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Immunology of Alzheimer's disease

*Lucila I. Sosa-García[1], Janeth Hernández-Jiménez[1], Diana I. Del Moral-Huerta[1], Charles Duyckaerts[2] and Ana L. Calderón-Garcidueñas[3]**

[1]Doctoral Program in Biomedical Sciences, Institute of Biomedical Research, Universidad Veracruzana, Xalapa; [2]Departament of Neuropathology, Hôpital Universitaire Pitié-Salpêtrière, Paris, France; Faculty of Medicine, Universidad Veracruzana, Región Veracruz. Mexico

Abstract

Alzheimer's disease (AD) is a multifactorial neurodegenerative pathology. Neuroinflammation is an early event of the presymptomatic stages in AD and contributes to its progression. We review the participation of astrocytes, microglia and blood-brain barrier cells, the mechanisms of cell death and the inflammatory factors such as chemokines, interferons and Toll-like receptors involved in progression and perpetuation of AD. Some of its prognostic and therapeutic possibilities are also mentioned. Identifying the different actors involved in inflammation and the main mechanisms of damage might allow the development of preventive strategies and treatments to fight against this devastating disease.

Key words: *Immunology. Alzheimer's disease. Microglia. Innate immunity. Lymphocytes.*

Inmunología de la enfermedad de Alzheimer

Resumen

La enfermedad de Alzheimer (EA) es una patología neurodegenerativa multifactorial. La neuroinflamación es un evento temprano de las etapas presintomáticas en la EA y contribuye a su progresión. En este trabajo revisamos la participación de astrocitos, microglia y células de la barrera hematoencefálica, los mecanismos de muerte celular y los factores inflamatorios como las quimiocinas, los interferones y los receptores tipo Toll que participan en la progresión y la perpetuación de esta enfermedad. También se mencionan algunas de sus posibilidades pronósticas y terapéuticas. La identificación de los diferentes actores involucrados en la inflamación y de los principales mecanismos de daño podrían permitir el desarrollo de estrategias y tratamientos preventivos para combatir esta enfermedad devastadora.

Palabras clave: *Inmunología. Enfermedad de Alzheimer. Microglia. Inmunidad innata. Linfocitos.*

Correspondencia:
*Ana Laura Calderón-Garcidueñas
Facultad de Medicina
Agustín de Iturbide, s/n
Zona Centro
C.P. 91700, Veracruz, México
E-mail: acald911@hotmail.com

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Introduction

Alzheimer's disease (AD) is the most common dementia. It is characterized by abnormal protein aggregates of tau protein (tubulin-associated) and β-amyloid (Aβ). Tau aggregates acting as "seeds" may propagate pathology by spreading from cell to cell in a "prion-like" manner[1]. It occurs in two forms, early onset, that is, genetically determined and late onset that is more frequent and mutifactorial[2]. Late-onset AD is genetically complex with 56-79% heritability[3]. Regardless of the initial trigger that initiates the abnormal aggregation of proteins, there seems to be an inflammatory background that contributes to the perpetuation of neuronal damage[2]. The importance of the immune response in AD has been evidenced with genomic studies in late-onset AD. These studies have shown at least four functional pathways of susceptibility to AD, the immune response, the regulation of endocytosis, the transport of cholesterol, and the ubiquitination of proteins[4]. The aim of this work is to review the most important immunological aspects in AD and its possible therapeutic implications.

Development

The immune system identifies foreign elements (i.e., different from the self) to mount a defense response against them. Natural or innate immunity is not specific and does not require an external challenge to be involved; acquired immunity is specific and keeps the memory of previous challenges. The immune system seems to contribute to the perpetuation of damage in Alzheimer's disease (AD). Some recent research suggests that the manipulation of some of these participants in the immune response such as microglia and cytokines could have beneficial therapeutic effects. Inflammation in AD involves both the innate and the acquired immune system[5].

