Sultan Qaboos University Med J, August 2015, Vol. 15, Iss. 3, pp. e305–316, Epub. 24 Aug 15. doi: 10.18295/squmj.2015.15.03.002.
Submitted 18 Aug 14
Revisions Req. 20 Oct 14 & 26 Jan 15; Revisions Recd. 17 Dec 14 & 9 Feb 15
Accepted 19 Mar 15

REVIEW

The Role of Inflammatory Mediators in the Pathogenesis of Alzheimer's Disease

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دور وسائط الالتهاب في الآلية المرضية لداء الزهايمر

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ABSTRACT: Alzheimer's disease (AD), a neurodegenerative disorder associated with advanced age, is the most common cause of dementia globally. AD is characterised by cognitive dysfunction, deposition of amyloid plaques, neurofibrillary tangles and neuro-inflammation. Inflammation of the brain is a key pathological hallmark of AD. Thus, clinical and immunopathological evidence of AD could be potentially supported by inflammatory mediators, including cytokines, chemokines, the complement system, acute phase proteins and oxidative mediators. In particular, oxidative mediators may actively contribute to the progression of AD and on-going inflammation in the brain. This review provides an overview of the functions and activities of inflammatory mediators in AD. An improved understanding of inflammatory processes and their role in AD is needed to improve therapeutic research aims in the field of AD and similar diseases.

Keywords: Alzheimer's Disease; Inflammation Mediators; Cytokines; Chemokines; Complement System Proteins; Acute Phase Proteins.

الملخص: داء الزهايمر هو انتكاسة عصبية تحدث مع التقدم في العمر وهي أكثر أسباب خرف الشيخوخة شيوعا. ويتميز المرض بحدوث خلل إدراكي، وترسب لويحات اميلويدية، وتشابك الألياف العصبية مع ألتهاب عصبي. والسمة المميزة لداء الزهايمر هي حدوث إلتهاب المخ. وبالتالي فإن الأدلة السريرية والمناعية المرضية قد يتم دعمها بالوسائط الالتهابية، مثل السيتوكينات والكيموكينات، ونظام الكومبليمنت (المتممة)، وعلامات الالتهاب الحاد، والوسائط المؤكسدة. وعلى وجه الخصوص فإن الوسائط المؤكسدة قد يكون لها دور نشط في تفاقم داء الزهايمر والتهاب المخ الجاري. وهذا الاستعراض يقدم لمحة عامة على وظائف وأنشطة وسائط الالتهاب في داء الزهايمر. إن تحسن فهمنا لدور الألتهاب في حدوث داء الزهايمر سيؤدي إلي تقدم البحث العلمي في إمكانية علاج هذا المرض وبالتالي أمراض أخرى مشابهة.

مفتاح الكلمات: داء الزهايمر؛ وسائط الألتهاب؛ السيتوكينات؛ الكيموكينات؛ بروتينات نظام الكومبليمنت؛ علامات الالتهاب الحاد.

Alzheimer's disease (AD) is a chronic neurodegenerative disease considered to be the most common cause of dementia.[1] AD is characterised by visuospatial *dysgnosia* and memory, language, emotional, personality and complex cognition impairment. The primary sign of AD is the gradual deterioration in an individual's ability to remember recent events, likely due to the perturbation of neuronal function in the temporal lobes.[1,2] More than 44 million people worldwide were estimated to be suffering from AD in 2014 and this number is projected to double by 2030.[3] There is a direct correlation between the incidence of dementia and ageing, with the highest rates of AD seen in the seventh and eighth decades of life. In addition, it is proposed that the incidence of AD may dramatically rise every five years after the age of 65 years.[4]

The most common neuropathological hallmarks of AD are deposition of amyloid β (Aβ) in a compact structure outside the neurons, intracellular neurofibrillary tangles (NFTs) and inflammatory processes. Aβ is derived from the amyloid precursor protein (APP) by processing enzymes (α-, β- and γ-secretases). These altered proteins are deposited as extracellular plaques called senile plaques.[5–7] Intracellular NFTs, which are composed of microtubule-associated protein tau, are another pathological aspect of AD-affected brains. Following chemical changes such as hyperphosphorylation, these aggregates often pair with other threads and accumulate inside the neurons, consequently causing microtubule destabilisation.[5,8,9]

Histopathological evidence from patients with AD shows cerebral atrophy, deposition of Aβ in plaques and neuritic changes, such as neuritic plaques and

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Table 1: Inflammatory components contributing to the pathology of Alzheimer's disease

Inflammatory component	Examples
CNS cells	Microglia, astrocytes and neurons
Cytokines	TNF-α, IL-1β, IL-6, IFN-γ and IL-18
Chemokines	MCP-1, CXCL8, CXCL12, CX3CL1 and MIP
Complement system	Classical and alternative pathways
Acute phase proteins	CRP and SAA
Oxidative mediators	ROS, RNS, NO, $O2^{-}$ and $ONOO^{-}$

CNS = central nervous system; TNF-α = tumour necrosis factor-α; IL = interleukin; IFN-γ = interferon-γ; MCP-1 = monocyte chemoattractant protein-1; CXCL = C-X-C motif ligand; CX3CL1= C-X3-C motif ligand 1; MIP = macrophage inflammatory protein; CRP = C-reactive protein; SAA = serum amyloid A; ROS = reactive oxygen species; RNS = reactive nitrogen species; NO = nitric oxide; $O2^{-}$ = superoxide anion radical; $ONOO^{-}$ = peroxynitrite anions.

