We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

186,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter

Astrocytes and Inflammatory Processes in Alzheimer's Disease

Soraya L. Valles, Federico Burguet, Antonio Iradi, Martin Aldasoro, Jose M. Vila, Constanza Aldasoro and Adrián Jordá

Abstract

A significant increase in inflammation has been shown to be a crucial factor in the progression of the Alzheimer's disease (AD). Moreover, inflammatory signals are already present in mild cognitive impairment (MCI) patients before they develop AD. The amyloid hypothesis argues that in AD, there is an increase in oxidative stress caused by the accumulation of β-amyloid (Aβ) and that its elimination should be a priority. Also, hyperphosphorylation of the protein TAU occurs, which is characteristic of this disease. In AD oxidative stress processes occur and also inflammation. The basal chronic inflammation produces a cascade of cellular, such as astrocytes and microglial cells, and molecular processes in AD patients. We here have tried to explore the action of the inflammatory process and its implication in the neurodegenerative process of the AD. We can see that the role of Aβ is only one component that gives rise to inflammation, probably mediated by activation of microglia and astrocytes with the goal of getting rid of these brain waste products. In fact, it is related to a greater degree with the progression of the disease and worsening of the symptoms with the increase of phosphorylated TAU in different parts of the brain.

Keywords: astrocytes, microglia, neuroprotection, Alzheimer's disease, inflammation, oxidative stress

1. Introduction

Inflammation is a physiological process in response to various factors such as infection, trauma, and a long list of diseases that can promote it [1]. It is not uncommon to think that changes or failures that occur in their action mechanisms can lead to fatal consequences for humans. The inflammation originates because of a set of immune cells involved in the process that causes different changes in the inflamed area through signaling pathways composed of different groups of pro and anti-inflammatory molecules [2]. The resolution of the inflammatory process happens after the neutralization of the trigger. The cells of the immune system generate an anti-inflammatory activity, including lipoxins (for example, LXA4, RvE1) and cytokines such as interleukin-10 and interleukin-37, transforming growth factor-beta (IL-10, IL-37, TGF-β) [3]. Acute inflammatory processes will be resolved relatively quickly, while, however, resolution processes are not achieved in chronic inflammation [4].

The differences between both types of inflammation, acute and chronic, reside at different levels. Regarding the cells involved in acute inflammation, neutrophils intervene in an infection context and eosinophils and mast cells in the case of allergies [5]. The chemical mediators involved in acute inflammation would be the complementary system, the kinins, the prostaglandins, the leukotrienes, the cytokines coming from several immune cells, and the gamma interferon of the T lymphocytes [6]. The lesions that are produced in this type of inflammation are itching, pus, and abscesses [7]. On the other hand, in chronic inflammation, we would have the participation of macrophages and lymphocytes mainly, which would produce cytokines as the main chemical mediators of this type of inflammation. As alterations, we would also have a rash (in the context of a cutaneous disease), and unlike the findings we had in the acute, in chronic we can have fibrosis and granuloma. These last two injuries are ultimately responsible for the effects of deterioration at central nervous system (CNS) and peripheral (SNP) level [8]. The study of neurodegenerative diseases excluded inflammation as an etiological agent of the disease. This was because there were no infiltrates of inflammatory cell similar to those that occur in infectious or autoimmune diseases [9]. Nowadays, there is an increasing amount of studies that position inflammation as being responsible for neurodegeneration through the participation of macrophages and the complementary system [10].

2. Specification of the process at the brain level

In the brain there is no reddening, local heat, or pain after acute inflammation. In the case of chronic inflammation in another organ, the participation of different immune cells takes place. But in the CNS, macrophages are essentially the representatives of the immune system [11].

In the CNS, the derivatives of tissue macrophages would be the microglia of the central nervous system. Microglia participate in numerous maintenance functions such as synapse management, neurogenesis, regulation of certain cognitive processes, and immunological protection [12]. Thus, the main hypothesis on the pathogenesis of Alzheimer's disease (AD) is that the plaques of β-amyloid (Aβ) and neurofibrillary tangles produce an acute inflammation in the brain, which activates these cells causing different inflammatory mediators, such as: proinflammatory cytokines, chemokines, macrophage inflammatory proteins, monocyte chemoattractant proteins, prostaglandins, leukotrienes, thromboxanes, coagulation factors, reactive oxygen species (and other radicals), nitric oxide (NO), complement factors, proteases, protease inhibitors, pentraxins, and C-reactive protein [13]. Due to the chemical composition of the Aβ plaques and neurofibrillary tangles, they stimulate a chronic inflammatory reaction with the intention of eliminating these brain structures [13]. Finally, this inflammatory reaction will produce a neuronal dystrophy mediated by the inflammatory mediators that are secreted by the microglial and astrocyte cells, as well as by the aggregates of amyloid fibrils [14].

3. Pathophysiology of Alzheimer's disease

The pathophysiology of Alzheimer's disease is very varied and there are different hypotheses on how it develops: the most accepted hypothesis in recent years was the amyloid hypothesis. The amyloid precursor protein (APP) will be able to be processed by either α-secretase, β-secretase, or γ-secretase. Depending on which enzyme does the app cut, we can have more or less neuroprotective profile; the α-secretase cleave produced a more neuroprotective one, while on the other hand,

if the β- and γ-secretase participate sequentially, we will obtain metabolites that are harmful to neurons, producing greater amount of Aβ [13].

3.1 Role of α-secretase

α-Secretases are a family of proteolytic enzymes that adhere to APP in their transmembrane region. The secretases adhere to the fragment that, however, is processed by β-secretases and γ-secretases and that increases the β amyloid peptide [15]. These enzymes are members of the ADAM (disintegrin and metalloprotease domain) family that are expressed on cell surfaces. Furthermore, a metabolite by the action of secretase is APPsα, which has a not only neuroprotective action, but also neurotrophic effects have been observed and, therefore, neuroplasticity can be favored [16].

3.2 Role of β- and γ-secretases

The amyloid plaques are composed of a fragment of the APP: the 4-kD amyloid-β protein. The enzymatic processing of APP, resulting in Aβ, requires two enzymes: the γ-secretase, which is dependent on presenilin, and β-secretase, which is an aspartyl protease β-site APP-cleaving enzyme (BACE) (also known as Asp2, memapsin 2) [17, 18]. The BACE1 will function to split the APP, giving as result the βCTF (beta C-terminal fragment), which will later be cleaved again by γ-secretase to give rise to Aβ. On the other hand, this second excision could be caused by a mechanism different from that carried out by γ-secretase, which would be dependent on a 20S proteasome and whose malfunction would lead to an overproduction of Aβ in the same way [19].