Participating cells

Astrocytes

Astrocytes are the most abundant glial cells. They contribute to the support of the neurons, but it is now known that they can perform other functions including providing the biochemical support of the endothelial cells that are part of the blood–brain barrier (BBB); they participate in the maintenance of the extracellular ionic balance and the repair and healing process of the brain parenchyma. The astrocytes can clean detritus by phagocytosis and support neuronal nutrition; but also, they are mediators of inflammation and are involved in the formation of reactive oxygen species. They have multiple roles in the development of AD: astrocytes degrade Aβ without the need for opsonins or cytokines[6]. They contribute to the clearance of β-amyloid protein (Aβ) and limit brain inflammation. If they dysfunction, they can also participate in neurodegeneration, releasing toxins, and altering basic metabolic pathways[7].

Astrocytes, as well as monocytes/macrophages and endothelial cells, secrete, monocyte chemoattractant protein-1 (MCP-1); this secretion is mediated by the stimulation of Aβ and depends on the physical contact between monocytes and astrocytes. MCP-1 facilitates the formation of Aβ oligomers in microglia. The concentration of MCP-1 in serum and cerebrospinal fluid (CSF) is elevated in patients with AD; the higher plasma concentration of MCP-1, the greater the severity of the disease, and the greater the cognitive deterioration[8].

In cell cultures of astrocytes, it has been shown that it is possible to inhibit inflammation induced by Aβ by pyrrolidine dithiocarbamate acid, indicating that nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is probably involved in the inflammatory process[9]. Resveratrol reduces inflammation in rat astrocytes probably by inhibiting NF-κB[9].

Interleukin 8 (IL-8) was the first chemokine identified in the brain. Astrocytes, neurons, and microglia are capable of producing IL-8 *in vitro*, whereas IL-8 receptor or CXCR2 is located in the neuritic portion of the plaques around Aβ deposits in tissues of patients with AD. Type 2 diabetes *mellitus* is a risk factor for dementia. It has been shown that hyperglycemia increases the expression of IL-6 mRNA and the astrocytic secretion of IL-6 and IL-8, contributing to astrocyte-mediated neuroinflammation[10].

Microglia

Microglia are resident myeloid cells of the brain capable of recognizing endogenous and exogenous insults and initiating an immune response. They promote phagocytic cleaning and provide trophic support to ensure tissue repair and maintain homeostasis. In addition, they participate actively in the remodeling of synapses with the release of brain-derived neurotrophic factor (BDNF) that contributes to the formation of memory circuits.[11] Microglial cells originate from the yolk sac during primitive hematopoiesis[12]. Their differentiation need the PU.1 transcription factor and the regulatory factor of interferon 8 or IRF8; to survive, they also require the signaling of the colony stimulating factor 1 receptor (CSF1R)[13]. The release of IL-10 by the microglia causes an increase in the number of dendritic spines. AD is associated with apolipoprotein E ε4 (APOE4) while APOE2 has a protective nature. Both astrocytes and microglia express APOE under the control of nuclear hormone receptors. In AD, the inflammatory activity of the microglia is increased. The microglial cells mount an immune response against the misfolded Aβ protein. The deposit of Aβ induces inflammatory changes in the brain parenchyma, and activation of the microglia has been demonstrated with an increase in the levels of pro-inflammatory cytokines in the regions characteristically most affected in the disease[14]. If the problem is not solved and the stimulus continues, the activity of the microglia deviates from its physiological and beneficial functions. To recognize aggressions, the microglia have different types of receptors, some designed to identify molecular patterns associated with pathogens (PAMPS) and damage, known as PAMPS/DAMPS. It also presents the class 1-scavenger receptor, CD36 (Cluster designation/differentiation), CD14, integrin α6β1, CD47 (integrin-associated protein), and Toll-like receptors (TLR2, TLR4, TLR6, and TLR9)[14]. The amyloid precursor protein (APP) is an integral membrane protein expressed in many tissues and concentrated in the neuronal synapse where it probably has a trophic and regulatory function with both extracellular and intracellular interaction with different signal transduction pathways[15]. It seems to participate in the development of the neural stem cell, in neuronal survival, and the growth and repair of neurites. APP is cut by some enzymes, giving rise to peptides, some of which are released outside the cell[16]. Two of these fragments, or peptides that leave the cell are:

– Soluble sAPP that promotes the growth of nerve cells and can play an important role in the formation of neurons, both before and after birth.
– Aβ, a peptide of 36-43 amino acids that activates kinases. Oligomeric Aβ42 enhances Ras (contraction of Rat Sarcoma)/ERK signaling cascade and glycogen synthase kinase-3 (GSK-3) activation. Both ERK and GSK-3 induce hyperphosphorylation of tau and APP at Thr668[17] and could be related to cholesterol metabolism. In fact, inhibition of cholesterol biosynthesis reduces γ-secretase activity and Aβ generation[18] It is also believed that it may have some antimicrobial activity (it intervenes in the inflammatory action)[16].