NFTs. Although the brains of people diagnosed with AD have increased Aβ deposition, these findings are not specific to AD alone and may be found in elderly people not suffering from dementia.[10,11] Although the amyloid cascade theory is the most widely accepted explanation for the aetiology of AD, other theories have also been described to illustrate the role of inflammation in actively contributing to the progression of the disease.[12] It is often assumed that the accumulation of Aβ in the brain results in the development of systemic inflammatory reactions by prompting immune responses.[13,14] This article reviews the major role of inflammatory mediators in the immunopathogenesis of AD.

Immunopathology of Alzheimer's Disease

Cells of the adaptive immune system can migrate to the brain through the blood-brain barrier (BBB), which is structurally different in people with AD in comparison to healthy individuals.[15] Based on electron microscope observation, most Aβ plaques in the brains of AD patients are associated with activated microglial cells (central nervous system [CNS]-resident macrophages). These cells seem to be responsible for on-going neuro-inflammatory processes in AD through the release of cytokines, chemokines and neurotoxins. Moreover, microglial cells can produce several pro- and anti-inflammatory cytokines via direct inter-action with infiltrated T lymphocytes.[15] Interestingly, Bromley *et al.* reported that some chemokines are able to restrain immunological synapse formation and T cell activation.[16] They indicated that the immunosuppressive effect of chemokines occurred with C-X-C motif receptor (CXCR) 3 and C-C motif receptor (CCR) 7 chemokines, but not with CCR2, 4 and 5 or CXCR4 chemokines.[16]

Inflammation commences when innate immune mediators detect damaged tissue or other molecules on the surface of cells. Chemokines and other inflammatory mediators are responsible for the recruitment of immune cells to the damaged area.[17,18] Various inflammatory processes in AD contribute to the pathology of the disease [Table 1]. Degenerated cells and tissues, as well as an accumulation of abnormal insoluble materials, are the most common stimuli for inflammation. Likewise, in the brain of AD patients, damaged neurons and neurites, along with NFT and insoluble Aβ peptide deposits, can act as potent triggers of inflammation.[19]

Accordingly, inflammation may contribute to the pathogenesis of AD by two mechanisms. The first is a preliminary innate immune response to the alterations in the AD brain; inflammation is involved in the recruitment of immune cells to the site of injury as a result of the initial signalling of cytokines and chemokines and complement system activation. The second mechanism involves a minor amount of on-going inflammation in the brain, which can result in the pathogenesis of AD. This inflammation can be considered a sign of an impaired adaptive immune response and leads to chronic inflammation.[19,20]

GLIAL CELLS AS A TRIGGER OF IMMUNE RESPONSES

Microglial cells have the ability to induce neuronal damage through the following processes: (1) phagocytosis; (2) the release of cytokines/chemokines/prostaglandins and reactive oxygen species (ROS); and (3) the expression of innate and adaptive immune function molecules such as Toll-like receptors (TLRs), immunoglobulin fragment crystallisable gamma receptors, major histocompatibility complex class II (MHC II) molecules, complement receptors and purinergic receptors (e.g. P2X purinoceptor 7).[21–23] The activation of microglia with Aβ can occur either via the internalisation of soluble Aβ through phagocytosis while fibrillary Aβ binds to TLR2 and TLR4 or through the activation of a mitogen-activated protein kinase pathway, stimulating pro-inflammatory gene expression leading to the secretion of cytokines and chemokines.[24] Moreover, Aβ may be presented by activated microglial cells to T lymphocytes, eventually causing Aβ-specific T cells to enter the brain [Figure 1]. It should be noted that while Aβ-reactive T cells are present in healthy individuals, T cells are vital for protecting against AD pathogenesis by cooperating with and modulating the innate immune system.[25]

