes has been prominently positioned in recent studies of pathological CNS conditions, where it was demonstrated that microglial-derived cytokines can induce deleterious phenotypes in astrocytes, which serve in return as the actual toxic insult to neurons.^{102–105} It is conceivable that the more abundant population of astrocytes is the major effector cell and microglia serve as mere mediators in the pathological cascade. Oligodendrocytes and myelin also are affected by altered microglia functions.^{106–108} This is illustrated by the fact that some of the variants in the TREM2 gene associated with Frontotemporal dementia (FTD) cause dominant degeneration of white matter tracts without major pathological protein deposits⁷⁸ and the progressive leukoencephalopathy in HDLS associated with reduced microglia

function.⁷⁷ Recent large scale genomic analyses also suggest a role for myelination defects in AD and other neurodegenerative diseases,⁷⁷ making the interactions of microglia with oligodendrocytes and white matter tracts an even more interesting area for future study.

Besides the impact of the innate immune system, evidence exists that the adaptive arm of the immune system also may play a role in neurodegenerative diseases. Changes in T cell subtypes, as well as B cells, have been reported in peripheral blood of AD patients compared to controls^{109–117} and it has been speculated that a general aging of the immune system may predispose to development of neurodegenerative diseases.^{118,119} While major lymphocyte infiltrations are not a feature of neurodegenerative diseases, focal infiltrates of lymphocytes have been observed in brains of AD patients and murine model systems.^{120–123} Evidence from studies in animal models suggests that manipulating peripheral lymphocyte populations, including lymphocytes residing in periventricular and perivascular locations, will impact microglial and astrocyte functions via secreted mediators.^{124–127} Manipulating T cells with checkpoint inhibitors¹²⁸ or using genetically modified T cells to target cancer cells¹²⁹ has shown great promise in cancer therapy, including brain tumors,¹³⁰ but it remains doubtful that these approaches are applicable to neurodegenerative diseases, although some studies report success with checkpoint inhibitors in animal models.^{131,132} The brain is regarded as an immune privileged site and therefore infiltrates of lymphocytes are not desirable and potentially harmful, which is illustrated by serious side effects in early trials of A β vaccination,¹³³ where the intervention induced a prominent T cell response leading to meningoencephalitis and a detrimental outcome for the patients.¹³⁴ Furthermore, the changes in neurodegenerative diseases are diffuse and consist of extracellular and intracellular protein aggregates as well as damaged cells or structures, which poses a difficult target and may expose self-antigens and trigger unwanted auto-immune responses.

5. Challenges moving forward

In recent years, the notion that the immune system is a component of the pathogenetic cascade in neurodegenerative diseases, sometimes referred to as “cellular phase,”¹³⁵ has been solidified and changes in immune functions have been demonstrated to be the pathogenetic driver in some neurodegenerative disease conditions. Given its central role in the disease course, the immune system is a prime target for therapeutic interventions, but the road to progress is littered with challenges. A major problem is uniqueness of the neurodegenerative process in humans when compared to common animal models used for experimental studies. Pathological protein deposits begin decades before symptom onset and the immune system’s response to these changes also lasts for long periods of time. These processes are hard to mimic in short-lived animal models. Furthermore, the human disease condition is complicated by multiple coexisting protein pathologies and also a multitude of contributing underlying disease conditions.¹³⁶

Recent studies have underscored similarities and differences between murine and human microglia on a single cell transcriptomics level, with the differences being most apparent with respect to aging.^{137–141} Thus, translational studies in human tissue specimens, taking advantage of the immense efforts of AD research centers in collecting fluid specimens as well as brain tissue are more important than ever to validate findings from animal model

systems and improvements in technology. In particular, possibilities that allow for a detailed, multiplexed protein analysis, as well as spatially resolved protein and gene expression analysis in post mortem brain tissue specimens, will aid these endeavors in the future.

Another important aspect of studying immune cell functions, in particular in the brain, is that context matters. Microglia are a prominent example of isolated cells in culture behaving differently than cells in the context of tissue with major differences in basic cellular functions like migration, process movement, phagocytosis, response to stimuli and cytokine secretion.^{139,142} This calls for the development and more frequent use of novel model systems mimicking the cellular context in the brain like organotypic slice cultures^{143,144} and induced pluripotent stemcell (iPSC) derived three-dimensional systems.^{145,146}

It will be important moving forward to think about what to expect from manipulations of the immune system in patients suffering from symptomatic neurodegenerative diseases. In animal models, existing aggregates of misfolded proteins can be cleared and cognitive deficits reversed by manipulations of immune factors, which is unlikely to happen in the complex human disease condition. But it is reasonable to expect symptom improvement and slowing down of the neurodegenerative cascade through targeted interventions in the immune system. These interventions will have to strike a delicate balance between inhibition of toxic or harmful effects and overactivation of desired immune effects, which can then become toxic.¹⁴⁷ Furthermore, when immune manipulations should be initiated needs to be considered when choosing the intervention and therapeutic strategies that may vastly differ between different stages of disease,¹⁴⁸ including preventative efforts in asymptomatic subjects decades before the anticipated onset of disease. These are exciting times for neurodegenerative disease research and studies of the immune system, at a juncture in AD research progress when overcoming some of the hurdles presented to the field will prove important for a deeper understanding of disease mechanisms and guide the way to successful interventions in these devastating conditions.

