Beyond the neuron-cellular interactions early in Alzheimer disease pathogenesis

Christopher M. Henstridge[1], **Bradley T. Hyman**[2], and **Tara L. Spires-Jones**[1,*]

[1]The University of Edinburgh Centre for Discovery Brain Sciences, UK Dementia Research Institute, Edinburgh, UK.

[2]MassGeneral Institute for Neurodegenerative Disease, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, USA.

Abstract

The symptoms of Alzheimer disease reflect a loss of neural circuit integrity in the brain, but neurons do not work in isolation. Emerging evidence suggests that the intricate balance of interactions between neurons, astrocytes, microglia and vascular cells required for healthy brain function becomes perturbed during the disease, with early changes likely protecting neural circuits from damage, followed later by harmful effects when the balance cannot be restored. Moving beyond a neuronal focus to understand the complex cellular interactions in Alzheimer disease and how these change throughout the course of the disease may provide important insight into developing effective therapeutics.

Alzheimer disease (AD), the most common cause of dementia in elderly individuals, poses a growing problem for society as the population ages[1]. The overwhelming evidence that neuronal damage downstream of key pathological players causes cognitive decline has led to a 'neurocentric' view of AD pathogenesis. However, advances in our understanding of the molecular pathogenesis of AD approached from this neurocentric perspective have not translated into effective therapies. This failure reflects in part a lack of consideration of the effects of primary pathological changes on all cell types involved in neural system integrity and the consequent perturbations of many key intercellular interactions.

In this Review, we discuss the evidence supporting a role for interactions of multiple cell types in early AD pathogenesis and how this can inform development of therapeutic strategies. Both the advances in the fundamental understanding of disease and the outcomes

of clinical trials over the past decade indicate the importance of cellular interactions early in the disease process[2].

Early brain changes in AD

AD is pathologically defined by the presence of amyloid-β (Aβ) accumulation in amyloid plaques, tau aggregation in neurofibrillary tangles and brain atrophy caused by loss of neurons and synapses (Box 1). In addition to these definitive pathological lesions, the brain undergoes an innate immune response including large changes in the phenotypes of microglia and astrocytes. A substantial amount of evidence supports the amyloid cascade hypothesis of disease pathogenesis, which states that alterations in Aβ initiate the disease and set off a chain of events including accumulation of toxic forms of tau that cause downstream neuron death[3,4]. This hypothesis is strongly supported both by the genetics of familial AD implicating Aβ production and aggregation in causing disease and by the pathological accumulation of Aβ deposits beginning many years before symptom onset. Along with the changes in Aβ early in disease, there is an early loss of synapses that tracks with disease progression. There are also early changes in non-neuronal cell types, including an inflammatory response of glia around plaques and disruptions to vascular function, including reduced cerebral blood flow and blood-brain barrier (BBB) disruptions (Table 1).

Risk factors point to multiple cells.

The interest in cellular interactions in AD pathogenesis is increasing as both genetic and epidemiological evidence point to a causative role for changes in the innate immune system, metabolism and vasculature. These have initiated a boom of research in the field to understand the non-neuronal contributors and cell-cell interactions in initiating changes in the brain in the early stages of disease[2,5–8]. Early genetic evidence implicated the apolipoprotein E ε4 allele (APOE4) as a potent risk factor for AD[9]. APOE is highly expressed in astrocytes and disease-associated microglia (or DAMs) in the brain, implicating a role for these cell types in pathogenesis. However, it was not until the more recent genome-wide association, whole-genome and whole-exome sequencing studies implicating multiple AD risk genes expressed predominantly in non-neuronal cells that the interest in non-neuronal contributors to AD has really taken hold (TABLE 2). In particular, genetic evidence has directly linked microglial function to AD. Several genes involved in the innate immune system and inflammation increase AD risk, including those encoding triggering receptor expressed on myeloid cells 2 (TREM2), complement receptor 1 (CR1), CD33 (also known as sialic acid binding Ig-like lectin 3; SIGLEC3) and inositol polyphosphate-5-phosphatase (INPP5D). Astrocytic metabolism gene variants, in addition to APOE4, have also been implicated in AD pathogenesis, including those encoding clusterin (CLU; also known as apolipoprotein J) and sortilin-related receptor 1 (SORL1). Interestingly, several genes that are highly expressed in oligodendrocytes or oligodendrocyte precursor cells (OPCs) have also been implicated in AD risk, although the role of these cells in the disease is much less studied than that of neurons, microglia and astrocytes.

Non-genetic risk factors also point to an important role of interactions of multiple cell types in disease pathogenesis. The mantra 'what is good for your heart is good for your brain' is

central advice for dementia prevention on the basis of a large amount of evidence implicating vascular risk factors such as high blood pressure, obesity, type 2 diabetes and a sedentary lifestyle in substantially increasing AD risk[6]. More recently, direct interactions of AD pathological proteins with the vasculature have suggested changes in vascular function and stability[10,11]. All of these risk factors implicate non-neuronal cell types, including vascular cells and glia in disease. Although the mechanisms of neurodegeneration initiated by interactions between cell types and the timing of these interactions remain unclear, many recently discovered pathways converge on synapse degeneration, as will be discussed later.

Inflammation and the immune response

The brain's inflammatory response to toxic stimuli involves multiple cell types and cellular interactions. Both microglia and astrocytes respond to toxic stimuli in the brain by altering their gene expression, morphology and secretomes, which have cascading effects on other cell types, including neurons. The dramatic envelopment of amyloid plaques by glial cells, and the evidence supporting inefficient Aβ clearance as a pathogenic pathway in sporadic AD, have driven much of the work surrounding inflammation to focus on the role of glia in clearing Aβ. Clearing toxic forms of Aβ from the brain should be neuroprotective; however, Aβ also has effects on glial function, which can render them neurotoxic.

Role of glia in amyloid clearance.

Microglia accumulate around plaques in AD and are well known for their ability to phagocytose Aβ. This process begins at the early stages of disease as plaques accumulate in the neocortex. Many mouse models of this early stage of disease exist that express familial-AD-associated mutations in APP and PS1 and develop plaques and associated gliosis in the absence of neurofibrillary tau pathology or overt neuron loss. In one such model, microglia form a barrier around plaques, which prevents accumulation of toxic oligomeric Aβ 'hot spots'[12]. However, chronic microglial activation leads to a more damaging pro-inflammatory state[13]. For example, activated microglia are thought to recruit and activate other microglia through a self-perpetuating loop of cytokine release and receptor expression[14]. Ablating CX_3CL1 (also known as fractalkine)-positive microglia in plaque-bearing mice results in plaque growth, but no change in number, in support of an important role for these cells in limiting plaque expansion[15]. However, this finding is inconsistent as previous work in the same APP/PS1 model showed that a 90% pharmacological reduction in CD11b-positive microglia had no effect on plaque formation or maintenance[16]. Furthermore, ablating CSF1R-positive microglia in 5xFAD mice has no effect on amyloid burden but does improve spine loss, neuron death and cognition[17,18]. Soluble Aβ is thought to be much more neurotoxic than plaque fibrils, and recent evidence also supports a role for microglia in clearing soluble Aβ by secreting Aβ-degrading enzymes in a process regulated by CR3 (Ref[19]). In contrast to the data showing microglial ablation results in plaque growth, other data indicate that blocking proliferation of microglia may be beneficial to cognition in mice[17,18]. Thus, despite a clear role for microglia in clearing Aβ, it is not yet known whether microglial activation is protective or harmful or, more likely, whether this depends on the stage of the disease. Further, in many of the studies examining microglia in AD models discussed here, it has not been possible to distinguish between microglia, brain macrophages

and infiltrating bone-marrow-derived cells. More detailed investigations will be needed to determine whether the effects observed are due to microglia or other myeloid cells.