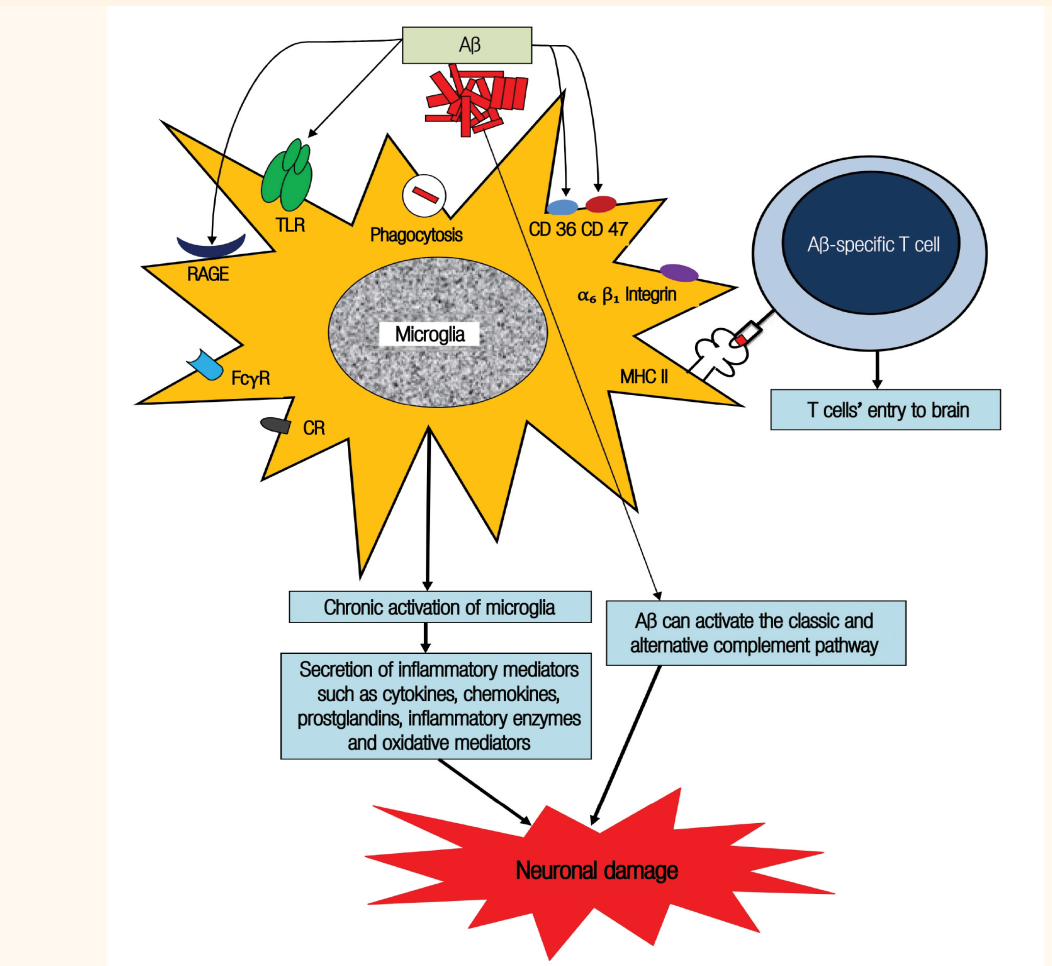

Figure 1: The immunological function of microglia in Alzheimer's disease.
Aβ = amyloid β; TLR = Toll-like receptors; CD = cluster of differentiation; RAGE = receptor for advanced glycation end-products; FcγR = fragment crystallisable gamma receptor; MHC II = major histocompatibility complex class II; CR = complement receptor.

However, T cells are more susceptible to ageing than innate immune components. Fulop *et al.* demonstrated that adaptive immune responses in the elderly were less effective in eliminating Aβ deposition than an innate immune response.[25] Therefore, once the immune system is overwhelmed with Aβ deposition, inflammation becomes chronic and adverse, resulting in accelerated neurodegeneration.[26]

ROLE OF LYMPHOCYTES

Several studies have evaluated the function of T cells in AD so as to determine AD-related abnormalities in the immune system.[27,28] Richartz-Salzburger *et al.* reported the general decline of immune function among patients with AD due to a decreased number of T and B cells.[27] In addition, another study noted the hyporesponsiveness of T cells to certain intrinsic functional defects in AD patients when compared with control subjects.[29] Some alterations, such as accelerated telomere shortening, can serve as an important factor in the impairment of normal lymphocyte activity in AD patients.[30] This finding was confirmed by Zhang *et al.*; their research indicated that the increase of telomerase activity in the lymphocytes of AD patients can lead to diminishing lymphocyte proliferation activity, consequently resulting in the loss of immune function.[31]

As yet, the precise mechanism regarding the activation, migration and survival of T cells in the brains of AD patients is not clear. As previously mentioned, antigen-presenting cells with a high expression of MHC II molecules, which either differentiate from microglia in the brain or are recruited from the blood, can present Aβ to T cells. In addition, interferon-γ (IFN-γ) plays a key role in facilitating T cell migration as well as promoting an immune regulatory process within the brain.[32] The amount of IFN-γ in the brain determines its effect as it is adverse at high levels and beneficial at low levels.[33] Research has demonstrated the pathogenic reaction of both T and B cells against Aβ as well as the risk of meningoencephalitis, caused by the entry of

cluster of differentiation (CD) 8 cytotoxic T cells to the brain followed by the secretion of pro-inflammatory cytokines by CD4 T cells.[33,34]

