Neuroprotective and neurotoxic properties of glial cells in the pathogenesis of Alzheimer's disease

D. Farfara, V. Lifshitz, D. Frenkel *

Department of Neurobiology, George S. Wise Faculty of Life Sciences, Tel Aviv University, Tel Aviv, Israel

Abstract

Alzheimer's disease (AD) affects more than 18 million people worldwide and is characterized by progressive memory deficits, cognitive impairment and personality changes. The main cause of AD is generally attributed to the increased production and accumulation of amyloid-β (Aβ), in association with neurofibrillary tangle (NFT) formation. Increased levels of pro-inflammatory factors such as cytokines and chemokines, and the activation of the complement cascade occurs in the brains of AD patients and contributes to the local inflammatory response triggered by senile plaque. The existence of an inflammatory component in AD is now well known on the basis of epidemiological findings showing a reduced prevalence of the disease upon long-term medication with anti-inflammatory drugs, and evidence from studies of clinical materials that shows an accumulation of activated glial cells, particularly microglia and astrocytes, in the same areas as amyloid plaques. Glial cells maintain brain plasticity and protect the brain for functional recovery from injuries. Dysfunction of glial cells may promote neurodegeneration and, eventually, the retraction of neuronal synapses, which leads to cognitive deficits. The focus of this review is on glial cells and their diversity properties in AD.

Keywords: Alzheimer's disease ● microglia ● astrocyte ● endothelial cells neurodegeneration ● immunotherapy

Introduction

Alzheimer's disease (AD) has emerged as the most prevalent form (70%) of late-life mental failure in humans, which is characterized by progressive memory deficits, cognitive impairments and personality changes. At gross examination, the Alzheimer's brain shows severe atrophy and a reduction in brain weight of usually more than 35%. The histopathological hallmarks include the presence of extracellular

*Correspondence to: Dan FRENKEL,
Department of Neurobiology,
George S. Wise Faculty of Life Sciences,
Sherman building, Room 424,

Tel Aviv, 69978, Israel.
Tel.: +972-3-6409028
Fax: +972-3-6406743
E-mail: dfrenkel@post.tau.ac.il

deposition of Aβ, neurofibrillary tangles (NFT), progressive synaptic dysfunction and, much later, neuronal death, especially in the hippocampus [1–3].

Most cases of AD are sporadic, while less than 5% of cases are early onset familial Alzheimer's disease (EOFAD; age at onset < 65 years) with an autosomal dominant pattern of inheritance [4]. Among all the known cases of EOFAD, the genetic mutations are found to affect the expression levels of Aβ peptide, which was named amyloid after its starchy appearance following its aggregation. Aβpeptide is a 4-kD peptide, 40–43 aa, derived from proteolytic amyloid-cleavage of the amyloid precursor protein (APP), which maps to chromosome 21 and is found to be spread on neuronal cells [5–7]. The main role of Aβ as a mediator in AD is derived from the fact that it accumulates in the brain several decades before the disease is evident. Furthermore, Down syndrome patients that have tri-chromosome 21 suffer from AD symptoms in their late 30s. This evidence led to the establishment of the amyloid hypothesis in AD. While in early research the fibril form of Aβ was considered the toxic form, in more recent papers, the toxicity to the neurons seems also to be derived from soluble Aβ oligomers [8, 9]. The classical view is that Aβ is deposited extracellularly, however, emerging evidence from transgenic mice and human patients indicates that this peptide can also accumulate intraneuronally, which may contribute to disease progression [10].

Although Aβ is the major component of the amyloid deposits, other molecules are also associated with these deposits (*e.g.* ferritin, components of the complement pathway, α1-antichymotrypsin, α2-macroglobulin, low-density lipoprotein [LDL] receptor-related protein, APP, acetylcholinesterase, laminin, glycosaminoglycans and the apolipoproteins E and J) [11–13]. Aβ can adversely affect distinct molecular and cellular pathways, thereby facilitating tau phosphorylation, aggregation, mislocalization and accumulation. Intracellular abnormally phosphorylated tau and Aβ exhibit synergistic effects that finally lead to an acceleration of neurodegenerative mechanisms involved in metabolism, cellular detoxification, mitochondrial dysfunction and energy deficiency, which result in the formation of neuritic plaques [1]. Such plaques are also closely associated with microglia that express surface antigens associated with activation, and surrounded by reactive astrocytes displaying abundant glial filaments. The microglia are usually within and adjacent to the central amyloid core of the neuritic plaque, whereas the astrocytes often ring the outside of the plaque with some of these processes centripetal to the amyloid core [14] (Fig. 1). The time extent that it takes to develop such a neuritic plaque is unknown, but these lesions probably evolve very gradually over a substantial time, perhaps several years. The dialogue between the microglia and astrocyte play an important role in shaping the immune response surrounding the amyloid plaques.

Innate immune response in the brain of AD

Although inflammation is not necessarily a hallmark of AD, an increased amount of findings suggests that Aβ deposition and NFT activate a potentially pathological innate immune response in the disease (Fig. 1). These investigations demonstrate that serum and cerebrospinal fluid (CSF) from AD patients contained antibodies that recognized human senile plaques in the central nervous system (CNS) [15, 16]. The mechanism underlying the innate immune system is based on the detection of different ligands that are not self-initiated and express highly conserved pattern recognition receptors (PRRs) to facilitate the clearance of debris (Table 1, Fig. 1). Among these highly conserved receptors, the most abundant factors expressed on glial cells are the complement receptors [17, 18], Toll-like receptors (TLRs) and scavenger receptors (SRs) [19–21] (Table 1).