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References

1. Glenner GG, Wong CW. Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. *Biochem Biophys Res Commun.* 1984;120:885–890. 10.1016/s0006-291x(84)80190-4. [PubMed: 6375662]
2. Grundke-Iqbal I, Iqbal K, Quinlan M, Tung YC, Zaidi MS, Wisniewski HM. Microtubule-associated protein tau. A component of Alzheimer paired helical filaments. *J Biol Chem.* 1986;261:6084–6089. [PubMed: 3084478]
3. Kosik KS, Joachim CL, Selkoe DJ. Microtubule-associated protein tau (tau) is a major antigenic component of paired helical filaments in Alzheimer disease. *Proc Natl Acad Sci.* 1986;83:4044–4048. 10.1073/pnas.83.11.4044. [PubMed: 2424016]
4. Wood JG, Mirra SS, Pollock NJ, Binder LI. Neurofibrillary tangles of Alzheimer disease share antigenic determinants with the axonal microtubule-associated protein tau (tau). *Proc Natl Acad Sci.* 1986;83:4040–4043. 10.1073/pnas.83.11.4040. [PubMed: 2424015]

5. Spillantini MG, Schmidt ML, Lee VM-Y, Trojanowski JQ, Jakes R, Goedert M. α -Synuclein in lewy bodies. *Nature*. 1997;388:839–840. 10.1038/42166. [PubMed: 9278044]
6. McGeer PL, Itagaki S, Boyes BE, McGeer EG. Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains. *Neurology*. 1988;38:1285 10.1212/WNL.38.8.1285. [PubMed: 3399080]
7. McGeer PL, Itagaki S, McGeer EG. Expression of the histocompatibility glycoprotein HLA-DR in neurological disease. *Acta Neuropathol*. 1988;76:550–557. [PubMed: 2974227]
8. Perlmuter LS, Barron E, Chui HC. Morphologic association between microglia and senile plaque amyloid in Alzheimer's disease. *Neurosci Lett*. 1990;119:32–36. 10.1016/0304-3940(90)90748-x. [PubMed: 2097581]
9. Wisniewski HM, Wegiel J, Wang KC, Kujawa M, Lach B. Ultrastructural studies of the cells forming amyloid fibers in classical plaques. *Can J Neurol Sci*. 1989;16:535–542. [PubMed: 2553231]
10. 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. *J Biol Chem*. 1999;274:32301–32308. 10.1074/jbc.274.45.32301. [PubMed: 10542270]
11. Banati RB, Gehrmann J, Czech C, et al. Early and rapid de novo synthesis of Alzheimer β A4-amyloid precursor protein (APP) in activated microglia. *Glia*. 1993;9:199–210. 10.1002/glia.440090305. [PubMed: 7507467]
12. Cras P, Kawai M, Siedlak S, et al. Neuronal and microglial involvement in beta-amyloid protein deposition in Alzheimer's disease. *Am J Pathol*. 1990;137:241–246. [PubMed: 2117395]
13. Giulian D, Haverkamp LJ, Li J, et al. Senile plaques stimulate microglia to release a neurotoxin found in Alzheimer brain. *Neurochem Int*. 1995;27:119–137. [PubMed: 7655344]
14. Giulian D, Haverkamp LJ, Yu JH, et al. Specific domains of beta-amyloid from Alzheimer plaque elicit neuron killing in human microglia. *J Neurosci*. 1996;16:6021–6037. [PubMed: 8815885]
15. Wu Q, Combs C, Cannady SB, Geldmacher DS, Herrup K. Beta-amyloid activated microglia induce cell cycling and cell death in cultured cortical neurons. *Neurobiol Aging* 2000;21:797–806. [PubMed: 11124423]
16. Beard CM, Waring SC, O'Brien PC, Kurland LT, Kokmen E. Nonsteroidal anti-inflammatory drug use and Alzheimer's disease: a case-control study in Rochester, Minnesota, 1980 through 1984. *Mayo Clin Proc*. 1998;73:951–955. 10.4065/73.10.951. [PubMed: 9787743]
17. Breitner JC, Gau BA, Welsh KA, et al. Inverse association of anti-inflammatory treatments and Alzheimer's disease: initial results of a co-twin control study. *Neurology*. 1994;44:227–232. 10.1212/wnl.44.2.227. [PubMed: 8309563]
18. in 't Veld BA, Ruitenberg A, Hofman A, et al. Nonsteroidal antiinflammatory drugs and the risk of Alzheimer's disease. *N Engl J Med*. 2001;345:1515–1521. 10.1056/NEJMoa010178. [PubMed: 11794217]
19. in 't Veld BA, Launer LJ, Hoes AW, Ott A, Hofman A, Breteler MM, Stricker BH. NSAIDs and incident Alzheimer's disease. The Rotterdam Study. *Neurobiol Aging*. 1998;19(6):607–611. [PubMed: 10192221]
20. ADAPT-FS Research Group. Follow-up evaluation of cognitive function in the randomized Alzheimer's disease anti-inflammatory prevention trial and its follow-up study. *Alzheimers Dement*. 2015;11:216–225.e1. 10.1016/j.jalz.2014.03.009. [PubMed: 25022541]
21. ADAPT Research Group, Lyketsos CG, JCS B, et al. Naproxen and celecoxib do not prevent AD in early results from a randomized controlled trial. *Neurology*. 2007;68:1800–1808. 10.1212/01.wnl.0000260269.93245.d2. [PubMed: 17460158]
22. Aisen PS, Schafer KA, Grundman M, et al. Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression. *JAMA*. 2003;289:2819 10.1001/jama.289.21.2819. [PubMed: 12783912]
23. Breitner JC, Baker LD, Montine TJ, et al. Extended results of the Alzheimer's disease anti-inflammatory prevention trial. *Alzheimers Dement*. 2011;7:402–411. 10.1016/j.jalz.2010.12.014. [PubMed: 21784351]