3.3 The β-secretase: BACE

There are two BACEs, BACE1 and BACE2. BACE2 is a homolog discovered later than the enzyme BACE1 and shares 64% of similarity in its structure. By contrast, BACE2 is expressed at low levels in neurons and does not have the same activity against APP as BACE1 [20]. The BACE1 is doubly increased in the brains of patients with AD, compared to the brains of individuals without the disease. For this reason, it is considered that this enzyme is responsible for the initiation or acceleration of AD. Other studies show how BACE1 is also increased in response to stress: during oxidative stress, hypoxia ischemia, apoptosis, and brain trauma [18].

3.4 The γ-secretase

Research on the proteolytic processing of APP has provided information on the pathogenesis of Alzheimer's disease and on an unusual form of regulation of proteolytic processing within the domains of some membrane proteins, including APP, Notch, and ErbB4 [21]. Some of the enzymes responsible for α and β cleavage are already known. However, the molecular events that are involved in the cleavage produced by the γ-secretase, within the transmembrane domain of these proteins, are much more complex. Presenilins and nicastrin are necessary for this process. While the role of presenilins, in some cases, supports the idea that presenilins are found in the active site of the γ-secretase, other data indicate that they could have a more indirect function, as for example in the transport of substrates to the subcellular compartment for cleavage by the enzyme γ-secretase [22].

3.5 Role of β-secretase: BACE1 and γ-secretase in voltage regulation by sodium channel

The sodium channels Na1s are responsible for regulating for regulating the passage of Na^+ in the initial axonal fragments, Ranvier nodes, and neuromuscular junctions. These channels are formed by an α-subunit in the form of pore and two accessory β subunits which are transmembrane that modify the localization, surface cell expression, and inactivation of the alpha subunit by direct interaction, specially β2 subunit of the Na-1 channel that plays an important role since it undergoes degradation by BACE1 and γ-secretase [23]. These enzymes cleave an intracellular fragment of the C-terminal fraction that results in a transcription factor for Na1.1 mRNA and other protein levels, so that Na 1.1 levels accumulate intracellularly [23]. This fact explains the decreased expression of sodium channels on the surface of the hippocampal neurons of patients with AD, as well as in neuroblastoma cells producing BACE1, resulting in a lower sodium current density [23].

3.6 Differences between Aβ40 and Aβ42

To better understand the fact why Aβ42 promotes, to a greater extent, inflammation in AD than the Aβ40 peptide, it is necessary to emphasize its greater propensity to form amyloid plaques [24]. Studies performed by combining molecular dynamics and nuclear magnetic resonance (NMR) experiments with respect to the behavior of both peptides in water have shown that the Aβ42 peptide forms tangles more prominently [24, 25]. The differences that exist at the level of the chemical formula between the two peptides are only two amino acid residues at the C-terminus. However, at the level of biochemical and conformational interactions, there are clear differences [25]. In addition, while the N-terminal half presents a much smaller spectrum of possible conformations in its secondary structure, the C-terminal half of the Aβ42 peptide allows a greater number of possible conformations. Despite this, these studies showed that Aβ42 is more structured in water than Aβ40 [24]. Specifically, it is appreciated that the Aβ42 form has less flexibility than Aβ40 in its C-terminal half. This fact is produced by the formation of a beta hairpin in the sequence IIGLMVGGVVIA, involving short fragments of the structure between the residues of amino acids 31–34 and 38–41, reducing the flexibility in the Aβ42 peptide. Specifically, this must be the cause of the greater capacity to form amyloid plaques. On the other hand, a β-turn type VIB, centered on residues 35 and 36, is important for the alignment of the threads involved. In addition, the existence of hydrogen bonds between the pairs A30-A42, I32-V40, and L34-G38 adds stability to the structure of the beta fork [24, 25].

4. Identification and definition of the problem-question

In epidemiological studies of Alzheimer's disease, a significant increase in inflammation has been shown to be a crucial factor in the progression of the disease, as well as in the activation of microglia and in the increase of reactive astrocytes in these patients [26]. It should be noted that inflammatory signals are already present in mild cognitive impairment (MCI) patients before they develop AD [27]. In this study, we have tried to explore the action of the inflammatory process associated with Alzheimer's disease and its implication in the neurodegenerative process of the disease.

5. Interest of the review

Glial cells have a very important role in the protection of the central nervous system against damage and also in the repair of damaged nerve tissue [28]. Within the glia, astrocytes are the cell type prevalent in the brain [29]. Astrocytes increase neuronal viability and mitochondrial biogenesis, protecting neural cells from oxidative stress and inflammation induced by the toxic amyloid peptide [30–32]. Conversely, if chronic inflammation occurs, astrogliosis is triggered, produced by a reaction to inflammation and oxidative stress caused by toxic and inflammatory agents [33]. In Alzheimer's disease, complex changes and specific conflicts occur in different brain regions. The number of reactive astrocytes increases, engulfing and reducing the amyloid plaques. In addition, astrocytes surround the amyloid plaques and secrete proinflammatory factors, such as tumor necrosis factor (TNF) or interleukin 1 (IL-1) [34]. Currently, no hypothesis about what causes Alzheimer's disease has obtained favorable results. For years, it has been believed that the amyloid theory was the correct one and it was the most supported and financed by almost all the pharmaceutical companies around the world. The amyloid hypothesis argues that in AD, there is an increase in oxidative stress caused by the accumulation of Aβ and that its elimination should be a priority. There is a lot of research showing that increased levels of ROS have been linked to Alzheimer's disease [30, 35] but the effects of antioxidants in clinical studies have been disappointing either because high concentrations of antioxidants are pro-oxidants, or because the oxidative stress occurs relatively early in the course of the disease.

5.1 Mediators of the inflammatory process in AD

5.1.1 Cytokines

In AD, different cytokines have been detected, such as IL-1α, IL-1β, IL-6 and, similarly, higher amounts of the type B receptor IL-8 (IL-8RB) have also been found (in neurons in addition to the rest immune cells), unlike the type A receptor for IL-8RA that is only found in immune cells [36, 37]. It was already demonstrated that inflammatory signals are previously present in patients with mild cognitive impairment or with MCI before they develop AD [27].

The cytokine IL-1β constitutes one of the first secreted cytokines in response to lesions, as it is an important mediator of proliferation, differentiation, and apoptosis [38, 39]. The concentration of the said cytokine has been increased near the sites where the amyloid plaques are located [40]. More recently, it was observed that old mice had an increased basal neuroinflammation and they express IL-1β and IL-10 in the hippocampus compared to adult mice [41].

A study conducted in autopsies of 10 patients clinically diagnosed with AD showed that they had amyloid plaques and immunoreactivity for the cytokine IL-6. On the other hand, the control patients did not have immunoreactivity for IL-6 whether they presented plaques or not. From the plaques that were positive for the cytokine IL-6, it could be observed that they were most frequently found in diffuse plaques, less frequently in primitive plaques, and rarely found in compact and classic plaques [42].