The complement system provides an innate immune response against pathogenic features and contributes to the local inflammatory response triggered by Aβ deposition and NFT in AD [17, 22]. The CNS contains components of the complement system that are synthesized by astrocytes, microglia and neurons [17]. Complement component 1q (C1q) has been shown to colocalize with most of the amyloid deposits in brains of AD patients [23–25] and triggers a complement cascade, including the formation of the membrane attack complex (MAC), C5b–C9 [26]. In brain regions that have dense accumulations of plaques and tangles (*e.g.* hippocampus and cortex), C1q mRNA level is increased up to 80-fold compared to control levels [27]. Furthermore, the absence of C1q leads to less neuropathology in transgenic mouse models of AD [28]. Therefore, the activation of the classic complement pathway through C1q may
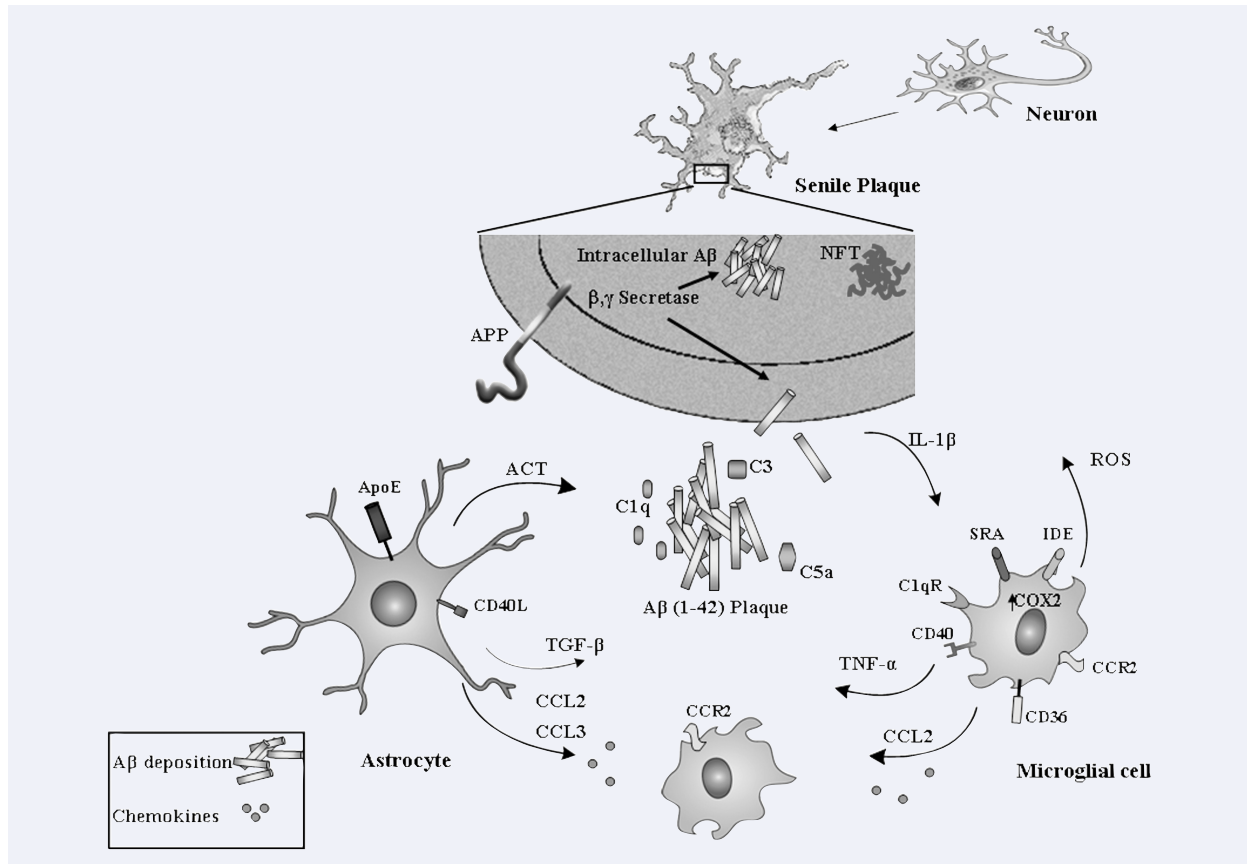
Fig. 1 Activation of the glial cell response toward the formation of senile plaque in Alzheimer's disease. The overproduction and extracellular deposition of amyloid β-peptide (AβP) and an intracellular deposition of neurofibrillary tangles (NFT) initiates the pathogenesis of Alzheimer's disease (AD). The production of complement components (C1q, C3 and C5) is the first stage in response to Aβ deposition, resulting in the attraction and activation of microglial cells. Both microglial cells and astrocytes produce multiple pro-inflammatory and neurotoxic factors: transforming growth factor (TGF)-1; tumour necrosis factor (TNF)-α; interleukin-1 (IL-1); CC-chemokine ligand (CCL); antichymotrypsin (ACT); reactive oxygen species (ROS) and cyclooxygenase 2 (COX2). Activated microglial cells express various scavenger receptors (SRs) that mediate phagocytosis of Aβ, such as CD36, SR-A. Microglial cells can also degrade Aβ by releasing Aβ-degrading enzymes, such as insulin-degrading enzyme (IDE).

provide a specific mechanism for recruiting reactive glial cells to the sites of the Aβ plaque and lead to inflammatory events, neuronal dysfunction and degeneration through production of pro-inflammatory cytokines and oxidative products such as nitric oxide [22, 29]. Nevertheless, the complement system serves in eliminating aggregated and toxic proteins associated with neurological disorders, and thus has a protective effect. Thereby activation of the complement system can lead to increased phagocytosis of Aβ by microglial cells [30]. Inhibition of complement C3 activation in the brains of hAPP mice, by expressing soluble complement receptor-related protein y (sCrry), a complement inhibitor, led to marked increases in Aβ accumulation and neuronal degeneration compared to the hAPP mice [31]. Moreover, blocking complement activation diminished microglial cell activity in APP-transgenic mice and led to an increase in amyloid loads [31]. It is likely that a balanced complement activation is necessary for efficient clearance of Aβ without damaging the brain, and hence a successful clinical outcome.