Advances in single-cell profiling technology are starting to unravel some of these microglial mysteries both by helping to differentiate the different myeloid cell types and to tease out how these cells change upon activation. Recent data indicate that there are likely not just on or off states but a continuum of glial activation[20–23]. Single-cell RNA sequencing (RNAseq) in an AD mouse model revealed DAMs, which accumulate around plaques and exhibit reduced expression of homeostatic genes and increased expression of genes involved in phagocytosis[23]. Interestingly, two of the upregulated genes in DAMs are genetic risk factors for AD — *APOE* and *TREM2* — providing a link between these molecules and microglial activation that may explain some of the risk these polymorphisms confer. More detail on the link between TREM2 and APOE recently emerged in a transcriptomic analysis of microglia showing that TREM2 can be activated by APOE signalling in DAMs[24]. Interestingly, TREM2 binds to APOE and CLU (another known risk factor) and facilitates microglial uptake of Aβ, which is impaired by AD associated variants, at least in cell culture[25]. A more complex disease-stage-dependent role of TREM2 is becoming evident from in vivo studies. In one model of AD, TREM2 knockout was found to ameliorate amyloid pathology early in disease but exacerbate pathology later in the disease process[26], highlighting the variability in effects of microglial phenotypes at different stages of disease. Although the data are not yet all in agreement, several studies suggest a protective role in which upregulation of TREM2 causes microglia to phagocytose Aβ. In support of this idea, genetic reduction in TREM2 levels in mice and the R47H TREM2 mutation in both mice and humans reduced microglial or monocyte association with plaques[26–30], implying that reductions in TREM2 reduce the 'barrier' of microglia around plaques that may protect surrounding tissue[31]. Lack of TREM2 appears to reduce the ability of microglia to sense their environment and respond appropriately, resulting in reduced phagocytosis[32].

Reactive astrocytes accumulate around plaques and are thought to play a role in Aβ degradation, thus appearing to act in a neuroprotective manner[33]. This effect may be due to the increased expression of insulin-degrading enzyme (IDE), which is observed in vitro in cultured astrocytes and in vivo in astrocytes near amyloid plaques[34]. Alternatively, astrocytic matrix metalloproteinases (MMPs) may be involved in extracellular Aβ breakdown. Numerous MMPs are expressed in astrocytes, and their levels increase following Aβ exposure in vitro[35] and in the brains of AD mice[36]. Conversely, astrocytes may contribute to periplaque pathology by releasing pathological factors such as S100β. This protein is enriched in the AD brain, and levels positively correlate with the number of dystrophic neurites within plaques[37]. APOE is also expressed in astrocytes and is thought to play a role in astrocytic amyloid clearance (as well as initial deposition and remodelling of Aβ into dense core plaques). Expressing human APOE isoforms indicates that APOE4 exacerbates plaque deposition in mouse models of AD compared with APOE2 or APOE3 (REF[38]). By contrast, complete ablation of APOE in mice reduces plaque deposition[39,40]. These APOE-null data remain incompletely understood but may have more to do with amyloid production and seeding in neurons than with amyloid clearance by astrocytes. Aβ also induces Ca^{2+} dysregulation in astrocytes in vitro[41,42] and in vivo[43], and astrocytes from human post-

mortem AD brains show alterations in the expression of genes associated with Ca^{2+} signalling, contributing to impaired astrocyte function.

Glia and tau pathology.

Tau pathology correlates more strongly with neuron loss and cognitive decline in AD than amyloid pathology, and extensive tau pathology throughout the brain is present only at later stages of the disease process downstream of initial insults. However, tau pathology does accumulate in the entorhinal region early in the disease, and the spread of tau out of the medial temporal lobe is thought to be important for moving from the early stages of the disease, in which brain circuits compensate well for pathology, to the later stages of progressive worsening of symptoms[44]. There is some evidence that non-neuronal cell types may play a role in tau-induced neuron death and perhaps also in its spread through neural circuits. In addition to their well-known plaque associations, glia accumulate in the vicinity of neurofibrillary tangles, and the burden of glia positively correlates with tangle burden in human AD brain[45]. Further, gliosis occurs in non-AD tauopathies and tau pathology can accumulate in astrocytes[46]. In support of interactions of glia with tau-induced neuro-degeneration, transplantation of human neural precursor cells into a mouse model of tauopathy resulted in glial cell differentiation that protected mice from neuron loss[47]. Both APOE and TREM2 have also recently been linked to inflammation in tau models. TREM2 deficiency in a mouse model of tauopathy reduced inflammation and prevented neurodegeneration at late stages of disease[46]; however, TREM2 reduction in a different tauopathy model examined at an earlier stage showed an exacerbation of tau phosphorylation[48]. Furthermore, overexpression of TREM2 in the microglia of P301S mice (a model of tauopathy) reduced tau phosphorylation and suppressed secretion of pro-inflammatory cytokines[49]. These emerging data on TREM2 indicate that it may have different effects on tau pathology at different stages of disease (similar to the emerging story with Aβ), or at least that it has different effects in different mouse models. Although the data examining the relationship between TREM2 and tau are still sparse, they do urge caution in pursuing therapeutic strategies to activate TREM2 before we fully understand the role of this molecule in the disease.

Similarly, most work examining effects of APOE4 on AD have focused on Aβ or synapse loss, but there are now hints that APOE may also affect tau pathology, likely through modulating glial function. In a mouse model overexpressing frontotemporal dementia (FTD)-associated P301S mutant tau, knocking out APOE protected mice from neurodegeneration, while knocking in human APOE exacerbated neurodegeneration in an isoform-specific manner with APOE4 being most toxic[50]. Furthermore, profiling of gene expression showed an increase in pro-inflammatory and a decrease in homeostatic gene expression in microglia and an increase in inflammatory profiles in astrocytes[50].It remains to be seen which cell types are important in mediating these APOE isoform-dependent effects on neurodegeneration, as APOE is largely produced in astrocytes and microglia but its expression is also induced in other cells in the CNS.

Microglia may contribute to tau spreading through the brain. One recent study reported that after tau virus injection into the entorhinal cortex, ablation of microglia reduced

phosphorylated tau, reduced tau spread from the entorhinal cortex to the dentate gyrus and lowered pro-inflammatory cytokine levels[51]. Other studies have increased microglial activity by blocking or genetically removing the fractalkine receptor, which is constitutively activated by neuronally released CX_3CL1 to suppress microglial activation. Genetic removal of CX_3CL1 results in increased tau phosphorylation in wild-type and tau-overexpressing mice via microglia-derived soluble factors[52]. In support of this, CX_3CL1 overexpression in the rTg4510 model suppressed microglial activation and subsequent tau pathology[53]. Although interesting, there are caveats to these studies including small animal numbers and the possibility that reducing microgliosis likely reduced levels of inflammatory cytokines, which themselves could contribute to the spread of tauopathy. Further work is necessary to understand the potential role of microglia and astrocytes in the early spread of tau through neural circuits.

Glial phenotypes change during ageing.