5.1.2 Role of lipopolysaccharide (LPS)

The role of lipopolysaccharides in Alzheimer's disease has been studied by several research groups and it has been observed that treatment with these LPS induces chronic neuroinflammation [43, 44] and can contribute to deficits in learning

and memory [44–46]. As previously known, LPS is an activator of microglia in the central nervous system and can induce a 2-fold increase in the expression of APP in the brains of mice with the Swedish mutation for APP [47]. In addition, it also caused an 18-fold increase in βCTF, suggesting an increased activity in turn of BACE1 and in turn an increase by up to three times in the amount of Aβ40 and Aβ42 [47]. While the previous study observed an increase in the brain in a non-specific manner, another study specifically analyzed the increase in glial fibrillary acidic protein (GFAP)-positive astrocytes in the cortex and hippocampus after treatment with LPS [48].

5.2 Alzheimer's disease as taupathy

5.2.1 Structure of the TAU protein

In electrophoresis gels, the TAU protein has been found in different isoforms depending on how the RNA has been processed and different levels of phosphorylation. This RNA is located on chromosome 17, it has at least 16 exons [49]. Other proteins besides tubulin have been described that can bind to the TAU protein: spectrin protein phosphatase 1, protein phosphatase 2a, presenilin 1, α-synuclein. Recent studies that have used mass spectrophotometry techniques indicate that it is more appropriate to measure the bacterially expressed MT-binding region (MTBR) domain of TAU, instead of the total TAU protein, this technic is more accurate to calculate the amount of TAU neurofibrillary tangles [50].

5.2.2 AD as taupathy

The TAU protein is a member of the microtubule-associated proteins (MAPs). The microtubules in the cells have a multitude of functions, among which we can highlight at the level of the neurons the formation of dendrites, axons, and their specific contacts [51]. Therefore, the TAU protein is necessary for the functioning and development of the nervous system and the presence of modified forms of the TAU protein gives rise to important pathological effects in the neurons that leads to neurodegeneration. Specifically in AD, phosphorylation of TAU protein is produced by glycogen synthase 3ß (GSK3) [49]. This TAU protein is abnormally phosphorylated and will form the neurofibrillary tangles in the neuronal cytoplasm, constituting one of the most important histological features of Alzheimer's disease. As previous works demonstrated, the number of these balls will be directly related to the severity of the symptoms of the disease [52]. The structure of these microtubules will be formed by double helix subunits that are intertwined with levorotatory filaments that are composed of the following proteins: intermediate filaments, neurofilaments of medium and high molecular weight; proteins associated with microtubules MAP2 and TAU; actin; and ubiquitins [53, 54], which show characteristics different from normal neurofilaments and normal microtubules.

In 1995, a study in autopsies done with eight patients with diagnostic criteria for Alzheimer's disease and six control patients of similar ages indicated important changes between TAU and inflammation. The brain of these 15 subjects was extracted without exceeding 15 h of postmortem and, later, samples were taken from the hippocampus; from the frontal, temporal, and occipital lobes; and from the cerebellum. AD patients presented a direct relationship between higher concentrations of the activated IL-α and higher load of neuritic plaque TAU2+ (TAU 2-immunoreactive). There is a strong association between the presence of IL-1α +, microglia, and TAU protein plates in patients with Alzheimer's disease [55]. Recently, it was observed in a microglial culture model together with neurons that the inflammatory response mediated by LPS-induced microglia leads to

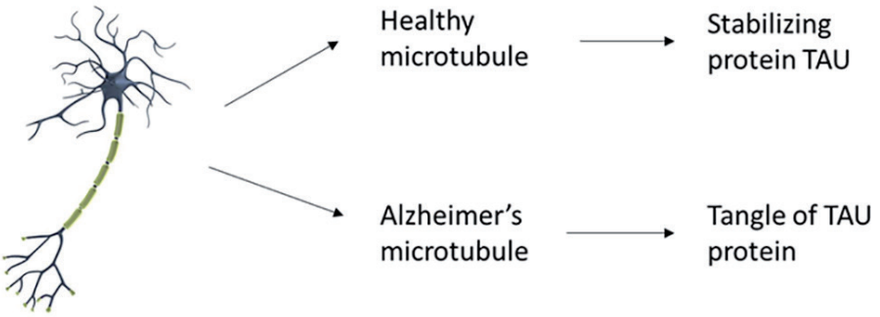

Figure 1.
TAU protein in health and Alzheimer's disease.

hyperphosphorylation of TAU mediating the greater kinase of the TAU protein, GSK3β (kinase glycogen synthase kinase 3β) [56]. On the other hand, chronic inflammation causes phosphorylation of TAU and worsens pathology in neurons that express many inflammatory receptors and molecules, including, MHC-I, TNFR1, IL-1R, and TLR. As a result of this, it allows them to interact directly with microglia [57]. Inflammatory signals can consequently directly activate neuronal protein kinases and phosphatases, such as cyclin-dependent kinase 5 (CDK5), glycogen synthase kinase-3β (GSK3β), ERK, and protein-phosphatase 2A (PP2A), which regulates phosphorylation of TAU and the assembly of neuronal microtubules [43, 44, 58, 59] (**Figure 1**).

TAU, and its function regarding neuronal and microglial interactions in brain immune chain reactions, as in AD and its progression, could be initiated, by age-related chronic inflammation. There is an increase in scientific evidence suggesting the importance of the mechanism in the synaptic pruning regulation, neurogenesis, immunological chain reaction-mediated cognitive functions in brain cells, and LTP, even if its complete relevance is still to be confirmed [44].

The mechanisms of inflammation effects on TAU and its pathological influx remain constant even if broad investigations have been carried out on Aβ and inflammation pathway. Persistent microglial activity and inflammation are established to be the causes of a broad release of TAU sub-species [44–47]. As for the mechanisms of TAU-induced inflammatory responses leading to pathology, several sources point to an acceleration of the onset of main protein kinases, which take care of the phosphorylation of the TAU protein. Microglia-perpetuated liberation of TNF-α has proven to provoke the accumulation and aggregation of TAU in in vitro neurons [48]. On the other hand, blocking microglia with minocycline reduces the inflammatory response and propagation of pathology related to TAU in experiments performed with hTau mouse models [60]. Moreover, the inhibition of inflammation by arginase-1 overexpression counteracts the activity of nitric oxide synthases, and facilitates autophagy and the decrease of TAU pathology in the TAU-transgenic mouse model rTg4510 [61]. A process that has been reported as important in stress-induced mechanisms and which can be genetically suppressed by the corticotropin-releasing factor receptor is the stimulation of toll-like receptor 4 (TLR4), which increases GSK-3β and CDK-5, which phosphorylate TAU [62].