Chemokines are secreted proteins that play an important role in mediating the innate immune response in the CNS. Chemokines can recruit immune cells from the blood or from within the brain.

Table 1 Glia and endothelial receptors that mediate interaction with Aβ

Cell surface receptor	Microglia	Astrocyte	Endothel	Reference
Antibody receptor:				
FcRγ	+			[171–173]
Toll-like receptor:				
TLR2	+	+	+	[174]
TLR3	+	+		[19, 175, 176]
TLR4	+	+		[176, 177]
TLR9	+	+		[146]
Scavenger receptor:				
SRA	+	+	+	[20, 178]
SRBI	+	+		[179, 180]
SR-MACRO	+	+		[181]
SRCL			+	[148]
CD36	+		+	[53, 182, 183]
Glycoprotein receptor:				
Lactadherin	+	+	+	[149]
Lipoprotein receptor:				
APOE		+		[93]
LRP	+	+	+	[99, 184]
CD14	+	+	+	[185]
Advanced glycation end products receptor:				
RAGE	+	+	+	[104, 105]
Formyl peptide receptor:				
FPRL1	+			[186–188]
Complement receptor:				
C1q receptor	+	+		[23, 25]
CD11b (C3 receptor)	+			[31]
Chemokine receptor:				
CCR3	+	+		[72]
CCR2	+	+		[65]
CCR5	+	+		[72]
CXCR2	+	+		[34]
CXCR3	+	+		[89]
T-cell receptor:				
CD40	+			[189]
CD40L		+	+	[190, 191]
MHC-II	+	+		[62, 192]
Mannose receptor:				
MR	+	+		[193]

The source of the chemokines in the CNS can be glia cells, especially microglia or astrocytes. Several chemokines and chemokine receptors have been found to be up-regulated in the AD brain [32]. Those chemokines were clusters from the CC and CXC families, of which most are related to glial cell activity [32]. Immunohistochemical analysis of human AD brains revealed an expression of four chemokine receptors: CCR3, CCR5, CXCR2 and CXCR3 (chemokine receptors of macrophage inflammatory protein-1α (MIP-1α; also known as CCL3), RANTES (also known as CCL5), MIP-2 and CXCL10, respectively [32–34]. Furthermore, increased levels of MCP-1 and IL-8/CXCL8 can be found in the CSF in the majority of AD patients, therefore chemokines in the CSF may provide a useful diagnosis for AD progression [35].

Pro-inflammatory cytokines, such as interleukin-1β (IL-1β/ [36, 37], tumour necrosis factor-α (TNF-α) [38] and IL-6 [39], may play an important role in AD pathology and lead to an increased production of inducible nitric oxide synthase (iNOS), neuronal stress and further neuronal dysfunction and death [40]. Moreover, recent research of plasma signalling proteins suggests a correlation between the immune response mediating cytokines such as IL-1β and TNF-α within patients with pre-symptomatic Alzheimer's or mild cognitive impairment (MCI) and a greater risk of developing AD [41]. Interestingly, other evidence demonstrates that triggering localized hippocampal IL-1β overexpression mediates a substantial reduction in plaque pathology through microglial cell activation suggesting a dual effect of IL-1β in mediating inflammation in AD [42].

Transforming growth factor β (TGF-β) is a cytokine with neuroprotective features that can be released by both neurons and glia in response to stress [43]. Brain TGF-β1 is increased in AD brains compared with controls and positively correlates with the extent of cerebrovascular brain amyloid deposition and cerebral amyloid angiopathy (CAA) [44]. Interestingly, coexpression of TGF-β1 with hAPP/Aβ in bigenic mice resulted in reduction of brain Aβ while elevating cerebrovascular and meningeal amyloid deposition at 2–3 months of age [45].

Microglia

Activated microglia represent the major source of inflammatory factors in the brain in neurodegenerative disorders such as AD [46]. In AD, activated microglia diffusely situate throughout the cerebral cortex, and focally concentrate in Aβ plaques [47]. Microglia accumulate in plaques containing Aβ fibrils, but not in plaques containing amorphous non-fibrillar amyloid [47]. It is possible, however, that small soluble aggregates of Aβ trigger local activation of glial cells, as suggested by a recent study of the young thymus cell antigen 1 (Thy1)-APP mice that had not yet developed Aβ deposits [48]. Furthermore, studies found activated microglia *in vivo* (in the brains of AD patients), by using positron emission tomography and 11C®-PK111995, which is a marker of peripheral benzodiazepine binding sites that are upregulated on the activated microglia [49, 50].

An accumulation of damaged neuronal DNA fragments can be potent promoters of microglial activation in AD [51]. Activated microglia were found to contain fragmental DNA (fDNA) in their cytoplasm (AD brains and in culture) [51]. Furthermore, Aβ fibril interacts with numerous microglial membrane receptors including scavenger receptor A (SRA) [20, 52] and B [20], CD36 [53], CD40 [54], α6/β1 integrin-CD36-CD47 complex [55] and complement receptors [56] (Table 1). Soluble Aβ can be directly bound by microglial cell receptors, including the heparan sulphate proteoglycans (HSPGs) [57], insulin receptors [58], proteinase inhibitor (serpin)–enzyme complex receptor (SEC-R) [59] and an accumulation of the receptor for advanced glycation end products (RAGE) [60, 61].