In addition to their effects on amyloid and tau pathology, glial changes may be important for other aspects of AD pathogenesis independent of the amyloid cascade. Age is the largest risk factor for AD, yet we do not fully understand why age renders the brain susceptible to neurodegeneration. A recent genome-wide analysis of microglia in mice showed distinct region-dependent transcriptional identities that changed with age[54]. Similarly, analysis of astrocytes from different regions of mouse brain during ageing showed age-associated and region-specific transcriptional changes[55]. Interestingly, these age-associated astrocyte changes were reduced in mice lacking microglial secreted cytokines, indicating important interactions between microglia and astrocytes during ageing[55]. In support of the translational relevance of these age-associated changes observed in mice, we observed differences in the distribution of microglia and astrocytes in different brain regions in healthy aged human brain[56], suggesting that regional differences in the ageing of glia could contribute to selective vulnerability in age-related neurodegenerative diseases such as AD. In a recent mouse study profiling the translatome of microglia, ageing, APP/PS1 overexpression and P301L tau overexpression all induced a similar network of translational changes strongly implicating APOE in driving a network of changes resulting in production of the cytokines CCL3 and CCL4 (REF.[57]). The effects in this study were more pronounced in microglia from female mice. Although this is a single paper utilizing AD animal models, it points to the intriguing idea that the AD risk factors of age, APOE isoform and female sex may converge on similar inflammatory pathways that are induced by the pathological proteins that accumulate in the disease.

Glial effects on neuron death.

Neurons begin to die early in AD pathogenesis. By the time symptoms are detectable, estimates indicate that over half of neurons in layer II of the entorhinal cortex are lost[58]. Microglial phenotypes and their effects on neuron death have recently been shown to change with disease stage. In a mouse model of neurodegeneration downstream of p25 overexpression, microglia appear to proliferate early then later initiate a harmful host of innate immune responses[59]. Microglia also influence neuron death in a human cell tri-culture system in which neurons and astrocytes expressing mutant APP are cultured in a 3D chamber and microglia are added in a surrounding, connected chamber at later time points[60].

In this system, infiltrating microglia contribute to neuron death in a pathway involving Toll-like receptor 4 and interferon-γ (IFNγ). This study has several limitations, including overexpression of mutant APP and the use of an immortalized microglial cell line, but it does support a role for microglia in inducing death of human neurons[60,61]. Although these results from model systems are intriguing, it will be important to examine other models and human brain to fully understand how microglia change with disease stage and which changes may contribute to neurodegeneration. It will also be important moving forward to distinguish microglia from infiltrating microglia-like macrophages, which enter the brain during disease and may have distinct roles compared with resident microglia[62–64].

Astrocytes are also able to modulate neuron death via their expression of APOE. In mice, APOE3 expression in neurons or astrocytes and APOE4 expression only in astrocytes protected APOE-null mice from excitotoxicity, whereas neuronal expression of APOE4 was not protective and led to neuron death after excitotoxic challenge[65]. Although excitotoxicity has not been established as the cause of cell death in AD, this study provides proof of principle that the cellular source of APOE4 influences neuronal susceptibility to neurodegeneration and indicates that glia may affect cell death independently of amyloid.

Cellular crosstalk in inflammation.

Along with their independent roles in neuroinflammation, there is increasing evidence for interactions between microglia and astrocytes in destructive feedforward loops in AD. Work from Ben Barres' group showed that secretion of cytokines by microglia can activate astrocytes, causing them to lose some of their physiological functions and become toxic to neurons[66]. In AD models, two studies showing that IL-10 worsens amyloid-related phenotypes in mice also implicate microglial IL-10 in boosting astrocytic expression of APOE, which then looped back to decrease microglial appetite for Aβ[67,68]. The complement system also plays a role in microglia-astrocyte crosstalk. In a recent study examining both plaque-bearing transgenic mice and cultured astrocytes and microglia, Aβ was found to activate astrocyte expression of NF-κB, which caused extracellular release of complement C3. In turn, this extracellular release caused microglial and neuronal C3a receptor activation, which impaired cognitive function and altered microglial Aβ phagocytosis[69]. Immune-system-related genes including those encoding CLU and complement C3 are differentially expressed in laser-captured astrocytes from human AD brain compared with control brains[70], further implicating an inflammatory immune response in multiple cell types in AD.

Microglia and astrocytes both secrete cytokines in the AD brain. Treating cultured microglia with amyloid induces secretion of numerous pro-inflammatory mediators such as IL-1β, IL-6 and TNFα as well as reactive oxygen species (ROS)[71]. All of these factors can be released in differing combinations depending upon the pathological context and have significant detrimental effects on the surrounding milieu. Importantly, some of these molecules can induce the activity of γ-secretase, leading to increased Aβ production[72]. Exposure of cultured astrocytes to oligomeric Aβ similarly induces astrocyte activation[73] and the release of pro-inflammatory cytokines such as IL-1β and TNFα as well as the gaseous synaptic modulator nitric oxide (NO)[74]. APOE genotype influences the inflammatory response of glia to Aβ exposure. APOE4 expression in a mouse model of AD

with plaque deposition resulted in increased microglial and astrocytic reactivity and increased release of inflammatory cytokines, particularly in plaque-associated microglia[75]. TNFα has received much attention as mice in which TNF receptor 1 has been knocked out have significantly lower levels of amyloid production and deposition in an AD mouse model[76]. In mouse models of familial AD that develop plaques and in wild-type animals injected with oligomeric Aβ, Aβ is associated with increasing levels of cytokines, confirming that Aβ induces cytokine release in vivo[77,78]. Although much work focuses on pro-inflammatory cytokines, there is also evidence that the anti-inflammatory cytokine IL-10 worsens amyloid pathology and cognition in mouse models[67,68]. Understanding the complex role of cytokines will be important, particularly because cytokines may contribute to neuron death[79].

Complex cellular responses to systemic infection may also contribute to disease pathogenesis. The controversial idea that pathogens contribute to the initiation of AD has been around for decades[80,81] but has received a recent boost from two papers examining herpes infection in human AD and in a mouse model of disease. An extensive analysis of multiple human cohorts found higher levels of herpesvirus 6 and 7 in brain tissue from patients with AD than in controls, and computational analyses indicate that the viruses may regulate known AD genes[82]. The increase in virus in the brains of people with AD could plausibly be due to the known disruption of the BBB in disease, which allows these very common viruses to enter the brain. More mechanistically convincing is the recent study that showed that herpes simplex virus 1 infection leads quickly to amyloid deposition in an AD mouse model and a human stem-cell-derived neuronal culture model[83]. This observation builds on work indicating that Aβ has antimicrobial properties[84]. Whether this is important to AD pathogenesis remains controversial, particularly because plaque deposition is not sufficient to initiate full-blown AD[44]. However, it is possible that these processes may turn out to play a causative role in disease initiation, and there is no doubt that interactions of multiple cell types from the vasculature through glia and neurons are involved in this type of response to infection.

White matter and oligodendrocytes.

Although there is substantial evidence supporting a role for microglia and astrocytes in AD pathogenesis, there has to date been less investigation of a potential role for oligodendrocyte precursor cells (OPCs). White matter changes, as observed by MRI scans, are frequent in AD, with recent studies showing associations of white matter damage with both amyloid[85] and tau pathology[86]. Intriguingly, neuropathological studies do not generally reflect substantial white matter changes, although post-mortem evidence of volume changes would be difficult to observe.

Early on, Braak observed that the pattern of neurofibrillary tangle deposition in AD parallels the developmental pattern of myelination[87], indicating that neurons with late-myelinating axons may be more vulnerable to degeneration, although the molecular link between these observations remains uncertain. Some gene variants that increase AD risk are predominantly expressed in oligodendrocytes or OPCs (TABLE 2) and emerging evidence suggests that myelination is involved in neuronal plasticity[88], indicating that changes in these cells may

contribute to the disease. Incubation of cultured oligodendrocytes with amyloid peptides leads to apoptotic cell death[89], and injection of amyloid into the rat corpus callosum leads to axon damage, oligodendrocyte death and reactive gliosis around the injury[90]. Inflammatory conditions such as those observed in AD can hinder the remyelination process and prevent OPCs from differentiating to oligodendrocytes[91]. Although not yet fully substantiated, these potential oligodendrocyte processes provide further support for the importance of interactions between cell types in disease.