APP undergoes two consecutive cuts by two membrane-bound proteases. It is initially cut by BACE1 (β-site APP-cleaving enzyme 1). Subsequently, a second cut is made by the secretase γ (gamma) complex within the transmembrane region of the APP resulting in fragments of 37-42 amino acids at the C-terminal end called Aβ. In particular, the Aβ of 42 amino acids (Ab_{1-42}) has a tendency to form soluble oligomers and fibrils[16].

The binding of Aβ to CD36, TLR4, and TLR6 activates microglia and with it, the production of pro-inflammatory cytokines and chemokines. Microglial cells ingest Aβ fibrils that enter the endosomal/lysosomal pathway. However, these fibrils are resistant to enzymatic degradation unlike soluble Aβ that is degraded by extracellular proteases. Preliminary studies have demonstrated that CNP520, a BACE-1 inhibitor, reduced the amount of Aβ in CSF and in the brain parenchyma of healthy rats and dogs, and the deposit of Aβ in the plaques of transgenic-APP mice. In adults over 60, it was well tolerated and it reduced Aβ concentration in the CSF. These studies are still in progress[19].

Microglia are able to release the insulin-degrading enzyme (IDE) that degrades insulin, amylin, and Aβ. IDE seems to be the main regulator of Aβ levels in microglia and neurons. In animal models, the homozygous deletion of the IDE gene results in a 50% decrease in the degradation of Aβ and in a similar deficit in the breakdown of insulin in the liver with an accumulation of Aβ in the brain. A meta-analysis demonstrated recently that AD patients have lower protein levels of IDE in comparison with controls (mRNA levels were not systematically lower)[20].

It has also been shown that IDE degrades the APP intracellular domain (AICD). IDE regulates the levels of non-phosphorylated AICD. It seems that phosphorylation protects AICD from its breakdown by IDE. The IDE could be a therapeutic target in AD[21].

ApoE gene, which codes for ApoE, the most important genetic risk for AD seems to have an immunomodulatory function. This function is related to the activation of triggering receptor expressed on myeloid cells2 (TREM2) expressed by microglia[22].

Mutations in the extracellular domain of TREM2 confer an elevated risk of developing late-onset AD. A risk allele (R47H) of TREM2 had an effect similar to ApoE4 (odds ratio 2.90-5.05) in a Colombian population[23]. TREM2 is a receptor expressed in macrophages including microglia in the brain. TREM2 participates in the survival and proliferation of microglia, chemotaxis, and phagocytosis[23]. In murine models of AD, the loss of TREM2 causes increased deposits of Aβ in the hippocampus due to a dysfunctional response of the microglia to Aβ suggesting that TREM2 facilitates the clearance of Aβ by these cells[24].

The microglial response mediated by TREM2/DAP12 (DNA activation protein of 12kDa) limits the diffusion and toxicity of the amyloid plaques forming a protective barrier. TREM2 propagates its signal through the adapter protein DAP12, which, in turn, activates several signaling pathways including Spleen tyrosine kinase, phosphoinositide 3-kinase, and the mitogen-activated protein kinase (MAPK) which culminates in increased phagocytosis and an anti-inflammatory profile in the microglia[24]. On the other hand, dendritic cells deficient in TREM2 secrete more tumor necrosis factor-alpha (TNF-α), IL6 and IL-12 compared to wild type, especially when activated by lipopolysaccharides; this suggests that there may be a shift toward a more inflammatory profile in the absence of TREM2[25].

The loss of TREM2 in microglia confers an increased risk of developing late-onset AD and is associated with loss of endothelial homeostasis[25].