24. de Jong D, Jansen R, Hoefnagels W, et al. No effect of one-year treatment with indomethacin on Alzheimer's disease progression: a randomized controlled trial. *PLoS One*. 2008;3:e147510.1371/journal.pone.0001475. [PubMed: 18213383]
25. Reines SA, Block GA, Morris JC, et al. Rofecoxib: no effect on Alzheimer's disease in a 1-year, randomized, blinded, controlled study. *Neurology*. 2004;62:66–71. 10.1212/WNL.62.1.66. [PubMed: 14718699]
26. Soininen H, West C, Robbins J, Niculescu L. Long-term efficacy and safety of celecoxib in Alzheimer's disease. *Dement Geriatr Cogn Disord*. 2007;23:8–21. 10.1159/000096588. [PubMed: 17068392]
27. Prokop S, Miller KR, Heppner FL. Microglia actions in Alzheimer's disease. *Acta Neuropathol*. 2013;126:461–477. [PubMed: 24224195]
28. Jeffrey M, McGovern G, Barron R, Baumann F. Membrane pathology and microglial activation of mice expressing membrane anchored or membrane released forms of A β and mutated human Alzheimer's precursor protein (APP). *Neuropathol Appl Neurobiol*. 2015;41:458–470. 10.1111/nan.12173. [PubMed: 25131655]
29. Stalder M, Deller T, Staufenbiel M, Jucker M. 3D-reconstruction of microglia and amyloid in APP23 transgenic mice: no evidence of intracellular amyloid. *Neurobiol Aging*. 2001;22:427–434. [PubMed: 11378249]
30. Lopes KO, Sparks DL, Streit WJ. Microglial dystrophy in the aged and Alzheimer's disease brain is associated with ferritin immunoreactivity. *Glia*. 2008;56:1048–1060. 10.1002/glia.20678. [PubMed: 18442088]
31. Simmons DA, Casale M, Alcon B, Pham N, Narayan N, Lynch G. Ferritin accumulation in dystrophic microglia is an early event in the development of Huntington's disease. *Glia*. 2007;55:1074–1084. 10.1002/glia.20526. [PubMed: 17551926]
32. Streit WJ, Braak H, Xue Q-S, Bechmann I. Dystrophic (senescent) rather than activated microglial cells are associated with tau pathology and likely precede neurodegeneration in Alzheimer's disease. *Acta Neuropathol*. 2009;118:475–485. 10.1007/s00401-009-0556-6. [PubMed: 19513731]
33. Streit WJ, Sammons NW, Kuhns AJ, Sparks DL. Dystrophic microglia in the aging human brain. *Glia*. 2004;45:208–212. 10.1002/glia.10319. [PubMed: 14730714]
34. Prokop S, Miller KR, Labra SR, et al. Impact of TREM2 risk variants on brain region-specific immune activation and plaque microenvironment in Alzheimer's disease patient brain samples. *Acta Neuropathol*. 2019;138:613–630. 10.1007/s00401-019-02048-2. [PubMed: 31350575]
35. Cacabelos R, Barquero M, García P, Alvarez XA, Varela de Seijas E. Cerebrospinal fluid interleukin-1 beta (IL-1 beta) in Alzheimer's disease and neurological disorders. *Methods Find Exp Clin Pharmacol*. 1991;13:455–458. [PubMed: 1784142]
36. Sheng JG, Mrak RE, Griffin WS. Microglial interleukin-1 alpha expression in brain regions in Alzheimer's disease: correlation with neuritic plaque distribution. *Neuropathol Appl Neurobiol*. 1995;21:290–301. [PubMed: 7494597]
37. Fillit H, Ding WH, Buee L, et al. Elevated circulating tumor necrosis factor levels in Alzheimer's disease. *Neurosci Lett*. 1991;129:318–320. 10.1016/0304-3940(91)90490-k. [PubMed: 1745413]
38. Viel JJ, McManus DQ, Smith SS, Brewer GJ. Age- and concentration-dependent neuroprotection and toxicity by TNF in cortical neurons from β -amyloid. *J Neurosci Res*. 2001;64:454–465. 10.1002/jnr.1097. [PubMed: 11391700]
39. Vom Berg J, Prokop S, Miller KR, et al. Inhibition of IL-12/IL-23 signaling reduces Alzheimer's disease-like pathology and cognitive decline. *Nat Med*. 2012;18:1812–1819. 10.1038/nm.2965. [PubMed: 23178247]
40. Bhaskar K, Maphis N, Xu G, et al. Microglial derived tumor necrosis factor- α drives Alzheimer's disease-related neuronal cell cycle events. *Neurobiol Dis*. 2014;62:273–285. 10.1016/j.nbd.2013.10.007. [PubMed: 24141019]
41. Heneka MT, Kummer MP, Stutz A, et al. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. *Nature*. 2013;493:674–678. 10.1038/nature11729. [PubMed: 23254930]