Cellular interactions in synapse loss

For almost three decades, it has been known that the strongest neuropathological correlate with cognitive decline in AD is synapse loss[92]. Synapse loss occurs early in the disease and continues to parallel cognitive decline throughout disease progression[92–96]. The exact mechanisms driving this loss are yet to be fully elucidated, although it is evident that both amyloid and tau exert harmful effects on synapse integrity[97]. Strong focus has been placed on the neuronal components of the synapse as excitatory glutamatergic synapses have historically been considered dipartite structures, consisting of a presynaptic terminal and postsynaptic spine. However, detailed imaging studies have revealed that many exist as tripartite or even quadpartite structures, with glial processes found in close proximity to the synapse. These non-neuronal synaptic components play important roles in synapse development, maturation and disease. Before synapse loss in AD, amyloid and tau accumulate in the synapse, leading to disrupted function of glutamate receptors and synaptic kinases, altered calcium dynamics and spine disassembly[98]. These direct effects on the neuronal components of the synapse are well established and supported by a growing literature describing the presynaptic, postsynaptic and trans-synaptic effects of these pathological factors[97]. However, the disease-driven disruption of glial function and glia's subsequent influence on synaptic physiology remain an area of intense research.

Immune cascades and synapse loss in AD.

Over the past few years, data have emerged implicating both astrocytes and microglia in activity-dependent synaptic pruning during development[99–103]. The classical complement cascade has emerged as a key part of this developmental synaptic pruning[104–106]. In the developing mouse brain, synapses expressing high levels of complement components C3 and C1q are actively engulfed and phagocytosed by CR3-positive microglia[100,104]. Recent data indicate interactions between astrocytes and microglia in developmental synaptic elimination as microglial secretion of inflammatory molecules including C1q induces astrocyte activation, which causes neurotoxicity, at least in cultured cells[66]. Conversely, astrocytes can recruit microglia to eliminate synapses. By releasing transforming growth factor-β (TGFβ), astrocytes in the retina increase the expression of complement protein C1q on nearby synapses, thus priming them for complement-dependent phagocytosis by recruited microglial cells[107]. Intriguingly, the astrocytic elimination of synapses was also recently shown to be modified by APOE isoform. In young mice, APOE2 increased astrocytic phagocytosis of synaptic terminals, whereas APOE4 decreased astrocytic phagocytosis[108]. Complement C1q was also low in APOE2-expressing mice and high in APOE4-expressing

mice, suggesting that APOE4 may prevent astrocytes from performing physiological C1q-dependent synapse clearance, leading to a build-up of senescent synapses[108].

Although much of the evidence for the involvement of the complement cascade in synapse elimination comes from studies of developing retinal ganglion cells in rodents, this cascade may also be involved in synapse degeneration in AD. Several genes associated with the complement system have emerged as AD genetic susceptibility factors, including CR1 and CLU[109]. Furthermore, many components of the complement cascade are significantly upregulated in the AD brain[110]. Evidence from mouse models suggests that amyloid-induced complement activation leads to microglial phagocytosis of cortical synapses[111,112]. In mice, soluble amyloid drives the upregulation in C1q levels before the deposition of amyloid in plaques, and C1q knockout significantly reduced the synaptotoxic effect of amyloid[111]. Genetic removal of complement C3 from APP/PS1 mice (APP/PS1;C3-KO) rescued synapse loss in the hippocampus, and knocking out CR3 resulted in less synaptic engulfment by microglia following amyloid challenge[111]. APP/PS1;C3-KO mice have revealed some clues as to the roles of glia in amyloid clearance. In 16-month-old APP/PS1;C3-KO mice, plaque burden was increased compared with APP/PS1; however, they showed an altered glial response to amyloid plaques — namely, decreased glial infiltration of plaques and lower levels of pro-inflammatory cytokines such as TNFα and IFNγ[112]. This altered glial response associated with partial preservation of synapse density in the hippocampus and improved cognitive flexibility, suggesting that C3-mediated synapse loss is a feature in aged and AD brain[112]. The idea that microglia are phagocytosing synapses in the human AD brain remains controversial. Even in rodent slice culture, there is some debate about whether microglia actively eat postsynaptic dendritic spines, with one study proposing a role for microglia in synaptic circuit remodelling by 'nibbling' presynaptic terminals and facilitating postsynaptic filopodia formation[113]. On balance, the human genetic data and mouse model data strongly support a role for complement and microglia in synapse degeneration, but the details of this remain to be determined, particularly what is happening in human AD brain.

Immunological systems and cytokines beyond the complement system also contribute to synapse degeneration in AD. For example, the major histocompatibility complex 1 (MHC1) immune pathway has been shown to influence synapse function and formation[114]. MHC1 associates with PSD95 and can interact with a number of immunoreceptors, including paired immunoglobulin-like receptor B (PirB; also known as LILRB3)[114]. Neuronal PirB associates with synapses and plays a critical role in ocular dominance plasticity (ODP). When PirB is knocked out, ODP is enhanced[115]; however, in APP/PS1 models of AD, defective ODP is a very early marker of synaptic dysfunction[116]. It has since been discovered that PirB acts as a receptor for amyloid oligomers, and this interaction induces synaptic dysfunction and synapse loss by disrupting the synaptic cytoskeleton[117]. Removal of PirB could rescue synaptic plasticity deficits and behavioural changes in AD mice[117]. Importantly, amyloid oligomers have a nanomolar affinity for the human orthologue of PirB, leukocyte immunoglobulin-like receptor B2 (LILRB2; also known as LIR2), and although LILRB2 levels are not altered in AD brain, downstream signalling pathways are significantly upregulated[117]. This observation suggests that in human AD brain, amyloid activates LILRB2 and increases its downstream signalling, leading to altered neuronal actin

organization and ultimately synapse loss. Further support of a microglial role in Aβ-mediated synapse loss comes from a study of the APP/PS1 mouse model with knockout of TDP43 in microglia. TDP43 knockout increased microglial phagocytic activity and led to increased amyloid clearance and concomitant exacerbated synapse loss[118]. This finding provides an intriguing link between the pathological proteins involved in AD and amyotrophic lateral sclerosis (ALS), which also exhibits synapse loss associated with cognitive decline[119].

Excitotoxicity.

In addition to the potential involvement in innate immune cascades, astrocytic end feet at synapses are likely to play a role in synaptic dysfunction and loss in early AD through modulation of excitotoxicity. Adenosine A_{2A} receptors (A2ARs; also known as ADRA2As) are expressed on astrocytes and respond to synaptic adenosine by inducing a number of cellular changes, including a reduction in glutamate uptake[120]. Astrocytic A2ARs have a negative role in learning and memory processes in mouse models of AD, and high levels of these receptors are found on human astrocytes in AD[121]. Therefore, excitotoxicity in AD may be driven by increased astrocytic A2AR expression on astrocytes, leading to decreased glutamate clearance and excessive synaptic activity. Alternatively, genetically lowering glutamate transporter 1 (GLT1; also known as SLC1A2) expression in AD mice results in an earlier onset of cognitive deficits[122], and amyloid is known to increase the lifetime of synaptic glutamate by inducing the internalization of GLT1 from astrocytic membranes[123]. Furthermore, restoring GLT1 expression in an AD mouse model prevented synaptic pathology and cognitive decline[124]. Therefore, amyloid-induced alterations in GLT1 location and function may increase synaptic and extrasynaptic glutamate, thus driving excitotoxicity in AD. In support of this, it is believed that the beneficial role of memantine in patients with moderate to severe dementia may be due to the blockade of extrasynaptic NMDA (N-methyl-D-aspartate) receptors, which are activated by excess glutamate[125].