To perform the "synaptic pruning" by the microglia, a cytosine secreted by the neural cells called fraktalkine (CX3CL1) that is excreted in large quantities in the brain compared to the rest of the organs of the body is needed [63]. Its receptor CX3CR1 is expressed in large quantities by microglia [64]. Previously, it was demonstrated that neuroinflammation via the receptor deficiency for fractalkine (CX3CR1) promotes taupathy and neurodegeneration in mouse models in which systemic inflammation mediated by LPS had occurred. First, $Mapt^{+/+}$ neurons

showed high levels of Annexin V (A5) and TUNEL (markers of neurodegeneration) when they were grown together with microglia Cx3cr1$^{-/-}$ treated with LPS. Second, a population of positive neurons for TAU protein phospho-S199 (AT8) in the dentate gyrus is also positive for (CC3) for mice treated with Cx3cr1$^{-/-}$. Third, the genetic deficiency of TAU in Cx3cr1$^{-/-}$ mice resulted in reduced microglial activation, which altered the expression of inflammatory genes in those neurons positive for CC3 compared to Cx3cr1$^{-/-}$ mice [44]. These results suggest that pathological changes in TAU mediate the neurotoxicity induced by inflammation, while Mapt deficiency is neuroprotective. It was proposed that this earlier phenomenon was probably associated with the indirect reduction of microglial activity due to the decrease in the production of pathological species of TAU, observed in a transgenic mouse model rTg4510, which expresses the mutation in P310L (4R0N TauP301L) and initiates taupathy within 3–5 months. Brain stimulation of TLR4 by LPS in the aforementioned mouse model also produces activation of microglia and phosphorylation of TAU [65]. In another investigation using the 3xTg-AD transgenic mouse model, which develops both Aβ and taupathies, chronic treatment with LPS results in phosphorylation of CDK5-dependent TAU without affecting Aβ levels in adult animals (~6 months old). TAU phosphorylation was observed by immunohistochemistry techniques when treated with LPS and PBS samples of the aforementioned 3xTg-AD mice by two tests: in the first one in the Ser202/Thr205 residues that were recognized by AT8, they presented up to twice as much AT8 activity in the samples treated with LPS as those that were administered PBS; the second test detected that in the Thr231/Ser235 region, recognized by AT180, there was more activity this time of AT180 in the presence of LPS. However, the same did not happen in the Ser396/Ser404 region that was recognized by PHD finger protein 1 (PHF-1), where the sample with LPS was not altered to a greater extent compared to that which was administered PBS [66]. TLR4's activation has proven to initiate the TAU-mediated pathologies in a more powerful manner in aged 3xTg-AD mice (more than 12 months of age), which means that the influence of TAU over inflammatory mechanisms grows stronger with age. Older groups of 3xTg-AD, which received a chronic LPS treatment, showed TAU phosphorylation in AT8, AT180, and PHF-1 epitopes, as well as TAU accumulation and aggregation as neurofibrillary tangles and cognitive deterioration, appearing, though, no changes in platelet saturation of Aβ. In this tested, aged animals, TAU pathology modulation induced by TLR4 is principally dominated by GSK3β (glycogen synthase kinase-3ß), the latter data were verified through the inhibition with lithium of GSK3β, where a reduction was observed of the phosphorylation of TAU and the accumulation in its insoluble form together with the reversal of memory problems [67].

Another possible route deduced in a study done in the brains of patients with early onset of Alzheimer's disease (FAD) with the Swedish mutation for APP, corticobasal degeneration (CBD), and progressive supranuclear palsy (PSP) three well-known taupathies, which presented PS3 positive vesicles in the frontal cortex, which indicates that autophagic vesicles accumulated in the said location. In addition, LAMP1 (lysosomal-associated membrane protein 1) lysosomal markers were found in FAD and CBD, and cathepsin in the three mentioned diseases. Thus, this study presents a possible role of the autophagy-lysosome pathway that would contribute to the development of primary taupathies as well as FAD [68]. The unbalanced increase in IL-1β expression in 3xTg-AD models generated inverse effects in amyloid-based pathologies and TAU accumulation, by increasing the addition of its pathological forms while decreasing the total quantities of Aβ plaques. The elimination of such plaques is powered up by the effects of IL-1β in an increase in Aβ plaque surrounding activated microglia. This process also augments the proinflammatory status, in a directly proportional intensity to age, by means of its elimination. In

turn, it was also found in this experiment that it generates the activation of GSK3β and p38-MAPK, which leads to a higher level of phosphorylation in TAU [69].

It has been demonstrated in an experiment carried out in 3xTg-AD transgenic mice that the inhibition of IL-1 signaling decreases the activation of the kinases CDK5/p25, GSK3β, and p38-MAPK, as well as reduces the phosphorylation levels of TAU [66]. On the other hand, the blockade of IL-1R showed that it altered the inflammatory responses of the brain (related to a lower activity of NF-κB), reduces cognitive deficits, and notably attenuates the pathology attributed to TAU, and decreases the oligomeric and fibrillary forms of Aβ. Similarly, it was found that there was a reduction of the cytokine derived from astrocytes, S100β, and in neuronal signaling with Wnt/β-catenin in 3xTg-AD brains [66, 70]. In addition to the complex connection between inflammation and AD, it has been shown that opposite effects can be seen in Aβ and TAU produced with inflammation. For example, it was shown that the main risk factor for Alzheimer's disease, aging, seems to cause a decrease in the levels of sirtuin 1 (SIRT1), which is related to microglial aging. Thus, this deficiency in the microglial SIRT1 with age results in an excessive production of IL-1β, which in turn causes pathology through TAU in addition to cognitive deficits. The deficiency of microglial SIRT1 induces a hypomethylation of specific loci CpG in the promoter for IL-1β, with elevation of IL-1β transcription [71].

Parallel studies affirm what was previously stated. For example, CX3CR1 deficiency in mouse models of amyloidosis mitigates the accumulation of Aβ by altering microglial activation and promoting microglial phagocytosis [65, 72]. On the other hand, blockade of CX3CR1 signaling increases IL-1β/p38-MAPK-mediated TAU phosphorylation in the hTau taupathy model [43]. The genetic suppression of CX3CL1 anchored to the membrane, ligand of CX3CR1, in models of amyloid pathology and taupathy in the APP/PS1 mouse models also reduces the deposition of Aβ through the increase of phagocytosis mediated by microglia and at the same time induces phosphorylation of neuronal TAU [73], thus having similar effects as in the deficiency of the microglial receptor CX3CR1, as shown above. In addition, it was already studied that a loss of function was mediated by mutations of progranulin, which has been associated with frontotemporal dementia [74], and results in an increase in the activation signal of tyrosine kinase binding protein TYRO (TYROBP) and Aβ microglial phagocytosis in the APP/PS1 mouse model, while TAU pathology increases in mice expressing the human TA30 PIL mutation [75]. Obviously, these opposite effects induced by the immune signal in the accumulation of Aβ and TAU raise concerns as to the direction of the therapies relating to mitigate one or both of these effects by activating or inhibiting inflammation in the context of Alzheimer's disease. As we have seen in previous experiments, it is already known clinically and is explicitly stated in a research that TAU levels correlate better with cognitive deficits observed during the disease process [76]. The development of strategies to modulate the immune system to act in the deposition of Aβ and TAU hyperphosphorylation will probably produce better clinical results.