42. Tan M-S, Yu J-T, Jiang T, Zhu X-C, Guan H-S, Tan L. IL12/23 p40 inhibition ameliorates Alzheimer's disease-associated neuropathology and spatial memory in SAMP8 mice. *J Alzheimers Dis.* 2013;38:633–646. 10.3233/JAD-131148.
43. Sudduth TL, Schmitt FA, Nelson PT, Wilcock DM. Neuroinflammatory phenotype in early Alzheimer's disease. *Neurobiol Aging.* 2013;34:1051–1059. 10.1016/j.neurobiolaging.2012.09.012. [PubMed: 23062700]
44. Hu WT, Holtzman DM, Fagan AM, et al. Plasma multianalyte profiling in mild cognitive impairment and Alzheimer disease. *Neurology.* 2012;79:897–905. 10.1212/WNL.0b013e318266fa70. [PubMed: 22855860]
45. Magalhães TNC, Weiler M, Teixeira CVL, et al. Systemic inflammation and multimodal biomarkers in amnesic mild cognitive impairment and Alzheimer's disease. *Mol Neurobiol.* 2018;55:5689–5697. 10.1007/s12035-017-0795-9. [PubMed: 29039020]
46. Sue W, Griffin T. Clinical implications of basic research neuroinflammatory cytokine signaling and Alzheimer's disease. *N Engl J Med.* 2013;368:770–771. 10.1056/NEJMcibr1214546. [PubMed: 23425171]
47. Chakrabarty P, Jansen-West K, Beccard A, et al. Massive gliosis induced by interleukin-6 suppresses A β deposition in vivo: evidence against inflammation as a driving force for amyloid deposition. *FASEB J.* 2010;24:548–559. 10.1096/fj.09-141754. [PubMed: 19825975]
48. Chakrabarty P, Tianbai L, Herring A, Ceballos-Diaz C, Das P, Golde TE. Hippocampal expression of murine IL-4 results in exacerbation of amyloid deposition. *Mol Neurodegener.* 2012;7:36 10.1186/1750-1326-7-36. [PubMed: 22838967]
49. Chakrabarty P, Li A, Ceballos-Diaz C, et al. IL-10 alters immunoproteostasis in APP mice, increasing plaque burden and worsening cognitive behavior. *Neuron.* 2015;85:519–533. 10.1016/j.neuron.2014.11.020. [PubMed: 25619653]
50. Guillot-Sestier M-V, Doty KR, Gate D, et al. IL10 deficiency rebalances innate immunity to mitigate Alzheimer-like pathology. *Neuron.* 2015;85:534–548. 10.1016/j.neuron.2014.12.068. [PubMed: 25619654]
51. Paolicelli RC, Bolasco G, Pagani F, et al. Synaptic pruning by microglia is necessary for normal brain development. *Science.* 2011;333:1456–1458. 10.1126/science.1202529. [PubMed: 21778362]
52. Schafer DP, Lehrman EK, Kautzman AG, et al. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. *Neuron.* 2012;74:691–705. 10.1016/j.neuron.2012.03.026. [PubMed: 22632727]
53. Hong S, Beja-Glasser VF, Nfonoyim BM, et al. Complement and microglia mediate early synapse loss in Alzheimer mouse models. *Science.* 2016;352:712–716. 10.1126/science.aad8373. [PubMed: 27033548]
54. Lian H, Litvinchuk A, Chiang AC-A, Aithmitti N, Jankowsky JL, Zheng H. Astrocytemicroglia cross talk through complement activation modulates amyloid pathology in mouse models of Alzheimer's disease. *J Neurosci.* 2016;36:577–589. 10.1523/JNEUROSCI.2117-15.2016. [PubMed: 26758846]
55. Maier M, Peng Y, Jiang L, Seabrook TJ, Carroll MC, Lemere CA. Complement C3 deficiency leads to accelerated amyloid plaque deposition and neurodegeneration and modulation of the microglia/macrophage phenotype in amyloid precursor protein transgenic mice. *J Neurosci.* 2008;28:6333–6341. 10.1523/JNEUROSCI.0829-08.2008. [PubMed: 18562603]
56. Head E, Azizeh BY, Lott IT, Tenner AJ, Cotman CW, Cribbs DH. Complement association with neurons and β -amyloid deposition in the brains of aged individuals with down syndrome. *Neurobiol Dis.* 2001;8:252–265. 10.1006/nbdi.2000.0380. [PubMed: 11300721]
57. Morgan AR, Touchard S, Leckey C, et al. Inflammatory biomarkers in Alzheimer's disease plasma. *Alzheimers Dement.* 2019;15:776–787. 10.1016/j.jalz.2019.03.007. [PubMed: 31047856]
58. Stoltzner SE, Grenfell TJ, Mori C, et al. Temporal accrual of complement proteins in amyloid plaques in Down's syndrome with Alzheimer's disease. *Am J Pathol.* 2000;156:489–499. 10.1016/S0002-9440(10)64753-0. [PubMed: 10666378]