Risk genes influence synapse loss.

Astrocytes are also likely to influence synapse dysfunction and loss owing to their production of APOE and its effects on synaptic Aβ[126]. We demonstrated a role for APOE4 protein in targeting oligomeric Aβ to synapses, where it is associated with synapse degeneration in human AD brain[127]. In mouse models, it is clear that the synaptic effects of APOE4 are not cell autonomous, as we observed that bathing the cortex in APOE4 expressed by viral infection of ependymal cells worsens synaptic phenotypes[38]. APOE modulates Aβ metabolism and clearance[128,129], and APOE4 increases the oligomerization of Aβ[130], which is toxic to synapses[131,132]. Interestingly, the APOE4 effect is not just a feature of neurodegenerative disease but also plays a role in synaptic integrity in non-pathological cognitive ageing. APOE plays a role in dendritic spine maintenance[133], presynaptic terminal composition and glutamate synthesis[134] and synaptic plasticity[135], with APOE4 isoforms having significant detrimental effects in these studies. A recent study utilizing transgenic mice that express human APOE isoforms discovered an isoform-specific change in the phagocytic properties of astrocytes[108]. Non-demented individuals from the Lothian Birth Cohort in their ninth decade of life exhibit a faster rate of cognitive decline if they are APOE4 positive than those with APOE2 or APOE3 alleles[136]. Future work on the

well-characterized Lothian Birth Cohort subjects will help to clarify the role of factors such as APOE in cognitive ageing through deep phenotyping of genetic, psychosocial and neuropathological factors[56,137,138].

In addition to the clear links between Aβ, glia and synapse loss, there are indications that tau-mediated synapse loss also involves glia. Early studies in the P301S mouse model of tauopathy revealed that microglial activation coincided with the onset of synapse loss[139]. This occurred before neuron loss and tau tangle formation, placing active microglia at the right place and time to induce synaptic alteration[139]. The effects of TREM2 modulation of tau-induced synapse degeneration have not yet been fully explored, but one study showed that overexpressing TREM2 in microglia in these mice improves cognition and prevents loss of synaptic proteins[49]. There are also hints that astrocytes modulate synapse degeneration in tau mice. Cultured astrocytes from the P301S tauopathy model exhibit functional deficiencies that result in a failure to support neurons in culture[140]. GLT1 is decreased in P301L mice, indicating that astrocytic clearance of glutamate is impaired by tau expression in this model[141], which may contribute to excitotoxicity. Extracellular tau oligomers also disrupt astrocytic Ca^{2+} signalling, reduce astrocytic ATP release and impair neuronal synaptic function in culture[142].

Together, these data strongly support the notion that multiple cell types contribute to synaptic changes (FIG. 1). This view opens promising avenues to prevent or reverse synapse degeneration and potentially to prevent the spread of pathological proteins through neural circuits.

Role of the NVU in neurodegeneration

The brain is an energy-hungry organ, dependent upon blood vessels for delivering oxygen and nutrients and for waste removal. An intricate control system has evolved both to protect the brain from components in the blood that are toxic to brain cells (the BBB) and to regulate blood flow to different brain regions with fluctuating energy demands. This neurovascular unit (NVU) contains almost every cell type found in the brain, all working together in a tightly regulated manner. Vascular cells (endothelial cells, pericytes and vascular smooth muscle cells) form the walls of the vessels. These are surrounded by astrocyte end feet, the terminal processes of astrocytes. Perivascular microglia and macrophages survey the influx of blood-borne molecules into the brain[143].

The different cell types in the NVU communicate and are interdependent. For example, endothelial cells can promote proliferation and differentiation of both neural precursors and OPCs[144,145] and, via the release of trophic factors, also protect neurons from injury[146].

Strong epidemiological evidence shows associations between vascular risk factors and risk of AD and further that mid-life statin use to control high blood pressure is protective against AD[147]. Recent studies show reductions in incidence of AD in the United Kingdom[148], and although the causes for this remain unknown, scientists speculate that better access to health care and lowered cardiovascular risk factors may be contributing to reduced incidence. Disruptions in the NVU certainly cause vascular dementia7 and likely also contribute to the

early stages of AD pathogenesis. It has been proposed that damage to the NVU starts a cascade involving reduced cerebral blood flow and BBB disruption, which when followed by a 'second hit' of Aβ pathology leads to AD[8]. In animal models, vascular changes have been observed very early in the disease process. Reductions in cerebral blood flow and vascular reactivity are the first changes observed in a model overexpressing Swedish mutant APP[149,150], and APP/PS1 mice exhibit ultrastructural changes in microvasculature before cognitive impairment is observed[151]. Tau-overexpressing mice also develop vascular abnormalities, even those expressing wild-type human tau, which do not develop overt neurodegenerative phenotypes[11]. In humans, using dynamic contrast-enhanced MRI, decreases in hippocampal vascular volume have been observed in subjects with mild cognitive impairment[152], and increased BBB permeability has been observed even at an early stage of AD[153]. Brain glucose uptake measured by 18F-fluorodeoxyglucose-positron emission tomography (18FDG-PET) imaging is impaired in patients with AD very early in the disease process[154]. Although these imaging studies have fairly small sample sizes (6–15 subjects per group), they do point to a link between vascular damage and AD. Large biomarker studies also point to the role of vascular malfunction as an early event in AD. In the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort, a data-driven model spanning 30 years of disease progression suggests that vascular dysregulation is one of the earliest events in AD[155].

Along with direct effects of oligodendrocytes on myelin integrity discussed earlier, vascular changes can also affect white matter. White matter hyperintensities detected by T2-weighted MRI have emerged as an important biomarker of white matter damage. Although the pathological causes and consequences of these hyperintensities remain to be fully determined, they have been associated with small-vessel disease, glial cell death, microglial and endothelial cell activation, demyelination, axonal loss and tau pathology in the overlying cortex, linking many aspects of the NVU[86,156,157].

A well-powered imaging study from the Dominantly Inherited Alzheimer Network (DIAN) found white matter hyperintensities in people with familial AD mutations that began 6–22 years before symptom onset[158].

There are some hints at mechanisms linking vascular changes to AD, with the strongest evidence favouring defective clearance of Aβ from the brain to the periphery and chronic hypoperfusion as two of the contributors to sporadic AD. The routes of clearance of Aβ from the interstitial fluid (ISF), and indeed the routes of brain extracellular fluid drainage in general, are not entirely clear and have been fiercely debated over the past decades[159]. Although Aβ can be degraded in the parenchyma, a large part of Aβ clearance from the brain appears to be via the vasculature drainage, driven at least in part by para-arterial influx of cerebrospinal fluid (CSF) that causes convective fluid flux forcing ISF out through paravenous efflux (known as the glymphatic system)[10,160–163]. Meningeal lymphatics have also been recently implicated in Aβ clearance in rodents[164]. In this study, impairment of lymphatic drainage affected glymphatic exchange of CSF and ISF[164], implying that lymphatic and glymphatic drainage processes may be functionally linked — perhaps via effects on glia. Intriguingly, both production and clearance of Aβ change with the sleep-wake cycle, with higher levels of Aβ in CSF and ISF reported during periods of more brain

activity in mice and humans[165,166]. This observation is doubtless due in part to the increased secretion of Aβ with increasing neuronal activity[167], but astrocytes are most likely involved in this process as well because glymphatic clearance is enhanced during sleep[168]. Several genetic risk factors for AD including APOE, CLU and PICALM have been implicated in the vascular clearance of Aβ[169–171]. Polymorphisms in aquaporin 4 are associated with modulation of cognitive decline in AD[172], which could be important because of the role of aquaporin 4 in the influx of CSF into the brain as part of the glymphatic system[163]. Similarly, inducing pericyte loss in APP-overexpressing mice by knocking down pericyte-deficient platelet-derived growth factor receptor-β resulted in exacerbated amyloid pathology. Pericyte loss also caused accumulation of tau pathology and neurodegeneration[173]. However, the role of pericytes in regulating cerebral blood flow and protein clearance from the brain remains controversial[174].