5.2.3 Astrocytes and inflammation

Analogous to microglia, astrocytes play multiple roles in the organization and maintenance of brain structure and function. Multiple studies show that astrocytes dynamically modulate information processing, signal transmission, neural and synaptic plasticity. As well as, homeostasis of the blood-brain barrier, and its role in immune responses. The evidence shows us how during cerebral ischemia, it acts as a protector, whereas against inflammation mediated by the lipopolysaccharide of *Escherichia coli*, its intervention seems to be harmful [77]. In the cells of the retina, however, it has been proven that through the production of lipoxins, it has

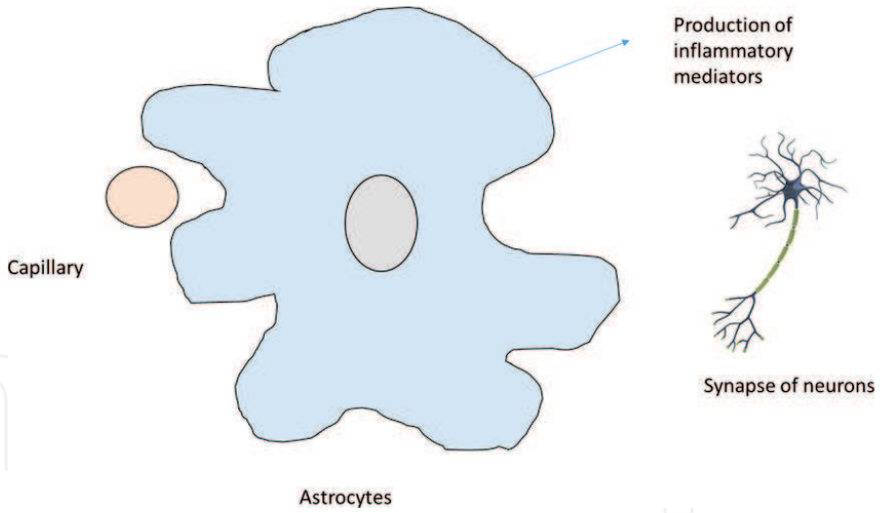

Figure 2.
Implication of astrocytes in inflammation.

an anti-inflammatory and neuroprotective effect against acute and chronic lesions [78]. Similarly, the role of the cytokine IL-33 produced by astrocytes has recently been demonstrated for the microglial approach to the synaptic terminals, as well as the development of neural circuits [79]. In previously mentioned studies describing the action of IL-1α^{+}, it is concluded that there is also a correlation between IL-1α and the greater number of GFAP^{+} astrocytes (GFAP-immunoreactive astrocytes) [80]. On the other hand, it has been demonstrated in an experiment carried out in mice with multiple sclerosis TNF-α alters synaptic transmission and produces interferences at the cognitive level [81]. Other studies have shown that the activation of certain transcription factors are also involved, developing protective effects (STAT3) [82] or injurious effects (NF-κB) [83] (**Figure 2**).

5.2.4 Role of astrocytes in amyloid production

The role of astrocytes in the amyloidogenic pathway is currently being widely studied. For a long time, it was thought that neurons were the only type of cell that expressed high levels of BACE1 and, therefore, that neuron was the only type of cell capable of producing Aβ [84]. However, studies have shown that astrocytes express BACE1 at sufficient levels to generate Aβ, and that expression can be increased by cell stress [85–89]. In addition, stressors can upregulate the expression of APP and, therefore, the secretion of Aβ. In contrast, the effect of cellular stress on the activity of γ-secretase in astrocytes has not yet been fully clarified.

The production of Aβ will lead to activation of the microglia and astrocytes in order to get rid of these brain waste products [90–92]. Similarly, genetic studies have identified polymorphisms of a single nucleotide in inflammatory genes that are associated with the risk of AD, highlighting the role of inflammation in AD [86, 93–95]. In addition, it has been observed that patients with Alzheimer's disease have more proinflammatory cytokines and activated inflammasomes [96]. As demonstrated in studies that claim an increase in both glial fibrillary acid protein (GFAP) and S100β expression, they lead to greater astrogliosis in postmortem tissues of human patients and experimental models in mice. In the same way, a correlation has been found, in different studies, between the degree of astrogliosis and cognitive deterioration [32, 96, 97]. As astrocytes substantially exceed the number of neurons in the brain, the identification of cellular environment factors (such as inflammation), which promote the production of astrocytic Aβ, could redefine our therapeutic targets when it comes to fighting Alzheimer's disease.

5.2.5 S100β and inflammation

The cytokine S100β is known to be an important neurotrophic agent during fetal development, both in neuroblasts and in the glia [98]. In addition to this known function, it is known that it directly contributes to the activation and subsequent gliosis, stimulating the proliferation of astrocytes and inducing morphological changes [70]. Furthermore, the IL-1 produced in the microglia, is the responsible for the overproduction of S100β.

The distribution of S100β contained in activated astrocytes by ELISA and immunohistochemistry was studied, as shown by many, few, or no neuritic plaques in the context of Alzheimer's disease. Postmortem samples were obtained from both patients diagnosed with AD and control patients from the hippocampus, temporal lobes, frontal lobes, occipital lobes, brain stem, and cerebellum. The results indicated that the density of cells that were $S100\beta^{+}$, identified with activated astrocytes, was higher around the neuritic plaques in certain areas of the brain. By order, the concentration was found to be more remarkable in the hippocampus > temporal lobe > frontal lobe > occipital lobe > protuberance, and no neuritic plaques were found in the cerebellum. The importance of these results lies in the fact that the regulatory role of the cytokine S100β contributes to the development or maintenance of dystrophic neurites observed in neuritic plaques. Furthermore, overexpression of S100β shows that it has been related to a higher degree of dysfunction and neural loss in AD caused by an intracellular increase in calcium levels [70].

5.2.6 Astrogliosis

Astrogliosis occurs in the presence of a central nervous system lesion. Inflammatory mediators made by microglia, neurons, oligodendrocytes, endothelial cells, leukocytes, and other astrocytes initially cause astrocytes to become reactive [77]. To better understand the process of astrogliosis, we must bear in mind that a series of changes occur at the phenotype level of astrocytes, which induce a specific expression. This was demonstrated in an experiment using arrays (Affymetrix GeneChip arrays) to define the genetic expression of different populations of reactive astrocytes isolated at different time periods using two models of injury (neuroinflammation and ischemic stroke) in mice. It was observed that this reactive gliosis had a rapid, but rapidly diminished, pattern of induction of gene expression after damage, where Lcn2 and Sertapina3n were identified as the major markers of reactive astrocytes. It was also seen that the pattern of expression experienced during ischemic stroke had a protective profile, whereas in the population of mice in which neuroinflammation was induced by the use of LPS, it turned out to be, on the contrary, detrimental [77]. Moreover, using high-density microarray, reactive astrocytes also produced detrimental effects (in vitro models from multiple sclerosis, neoplasms and stroke), and was identified up to 44 different transcription patterns present in the different pathological models mentioned [99].