59. Gyoneva S, Swanger SA, Zhang J, Weinshenker D, Traynelis SF. Altered motility of plaque-associated microglia in a model of Alzheimer's disease. *Neuroscience*. 2016;330:410–420. 10.1016/j.neuroscience.2016.05.061. [PubMed: 27288150]
60. Krabbe G, Halle A, Matyash V, et al. Functional impairment of microglia coincides with Beta-amyloid deposition in mice with Alzheimer-like pathology. *PLoS One*. 2013;8: e60921 10.1371/journal.pone.0060921. [PubMed: 23577177]
61. Lucin KM, O'Brien CE, Bieri G, et al. Microglial Beclin 1 regulates retromer trafficking and phagocytosis and is impaired in Alzheimer's disease. *Neuron*. 2013;79:873–886. 10.1016/j.neuron.2013.06.046. [PubMed: 24012002]
62. Orre M, Kamphuis W, Osborn LM, et al. Isolation of glia from Alzheimer's mice reveals inflammation and dysfunction. *Neurobiol Aging*. 2014;35:2746–2760. 10.1016/j.neurobiolaging.2014.06.004. [PubMed: 25002035]
63. Dagher NN, Najafi AR, Kayala KMN, et al. Colony-stimulating factor 1 receptor inhibition prevents microglial plaque association and improves cognition in 3xTg-AD mice. *J Neuroinflammation*. 2015;12:139 10.1186/s12974-015-0366-9. [PubMed: 26232154]
64. Grathwohl SA, Kälén RE, Bolmont T, et al. Formation and maintenance of Alzheimer's disease β -amyloid plaques in the absence of microglia. *Nat Neurosci*. 2009;12:1361–1363. 10.1038/nn.2432. [PubMed: 19838177]
65. Spangenberg EE, Lee RJ, Najafi AR, et al. Eliminating microglia in Alzheimer's mice prevents neuronal loss without modulating amyloid- β pathology. *Brain*. 2016;139:1265–1281. 10.1093/brain/aww016. [PubMed: 26921617]
66. Flanary BE, Sammons NW, Nguyen C, Walker D, Streit WJ. Evidence that aging and amyloid promote microglial cell senescence. *Rejuvenation Res*. 2007;10:61–74. 10.1089/rej.2006.9096. [PubMed: 17378753]
67. Streit WJ, Braak H, Del Tredici K, et al. Microglial activation occurs late during preclinical Alzheimer's disease. *Glia*. 2018;66:2550–2562. 10.1002/glia.23510. [PubMed: 30417428]
68. Tischer J, Krueger M, Mueller W, et al. Inhomogeneous distribution of Iba-1 characterizes microglial pathology in Alzheimer's disease. *Glia*. 2016;64:1562–1572. 10.1002/glia.23024. [PubMed: 27404378]
69. Watanabe S, Kawamoto S, Ohtani N, Hara E. Impact of senescence-associated secretory phenotype and its potential as a therapeutic target for senescence-associated diseases. *Cancer Sci*. 2017;108:563–569. 10.1111/cas.13184. [PubMed: 28165648]
70. Baker DJ, Childs BG, Durik M, et al. Naturally occurring p16Ink4a-positive cells shorten healthy lifespan. *Nature*. 2016;530:184–189. 10.1038/nature16932. [PubMed: 26840489]
71. Baker DJ, Wijshake T, Tchkonja T, et al. Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. *Nature*. 2011;479:232–236. 10.1038/nature10600. [PubMed: 22048312]
72. Bussian TJ, Aziz A, Meyer CF, Swenson BL, van Deursen JM, Baker DJ. Clearance of senescent glial cells prevents tau-dependent pathology and cognitive decline. *Nature*. 2018;562:578–582. 10.1038/s41586-018-0543-y. [PubMed: 30232451]
73. Yeh FL, Hansen DV, Sheng M. TREM2, microglia, and neurodegenerative diseases. *Trends Mol Med*. 2017;23:512–533. [PubMed: 28442216]
74. Guerreiro R, Wojtas A, Bras J, et al. TREM2 variants in Alzheimer's disease. *N Engl J Med*. 2013;368:117–127. 10.1056/NEJMoa1211851. [PubMed: 23150934]
75. Jonsson T, Stefansson H, Steinberg S, et al. Variant of TREM2 associated with the risk of Alzheimer's disease. *N Engl J Med*. 2013;368:107–116. 10.1056/NEJMoa1211103. [PubMed: 23150908]
76. 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. *Nat Genet*. 2017;49:1373–1384. 10.1038/ng.3916. [PubMed: 28714976]
77. Rademakers R, Baker M, Nicholson AM, et al. Mutations in the colony stimulating factor 1 receptor (CSF1R) gene cause hereditary diffuse leukoencephalopathy with spheroids. *Nat Genet*. 2012;44:200–205. 10.1038/ng.1027.