The role of the NVU in AD goes beyond protein clearance. Hypoperfusion, hypoxia and breakdown of the BBB are all thought to contribute to pathogenesis, all of which are processes that involve complex interactions of multiple cell types[8]. For example, in mouse models of early AD, hypertension increases Aβ-induced NVU dysfunction and promotes BACE activity and subsequent Aβ production[175]. Tau pathology has also recently been linked to changes in brain microvasculature. Mice overexpressing human wild-type tau or FTD-associated mutant tau both develop changes in blood vessel structure that are associated with obstructed blood flow[11]. These data indicate that changes in neuronal expression of tau affect endothelial cell biology, further supporting an important role for cell-cell interactions in AD.

As observed in parenchymal inflammation, perivascular microglia likely play a protective role early in the disease process by phagocytosing Aβ and potentially also phagocytosing extracellular tau as it propagates from cell to cell. In support of this idea, in Tg2576 mice, decreased microglial perivascular accumulation correlated with increased deposition of cerebral amyloid angiopathy (CAA) and decreased survival of the remaining microglia, which developed a pro-inflammatory phenotype and impaired the BBB[176].

Hypoperfusion due to vascular changes and neurotoxic changes including glial activation both lead to oxidative stress through generation of ROS, which can contribute to a negative spiral of degeneration. Accumulation of ROS can result from excessive production due to increased activity of superoxide-producing enzymes such as NADPH oxidase or inhibited function of antioxidant enzymes such as superoxide dismutase (SOD)[177]. This fine balance of pro-oxidant and antioxidant activity is particularly vulnerable in the brain owing to its high abundance of polyunsaturated fatty acids, high metabolic rate and fairly low expression of antioxidant molecules[178]. However, given the devastation observed in the human AD brain, it is no surprise that oxidative stress is evident; the important question is whether oxidative stress is a cause of AD pathogenesis or a result of it. Animal models suggest that oxidative stress occurs before or in tandem with amyloid plaque formation[179,180], and human studies suggest that oxidative stress represents an early pathological event in AD[181]. Oxidative stress can result in neuronal death; however, ROS can also have detrimental effects on other cell types in the brain.

CAA, the build-up of amyloid on cerebral vasculature, can lead to vascular oxidative stress via the generation of ROS, and this exacerbates vascular dysfunction. Animal models suggest that NADPH oxidase is the major source of toxic free radicals, as genetic removal of NOX2 (a catalytic subunit of NADPH oxidase) counteracts amyloid-induced, ROS-dependent, vascular dys-function[182]. Furthermore, vascular endothelial cells and perivascular microglia and/or macrophages express the amyloid-binding receptor CD36 (REF[183]). This receptor increases CAA and is important in the amyloid-induced oxidative stress within the NVU[183]. Interestingly, genetic removal of this receptor results in reduced CAA, reduced vascular dysfunction and improved cognitive function in Tg2576 mice despite no change in cortical amyloid plaque burden[183]. More recent animal work has suggested that the source of amyloid-dependent oxidative stress is CD36-positive perivascular macrophages[184]. Depleting perivascular macrophages in Tg2576 mice with clodronate led to decreased amyloid-dependent vascular dysfunction, and this was dependent on CD36 and NOX2 expression[184]. This confluence of ROS, loss of bioenergetics and inflammatory responses involving the neurovascular junction, as well as organ-level clearance mechanisms, may lead to an imbalance in Aβ homeostasis or in tau-spreading mechanisms that help 'tip the balance' towards progression of disease.

Therapeutic implications

Much of the clinical trial landscape for the past 20 years has been dominated by the amyloid cascade hypothesis, on the assumption that lowering Aβ levels will protect neurons. Although confidence in the validity of the amyloid cascade remains high, all trials targeting Aβ to date have failed to improve cognition, and it is now considered possible that anti-Aβ interventions will need to be carried out at very early stages of the disease, long before symptoms begin, to prevent neural system failure and cognitive impairments. These clinical failures and the emerging evidence of the importance of cellular interactions that affect AD have led to a broadening view of therapeutic targets that may prevent or reverse pathological changes in non-neuronal cell types.

Activation of microglia and astrocytes and the downstream effects on neurons are likely important players early in disease pathogenesis that offer potential therapeutic targets. Increasing APOE secretion by astrocytes could be beneficial owing to increasing clearance of Aβ and potentially enhancing synaptic function[185]. Bexarotene, a drug in clinical use to treat skin cancer, has generated interest owing to its ability to aid in the formation of APOE lipoprotein particles. A study published in 2012 indicated that bexarotene treatment increased brain APOE concentrations, reduced Aβ levels and reversed cognitive deficits in APP/PS1 mice[186]. This led quickly to clinical trials; however, subsequent mouse work has failed to replicate the full benefits seen in the original study[187–189]. The initial outcomes from clinical trials have similarly not shown much benefit, lowering brain Aβ levels only in people who do not have an APOE4 allele and increasing serum triglycerides, which could increase cardiovascular risk[190]. Despite these lukewarm results with bexarotene, there is promise in the idea of harnessing APOE levels as a therapeutic, and it may be that lowering APOE levels will be more helpful as a preventive strategy than raising them. Mouse work indicates that increasing levels of APOE2, lowering levels of APOE4 or lowering total

APOE levels in the brain may be beneficial to reduce amyloid levels, increase synaptic function and prevent tau-mediated toxicity[38,50,191].

Another potential therapeutic target based on cellular interactions in AD is inflammation. A large prospective study found that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with lowered risk of AD[192]. However, thus far, anti-inflammatory drugs have failed in clinical trials for AD despite protecting against many phenotypes in mouse models[193]. Human data indicate that anti-inflammatory treatment effects differ at different stages of disease[194], consistent with our conclusion that the role of glia likely changes during the disease course. Although it is still in very early stages, the development of C1q antibodies to treat AD will be of interest on the basis of the involvement of the complement system in synapse loss[195].

At the interface of vascular risk factors and inflammation, diabetes drugs have gained interest as potential therapeutics for AD[196]. Promising mouse work indicates that hyperinsulinaemia exacerbates AD pathology and that anti-diabetic drugs improve phenotypes in AD models[197,198]. However, clinical trials with two agonists of the peroxisome proliferator-activated receptor-γ (PPARγ), diabetes drugs used to control blood sugar, did not succeed in either symptomatic or prevention trials[199,200].

Despite disappointing clinical trial results, it is not clear whether therapeutics aimed at APOE, anti-inflammatories or lowering insulin levels have been adequately studied in humans to date.

Along with therapeutics that target non-neuronal cells, preventive strategies that address the entire neurovascular-glial unit are a promising approach. Recent population-based studies indicate that the incidence of dementia in many countries is stable or decreasing[201]. Although the reasons for this are not known, it is likely that improved cardiovascular health — through initiatives such as reducing smoking — is a contributing factor. Epidemiological studies show an association between exercise and reduced risk of cognitive decline and dementia during ageing[6,202]. However, to date, interventional trials to prevent or treat dementia by improving cardiovascular health via exercise have inconsistent results trending towards no benefit[203,204].