In astrocytes, the first morphological change is the process of hypertrophy that is intimately related to the greater expression of intermediate filaments, attributed to the action of GFAP [99]. Although the consequences of GFAP expression are not fully understood, it is known that they have a determining role in limiting the creation of Aβ plaques. The impact of this reactive astrogliosis is complex: reactive astrogliosis can be both harmful or beneficial at the time the cells are affected. Reagent astrocytes will surround the Aβ plaques and will express receptors such as receptor for advanced glycation end products (RAGE), receptor-like LDL protein (low-density lipoprotein), membrane-associated proteinglycans, as well as receptor-like scavenger receptors to bind to Aβ [100]. Reactive astrocytes will be neurotoxic when they generate

reactive oxygen species or proinflammatory cytokines [101]. In order to understand the role of cerebral gliosis, the balance between the mechanisms that orient toward the neuroprotective or neurotoxic effect must be taken into account.

Patients with AD showed reactive astrocytes as shown by PET images [102, 103] and also, before the formation of plaques in transgenic APP mice [104]. Reactive astrocytes, depending on the level of gliotransmitters (including glutamate, ATP, serine-d and GABA) can produce inhibition of neuronal activity [105]. There is a consensus that the role of GABA is to protect neuronal cells in the brain [106]. In the amyloid plaques, an increase in the GABA protein has been detected in the reactive astrocytes that surround the plaques and that cause a greater release in the extracellular space [105]. It has been studied that these investigations have their limitations, since normally studies are carried out in mouse models, while in the human species there are many more processes to take into account [107].

5.2.7 Astrocytes, chemokines, and cytokines

Astrocytes can sometimes release reactive oxygen species (ROS), chemokines, or cytokines (CCL3, CCL4, CCL1, IL-1, for example) [108, 109]. Normally, those responsible for expressing these substances are going to be the so-called reactive astrocytes that cause functional changes by the expression of genes and the formation of glial scars that can be beneficial [81] or harmful to cells [82]. By using lipopolysaccharide (LPS) as an inducer, astrocytes increase the expression of many genes (C3a, C3b, C5, lectin) in the complement cascade that can be harmful [82]. On the other hand, it has been shown that positive regulation of trophic factors after ischemic damage is a protective mechanism [81]. Following the same line, inflammation is an essential factor in the progression of Alzheimer's disease in humans, demonstrating that this inflammation promotes the activation of microglia and an increase in reactive astrocytes that change their shape and increase the ramifications to go to the place of injury [110].

Relating astrogliosis to inflammation, both resting astrocytes and reactive astrocytes can secrete numerous cytokines capable of inducing inflammation, such as IFNγ, IL-1β, TNFα, IL-6, and TGFβ [37, 111–113]. IFNγ is a potent regulatory cytokine that activates microglia and promotes inflammation in the brain and is overproduced in the brains of patients with AD [114] both by microglia and astrocytes, despite which it is produced in the first instance by T cells [115, 116]. On the other hand, TNFα is a cytokine involved in the acute phase of inflammation and is also elevated in the serum, cerebral cortex, and cerebrospinal fluid of patients with AD [117]. In a study conducted by scientists at the Rostkamp Institute of the Department of Psychiatry at the University of South Florida, it was demonstrated in mice that those which were deficient in CD40, which is a gene that codes for the receptor TNF (Tumor Necrosis Factor), had a reduced activity of BACE, Aβ, and gliosis in comparison to the samples that presented normal quantities of CD40 [118]. IL-6 can have both proinflammatory and anti-inflammatory effects and has also been found elevated in plasma, cerebrospinal fluid, and in the brains of Alzheimer's patients [39, 119–122]. IL-1β constitutes one of the first cytokines secreted in response to lesions, as it is an important mediator of proliferation, differentiation, and apoptosis. The concentration of the said cytokine has been increased near the sites where the amyloid plaques are located [38–40].

A specific polymorphism in the transforming growth factor β1 (TGFβ1), an immunosuppressive cytokine, is also related to the risk of developing AD [123]. In addition, postmortem brains analyzed from Alzheimer's patients contained higher levels of TGFβ, specifically in their plaques, suggesting their

involvement in the same disease [124, 125]. Other studies performed in older mice that overexpress TGFβ in astrocytes promoted the deposition of Aβ, and those astrocytes containing TGFβ1 were located in the vicinity of the Aβ deposits in those mice that overexpressed APP with Swedish mutation [126–129]. Finally, astrocytes release purines that can influence the development of AD and activate the production of inflammatory proteins, decreasing anti-inflammatory proteins [108].

5.2.8 Astrocytes and expression of APP

As it has been already mentioned before, APP is the substrate prior to Aβ after erroneous processing by the BACE1 and γ-secretase enzymes. The expression of APP by astrocytes has been demonstrated by the identification of APP695, APP751, and APP770 mRNAs found in non-neuronal cells [126] and in rat astrocytes [130]. In addition, it has been shown that multiple proinflammatory cytokines upregulate APP in both mouse and human brains (investigating neuroblastoma cells and other non-neuronal cells such as human astrocytes) [131]. These findings imply that neuroinflammation in reactive astrocytes expresses higher levels of APP than when mice are at rest and they, therefore, may end up producing more β amyloid. Similarly, in APP/PS1 mice, an increase in chemokines and their receptors, compared to wild type mice, such as CCL3, CCL4, CCL1 and the receptors CCR5 and CCR8 was detected [108].

Several studies have shown that the transcription factor for APP (AP-1) is found in the promoter region of many of the acute phase proteins of inflammation that are induced by the cytokines IL-1β and IL-6, suggesting that the expression of APP is regulated in the same way by these specific cytokines [132, 133]. Moreover, astrocytes stimulated with different combinations of cytokines (LPS + IFNγ, TNFα + IFNγ, and TNFα + IL-1β + IFNγ) increased the expression of APP [89].

5.2.9 Astrocytes and cancer

The type of tumor and its location are determined by age; for example, infratentorial astrocytoma and midline tumors, such as medulloblastoma and pinealoma, anaplastic astrocytoma, and glioblastoma predominate in adulthood [134]. Although meningiomas are the most frequently detected in the series of autopsies, glioblastomas are the most frequently detected in the brain. Some brain tumors such as schwannoma, sarcoma, glioma, and meningioma are detected after the patient has been exposed to cancer therapy with chemotherapy and/or radiotherapy. Until now it was thought that only glial cells and stem cells were responsible for the emergence of glioblastoma, but it is now known that mature neurons can also induce this type of cancer. This is due to the fact that these cells revert to an undifferentiated state that is directed to proliferate as an uncontrolled tumor [135].