78. Le Ber I, De Septenville A, Guerreiro R, et al. Homozygous TREM2 mutation in a family with atypical frontotemporal dementia. *Neurobiol Aging*. 2014;35:2419.e23–2419.e25. 10.1016/j.neurobiolaging.2014.04.010.
79. Giraldo M, Lopera F, Siniard AL, et al. Variants in triggering receptor expressed on myeloid cells 2 are associated with both behavioral variant frontotemporal lobar degeneration and Alzheimer's disease. *Neurobiol Aging*. 2013;34:2077.e11–2077.e18. 10.1016/j.neurobiolaging.2013.02.016.
80. Guerreiro R, Bilgic B, Guven G, et al. A novel compound heterozygous mutation in TREM2 found in a Turkish frontotemporal dementia-like family. *Neurobiol Aging*. 2013;34:2890.e1–2890.e5. 10.1016/j.neurobiolaging.2013.06.005.
81. Guerreiro RJ, Lohmann E, Brás JM, et al. Using exome sequencing to reveal mutations in TREM2 presenting as a frontotemporal dementia-like syndrome without bone involvement. *JAMA Neurol*. 2013;70:78 10.1001/jamaneurol.2013.579. [PubMed: 23318515]
82. Bianchin MM, Capella HM, Chaves DL, et al. Nasu–Hakola disease (polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy—PLOS): a dementia associated with bone cystic lesions. From clinical to genetic and molecular aspects. *Cell Mol Neurobiol*. 2004;24:1–24. 10.1023/B:CEMN.0000012721.08168.ee. [PubMed: 15049507]
83. Ginhoux F, Greter M, Leboeuf M, et al. Fate mapping analysis reveals that adult microglia derive from primitive macrophages. *Science*. 2010;330:841–845. 10.1126/science.1194637. [PubMed: 20966214]
84. Fügen P, Hefendehl JK, Veeraraghavalu K, et al. Microglia turnover with aging and in an Alzheimer's model via long-term in vivo single-cell imaging. *Nat Neurosci*. 2017;20:1371–1376. 10.1038/nn.4631. [PubMed: 28846081]
85. Tay TL, Mai D, Dautzenberg J, et al. A new fate mapping system reveals context-dependent random or clonal expansion of microglia. *Nat Neurosci*. 2017;20:793–803. 10.1038/nn.4547. [PubMed: 28414331]
86. Ginhoux F, Jung S. Monocytes and macrophages: developmental pathways and tissue homeostasis. *Nat Rev Immunol*. 2014;14:392–404. 10.1038/nri3671. [PubMed: 24854589]
87. Stalder AK, Ermini F, Bondolfi L, et al. Invasion of hematopoietic cells into the brain of amyloid precursor protein transgenic mice. *J Neurosci*. 2005;25:11125–11132. 10.1523/JNEUROSCI.2545-05.2005. [PubMed: 16319312]
88. Wang Y, Ulland TK, Ulrich JD, et al. TREM2-mediated early microglial response limits diffusion and toxicity of amyloid plaques. *J Exp Med*. 2016;213:667–675. 10.1084/jem.20151948. [PubMed: 27091843]
89. Mildner A, Schlevogt B, Kierdorf K, et al. Distinct and non-redundant roles of microglia and myeloid subsets in mouse models of Alzheimer's disease. *J Neurosci*. 2011;31:11159–11171. 10.1523/JNEUROSCI.6209-10.2011. [PubMed: 21813677]
90. Naert G, Rivest S. CC chemokine receptor 2 deficiency aggravates cognitive impairments and amyloid pathology in a transgenic mouse model of Alzheimer's disease. *J Neurosci*. 2011;31:6208–6220. 10.1523/JNEUROSCI.0299-11.2011. [PubMed: 21508244]
91. Simard AR, Soulet D, Gowing G, Julien J-P, Rivest S. Bone marrow-derived microglia play a critical role in restricting senile plaque formation in Alzheimer's disease. *Neuron*. 2006;49:489–502. 10.1016/j.neuron.2006.01.022. [PubMed: 16476660]
92. Town T, Laouar Y, Pittenger C, et al. Blocking TGF- β –Smad2/3 innate immune signaling mitigates Alzheimer-like pathology. *Nat Med*. 2008;14:681–687. 10.1038/nm1781. [PubMed: 18516051]
93. Prokop S, Miller KRR, Drost N, et al. Impact of peripheral myeloid cells on amyloid- β pathology in Alzheimer's disease-like mice. *J Exp Med*. 2015;212:1811–1818. 10.1084/jem.20150479. [PubMed: 26458768]
94. Hammond TR, Dufort C, Dissing-Olesen L, et al. Single-cell RNA sequencing of microglia throughout the mouse lifespan and in the injured brain reveals complex cell-state changes. *Immunity*. 2019;50:253–271.e6. 10.1016/j.immuni.2018.11.004. [PubMed: 30471926]
95. Keren-Shaul H, Spinrad A, Weiner A, et al. A unique microglia type associated with restricting development of Alzheimer's disease. *Cell*. 2017;169:1276–1290.e17. 10.1016/j.cell.2017.05.018. [PubMed: 28602351]

96. Li Q, Cheng Z, Zhou L, et al. Developmental heterogeneity of microglia and brain myeloid cells revealed by deep single-cell RNA sequencing. *Neuron*. 2019;101:207–223.e10. 10.1016/j.neuron.2018.12.006. [PubMed: 30606613]
97. Mathys H, Adaikkan C, Gao F, et al. Temporal tracking of microglia activation in neurodegeneration at single-cell resolution. *Cell Rep*. 2017;21:366–380. 10.1016/j.celrep.2017.09.039. [PubMed: 29020624]
98. Nimmerjahn A, Kirchhoff F, Helmchen F. Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. *Science*. 2005;308:1314–1318. 10.1126/science.1110647. [PubMed: 15831717]
99. De Biase LM, Schuebel KE, Fufeld ZH, et al. Local cues establish and maintain region-specific phenotypes of basal ganglia microglia. *Neuron*. 2017;95:341–356.e6. 10.1016/j.neuron.2017.06.020. [PubMed: 28689984]
100. Grabert K, Michoel T, Karavolos MH, et al. Microglial brain region dependent diversity and selective regional sensitivities to aging. *Nat Neurosci*. 2016;19:504–516. 10.1038/nn.4222. [PubMed: 26780511]
101. Mastroeni D, Nolz J, Sekar S, et al. Laser-captured microglia in the Alzheimer's and Parkinson's brain reveal unique regional expression profiles and suggest a potential role for hepatitis B in the Alzheimer's brain. *Neurobiol Aging*. 2018;63:12–21. 10.1016/j.neurobiolaging.2017.10.019. [PubMed: 29207277]
102. Clarke LE, Liddelow SA, Chakraborty C, Münch AE, Heiman M, Barres BA. Normal aging induces A1-like astrocyte reactivity. *Proc Natl Acad Sci*. 2018;115:E1896–E1905. 10.1073/pnas.1800165115. [PubMed: 29437957]
103. Liddelow SA, Guttenplan KA, Clarke LE, et al. Neurotoxic reactive astrocytes are induced by activated microglia. *Nature*. 2017;541:481–487. 10.1038/nature21029. [PubMed: 28099414]
104. Shi Y, Yamada K, Liddelow SA, et al. ApoE4 markedly exacerbates tau-mediated neurodegeneration in a mouse model of tauopathy. *Nature*. 2017;549:523–527. 10.1038/nature24016. [PubMed: 28959956]
105. Yun SP, Kam T-I, Panicker N, et al. Block of A1 astrocyte conversion by microglia is neuroprotective in models of Parkinson's disease. *Nat Med*. 2018;24:931–938. 10.1038/s41591-018-0051-5. [PubMed: 29892066]
106. Hagemeyer N, Hanft K-M, Akriditou M-A, et al. Microglia contribute to normal myelinogenesis and to oligodendrocyte progenitor maintenance during adulthood. *Acta Neuropathol*. 2017;134:441–458. 10.1007/s00401-017-1747-1. [PubMed: 28685323]
107. Lloyd AF, Davies CL, Holloway RK, et al. Central nervous system regeneration is driven by microglia necroptosis and repopulation. *Nat Neurosci*. 2019;22:1046–1052. 10.1038/s41593-019-0418-z. [PubMed: 31182869]
108. Schirmer L, Velmeshev D, Holmqvist S, et al. Neuronal vulnerability and multilineage diversity in multiple sclerosis. *Nature*. 2019;573:75–82. 10.1038/s41586-019-1404-z. [PubMed: 31316211]
109. Garfias S, Tamaya Domínguez B, Toledo Rojas A, et al. Fenotipos de linfocitos perifericos en las enfermedades de Alzheimer y Parkinson. *Neurologia*. 2019; pii:S0213–4853 (19)30013–1. 10.1016/j.nrl.2018.10.004.
110. Hu GR, Walls RS, Creasey H, McCusker E, Broe GA. Peripheral blood lymphocyte subset distribution and function in patients with Alzheimer's disease and other dementias. *Aust NZ J Med*. 1995;25:212–217.
111. Leonardi A, Arata L, Bino G, et al. Functional study of T lymphocyte responsiveness in patients with dementia of the Alzheimer type. *J Neuroimmunol*. 1989;22:19–22. [PubMed: 2521867]
112. Lueg G, Gross CC, Lohmann H, et al. Clinical relevance of specific T-cell activation in the blood and cerebrospinal fluid of patients with mild Alzheimer's disease. *Neurobiol Aging*. 2015;36:81–89. 10.1016/j.neurobiolaging.2014.08.008. [PubMed: 25277040]
113. Shalit F, Sredni B, Brodie C, Kott E, Huberman M. T lymphocyte subpopulations and activation markers correlate with severity of Alzheimer's disease. *Clin Immunol Immunopathol*. 1995;75:246–250. [PubMed: 7768042]