Concluding remarks

Healthy brain function relies on intact neural system integrity, which encompasses the intricately choreographed workings of multiple cell types. Here, we have outlined that in AD there are changes in multiple cell types, and we have discussed the interactions between them (FIG. 2). Strong data from genetic and epidemiological risk factors implicate vascular and glial changes in initiating AD. However, a disease that plays out over more than a decade might be expected to have multiple moving parts; the role of glia or vasculature abnormalities in each portion of this cascade may change over time and is likely to change in the context of ageing and other systemic and environmental factors. Although it is tempting to try to arrange 'cause-and-effect' arrows in cartoon models of hypotheses, it seems very likely that the complexities involved will be difficult to conclusively model in simple

systems. We believe that further evaluation of deeply phenotyped human material from patients at different stages of the disease, and with different genetic risk factors and predispositions, will be critical to advance understanding. Nonetheless, increasing evidence from cell and animal studies implicates the interactions between cell types in damaging synapses and neural circuits and emphasizes the need for further studies. There is hope that with a clearer understanding of the interactions between cells in the brain and the time course of the changes, we will be able to either prevent or treat AD.

Acknowledgements

Glossary

Amyloid cascade hypothesis
Initially proposed in 1992, this hypothesis posits that the accumulation of amyloid-β (Aβ) is the initiating factor in Alzheimer disease pathogenesis, leading to the formation of amyloid plaques, neurofibrillary tangles, neuron loss and clinical dementia

Innate immune system
Reactive response that utilizes chemical mediators to fight infection and clear foreign substances from the body by recruiting specialized immune cells. It can also activate a second wave of adaptive immune response by presenting antigens to adaptive immune cells

Secretomes
The secretome includes all secretable factors released from a cell

Oligomeric Aβ
Single molecules of Aβ are known as monomers. These monomers can aggregate to form oligomeric structures of two or more monomers, which can then accumulate into larger fibrillar forms of aβ and deposit as the hallmark amyloid plaques

Cytokine
Small releasable signalling proteins that often have immunomodulatory effects. These include chemokines, interleukins and interferons and they can be released by numerous immune cell types, endothelial cells and fibroblasts

Homeostatic genes
Genes encoding a protein involved in a homeostatic mechanism within the cell

Glymphatic system
Drainage pathway found in the vertebrate CNS that allows cerebrospinal fluid to enter the brain alongside penetrating arteries and facilitates the removal of interstitial fluid and waste products from the brain

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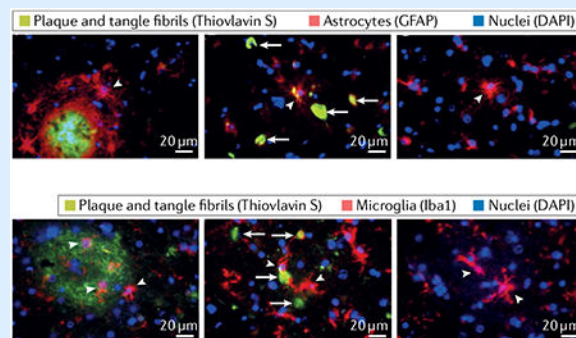
Box 1 |

Alzheimer disease pathology — neurons and beyond

Degenerative changes in the brains of patients with Alzheimer disease (AD) include the accumulation of 'positive' lesions such as amyloid plaques, neurofibrillary tangles, neuropil threads, dystrophic neurites, cerebral amyloid angiopathy and glial responses as well as the 'negative' lesions of synapse and neuronal loss[205–207]. Plaques are extracellular deposits of the amyloid-β (Aβ) peptide, which is generated from the sequential cleavage of the amyloid precursor protein by β-secretase and γ-secretase enzymes[208,209]. Plaque deposition begins in the neocortex years before symptom onset, then progressively spreads to the hippocampus, diencephalon and striatum, brainstem and finally the cerebellum[210]. Soluble oligomeric forms of Aβ rather than plaque fibrils are toxic to neurons and synapses, but the exact forms of the toxic oligomers and how they confer toxicity remain fiercely debated[211].

Neurofibrillary tangles are intracellular lesions composed of misfolded, hyperphosphorylated tau protein[212,213]. Tangle accumulation occurs early in the trans-entorhinal cortex then spreads to the entorhinal cortex and hippocampal formation and later to the neocortex[214,215]. Unlike plaque accumulation, the presence of tangles correlates with neuron loss, synapse loss and cognitive decline[216,217]. Similar to amyloid, it is likely that soluble forms of tau are toxic, but the precise toxic forms remain unknown[218,219].

Drastic brain atrophy occurs in AD, particularly in the medial temporal lobes and later in the frontal lobes[205]. This progressive atrophy can be observed longitudinally in vivo with structural MRI[219], which is increasingly used as a biomarker of disease progression.

Reactive astrocytes (GFAP-labelled; top of figure) and activated microglia (Iba1-labelled; bottom of figure) accumulate around plaques (arrowheads) and in the vicinity of tangles (arrows)[45,205]. Figure adapted with permission from REF[45], Elsevier.

DAPI, 4′,6-diamidino-2-phenylindole.

- Ageing
- Early Aβ accumulation
- Early changes in tau
  (phosphorylation and oligomerization)

Microglia
- Increase inflammatory cytokine secretion
- Increase APOE and TREM2 expression
- Increase phagocytosis

Synapse loss
- Aβ accumulation
- Excitotoxicity
- Tagging with markers for phagocytes

Astrocytes
- Secrete APOE and clusterin
- Increase neurotoxic phenotypes
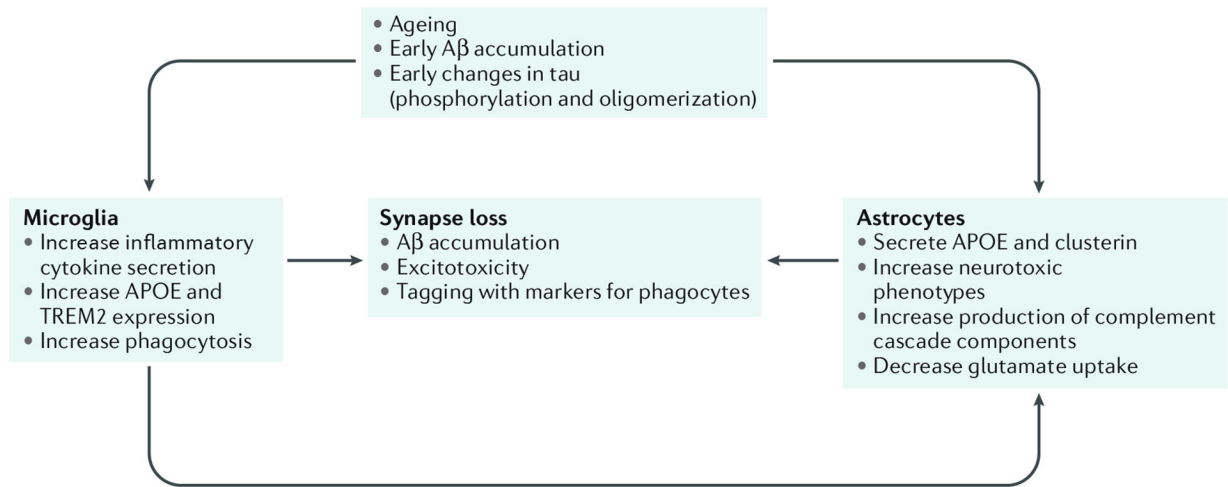- Increase production of complement cascade components
- Decrease glutamate uptake