Activated microglia bearing major histocompatibility complex (MHC) type II antigens on their surface are associated with Aβ fibrils in AD brain samples, and may interact with infiltrated T cells to induce inflammation as observed in autoimmune diseases [62]. Isolated microglia from postmortem AD and control (non-demented) patients' brain tissue exhibit pro-inflammatory cytokine expression profiles, in the form of a significantly increased expression of IL-1β, TNF-α, IL-6 and IL-12, following an exposure to Aβ peptides. These results strongly suggest that either the Aβ peptides or the plaques can initiate the activation of microglia and subsequent release of pro-inflammatory molecules in the AD brain [62–64].

The possible function of the activated microglia may be scavenger cells, since they represent macrophage-derived cells in the CNS and therefore are capable of rapidly responding to the accumulation of foreign material, such as Aβ deposits [47] (Table 1). A defi-

ciency in the activation of microglia in transgenic mouse models of AD promotes Aβ deposition and increases mortality in these mice [65]. Furthermore, a recent study reports that microglial cells exhibit significant telomere shortening and a reduction of telomerase activity in normal aging rats [66], and that in humans there is a tendency toward microglial cell telomere shortening with a presence of dementia [66]. Human brains containing high-amyloid loads demonstrate a significantly higher degree of microglial dystrophy than non-demented, amyloid-free control subjects [66]. This suggests that degeneration of microglia is a factor in the pathogenesis of AD [47].

Neurons can influence microglial functions, through direct cell-to-cell interactions as well as with the release of soluble mediators, such as neurotransmitters [67]. A recent article describes the up-regulation of nicotinic acetylcholine receptor α7 in cholinergic basal forebrain neurons in AD [68]. This receptor is also expressed by microglial cells and its activation weakens the pro-inflammatory response of microglial cultures, suggesting that acetylcholine may control brain inflammation [68].

Microglial cell activation can target Aβ plaques in the brain using many different mechanisms, and the source of the microglial cells can be brain resident or bone marrow-derived microglial cells [69]. Microglia cultured from rapid autopsies of AD and non-demented patients reveal an increased expression of chemokines such as IL-8, monocyte chemoattractant protein-1 (MCP-1; also known as CCL2) and macrophage inflammatory MIP-1α (CCL3) after experimental exposure to Aβ [70]. Neuropathological studies have found MCP-1 [71] and an increased expression of the chemokine receptors CCR3 and CCR5 in reactive microglia [72]. Recent evidence shows that a deficiency of CCR2, a chemokine receptor expressed on microglia and important for cell migration, accelerates early AD disease progression and markedly impairs microglial cell accumulation in a transgenic mouse model of AD. Furthermore, AD mice deficient in CCR2 accumulated Aβ earlier and died prematurely [65].

It is likely that once Aβ is deposited in an area of the brain, locally present microglia, which are constantly sampling their environment, interact with these Aβ peptides using one or more specific receptors. This interaction initiates a local inflammatory response that recruits additional microglia and astro-cytes (Fig. 1). Microglial cells do not have uniform properties and, it is probable that there are different microglial cell phenotypes that have the potential to be beneficial or harmful in AD [73].

Astrocyte

Astrocytes are the most abundant cells in the CNS and play an important role in the homeostasis and maintenance of the brain [74, 75]. Astrocytes display an array of receptors involved in innate immunity, including TLRs, nucleotide-binding oligomerization domains, double-stranded RNA-dependent protein kinase, SRs, mannose receptor and components of the complement system [76] (Table 1). In an AD patient's brain, reactive astrocytes are integral components of neuritic plaques [77, 78]. Astrocyte activation seems to be particularly prominent around Aβ deposits both in the brain parenchyma and in the cerebrovasculature [63]. Astrocyte activity is marked by hypertrophy [79], resulting in an expression of proteins such as glial fibrillary acidic protein (GFAP), S100B [78, 80], adhesion molecules and antigen presenting capabilities, including MHC antigens [81, 82]. Tissue levels of S100B correlates with the number of neuritic plaques in the temporal lobe [78, 83] but not in the cerebellum where there is no evidence of neuritic plaques, suggesting a correlation between AD pathology and activated astrocyte.

Exposure of human astrocytes to LPS and IL-1β stimulates inflammatory mediators. These include TNF-α [84], IL-6 [85] and IL-12 [85]. Furthermore, an astrocytic response to IL-1β and TNF-α results in an elevation of colony stimulating factor 1 (CSF-1) [86], granulocyte-macrophage CSF (GM-CSF) [86], granulocyte CSF (G-CSF) [86], MCP-1 and MIP-1α [33, 87], which can lead to the recruitment of microglial cells to Aβ plaques [88]. The CXCL10 ligand for CXCR3 can be present in subpopulations of astrocytes associated with senile plaques in AD brains compared with controls [89].