In AD, there is over-regulation of TREM2 that seems to serve as a compensatory response to $A\beta_{1-42}$ and protects against the progression of the disease by modulating the functions of microglia. TREM2 promotes the survival of microglia by activating the Wnt/β-catenin signaling pathway. The manipulation of TREM2/Wnt/β-catenin may be a therapeutic target in AD[26].

It is known that all isoforms of apoE are an agonist of TREM2[27]. APOE3 maintains lipid homeostasis and has a protective cardiovascular effect. APOE2 is associated with dysbetalipoproteinemia and APOE4 is a risk factor for AD[27]. Microglial cells are able to produce nitric oxide (NO), TNF-α, and IL-1β and promote the generation of antibodies against Aβ, stimulating the clearance of amyloid plaques. The soluble Aβ oligomers and the Aβ fibrils have the ability to bind to receptors expressed in the microglia, such as CD14, CD36, CD47 integrin α6β1, the Class A eliminator receptor, the receptor for advanced glycation end products (RAGE), and TLR. In macrophages and microglia, classical M1 activation is characterized by a pro-inflammatory profile of cytokines including TNF-α, interleukins 1 (IL-1), 6 (IL-6), 12, and 18, and it is accompanied by a deficient phagocytic capacity, while the M2 profile is characterized by secretion of anti-inflammatory cytokines IL-4, IL-10, and IL-13 and transforming growth factor-beta (TGF-β) and by a high phagocytic capacity without NO production. A third phenotype is a deactivated state associated with corticosteroids or with TGF-β. *In vitro*, bipolar/rod-shaped microglia are highly proliferative, express various M1/M2 markers and are quickly transformed into amoeboid microglia within 30 min of lipopolysaccharide treatment, leading to the upregulation of pro-inflammatory cytokine gene expression and the activation of Jak/STAT *signaling pathway* **(**Janus kinase-signal transducer and activator of transcription)[28]. Markers of microglial phenotypes in human brains are still limited; the most widely used marker to describe activated microglia, particularly in diseased brains, has been HLA-DR, or major histocompatibility complex II protein. Ionized calcium binding adaptor molecule-1 (IBA1) and CD68 are generic markers of microglia and recruited monocytes[29]. In patients with AD, Stages V-VI of Braak, degeneration of the microglia has been observed, especially in the dentate gyrus, probably due to the accumulation of toxic tau-soluble species[30]. There are agents capable of increasing phagocytosis of Aβ in phagocytic cells, such as Lipoxin A4 (LXA4), an endogenous lipid mediator with anti-inflammatory properties. It has been shown in mice that the administration of aspirin (15 μg/kg) twice a day, through the activation of LXA4, reduces the activation of NF-κB and the levels of pro-inflammatory cytokines, and produces an increase in IL-10 with anti-inflammatory action and in TGF-b. This was translated to the brain level in the recruitment of microglia with a phenotype characterized by the upregulation of YM1 lectin protein, and arginase 1 and low-regulation of the inducible synthase expression of NO. With this phenotype, the microglia presented a better phagocytic function with an efficient clearance of Aβ, reduction of synaptotoxicity, and improvement of cognition[31].

In transgenic mice bearing a mutated gene of tau (p301s MAPT), the elimination of astrocytic and microglial senescent cells (that accumulate $p16^{INK4A}$), with first-generation senolytics drugs (drugs that cause senescent cells to become susceptible to their own pro-apoptotic microenvironment)[32], preserves the cognitive function; a therapy focused on senescent cells (with irreversible arrest of the cell cycle) could be useful in AD[33].

BBB

The BBB protects the central nervous system from the entry of substances that can be potentially harmful and maintains homeostasis and communication between the brain and the peripheral blood. In addition to affecting neurons, astrocytes, and microglia, AD also damages the vascular cells of the neurovascular unit such as endothelial cells, pericytes, and vascular smooth muscle cells[34]. The interaction of Aβ with endothelial cells produces structural and functional changes in the BBB. It is now known that C-reactive protein (CRP), a member of the pentraxin superfamily involved in innate immune response, acts as a direct mediator of inflammatory reactions. The inert circulating pentameric form (pCRP) is transformed into the pro-inflammatory isoform pCRP and finally into the monomeric form (CRPm) in the presence of amyloid beta and activated endothelial cells. It will then contribute to the inflammation in AD[35].