ROLE OF INFLAMMATORY CYTOKINES AND CHEMOKINES

There is growing evidence that inflammatory mediators in the CNS contribute to cognitive impairment through cytokine-mediated interactions between glial cells and neurons. Moreover, it has been demonstrated that AD is associated with the upregulation of pro-inflammatory cytokines, which can initiate plaque production and enhance nerve cell degeneration.[6,15] Some of these mediators—including tumour necrosis factor (TNF)-α, interleukin (IL)-6, IFN-γ, inducible protein-10, monocyte chemoattractant protein (MCP)-1 and C-X-C motif ligand (CXCL) 8—increase in the prodromal stage of AD. Elevation of these cytokines occurs during the initiation of AD. This may explain the failure of clinical trials using anti-inflammatory drugs against severe AD.[35] This idea is supported by immunohistochemistry examinations performed by Sokolova *et al*. which confirmed the increase of MCP-1, IL-6 and CXCL8 in AD brains and determined that these mediators were localised in neurons (IL-6, MCP-1 and CXCL8), astrocytes (IL-6 and MCP-1) and plaques (CXCL8 and MCP-1).[36] Moreover, logistic linear regression modelling determined that, of the cytokines, MCP-1 was the most accurate for the prediction of AD.[36] Hence, these findings support the importance of IL-6, MCP-1 and CXCL8 in AD and also show that MCP-1 may play an important role in the progression of chronic inflammation in AD. As a result of these observations, some cytokines (such as IL-1, -4, -6, -10, -12 and -18, IFN-γ, TNF and transforming growth factor [TGF]-β) have been proposed as AD biomarkers.[6]

Interleukin (IL)-1ß, IL-6 and Tumour Necrosis Factor-α

The elevation of IL-1β, IL-6 and TNF-α is widely recognised as a critical component of neuro-inflammation and leukocyte recruitment to the CNS.[6] This response is characterised by promoting deposition of Aβ in the brain and astrocytic and microglial activation. Moreover, IL-1β and TNF-α are potent stimuli for inducible nitric oxide (NO) synthase (NOS) expression and activity in the brain and NO metabolite overflow into the cerebrospinal fluid.[5] Importantly, Belkhelfa *et al*. revealed recently that a high level of NO is associated with the rise of TNF-α levels in patients in the severe stages of AD.[37] In response to numerous intrinsic and extrinsic stimuli, TNF-α is produced by microglia, astrocytes and neurons in the brain. In addition, genetic and epidemiological findings have implicated augmented levels of TNF-α in the brain as a risk factor for AD.[37]

TNF-α can mediate neuronal dysfunction as well as Aβ-induced disruption of the molecular mechanisms involved in memory function. Likewise, TNF-α can stimulate accumulation of the tau proteins in neurites through induction of ROS.[5] In another recent study, Lin *et al*. observed a significant decrease of TNF-α, IL-1α, -6 and -12 in sera after vaccinating transgenic mice.[38] Remarkably, the decrease in TNF-α and IL-6 levels correlated with cognitive and behavioural improvements in the transgenic mouse model of AD.[38] In contrast, it has been reported that some inflammatory cytokines, such as IL-1β, IL-6 and IFN-γ, have also had beneficial and protective effects against AD.[6,39] Overexpression of IL-1 and IL-6 in the brain results in extensive *gliosis* which may be beneficial in the disease process by stimulating increased amyloid phagocytosis rather than mediating a neurotoxic feedback loop.

Interleukin-18 and Interferon-γ

Several studies have highlighted a critical role for IL-18 in mediating neuro-inflammation and neurodegeneration in the brains of AD patients.[40,41] Notably, an imbalance of IL-18 and its endogenous inhibitor, IL-18 binding protein (IL-18BP), has been shown in AD, with an elevated IL-18:IL-18BP ratio that might be involved in the disease immunopathogenesis.[42] In the brain, IL-18 is produced by microglial, astrocyte and ependymal cells as well as by neurons of the medial habenular nucleus.[43] Through the induction of IFN-γ and expression of MHC II molecules in microglial cells, IL-18 can initiate a neural-immune cell interaction which may play a key role in the induction of autoimmunity in the CNS environment.[44] Moreover, IFN-γ can enhance Aβ deposition through β-secretase 1 expression as well as stimulate the upregulation of MHC II molecules in a subpopulation of microglia and induce auto-immune processes in the CNS. Importantly, significant IFN-γ levels are only detected in mild cases of AD. Collectively, this suggests that NO production is IFN-γ-dependent in AD.[37] On the other hand, IFN-γ is a known inhibitor of APP fragment production. IFN-γ can prevent amyloid deposition during inflammatory processes in both non-neuronal and neuronal tissues. Furthermore, IFN-γ has a strong suppressive effect on the production and metabolism of APP.[5,45]