In AD, activated astrocytes can contain Aβ fragments, providing further evidence of their role in Aβ degradation [90]. Furthermore, Wyss-Coray *et al.* [91] demonstrate that astrocytes plated on Aβ brain sections (from a mouse model of AD) reduce overall Aβ levels in these sections. Apolipoprotein E (APOE), postulated to be a major lipid carrier protein
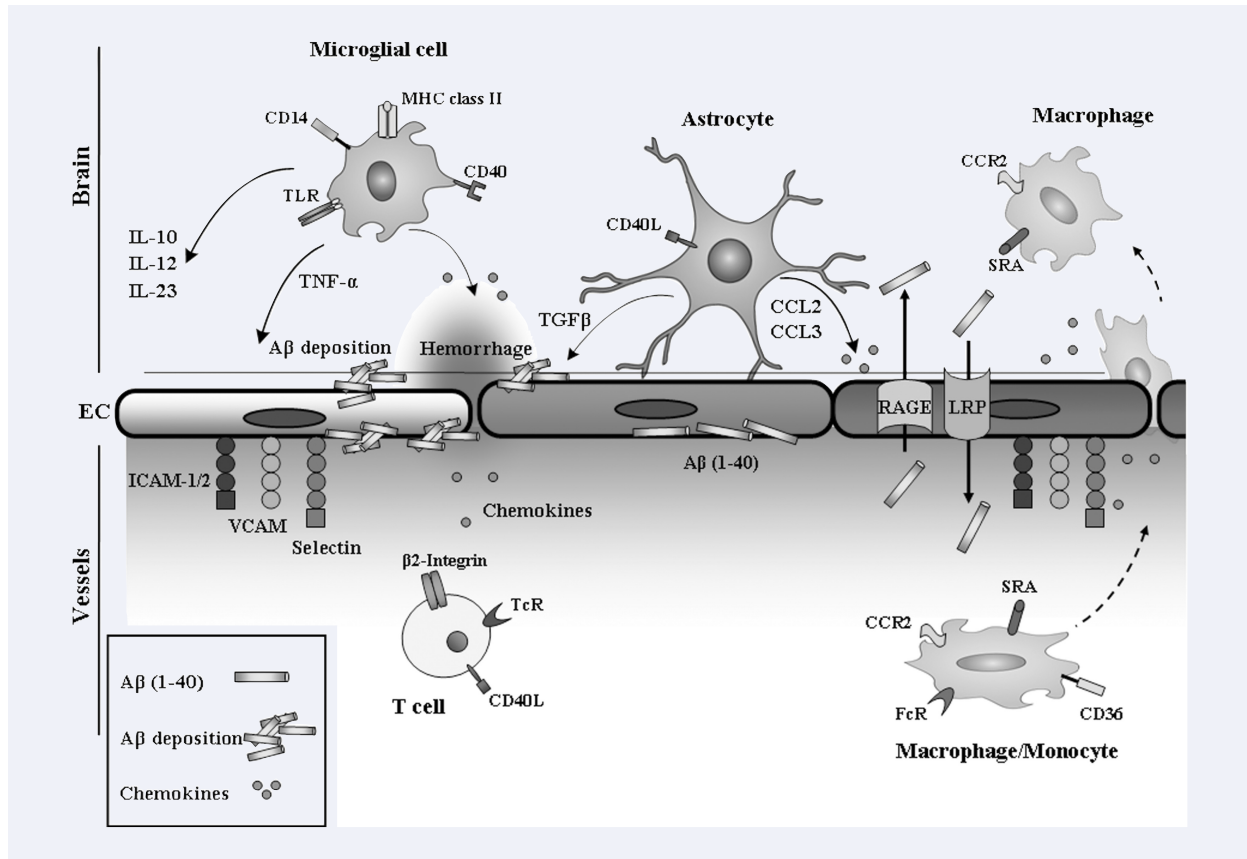
Fig. 2 Glia–endothelia cell interaction in AD pathogenesis. Mediators released by astrocytes activate neighbouring cells and amplify the local, initial innate immune response further, modify BBB permeability and attract immune cells from the blood circulation into the neural tissue, thus supporting an adaptive immune response. Activated microglia up-regulate: MHC class II molecules, CD14, Toll-like receptors (TLRs) and CD40; and produce cytokines: transforming growth factor-β (TGF-β); tumour necrosis factor-α (TNF-α); interleukins and chemokines. TGF-β1 potentiates Aβ production in human astrocytes and thus favouring continuing deposition of Aβ, which in turn activates glial cell synthesis and the release of a number of cytokines. Low-density lipoprotein (LDL) receptor-related protein (LRP-1) and receptor for advanced glycation end products (RAGE) perform opposite functions in transporting Aβ. The weakening of the vessel wall is the likely cause of intracerebral haemorrhage.

in brain, is synthesized and secreted primarily by astrocytes and is involved in brain development and repair [92]. The isoform apolipoprotein E4 (APOE4) is a risk factor for developing AD at an earlier age and might contribute to this effect [92]. The putative clearance mechanism of Aβ by astrocyte may depend on their expression of APOE3 [93]. Furthermore, high expression of APOE4 in astrocytes can reduce their response to Aβ deposits [94, 95]. Thus, APOE3 seems to be important in the degradation and clearance of deposited Aβ species by astrocytes, a process that may be impaired in AD [93].

Glial cells mediate the peripheral immune response in AD

Glial cells are important cells in maintaining the integrity and homeostasis of the brain. However, upon stress, glia can mediate the permeability of the blood-brain barrier (BBB) to recruit specialized immune cells from the periphery, such as T cells (Fig. 2). Thus, understanding the dialogue between glial cells to peripheral immune cells is key to the success of any future immune intervention treatment of neurodegenerative diseases.

Glial cell interaction with endothelial cells

The interaction of glial cells, particularly astrocyte, with endothelial cells, support and maintain the BBB [96]. The BBB is critical for mammalian brain homeostasis. The BBB regulates Aβ transport to and from the brain, using two main receptors, the LDL receptor-related protein (LRP)-1 and RAGE (Table 1, Fig. 2) [97–99]. LRP-1 and RAGE perform opposite functions in transporting Aβ [97]; RAGE transports Aβ into the brain and LRP transports Aβ out of the brain.