Aβ in CSF is rapidly cleared into the bloodstream. Aβ in the brain parenchyma is cleared across the BBB through the low-density lipoprotein receptor-related protein-1 (LRP-1)[36].

The luminal-to-abluminal transcytosis of Aβ is mediated by a transporter identified as the receptor for advanced glycation end products (RAGE). RAGE upregulation has been observed in the CNS microvasculature of humans with AD by histochemical methods in autopsy material[37].

Decreased expression of low-density lipoprotein receptor-related to protein 1 (LPR-1) in the outer or abluminal part of cerebral capillary cells and decreased levels of multidrug transporter p-glycoprotein (P-gp) in the luminal plasma membrane of the capillaries lead to a decrease in the flow of Aβ from the brain to the blood[38].

On the other hand, it has been observed that Catalpol, an iridoid glycoside extracted from the root of *Rehmannia glutinosa* Libosch, has a neuroprotective effect in AD. The protective mechanism seems to depend on a decrease in the levels of metalloproteinases (MMPs), MMP-2, MMP-9, and RAGE, as well as an increase in the concentration of proteins of the narrow junctions (zonula occludens-1, ocludin, and claudin-5), the LPR-1 and the glycoprotein P, so that the Catalpol could have utility in the early treatment of AD[39]. The endothelial cells of the BBB can also be damaged by high concentrations of low-density proteins (LDL). Statins decrease the inflammatory effects of oxidized LDL in the microvasculature[40].

Lymphocytes

AD appears to be a systemic pathology in which some of the dysfunctions found in the brain are present in peripheral tissues. Lymphocytes from patients with AD have an increased susceptibility to death induced by hydrogen peroxide (H_2O_2) that is related to the severity of dementia and appears to depend on deregulation of the p53 pathway with increased expression of p53[41]. Various alterations in the lymphocytes of patients with AD have been described, including a systemic decrease in B and T lymphocytes. The peripheral CD4 + and CD19 + lymphocytes in the early stages of AD show mitochondrial depletion. Lymphocytes T-helper 17 are found in the brain parenchyma of AD and IL-17A is located around the Aβ deposits. Overexpression of IL-17 improves glucose metabolism, amyloid angiopathy and learning in rats exposed to ozone, a murine model of oxidative stress and decreases soluble Aβ in the hippocampus and the CSF[42]. More recently, it has been found that micro-RNA Let-7b levels increase with the progression of the disease and this is parallel to the increase in the number of CD4 + T lymphocytes in the CSF. This microRNA correlates positively with the expression of t-Tau and p-Tau and is being studied as a possible biomarker of progression[43].

In the late stages of the disease, CD8 + T lymphocytes are increased in number in the hippocampus of subjects with AD compared to subjects without dementia. The numerical density of T-lymphocytes correlates with the tau pathology (AT8 staining)[44].

It is known that Vitamin D deficiency is a risk factor for cognitive deterioration and that this vitamin is involved in the clearance of Aβ from the brain. In subjects with mild cognitive impairment, their lymphocytes are more susceptible to oxidative damage, which improves with treatment with Vitamin D for 6 months as well as the plasma concentration of Aβ and cognitive function[45].

It has been proposed that the T cell profile may change depending on the stage of the evolution of AD, with an increase in pro-inflammatory activity as the disease progresses. Neurodegeneration, in general, has been linked to an imbalance between effector T cells that release IFNγ or IL17 and T-lymphocytes reg, which leads to a decrease in neuroprotection and increases neuronal damage[46].

Mechanisms of Cell Death

Apoptosis and necrosis

In the context of AD, although death due to apoptosis seems to prevail, necrosis also contributes to neurodegeneration. In familial Alzheimer's, some genes involved (presenilin 1 and 2) make neurons more susceptible to apoptosis[2].

On the other hand, greater expression of Bak and Bad pro-apoptotic proteins, activation of caspases and decreased expression of the antiapoptotic gene NCK-associated protein 1 has been demonstrated in affected brains[2].