114. Skias D, Bania M, Reder AT, Luchins D, Antel JP. Senile dementia of Alzheimer's type (SDAT): reduced T8+-cell-mediated suppressor activity. *Neurology*. 1985;35:1635-1639. [PubMed: 2932656]
115. Stevenson AJ, McCartney DL, Harris SE, et al. Trajectories of inflammatory biomarkers over the eighth decade and their associations with immune cell profiles and epigenetic ageing. *Clin Epigenetics*. 2018;10:159. [PubMed: 30572949]
116. Tajuddin SM, Schick UM, Eicher JD, et al. Large-scale exome-wide association analysis identifies loci for white blood cell traits and pleiotropy with immune-mediated diseases. *Am J Hum Genet*. 2016;99:22-39. [PubMed: 27346689]
117. Tramutola A, Abate G, Lanzillotta C, et al. Protein nitration profile of CD3+ lymphocytes from Alzheimer disease patients: novel hints on immunosenescence and biomarker detection. *Free Radic Biol Med*. 2018;129:430-439. [PubMed: 30321702]
118. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J Gerontol A Biol Sci Med Sci*. 2014;69:S4-S9. [PubMed: 24833586]
119. Goldberg EL, Dixit VD. Drivers of age-related inflammation and strategies for healthspan extension. *Immunol Rev*. 2015;265:63-74. [PubMed: 25879284]
120. Ferretti MT, Merlini M, Späni C, et al. T-cell brain infiltration and immature antigen-presenting cells in transgenic models of Alzheimer's disease-like cerebral amyloidosis. *Brain Behav Immun*. 2016;54:211-225. [PubMed: 26872418]
121. Merlini M, Kirabali T, Kulic L, Nitsch RM, Ferretti MT. Extravascular CD3+ T cells in brains of Alzheimer disease patients correlate with tau but not with amyloid pathology: an immunohistochemical study. *Neurodegener Dis*. 2018;18:49-56. [PubMed: 29402847]
122. Rogers J, Lubner-Narod J, Styren SD, Civin WH. Expression of immune system-associated antigens by cells of the human central nervous system: relationship to the pathology of Alzheimer's disease. *Neurobiol Aging*. 1988;9:339-349. [PubMed: 3263583]
123. Togo T, Akiyama H, Iseki E, et al. Occurrence of T cells in the brain of Alzheimer's disease and other neurological diseases. *J Neuroimmunol*. 2002;124:83-92. [PubMed: 11958825]
124. Baruch K, Rosenzweig N, Kertser A, et al. Breaking immune tolerance by targeting Foxp3+ regulatory T cells mitigates Alzheimer's disease pathology. *Nat Commun*. 2015;6:7967. [PubMed: 26284939]
125. Dansokho C, Ait Ahmed D, Aid S, et al. Regulatory T cells delay disease progression in Alzheimer-like pathology. *Brain*. 2016;139:1237-1251. [PubMed: 26912648]
126. Koronyo-Hamaoui M, Ko MK, Koronyo Y, et al. Attenuation of AD-like neuropathology by harnessing peripheral immune cells: local elevation of IL-10 and MMP-9. *J Neurochem*. 2009;111:1409-1424. [PubMed: 19780903]
127. Marsh SE, Abud EM, Lakatos A, et al. The adaptive immune system restrains Alzheimer's disease pathogenesis by modulating microglial function. *Proc Natl Acad Sci*. 2016;113:E1316-E1325. [PubMed: 26884167]
128. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363:711-723. [PubMed: 20525992]
129. June CH, O'Connor RS, Kawalekar OU, Ghassemi S, Milone MC. CAR T cell immunotherapy for human cancer. *Science*. 2018;359:1361-1365. [PubMed: 29567707]
130. Choi BD, Maus MV, June CH, Sampson JH. Immunotherapy for glioblastoma: adoptive T-cell strategies. *Clin Cancer Res*. 2019;25:2042-2048. [PubMed: 30446589]
131. Baruch K, Deczkowska A, Rosenzweig N, et al. PD-1 immune checkpoint blockade reduces pathology and improves memory in mouse models of Alzheimer's disease. *Nat Med*. 2016;22:135-137. [PubMed: 26779813]