LRP plays an important role in the balance between Aβ synthesis and clearance mechanisms [99]. LRP is expressed in reactive astrocytes and in the brain capillary endothelium [99, 100]. Glial cells secrete the LRP ligand, ApoE-containing lipoproteins (ApoE-LPs) [101], which have an important role in lipid homeostasis in the CNS. Glia-derived APOE-LPs also promote synaptogenesis and stimulate axon growth of CNS neurons [101]. In addition, binding APOE-LPs to LRP initiates the prevention of neuronal apoptosis [102]. The protective effect was greater for ApoE3 than for ApoE4, the expression of which is a risk factor for AD [103]. ApoE3 might be involved in the up-regulation of LRP and increase clearance of Aβ from the brain [103] (Table 1). These findings support the hypothesis that glial cells may play an important role in mediating Aβ transport through the endothelial cells.

RAGE is a multi-ligand receptor of the immunoglobulin super family of cell surface molecules and is expressed on endothelial and glial cells [104, 105]. RAGE is implicated in the development of the Alzheimer's neurovascular disorder by mediating circulating Aβ transcytosis across the BBB. After BBB transport, the circulating Aβ is rapidly taken up by neurons thereby inducing cellular stress. Hence, the RAGE–Aβ interaction in brain endothelium leads to an expansion of endothelin-1, a potent vasoconstrictor, resulting in a suppression of blood flow [97].

Dysfunction in the BBB clearance of Aβ through deregulated LRP1/RAGE-mediated transport, aberrant angiogenesis and arterial dysfunction may initiate neurovascular uncoupling, Aβ accumulation, cerebrovascular regression, brain hypoperfusion and neurovascular inflammation [106]. Severe AD is associated with significant changes in the relative distribution of RAGE and LRP-1 in the human hippocampus, as compared with age-matched controls [100].

TGF-β1 is a multi-functional cytokine that is a major regulator of the immune response and has profound affects on vasculogenesis, angiogenesis and the maintenance of vessel wall integrity [43]. Overexpression of TGF-β1 by the promoter of the GFAP, a specific marker of astrocytes, within the CNS can result in cerebrovascular amyloid and enhance immune cell infiltration from peripherally triggered autoimmune responses [107] (Fig. 2). In AD, the deposition of amyloid around cerebral blood vessels can lead to CAA which occurs in 80% of AD cases [108]. Aβ deposits in the cerebrovasculature are associated with the alteration of smooth muscle cells [109], the thinning of endothelial cells [110] and the loss of endothelial mitochondria [110]. The deposits cause intraparenchymal and subarachnoid bleeding, which leads to haemorrhage, stroke with hemosiderin deposits, multiple infarcts and cognitive impairment [109] (Fig. 2). Aβ increases endothelial monolayer permeability [111, 112], stimulates secretion of inflammatory cytokines [113] and up-regulates vascular cell adhesion molecules (Fig. 2).

Glial cell interaction with T cells

Although there is no clear T-cell response in the brains of AD patients, understanding T-cell responses and adaptive immunity has become important in AD immunotherapy. Studies show a stronger T-cell response to Aβ, in a proportion of healthy elderly individuals and patients with AD, than in middle-aged adults [114]. In the human trial of Aβ-peptide vaccination in which meningoencephalitis followed immunization with Aβ peptide [115, 116], the inflammatory response following immunization was composed of CD8^{+}, CD4^{+} and CD3^{+} T cells. Recent works suggest that the final maturation of T cells might occur in the CNS through an interaction with resident antigen presented cells. Therefore, glial cells have an important role in facilitating the response to T cells. The glial cell–T cell interaction occurs through different receptors and the first type of signal mediates the fate of the immune response [117].

Different types of T cells would be expected to have different effects on microglial cell activation and therefore on amyloid clearance. Th1 cells can promote microglial cell activation through the secretion of IFN–γ, which also up-regulates the expression of

MHC class II molecules by microglial cells, thereby enhancing the T cell–microglial cell interaction. Recent evidence has shown that the interaction of CD40 (expressed on the surface of microglia) with CD40L (T-cell receptor) promotes pro-inflammatory microglial cell activation in response to Aβ [118]. Transgenic mice overproducing Aβ, but deficient in CD40L, show reduced Aβ levels and Aβ plaque load [118]. This finding suggests several possible mechanisms underlying mitigation of AD pathology in response to CD40L and validates the CD40–CD40L interaction as a target for therapeutic intervention in AD [54, 118] (Table 1). As part of the defence mechanism of preventing brain inflammation, glial cells can facilitate apoptosis of the infiltrating T cells through signalling pathways initiated by CD95L, CD95L (FasL)/CD95 (Fas), perforin and the TNF receptor 1 (TNFR1) pathway [119–121].

T-cell responses might also be beneficial by aiding the clearance of Aβ, most likely through the activation of microglial cells. Hence, understanding the interaction between glial cells and T cells may reveal a new target for modulating brain inflammation and help in developing novel immunotherapeutic approaches to AD.

Glial cell activation as therapeutic target in AD

Glial cells provide a natural mechanism by which protein aggregates (including amyloid) and debris can be removed from the brain. In addition to their innate ability to phagocytose and clear Aβ, glial cells can also be activated to promote the clearance of Aβ and prevent neuronal death in AD [65, 117, 122, 123] (Table 1).