Radial glia are stem cells that develop from a progenitor stem cell in the embryo and adult brain [136]. The neuroblastoma cells are radial glia or precursors of astrocytes that can develop before their differentiation into neurons. In the same way, glial cells can also develop different types of cells besides neurons such as oligodendroglia and astrocytes [137]. All these types of cells can turn into cancer and affect the normal function of the brain. Then, astrocytes and their progenitor cells can cause cancer and destroy many functions in the brain. It is interesting to note that in some astrocytomas, the patients increase their cognitive capacity, memory, and spatial vision, before the disease begins and also when the cancer is present [138], which makes us think and throws more evidence to the role of astrocytes in modulating cognitive brain functions or memory.

5.3 Protective role of astrocytes

5.3.1 Oxidative stress, AD, and the protective role of astrocytes against oxidative stress

Hydrogen peroxide (H_2O_2), superoxide (O_2^-) and hydroxyl radicals (OH^-) are the aforementioned reactive oxygen species (ROS). Due to the rate of oxidative metabolism, the SNC is especially susceptible to the damage suffered by them [139]. Under stable physiological conditions, the homeostasis of ROS is under control and this is crucial for the proper organic functions. ROS stimulates the proliferation of brain cells, but at high concentrations, ROS has harmful effects on different cellular structures such as membranes, DNA, and enzymes, which can lead to cell death [140]. The reduction of molecular oxygen is not complete in the respiratory chain, producing ROS continuously and thus affecting different cellular components such as proteins or lipids [141]. To return to the state of physiological equilibrium, the brain has several enzymes, such as peroxidase, superoxide dismutase (SOD), oxidase, and NADPH oxidase (NOX). Neurons have fewer defenses against ROS than astrocytes and cooperation between them is important for neuronal resistance against ROS [30, 142, 143]. Astrocytes contribute to the survival of neurons by detoxifying the ROS enzymes (GSH peroxidase and catalase), increasing antioxidant proteins (GSH or glutathione, vitamin E and ascorbate) and the biogenesis of mitochondria and reducing the activity of metals which can produce redox [31, 144–146]. The most powerful antioxidant protein in the brain is GSH produced by astrocytes and neurons, but neurons depend on astrocytes because they do not use extracellular cysteine efficiently and, therefore, need astrocytes to supply it. In addition, with respect to ascorbic acid, another important antioxidant in the nervous system, we depend on diet to obtain it [147].

Ascorbic acid is released by the astrocytes in the extracellular space and is absorbed by the neurons, where thanks to ascorbate the formation of ROS diminishes and its oxidized form is converted to be recovered by the astrocytes and converted again to ascorbic acid [148]. In addition, the lactate shuttle between astrocytes and neurons is favored by ascorbic acid [149]. Changes in ascorbic acid homeostasis are actually involved in different neurodegenerative diseases and have been analyzed for the treatment of diseases, such as Parkinson's and Huntington's disease [148]. In addition, astrocyte prevention in redox production caused by active metals has been demonstrated as a result of the ability to sequester metals by this cellular type [144].

The increase in ROS levels is related to AD [35], but the effects of antioxidants in clinical studies have been disappointing because the high concentration of antioxidants acts, in many cases, as pro-oxidants. It may also be due to the fact that oxidative stress occurs relatively early in the course of AD and therefore, by its administration at later stages, no results are obtained, or else that the combination of antioxidants does not work in clinical situations in humans [150]. As already shown, astrocytes protect neurons from oxidative stress, producing antioxidant proteins. The toxic amyloid beta peptide causes the production of hydrogen peroxide by astrocytes [151], as shown previously [30], and they release ROS in response to beta amyloid through the pentose-phosphate pathway [151]. In addition, in patients with Alzheimer's disease, there is a fall in the brain cleansing process produced by astrocytes during the sleep period. On the other hand, Haydon showed that the sleep/wake cycle is modulated by astrocytes and is also altered in AD [152]. This finding also demonstrates the close relationship between astrocytes and Alzheimer's disease.

After demonstrating the important role of astrocytes in protecting neurons from oxidative stress, we can deduce that all those conditions mentioned where the astrocyte undergoes changes in its function, beyond the strictly physiological, will result in poor protection of the said neurons and the rest of brain structures in front of different harmful agents and neuronal damage.

5.3.2 Prejudicial and protective role of astrocytes

As we have seen previously, the role of astrocytes is essentially protective. This was also demonstrated by another group finding a mechanism different from those previously studied by cytokines and other inflammatory agents, in which it was shown that the astrocytes surrounding the plates increase the release of ATP in transgenic APP/PS1 mice and this happens because the Ca^{2+} concentration increases within the cell [153]. This last fact gives us the idea that an increase in ATP in astrocytes and neurons could help to reduce the neuronal death that occurs in Alzheimer's disease. The increase in the production of ATP by the mitochondria of astrocytes could help to recover and reduce the development of the disease [153]. The neurotransmitter glutamate is released by astrocytes in the presence of Aβ and can cause neuronal loss as well as synaptic damage by activation of NMDA receptors [154, 155]. In addition, astrocytes release purines that can influence the development of AD and activate the production of inflammatory proteins, decreasing anti-inflammatory proteins, such as PPAR-γ [108, 156]. This is probably due to the effect of reactive astrogliosis that may have beneficial effects [82] or detrimental effects [83] for neurons, and because these two different reactions depend on the type of triggering of the astrogliosis. Nevertheless, in our laboratory, we demonstrated that astrocytes play a significant role in neuron protection. Astrocytes promote neural viability and improve oxidative stress defense mechanisms with anti-inflammatory effects against $A\beta_{1-42}$ peptide toxicity. It is probable that the protective effects of astrocytes are related with the mitochondrial biogenesis (**Figure 3**). This could be a complex epigenetic process in Alzheimer's disease pathogenesis [30].