Fig. 1 |. Synapse loss occurs early in Alzheimer disease pathogenesis.
Emerging data indicate that microglia, astrocytes and crosstalk between these are involved in synapse degeneration. Ageing, early pathological changes in amyloid-β (Aβ) and tau and chronic hypoperfusion due to vascular impairments all directly and indirectly contribute to synapse loss via effects on microglia and astrocytes. Microglia and astrocytes also have direct effects on synapse degeneration, and there is crosstalk among the glial pathways affecting synapses. APOE, apolipoprotein E; TREM2, triggering receptor expressed on myeloid cells 2.
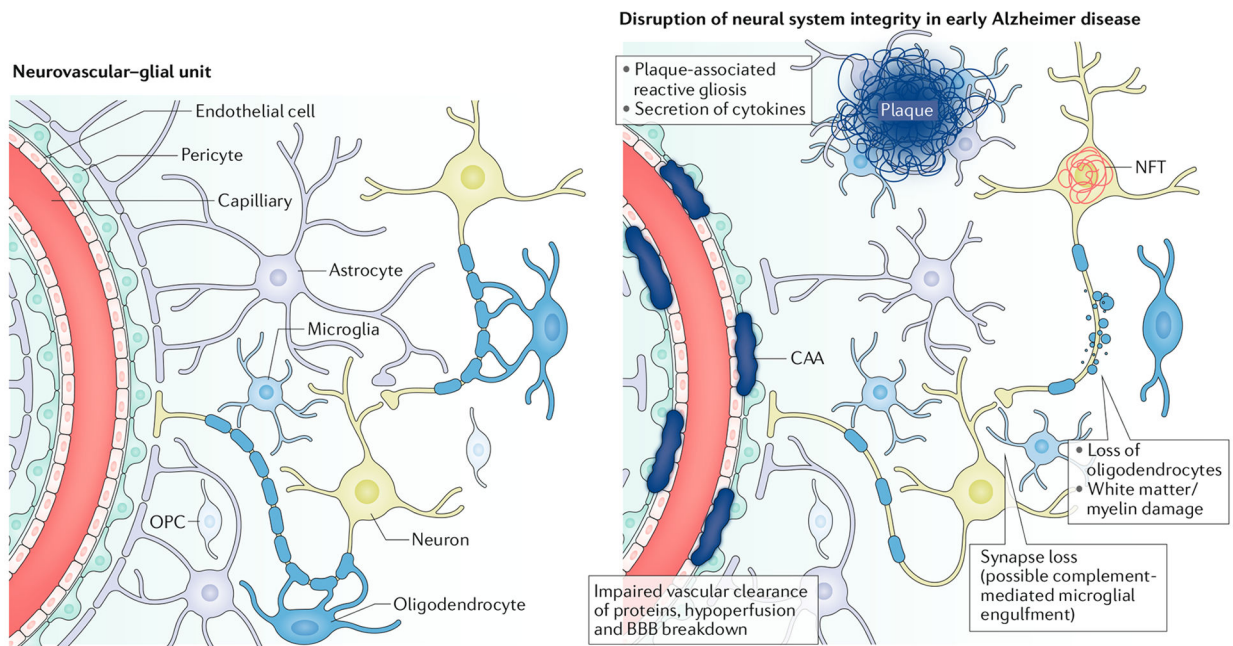
Fig. 2 |. Schematic of the neurovascular unit and early changes in Alzheimer disease.
All of the cell types in the brain interact in a complex web to maintain brain function (left).
During the early stages of Alzheimer disease (right), many of these homeostatic processes
are impaired, and synapses and neurons are damaged by pathways involving multiple cell
types. Vascular integrity is impaired by damage to endothelial cells, astrocytic end feet and
pericytes and by the build-up of amyloid-β (Aβ) along vessel walls in cerebral amyloid
angiopathy (CAA). These vascular changes cause impairments in the vascular clearance of
proteins, hypoperfusion and breakdown of the blood-brain barrier (BBB). Amyloid plaques
are surrounded by a halo of oligomeric Aβ, which damages nearby synapses and neuronal
processes. Plaques are also surrounded by astrocytes and microglia, which initially serve to
clear amyloid protein but after exposure to Aβ become reactive and secrete cytokines.
Within neurons, tau accumulates in neurofibrillary tangles (NFTs), which are associated
with gliaL accumulation and neuronal dysfunction and death. Synapses become
dysfunctional and disappear in a process that likely involves microglia. White matter
integrity is compromised owing to the loss of oligodendrocytes and damage to myelin
caused by chronic hypoperfusion. OPC, oligodendrocyte precursor cell.

Table 1 |

Changes in multiple cell types in the brain early in Alzheimer disease

Cell type	Normal function	Changes in early Alzheimer disease	Refs
Microglia	• Trophic support • Brain surveillance • Phagocytosis of debris	• Microgliosis • Beneficial and impaired clearance of amyloid and tau • Release of neurotoxic and pro-inflammatory factors • Excessive synaptic phagocytosis	13,220,221
Astrocytes	• Trophic support • Metabolic support • BBB component • Synaptic modulation	• Astrogliosis • Beneficial and impaired clearance of amyloid and tau • Release of neurotoxic and pro-inflammatory factors • Synaptic phagocytosis • Impaired synaptic homeostasis • BBB breakdown	221–223
Oligodendrocytes	• Trophic support • Myelin production	• Loss of oligodendrocytes • Myelin loss • Disrupted neuronal plasticity	224,225
Neurons	• Electrical and chemical transmission • Excitatory and inhibitory synaptic activity • Synaptic plasticity , circuit function and cognition	• Intracellular tau aggregation • Synaptic accumulation of amyloid and/or tau • Synaptic dysfunction • Synapse loss	2,97,226
Cerebral vascular cells • Endothelial cells • Pericytes and smooth muscle cells • Perivascularmacrophages	• Endothelial cells, pericytes and astrocytic end feet are essential components of the BBB • Smooth muscle cells control blood flow • Perivascular macrophages aid clearance of toxins	• Impaired amyloid clearance • Cerebral amyloid angiopathy • BBB breakdown • Obstructed blood flow • Decreased CNS glucose uptake • Oxidative stress	2,10,161

This table highlights the normal functions of several brain cell types and how these change in early Alzheimer disease pathogenesis. BBB, blood-brain barrier.

Table 2 |

Cell types expressing genetic risk factors for Alzheimer disease

Risk allele	Cell type(s)	Gene function(s)	Refs
AP0E4	Astrocytes and microglia	Lipid metabolism	9
A8CA7	All cell types	Lipid metabolism	227,228
CLU	Astrocytes and OPCs	Lipid metabolism and endocytosis	109,227,229
SORL1	Astrocytes	Lipid metabolism and endocytosis	227
TREM2	Microglia	Immune response	230–232
PLCG2	Microglia	Immune response	232
AB13	Microglia	Immune response	232
CR1	Microglia	Immune response	109,227
CD33	Microglia	Immune response	227,228
INPP5D	Microglia	Immune response	227
BIN1	Microglia, oligodendrocytes and neurons	Endocytosis	227
P1CALM	Microglia and endothelial cells	Endocytosis	227,229
ZCWPW1	OPCs, oligodendrocytes and microglia	Epigenetic regulation	227
NME8	All cell types	Cytoskeleton	227
EPHA1	Oligodendrocytes	Ephrin receptor	227,228
HLA-DRB5-HLA-DRB1	Microglia and macrophages	Immune response	227

For reviews with more exhaustive lists of risk genes and databases where we searched for cell types that express genes, see REFS[233–235]. OPCs, oligodendrocyte precursor cells.