Epidemiological studies have documented a reduced prevalence of AD among users of non-steroidal anti-inflammatory drugs (NSAIDs) [124, 125]. The main known target of NSAIDs are the cyclooxygenase (COX) enzymes [125]. However, studies by Weggen et al. [126] demonstrate that a subset of NSAIDs lower amyloidogenic Aβ independently of COX activity and appear to operate by decreasing the activity of γ-secretase, an enzyme linked to increased production of Aβ. These findings support the view that decreasing the inflammatory response is not necessarily beneficial in AD and may not be linked to a reduction of Aβ in the brain. In support of this, Jantzen and colleagues [127] suggest that microglial activation may be beneficial based on results of their studies of a nitric oxide-releasing NSAID, NCX-2216. Thus, specifically activating microglia for Aβ phagocytosis, while reducing their pro-inflammatory response, is a major aim for therapeutic applications in AD that target microglial cells.

The classical mechanism for enhancing microglial phagocytosis is through the Fc receptor (FcR). Engagement of the FcR by immune IgG initiates phagocytosis [117, 128, 129], which is characterized by an extension of pseudopodia and an envelopment of the phagocytic target by a mechanism of tyrosine kinases, Rac and Cdc42 [130]. Active immunization with Aβ in mouse models of AD [131], and immunotherapy by passive administration of amyloid-specific antibodies [132] induce microglial cell activation and markedly reduces amyloid levels in the brain and reverses behavioural impairment in these mice [133, 134]. Furthermore, restricting Aβ-specific antibodies with anti-inflammatory drugs, such as dexamethasone, reduces microglial cell activation and inhibits the removal of fibrillar amyloid deposits [135]. There is also evidence that intravenous immunoglobulin (IVIg), an FDA-approved purified immunoglobulin fraction from normal human donor blood, shows promise as a passive immunotherapy for AD, which enhances microglial cell migration toward Aβ deposits, and mediates phagocytosis of Aβ [136].

The first human clinical trial of immunizing AD patients with Aβ peptide led to the activation of T cells and meningoencephalitis in some patients so the trial was discontinued [115]. Nevertheless, the cases of meningoencephalitis did not correlate with the presence of highly elevated concentrations of antibody titres to Aβ, and it is now generally believed that the meningoencephalitis was due to a T-cell response against Aβ resulting from the type of adjuvant that was used [117]. Furthermore, as it was suggested, since the Aβ peptide antibody may lead to local microhaemorrhages associated with amyloid-bearing vessels, the Aβ immunotherapy success rate might be improved by screening patients for the presence and severity of CAA (once this can be accomplished), before such therapies are undertaken. Constructing a specific antibody immune response against Aβ, and avoiding complications seen in the first clinical trial of a vaccine against Aβ remains a promising path for future therapeutic applications in AD [137]. Passive administration of an Aβ-specific humanized monoclonal antibody is currently in a

phase II clinical trial of patients with AD [137, 138]. Additionally, there are also several other ongoing trials based on anti-Aβ antibodies, such as bapineuzumab (Elan/Wyeth), LY2062430 (Eli Lilly) and RN1219 (Pfizer) [138]. Furthermore, other routes of inducing autoantibodies toward Aβ, including the use of a viral envelope instead of an adjuvant or mucosal administration, might play an important role in shaping the beneficial types of glial cell activation toward the clearance of Aβ [139–141]. Nevertheless, a marked reduction of Aβ load in the brains of FcγR-deficient APP-transgenic mice following immunization with Aβ [142] indicates an additional *in vivo* mechanism besides FcR-mediated clearance.

Different types of T cells would be expected to have various effects on microglial cell activation and therefore on amyloid clearance [117]. A T-cell strategy would have to activate microglial cells without causing encephalitis. Recent reports [143, 144] suggest that this can be achieved in APP-transgenic mice by immunizing them with glatiramer acetate (GA) [145], which is a random amino acid copolymer of alanine, lysine, glutamic acid and tyrosine used for the treatment of multiple sclerosis that induces both Th2- and Th3-cell response. The immunization of APP-transgenic mice with GA activates microglial cells without inducing neurotoxicity and leads to Aβ clearance [143, 144]. Hence, understanding the interactions between glial cells and T cells may reveal a new target for modulating brain inflammation and help in developing novel immunotherapeutic approaches to AD.

TLRs are a family of PRRs in the innate immune system. Exogenous and endogenous TLR ligands activate microglia cell [146]. APP mouse models with TLR4 deficiency have an increase in insoluble Aβ in the cortex, as compared to TLR4 wild-type APP mouse models [146]. The activation of microglia with a TLR2, TLR4 or TLR9 ligand markedly boosted the ingestion of Aβ *in vitro* [146]. These results suggest that the TLR signalling pathways may be involved in the clearance of Aβ deposits in the brain and that TLRs can be a therapeutic target for application in AD [146].

Activated glial cells express various SRs that mediate phagocytosis of Aβ fibrils and oligomers. Targeting SRs can mediate the activation of glial cells towards Aβ clearance [147]. A recent study found that there is a low expression of the scavenger receptor with C-type lectin (SRCL), a member of the SR family, in a double transgenic mouse model of AD and in AD patients. The presence of a large number of SRCL together with Aβ double-positive particles in the intracellular compartments of reactive astrocytes and vascular or perivascular cells in APP mice suggests a role for SRCL in Aβ clearance [148]. Lactadherin is a secreted extracellular matrix protein expressed in phagocytes and contributes to the removal of apoptotic cells. In addition, lactadherin can be expressed on vascular smooth muscle cells, astrocytes and microglia. One study found that there is less lactadherin found in the brains of AD patients [149]. This suggests that a lactadherin deficiency significantly limits Aβ phagocytosis. Hence, alterations in lactadherin production or function may contribute to the initiation or progression of AD [149].