Neuronal autophagy

Excessive accumulation of autophagic vacuoles and toxic substances such as misfolded proteins or damaged organelles can lead to cell death by self-destruction. Autophagosomes are frequent in AD. The beclin-1 protein plays an important role in autophagy and is diminished in AD. In fact, patients with AD show accumulation of autophagy markers such as sequestosome 1/p62 (ubiquitin-binding protein) and LC3 (Microtubule-associated protein 1A/1B-light chain 3) and these markers colocalize with the Aβ marker-6E10 and hyperphosphorylated tau[47].

The intracellular Aβ alters the retrograde transport mediated by dynein. The neurons must transport the autophagosomes generated in the distal axons to the soma or neuronal body. This retrograde transport starts with the recruitment of the late endosome complex (LE)-loaded with dynein and with SNAPIN (SNAP-associated protein) after fusion of LE with autophagic vacuoles to form amphysomes. However, in AD, autophagic vacuoles accumulate massively within dystrophic neurites. Aβ is associated with an increased density of LEs or multivesicular bodies. It has been shown in animal models that Dynein intermediate chain 1, axonemal interacts with Aβ _ interacts with Aβ. This binding competitively disrupts the formation of dynein-SNAPIN complexes, and therefore the recruitment of dynein motors to LEs-loaded with SNAPIN (amphysomes), is markedly reduced[48].

Inflammation

In the development of AD, Aβ, and Tau protein can act as pro-inflammatory factors. In fact, the deposition of Aβ in the brain is associated with the activation of astrocytes and microglia. The soluble isoforms of Aβ are phagocytosed by microglia while the insoluble deposits activate microglia by binding to TLRs. In these cells, Aβ activates MAPKs and favors the expression of a pro-inflammatory profile with the secretion of cytokines and chemokines that amplify the inflammatory process[49]. The misfolded protein aggregates activate the NLRP3 (cryopyrin) inflammosome. NLRP3 inflammasome is a multiprotein complex expressed in myeloid cells and has an important role in the activation of caspase-1 by Aβ[50].

Glia maturation factor (GMF) is a regulator of the actin cytoskeleton with a unique role in remodeling actin network architecture; it does not bind actin but instead binds the Arp2/3 complex. GMF catalyzes the debranching of actin filament networks and inhibits actin nucleation by Arp2/3 complex. GMF is also a pro-inflammatory molecule present in glial cells and some neurons. Its over-expression causes inflammation. It is localized and expressed in the neighborhood of Aβ and tau in the temporal cortex of patients with AD. GMF could be a therapeutic target in AD[51].

Dendritic cells (DC) appear to regulate the entry of T-lymphocytes into the perivascular and leptomeningeal spaces. Their protective properties in AD are related to their ability to clear Aβ. Aβ significantly decreases the expression of brain-derived neurotrophic factor (BDNF) in DCs derived from AD patients but not from control subjects, AD-linked dysregulated immune mechanisms lead to dendritic cell-mediated over-activation of inflammation and impaired antigen presentation, thus supporting the idea that immune cell activation could play an important role in AD pathogenesis[52].

Recently, elevated levels of CSF biomarkers such as heparin and chitin-binding glycoprotein (YKL-40), intercellular adhesion molecule-1, vascular adhesion molecule-1, IL-15, and fms-related tyrosine kinase-1 have been described, both during the preclinical phase and in the dementia phase of AD. These levels correlate with the total concentration of tau in the CSF[53].

Chemokines

Chemokines, belonging to the cytokine family, are small proteins that bind to heparin and are chemoattractants; some are pro-inflammatory while others control the migration of cells during development. Chemokines are classified according to their primary protein structure that is based on the number of amino acids that separate two cysteine residues; thus, four groups are recognized, α (CXC), β (CC), γ (CX3C), and δ (C). Chemokine receptors are designated CXCR1-CXCR6, CCR1-CCR11, CX3CR1, and XCR. Chemokines and their receptors represented by MCP-1 (also called chemokine (C-C motif) ligand 2 [CCL[2]] and its receptor (CCR2) are considered biomarkers to monitor progression in AD since the progression of the disease seems to be related to the expression of chemokines[14].