Transforming Growth Factor-ß

Recent data have implicated anti-inflammatory cytokines as integral factors to the pathogenesis of AD.[6] Among them, TGF-β is emerging as a critical factor in regulating inflammatory responses. Three known

isoforms of TGF-β (TGF-β1, -β2 and -β3) are expressed in mammalian tissues. In AD, the expression of TGF-β2 is induced by toxic Aβ in both glial and neuronal cells; increased levels of TGF-β2 trigger the cell death pathway due to alterations in the morphology and number of lysosomes in neurons.[46] TGF-β2 causes lysosomal membranes to become unstable and leak and this effect is intensified with the accumulation of Aβ, as TGF-β2 rapidly targets the Aβ peptide in lysosomal compartments in cortical neurons, inducing cell death.[47] As a neurotrophic factor, TGF-β1 initiates and maintains neuronal differentiation and synaptic plasticity. In AD animal models, it has been suggested that a deficiency of TGF-β1 signalling may correlate with Aβ pathology and NFT formation.[48]

C-C Motif Ligand 2

C-C motif ligand (CCL) 2, also known as MCP-1, plays a significant role in AD pathogenesis. Increased levels of CCL2 in the brain result in the recruitment of activated monocyte cells into the organ where they differentiate into macrophages and produce neurotoxic and inflammatory mediators.[49–51] Immunohistochemistry findings have confirmed this increase in CCL2 levels and have determined localisation of these factors in astrocytes, neurons and plaques via pathology.[49] However, mononuclear phagocyte accumulation is regulated via the interaction of CCL2 with its receptor, CCR2; CCR2 deficiency in these cells therefore leads to diminished phagocyte cell recruitment to the brain which is associated with higher levels of Aβ in the brain, particularly around the blood vessels. This suggests that monocytes are initially recruited and accumulate at Aβ deposition sites in order to clear them and either halt or delay their associated neurotoxic effects. Indeed, an increase of mononuclear phagocyte recruitment to the brain delays the progression of AD in its early stages.[36,49]

C-C Motif Ligand 5

The role of CCL5, also known as the RANTES (regulates on activation, normal T cell expressed and secreted) protein, has been determined in neurodegenerative diseases such as AD and elevated levels of RANTES protein are commonly observed in the microcirculatory system of AD-affected brains.[52] The RANTES protein, as well as several other chemokines in astrocytes, is upregulated as a response to a cytokine-mediated increase of ROS.[53] Moreover, oxidative stress upregulates RANTES protein expression in endothelial cells in the brain.[52] In brain injury models, elevated levels of the RANTES protein contributed to immune cell recruitment that occurred concurrently with increased rates of neuronal death.[52,54,55]

C-X-C Motif Ligand 8

CXCL8 (IL-8) is a microglia-derived chemokine that is produced in response to pro-inflammatory signals such as Aβ. CXCL8 could be important for the recruitment of activated microglia and neutrophils into areas of the damaged brain during the late stages of AD, suggesting a role for this chemokine in phases with prevalent neurodegeneration. In addition, CXCL8 is continually upregulated in neurons and plaques.[19]

C-X-C Motif Ligand 12

The chemokine CXCL12 has been associated with neurogenesis and the recruitment of brain-resident and non-resident circulating cells to sites of lesions in the CNS.[56] Moreover, in Tg2576 mouse models of AD, CXCL12 messenger ribonucleic acid (mRNA) protein and its receptors were downregulated, with co-existing cognitive deficits.[57] Zhu *et al*. found that CXCL12 plasma levels in patients with early AD were low and that CXCR4 and CXCL12 had anti-inflammatory properties.[58] An *in vitro* study demonstrated that neurons pre-treated with CXCL12 were significantly protected from antibody-induced dendritic regression and *apoptosis* via protein kinase B and extracellular signal-regulated kinases 1/2 activation, as well as maintenance of A disintegrin and metalloproteinase 17, especially with CXCL12.[59]

C-X3-C Motif Ligand 1

C-X3-C motif ligand (CX3CL) 1, also known as fractalkine, is produced and expressed constitutively by neurons. CX3CL1 suppresses microglial activation and the CX3CL1/C-X3-C motif receptor (CX3CR) 1 complex may control neurotoxicity. Research has demonstrated that levels of plasma-soluble CX3CL1 are significantly greater in patients with mild to moderate AD than in those with severe AD.[60] These findings and other data suggest that CX3CL1 has a neuroprotective function that may potentially have therapeutic applications for several neurodegenerative diseases, including AD and Parkinson's disease, in which inflammation also plays an important role.[5,60] Cho *et al*. identified CX3CL1/CX3CR1 signalling as a central microglial pathway in protecting against AD; this pathway was associated with the inhibition of aberrant microglial activation and inflammatory cytokine elevation.[61]

Macrophage Migration Inhibitory Factor

The macrophage migration inhibitory factor (MIF) is a pleiotropic pro-inflammatory cytokine which increases the production of other inflammatory cytokines, such as TNF-α, IL-6 and IFN-γ, and has a pivotal regulatory role in the pathogenesis of numerous autoimmune and inflammatory disorders.[62,63] Cellular

sources for MIF are neurons and activated microglia; the clustering of microglia at amyloid deposition sites implies that this cell migrates to these locations and undergoes attempted removal of the amyloid protein.[64] In their study, Oyama *et al.* found that MIF was able to bind Aβ in AD-affected brains and that Aβ toxicity could thus be accredited directly to the increased expression of MIF.[65] However, microglial cells are seemingly unable to clear Aβ due to its insoluble nature and the fact that it is present in substantial quantities. Therefore, Aβ deposits are not phagocytised and remain present while microglial cells continue to be attracted to the sites for long periods of time.[66]