Complement components may modulate the phagocytosis of Aβ by microglia [150]. Moreover, the blocking of complement activation diminishes microglial cell activity in APP-transgenic mice and leads to an increase of amyloid loads [31]. Thus, mechanisms that enhance the binding of complement to microglia might accelerate Aβ ingestion by microglia and may be of therapeutic value.

Considerable data has emerged indicating that several enzymes, such as insulin-degrading enzyme (IDE) and neprilysin (NEP) play a role in regulating the clearance of Aβ in the brain [151, 152]. Genetic studies have also shown that IDE and NEP gene variations are associated with the clinical symptoms of AD [151, 152]. Glial cells can also degrade Aβ by releasing other Aβ-degrading enzymes, such as metalloproteases, and gelatinase A [153, 154].

The innate immune response can include cellular activation following recognition of microbial components such as lipopolysaccharide (LPS) or other highly hydrophobic structures. In AD, Aβ is highly hydrophobic and therefore possibly induces innate immune responses similar to those triggered by LPS. Microglial cell activation due to LPS administration may mimic some features of AD [155–157]. In these studies, LPS was given intravenously [155], intracerebroventricularly [156] or intraperitoneally [157]. However, others studies showed enhanced Aβ clearance through microglial cell activation when LPS was injected intrahippocampally [158, 159] or intracranial [160] to older APP-transgenic mice. LPS might lead to microglial cell activation through an interaction with TLR4. Furthermore, nasal administration of a proteosome-based adjuvant (Protollin) [161], composed of purified outer membrane proteins of Neisseria meningitides and LPS, also reduces Aβ in

an APP-transgenic mouse model in correlation with microglial cell activation [143]. Protollin might act by stimulating microglial cells both through LPS *via* TLR4 and through Por B, which makes up 70% of the proteosome protein and activates antigen-presenting cells *via* TLR2 [143].

Microtubules are the key component of the neuronal and glial cytoskeleton that regulates cell division, differentiation and protection. Tau proteins interact with tubulin to stabilize microtubules and promote tubulin assembly into microtubules. Increased tau hyperphosphorylation causes memory impairments in neurodegenerative diseases associated with tauopathies, including the most prevalent AD. Research of the activity-dependent neuroprotective protein (ADNP), a gene product essential for brain formation, shows that ADNP knockout is embryonic lethal and that an ADNP partial deficiency results in cognitive deficits that are paralleled by tau hyperphosphorylation [162]. Structure-activity studies identified a short peptide sequence in ADNP, known as a neuronal microtubule-interacting agent (NAP; amino acid sequence NAPVSIPQ), which mimics the neuroprotective activity of the parent protein and crosses the BBB after systemic or intranasal administration and can support the integrity of the astrocyte and microglial microtubules [163, 164]. ADNP/NAP can also play an important role in immune regulation and down-regulates the key inflammatory cytokines such as TNF-α and IL-12 [165]. The use of NAP may open up new horizons in research and development of protective compounds to both neurons and the supporting glial cells [166, 167]. NAP is currently in phase II clinical trials by Allon Therapeutics to assess the affects on MCI [162].

Adult hippocampal neurogenesis, the process that creates neurons, dramatically decreases with increasing age and it has been proposed that this decline may contribute to age-related memory deficits, such as in AD [168, 169]. While the causes of age-associated decline in neurogenesis have yet to be fully determined, a loss in growth factors in the microenvironment of the subgranular zone (SGZ) and subventricular zone (SVZ) are prime contributors to the reduced neurogenic potential in the hippocampus and cortex regions affected in AD [170]. The ability of glia to produce neurotrophic factors is one aspect that makes glial cells attractive as therapeutic tools. Glial cells produce their own repertoire of neurotrophic factors, including nerve growth factor (NGF), brain-derived growth factor (BDGF), glial cell-derived neurotrophic factor (GDNF), insulin-like growth factor-I (IGF-1) and vascular endothelial growth factor (VEGF) [170]. Recent works suggest that glial cells can mediate neurogenesis in neurodegenerative diseases, such as AD [144].

Conclusion

Glial cells are not only essential for maintaining a healthy well-functioning brain, but they also protect and aid the brain in the functional recovery from injuries. The activation of glial cells in the CNS is the first defence mechanism against pathological abnormalities that occur in neurodegenerative diseases. Different signals can mediate and influence the fate of glial cell activation. As discussed in this review, a dysfunction of glial cell receptors, which alters the glial cells' sense of their environment, can lead to the development of neurological diseases. Emerging evidences in literature suggest that changes in the dividing process of glial cells during aging might lead to their abnormality and may provide clues to the pathogenesis of devastating diseases, such as AD. Because glial cells make up the largest cell population in the brain and continually renew during a human being's lifetime, this makes them a perfect target for therapeutic intervention in neurological diseases. Nevertheless, because there is such diversity among each glia family (astrocyte, microglia and oligodendrocyte), they are still a mystery that holds the key to their modification. However, glial cell plasticity and diversity may allow the maturation of new functional cells, which can help the neuronal repair process. Yet, the basis of successful therapeutic application in neurodegenerative diseases depends on understanding the neuronal–glial cell interaction. Advanced analysis may shed light on genes involved in glial cell function thus leading to the development of new drug-target candidates. Furthermore, understanding the glial cells' continuous dialogue with cells from the peripheral immune response, may open up a new horizon for vaccine application. Hence, by modifying the activity of glial cells to reduce their neurotoxic properties and enhance their neuroprotective effects may pave the path for therapeutic interventions in neurodegenerative diseases, such as AD.

Acknowledgement

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