In studies of clinical follow-up of patients with a cognitive neurological deficit, it has been seen that those with the highest tertile of MCP-1 in CSF showed a significant cognitive decrease and developed dementia in a shorter time than those in the lowest tertile[14].

The chemotactic cytokines stimulate and control the movement of leukocytes from the blood to the tissues. In the context of AD, the most studied chemokine is CCL5 (RANTES) that regulates the expression and secretion of T cells[14]. Curcumin increases neuronal survival in the toxicity model induced by N-methyl-d-aspartic acid by inducing the expression of RANTES in astrocytes through the phosphatidylinositol 3-kinase and MAPK pathways[54].

In AD increased concentrations of CCL5 of astroglial origin have been described in the cerebral microcirculatory system in response to the increase in reactive oxygen species-mediated by cytokines.

It has been described in patients with AD that levels of MCP-1 and IL8 are increased in serum, CSF and parenchyma; on the other hand, levels of fractalkine and stromal cell-derived factor 1 are decreased in serum. Fractalkine (CX3CL1) is made by neurons, and its receptor (CX3CR1) is expressed by microglia; therefore, fractalkine/receptor interactions are a neuron–microglial signaling system[55].

MIP-1 and RANTES levels are elevated in the brain parenchyma. MCP-1, IL-6, and IL-8 are over-expressed in brain tissue in AD. Immunohistochemical studies have confirmed the increase and localization of these three factors in neurons[56], whereas in astrocytes MCP-1 and IL-6 were detected. MCP-1 and IL-8 have been observed in senile plaques.

Interferons (IFN)

IFN are cytokines made up of glycoproteins used for communication between cells; they activate the immune system in case of aggression. They are divided into three classes: types I, II, and III. Type I IFN in humans is IFN-α, IFN-β, IFN-ε, IFN-κ, and IFN-ω; produced by fibroblasts and monocytes; they are activated in viral infections. Type II or IFN-γ in humans is activated by IL-12 and produced by helper T-lymphocytes type 1 (Th1) and natural killer cells. Type III IFNs are characterized by having CRF2-4 and CRF2-12 receptors. The expression of IFNs Type I and III can be induced in virtually all cell types after recognition of viral components, while the production of IFN Type II is restricted to immune cells.

Type I IFNs are pleiotropic cytokines that control the secretion of pro-inflammatory cytokines and regulate the immune response that contributes to progression in AD. IFN beta 1a has been used in patients with AD in early stages; an improvement in the instrumental activities of daily life has been observed in these patients[57].

TLRs

TLRs are Type I transmembrane proteins with ectodomains that contain leucine-rich repeats that mediate the recognition of molecular PAMP; they are homologous to toll, a receptor found in insects, which participate both in the establishment of dorsoventral polarity during embryogenesis and in the immune response against fungal infections. 12 TRLs have been described in mice and 10 in humans; TLR1-9 are conserved in both. Fibrillar Aβ can interact directly with TLR2, TLR4, and CD14 to induce phagocytosis of Aβ by microglia in the early stages and neuroinflammatory responses in the advanced stages. In the early stages, the signal mediated by TLR3 increases the autophagy of Aβ; it increases neuronal apoptosis in the late stages. Furthermore, TLR7, TLR8, and TLR9 can increase phagocytosis of Aβ early, to later contribute to neuroinflammation. TLR2 and TLR4 can be a target of therapeutic intervention in AD[58]. It has also been described that the polymorphism of TLR2 -196-174del is a risk factor for late-onset AD in some populations[59].

It seems today well established that chronic inflammatory reactions are present in Alzheimer disease and are important factors that accelerate the progression of the disease. Receptors of innate immunity such as TLRs and RAGE play a central role in the perpetuation of inflammation. RAGE activation is a primary mechanism which determines self-perpetuated chronic inflammation, and RAGE cooperation with TLRs amplifies inflammatory signaling[49].

Conclusions

AD is multifactorial neurodegenerative pathology. Neuroinflammation is an early event of the presymptomatic stages in AD and contributes to the progression of the disease[53].

To identify the different actors participating in the inflammation and the mechanisms of damage involved can allow the development of treatments and preventive strategies in the fight against this disease.

Conflicts of interest

There are no potential conflicts of interest for any of the authors in this scientific report.

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