Macrophage Inflammatory Protein-1α

Macrophage inflammatory protein (MIP)-1α is a chemokine present in humans which has a significant part in the pathogenesis of AD mainly via its expression by astrocytes, microglia, neurons, infiltrated monocytes and T cells.[67] It has been demonstrated that higher MIP-1α expression in the peripheral T lymphocytes of AD patients results in CCR5 expression, a potential MIP-1α receptor on microvascular endothelial cells in the human brain, which subsequently leads to increased T cell transendothelial migration from the blood to the brain.[68] Li *et al.* found that serum MIP-1α levels were significantly higher in patients with the TA6/6 genotype of the *apolipoprotein E* gene and that this genotype seems to be a genetic risk factor for AD.[69] According to Passos *et al.*, the activation of the MIP-1α/CCR5 signalling pathway was one of the initial events following Aβ1–40 injections in AD mouse models; this seems to be a critical signal for activated glial cell accumulation, inflammatory responses, synaptic dysfunction and cognitive failure.[70]

CONTRIBUTION OF THE COMPLEMENT SYSTEM

In the AD-affected brain, levels of complement mRNAs and their protein products have been found to be significantly higher than those in the livers of healthy individuals; moreover, neurons of AD patients have been found to express complement proteins of the classical pathway to an increased degree in comparison to neurons in brains which were not affected by AD.[9] At the very first stages of amyloid deposition in AD, integral complement protein components of amyloid plaques and cerebral vascular amyloid material can be found; their activation occurs simultaneously with the clinical expression of AD.[71] Aβ can activate the classic and alternative complement pathways in areas of the brain associated with AD pathology, even in the absence of antibodies.[72] Moreover, it has been demonstrated that tau protein is an antibody-independent activator of the classical complement pathway.[9] This activation of the complement cascade not only causes substantial damage to the neurons, but can also lead to increased phosphorylation of tau proteins and formation of NFTs, resulting in elevated levels of membrane attack complex in AD brains.[9] Nevertheless, the complement cascade has both positive and negative aspects; although it is essential to maintaining the health of the brain, it may have adverse effects when unregulated and often exacerbates AD.

The complement protein C1q is induced in the brain in response to AD and blocks fibrillary Aβ neurotoxicity *in vitro*.[73] C1q binds to β-sheet fibrillary Aβ plaques and, when associated with C1r and C1s as in the C1 complex, activates the complement cascade that can have detrimental inflammatory consequences via production of the chemotactic factor C5a and following recruitment and activation of microglial cells to the site of injury. It also has a protective effect by increasing the clearance of Aβ through C1q- and C3-dependent opsonisation.[74] Benoit *et al.* showed that C1q protected both immature and mature primary neurons against fibrillary Aβ toxicity and prevented oligomeric Aβ toxicity.[75] In addition, gene expression analysis revealed that C1q-induced low-density lipoprotein receptor-related protein 1B and G protein-coupled receptor 6 expressed early in AD mouse models were vital for C1q-mediated protection against Aβ neurotoxicity.[75,76] Loeffler *et al.* noted that C3b and iC3b (a cleavage product of C3b) are also deposited on AD-affected neurons, much like C1q.[77]

FUNCTION OF ACUTE PHASE PROTEINS

Several prospective epidemiological studies have found that increased acute phase mediator serum levels can serve as a risk factor for AD, as detailed in a review article by Eikelenboom *et al.*[78] In addition, other clinical studies compiled in the review have suggested that increased peripheral inflammation is associated with a greater risk of dementia, mainly in patients with pre-existing cognitive impairments, and accelerates subsequent deterioration in patients with dementia.[78] Higher levels of serum C-reactive protein (CRP) in middle-aged patients are also associated with an increased risk of AD and vascular dementia, which may indicate that inflammatory factors are a reflection of both dementia-related peripheral disease and cerebral mechanisms.[78] Of note is the fact that these processes can be measured long before manifestations of dementia begin to be observed. Follow-up studies in the elderly have also revealed a correlation between serum CRP levels and an increased incidence of dementia and AD.[4] Kravitz *et al.* reported that high CRP levels were related to the increased likelihood of

all-cause dementia occurring in the elderly, particularly for females.[79] Moreover, Komulainen *et al*. found that elevated high-sensitivity CRP (hsCRP) serum concentrations were a predictor of poorer memory function in women 12 years after the measurements had been taken.[80] Therefore, hsCRP may be a useful biomarker to identify individuals with an increased risk for cognitive decline.