132. Rosenzweig N, Dvir-Szternfeld R, Tsitsou-Kampeli A, et al. PD-1/PD-L1 checkpoint blockade harnesses monocyte-derived macrophages to combat cognitive impairment in a tauopathy mouse model. *Nat Commun.* 2019;10:465. 10.1038/s41467-019-08352-5. [PubMed: 30692527]
133. Lee EB, Leng LZ, Lee VMY, Trojanowski JQ. Meningoencephalitis associated with passive immunization of a transgenic murine model of Alzheimer's amyloidosis. *FEBS Lett.* 2005;579:2564–2568. 10.1016/j.febslet.2005.03.070. [PubMed: 15862291]
134. Nicoll JAR, Wilkinson D, Holmes C, Steart P, Markham H, Weller RO. Neuropathology of human Alzheimer disease after immunization with amyloid- β peptide: a case report. *Nat Med.* 2003;9:448–452. 10.1038/nm840. [PubMed: 12640446]
135. De Strooper B, Karran E. The cellular phase of Alzheimer's disease. *Cell.* 2016;164:603–615. 10.1016/j.cell.2015.12.056. [PubMed: 26871627]
136. Robinson JL, Corrada MM, Kovacs GG, et al. Non-Alzheimer's contributions to dementia and cognitive resilience in the 90+ study. *Acta Neuropathol.* 2018;136:377–388. 10.1007/s00401-018-1872-5. [PubMed: 29916037]
137. Del-Aguila JL, Li Z, Dube U, et al. A single-nuclei RNA sequencing study of mendelian and sporadic AD in the human brain. *Alzheimers Res Ther.* 2019;11(1):71. 10.1186/s13195-019-0524-x. [PubMed: 31399126]
138. Galatro TF, Holtman IR, Lerario AM, et al. Transcriptomic analysis of purified human cortical microglia reveals age-associated changes. *Nat Neurosci.* 2017;20:1162–1171. 10.1038/nn.4597. [PubMed: 28671693]
139. Gosselin D, Skola D, Coufal NG, et al. An environment-dependent transcriptional network specifies human microglia identity. *Science.* 2017;356 eaal3222. 10.1126/science.aal3222. [PubMed: 28546318]
140. Mathys H, Davila-Velderrain J, Peng Z, et al. Single-cell transcriptomic analysis of Alzheimer's disease. *Nature.* 2019;570:332–337. 10.1038/s41586-019-1195-2. [PubMed: 31042697]
141. Srinivasan K, Friedman BA, Etxeberria A, et al. Alzheimer's patient brain myeloid cells exhibit enhanced aging and unique transcriptional activation. *bioRxiv.* 2019;610345. 10.1101/610345.
142. Bohlen CJ, Bennett FC, Tucker AF, Collins HY, Mulinyawe SB, Barres BA. Diverse requirements for microglial survival, specification, and function revealed by defined-medium cultures. *Neuron.* 2017;94:759–773.e8. 10.1016/j.neuron.2017.04.043. [PubMed: 28521131]
143. Croft CL, Cruz PE, Ryu DH, et al. rAAV-based brain slice culture models of Alzheimer's and Parkinson's disease inclusion pathologies. *J Exp Med.* 2019;216:539–555. 10.1084/jem.20182184. [PubMed: 30770411]
144. Falsig J, Julius C, Margalith I, Schwarz P, Heppner FL, Aguzzi A. A versatile prion replication assay in organotypic brain slices. *Nat Neurosci.* 2008;11:109–117. 10.1038/nn2028. [PubMed: 18066056]
145. Pamies D, Barreras P, Block K, et al. A human brain microphysiological system derived from induced pluripotent stem cells to study neurological diseases and toxicity. *ALTEX.* 2017;34:362–376. 10.14573/altex.1609122. [PubMed: 27883356]
146. Park J, Wetzel I, Marriott I, et al. A 3D human triculture system modeling neurodegeneration and neuroinflammation in Alzheimer's disease. *Nat Neurosci.* 2018;21:941–951. 10.1038/s41593-018-0175-4. [PubMed: 29950669]
147. Golde TE. Harnessing immunoproteostasis to treat neurodegenerative disorders. *Neuron.* 2019;101:1003–1015. [PubMed: 30897353]
148. Golde BTE, Dekosky ST, Galasko D. Alzheimer's disease: the right drug, the right time. *Science.* 2018;362:1250–1252. [PubMed: 30545877]

Fig. 1.
Activated microglia (Iba-1, green) surrounding A β plaques (NAB228, red) in the brain of a patient suffering from AD. Blue (DAPI). Scale bar=20 μ m. *Image courtesy of Stefan Prokop, MD.*