Strang *et al*. discussed the fact that no pathomechanistic link has yet been established between circulating pentameric CRP (pCRP) and AD, despite reports of an association between the two.[81] Their hypothesis was that Aβ plaques induce the dissociation of pCRP to single monomers, which have more potent pro-inflammatory properties than pCRP, and the inflammation is subsequently localised to the AD plaques.[81] Helmy *et al*. presented evidence that serum levels of IL-6 and CRP were significantly elevated among patients with vascular and Alzheimer's dementia in comparison to elderly subjects in good health.[82] Although IL-6 levels were higher in AD patients in comparison to those with vascular dementia, the difference was not found to be significant. Furthermore, α_1- and α_2-globulins were significantly higher in AD patients and researchers were able to distinguish vascular from Alzheimer's dementia.[82]

Elevations in CRP in middle-aged patients have been associated with an increased risk of AD development. O'Bryant *et al*. reported decreased CRP levels in AD patients; in fact, mean CRP levels were found to be significantly reduced in AD patients versus controls (2.9 versus 4.9 μg/mL, respectively).[83] However, Sundelöf *et al*. reported contradictory findings which indicated that hsCRP and serum amyloid A levels were not associated with AD risk in elderly men.[84]

OXIDATIVE STRESS

Cellular oxidative stress—including enhanced protein oxidation and nitration, glycoloxidation, lipid peroxidation and Aβ accumulation—is associated with AD.[85] The deposition of Aβ generates ROS, which is involved in the inflammatory and neurodegenerative pathology of AD. Oxidative stress can therefore exacerbate the progression of AD. When repair attempts are made by the brain to remedy oxidative damage, characterised by APP overexpression, adenosine triphosphate (ATP)-binding cassette sub-family G member 2 (ABCG2) is upregulated and activator protein-1 is activated. Not only do these proteins stop blood Aβ from entering the brain via the BBB but they also protect against oxidative stress by decreasing ROS production, boosting antioxidant activity and inhibiting the inflammatory response through the inhibition of the nuclear factor-κB signalling pathway in brain tissue. As a result, ABCG2 may have a protective function in the neuroinflammatory response of AD.[85–87] Additionally, the apparent end-product of APP, the formation and accumulation of Aβ, appears to be initiated by ABCG2.

This process can lead to increased free radical production—mainly superoxide anions via the mitochondria—which induces the interruption of oxidative phosphorylation and engenders a decrease in ATP levels. The mitochondrial dysfunction and damage that occurs with ageing correlates with the augmented intracellular production of oxidants and pro-oxidants. The extended oxidative stress in brain tissue, and the resultant hypoperfusion, stimulates the expression of NOS which subsequently drives the formation of ROS and reactive nitrogen species (RNS). ROS contributes to the dysfunction of the BBB and damage to the brain's parenchymal cells. Moreover, it has been shown that ROS is potentially toxic and may damage the proteins, lipids and nucleic acids of brain cells and mitochondria, including neurons and oligodendrocytes that may mediate toxicity.[88,89] Generation of ROS is controlled by sensitive genes called vitagenes. These genes encode proteins such as heat shock proteins, nutritional antioxidants which play a neuroprotective role.[90]

Oxidative stress could also lead to further damage in AD-affected brains through inducible NOS overexpression and constitutive neuronal NOS activity, which increases the production of NO and its derivative RNS. In an AD-affected brain, NO and superoxide anion radicals ($O2^-$) are produced by reactive astrocytes and microglia in response to Aβ.[91–93] Formed from NO and $O2^-$, peroxynitrite anions are another component of oxidative stress. These extremely reactive oxidising and nitrating agents lead to the oxidisation of cellular components, increased Aβ aggregation and a stimulated inflammatory response.[94]

In the early stages of AD, the pathology shows that inducible neuron-specific cyclooxygenase-2 (COX-2) enzymes are expressed and upregulated by neuronal cells which are closely linked with the Aβ-bearing cells. It has been suggested that Aβ can stimulate activity of COX-2 oxygenase and peroxidase in a cell-free system—this stimulation of the two-step action of COX-2 leads to the production of ROS and prostaglandin E_2.[85,95–97] In addition, recent findings in mouse models suggest a role for COX/prostaglandin E_2 signalling in the development of AD.[98]

Treatment and Immunotherapy for Alzheimer's Disease

There is currently no cure available for AD; however, drug and non-drug treatments may help with both

cognitive and behavioural symptoms of the disease. Two types of medications designed to treat the cognitive manifestations of AD have been approved by the Food and Drug Administration in the USA: cholinesterase inhibitors and a new N-methyl-D-aspartate receptor antagonist, memantine.[99] Three forms of cholinesterase inhibitor drugs are commonly prescribed: donepezil (approved to treat all stages of AD), rivastigmine and galantamine (both approved to treat only mild to moderate cases of AD).[100]

Inflammation is one of numerous hypotheses that have been proposed for the multifactorial aetiology of AD; indeed, inflammation may interact with other triggers in several ways. This network of mechanisms makes it difficult to identify any specific inflammatory process, causal factor or cell in order to determine their individual role in AD.[101] Risk factors for AD, which may include genetic, biological and environmental factors, contribute to neuro-inflammation and to subsequent neurodegeneration in the later stages of AD. However, they may have fewer effects on the early pathogenesis of the disease.[102,103] Therefore, due to the distinctive role of inflammation in the early versus late stages of AD, anti-inflammatory agents, such as non-steroidal anti-inflammatory drugs (NSAIDs), may potentially be a treatment option for AD patients, although this would be dependent on the stage of the disease.

Researchers have reported a decrease in AD development among subjects taking NSAIDs for long periods of time; thus, it has been proposed that NSAIDs could directly reduce the production of Aβ through several mechanisms.[9,104] Unfortunately, conflicting results have been reported in the literature and related clinical trials have not yet yielded promising findings. The toxic effects of NSAID treatments also prevent their widespread use.[9,104] Additionally, anti-inflammatory medications may have no effect on patients in later stages of the disease. This is because the most important aetiological factors for early-onset AD are the mismetabolism of APP along with the increased production of Aβ followed by the deposition of fibrillary Aβ, which can activate the innate immunity receptors leading to activation of microglia and reactive astrocytes. This exacerbates neurodegeneration through the release of inflammatory cytokines, ROS and other factors. Modifications of these factors can occur very early during the development of the disease; trials with anti-inflammatory agents may therefore be ineffective in patients with severe AD.[6] Furthermore, the efficacy of anti-inflammatory drugs such as aspirin, steroids and other traditional NSAIDs and COX-2 inhibitors in AD patients has not yet been proven; thus, these drugs cannot be recommended for AD treatment.[105]

Immunotherapy has been proposed as a potential candidate for the treatment of AD. Both active and passive Aβ immunotherapies have been developed to decrease the load of Aβ by enhancing its rate of elimination. Vaccinations, in the form of active immunisation with $A\beta_{42}$ (the common form of Aβ in amyloid plaques) or other synthetic peptides, have been successfully assessed in transgenic animal models of AD.[106] The basis of this approach is the priming of T, B and microglial cells, which provoke immune responses.

One type of passive immunotherapy, administering monoclonal antibodies against the Aβ fragment, diminishes the need for patients to mount immunity against Aβ peptides. An on-going clinical trial in the USA sponsored by a pharmaceutical company (Eli Lilly & Co., Indianapolis, Indiana, USA) is currently testing to see if treatment with solanezumab, a monoclonal antibody against Aβ, significantly slows the loss of awareness and cognitive and functional decline in patients with mild AD.[107] However, concerns exist regarding the use of related monoclonal antibodies as a therapeutic option. Firstly, new approaches are needed due to the poor penetration of antibodies into the brain and, secondly, recognition of the clearance pathways of Aβ/anti-Aβ immune complexes is essential to circumvent obstruction of these pathways during treatment.[106]

Recent Advances in Alzheimer's Disease

A prospective longitudinal study by Bateman *et al.* has indicated that Aβ deposition in the brain is detectable more than 20 years prior to the onset of AD symptoms.[108] In addition, although the production of Aβ in AD patients is similar to that of cognitively normal individuals, clearance of Aβ in the brain of AD patients is significantly reduced in comparison to control subjects.[109] Immunotherapy and the involvement of antibodies could therefore be a successful approach to facilitating this clearance process. Active immunisation with the DNA $A\beta_{42}$ vaccination may be effective in accomplishing this; the method involves injecting DNA encoding $A\beta_{42}$ where it is subsequently translated in the immunised individual to express Aβ peptide which then stimulates the respective immune responses against $A\beta_{42}$. Qu *et al.* found a 50% reduction in the level of $A\beta_{42}$ plaques in transgenic mouse models when using this approach; this reduction was later confirmed by another study.[110,111]

Currently, other approaches for AD therapy focus on clearance of Aβ fragments by different pathways, including chaperone-mediated and autophagocytic

clearance.[112] Chaperones are a specific cluster of proteins which can correct or prevent the misfolding of proteins. Autophagy is a normal cellular process in the body which preserves homeostasis or normal functioning through protein destruction and turnover of destroyed cell organelles for new cell formation. Several studies have noted the occurrence of autophagocytic vacuoles in the brains of patients with AD.[113,114] Caccamo *et al*. reported that the level of beclin 1, a protein involved in the formation of the autophagosome, is diminished in the brains of AD patients.[115] Moreover, Martorana *et al*. found an augmented subset of B cells with a memory double-negative phenotype in elderly people.[116] Interestingly, Colonna-Romano *et al*. reported that B cells are late memory or exhausted cells, which may be a manifestation of ageing or a dysregulation of the immune system.[117]

Conclusion

Numerous hypotheses have been proposed for the multifactorial aetiology of AD, including inflammation. Current evidence supports the potential role of inflammation in AD, although this factor may interact with other genetic, biological and environmental triggers in several ways. Immunotherapy and the use of antibodies could have applications for patients with AD. In order to improve the range and efficacy of therapeutic options for AD patients and those with similar neurodegenerative disorders, further research is recommended to advance the current knowledge of inflammatory processes with regards to this form of dementia.

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