In conclusion, we can see that the role of Aβ, which had been an essential pillar in the etiopathogenesis of Alzheimer's disease for decades, is only one component that gives rise to inflammation, probably mediated by activation of microglia and astrocytes with the goal of getting rid of these brain waste products, although this effect has already been shown to be produced in the same way by different

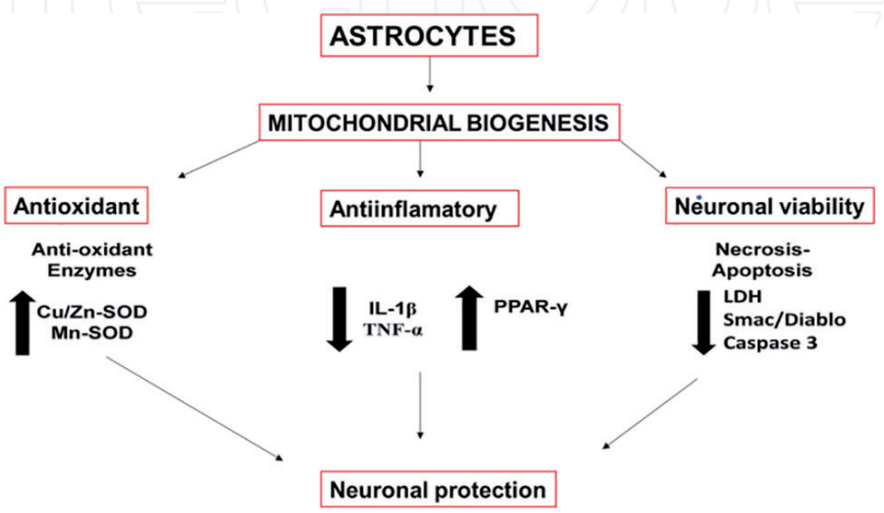

Figure 3.
Protective effects of astrocytes.

mediators. In fact, it is related to a greater degree with the progression of the disease and worsening of the symptoms with the increase of phosphorylated TAU in different parts of the brain. In the last years, the therapies have been focused on elimination of the Aβ from the brain of the Alzheimer's patient with poor results [157]. In addition, reactive astrocytes greatly increase NRF-2, which is an antioxidant protein and could produce beneficial effects in Alzheimer's disease [157]. The regulation of oxidative stress or inflammation could help the conservation of neurons located near astrocytes and microglia. Future therapies should be aimed at the development of specific drugs that control the formation of reactive astrocytes and that favor the correct resolution of the inflammation produced by Alzheimer's disease. The study of the genetic mechanisms that predispose to increase amounts of hyperphosphorylated TAU or those that decrease phosphorylation of TAU would be interesting in order to understand cellular mechanisms implicated in AD [157]. Furthermore, the study of the main trigger of this basal chronic inflammation that worsens the clinical symptoms of AD patients, should be crucial to find new therapeutic strategies. Finally, regarding the relationship that exists between the astrocytes and the cells of the nervous system, there would be a greater study of the functions of these cells in the healthy individual. The control of the mechanisms and the understanding of the relationship between astrocytes with other neural cells could help, in the same way, to the therapy of Alzheimer's disease.

Abbreviations

AD	Alzheimer's disease
IL-1β	interleukin 1β
TNF-α	tumor necrosis factor α
BACE	aspartyl protease β-site APP-cleaving enzyme
Aβ	β-amyloid
ADAM	disintegrin and metalloprotease domain
LXA4	lipoxin A4
IL-10	interleukin 10
IL-37	interleukin 37
TGF-β	transforming growth factor-beta
CNS	central nervous system
PNS	peripheral nervous system
APP	amyloid precursor protein
βCTF	beta C-terminal fragment
NO	nitric oxide
MCI	mild cognition impairment
ROS	reactive oxygen species
LPS	lipopolysaccharide
MAP	microtubule-associated proteins
CX3CL1	fraktalkina
GSK3β	glycogen synthase kinase-3 β
NF-κB	nuclear factor κB
SIT1	sirtuin 1
TLR4	toll like receptor 4

DOI: http://dx.doi.org/10.5772/intechopen.88701

IntechOpen

IntechOpen

Author details

Soraya L. Valles*, Federico Burguet, Antonio Iradi, Martin Aldasoro, Jose M. Vila, Constanza Aldasoro and Adrián Jordá
Department of Physiology, School of Medicine, University of Valencia, Spain

*Address all correspondence to: lilian.valles@uv.es

IntechOpen

© 2020 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. CC BY

References

[1] Ren Z, He H, Zuo Z, Xu Z, Wei Z, Deng J. The role of different SIRT1-mediated signaling pathways in toxic injury. Cellular & Molecular Biology Letters. 2019;**24**:36

[2] Cho K. Emerging roles of complement protein C1q in neurodegeneration. Aging and Disease. 2019;**10**(3):652-663

[3] Fullerton JN, Gilroy DW. Resolution of inflammation: A new therapeutic frontier. Nature Reviews. Drug Discovery. 2016;**15**(8):551-567

[4] Bollen J, Trick L, Llewellyn D, Dickens C. The effects of acute inflammation on cognitive functioning and emotional processing in humans: A systematic review of experimental studies. Journal of Psychosomatic Research. 2017;**94**:47-55

[5] Diwakar L, Cummins C, Lilford R, Roberts T. Systematic review of pathways for the delivery of allergy services. BMJ Open. 2017;7(2):e012647

[6] Serhan CN. Treating inflammation and infection in the 21st century: New hints from decoding resolution mediators and mechanisms. The FASEB Journal. 2017;**31**(4):1273-1288

[7] Kumari S, Pasparakis M. Epithelial cell death and inflammation in skin. Current Topics in Microbiology and Immunology. 2017;**403**:77-93

[8] Khiroya R, Macaluso C, Montero MA, Wells AU, Chua F, Kokosi M, et al. Pleuroparenchymal fibroelastosis: A review of histopathologic features and the relationship between histologic parameters and survival. The American Journal of Surgical Pathology. 2017;**41**(12):1683-1689

[9] Rose NR. Prediction and prevention of autoimmune disease in the 21st century: A review and preview. American Journal of Epidemiology. 2016;**183**(5):403-406

[10] Chitnis T, Weiner HL. CNS inflammation and neurodegeneration. The Journal of Clinical Investigation. 2017;**127**(10):3577-3587

[11] Franco R, Fernández-Suárez D. Alternatively activated microglia and macrophages in the central nervous system. Progress in Neurobiology. 2015;**131**:65-86

[12] Wolf SA, Boddeke HW, Kettenmann H. Microglia in physiology and disease. Annual Review of Physiology. 2017;**79**:619-643

[13] Arbor SC, LaFontaine M, Cumbay M. Amyloid-beta Alzheimer targets—Protein processing, lipid rafts, and amyloid-beta pores. The Yale Journal of Biology and Medicine. 2016;**89**(1):5-21

[14] Sarlus H, Heneka MT. Microglia in Alzheimer's disease. The Journal of Clinical Investigation. 2017;**127**(9):3240-3249

[15] Lammich S, Kojro E, Postina R, Gilbert S, Pfeiffer R, Jasionowski M, et al. Constitutive and regulated alpha-secretase cleavage of Alzheimer's amyloid precursor protein by a disintegrin metalloprotease. Proceedings of the National Academy of Sciences of the United States of America. 1999;**96**(7):3922-3927

[16] Fahrenholz F, Gilbert S, Kojro E, Lammich S, Postina R. Alpha-secretase activity of the disintegrin metalloprotease ADAM 10. Influences of domain structure. Annals of the New York Academy of Sciences. 2000;**920**:215-222

[17] Fukumoto H, Cheung BS, Hyman BT, Irizarry MC. Beta-secretase

protein and activity are increased in the neocortex in Alzheimer disease. Archives of Neurology. 2002;**59**(9):1381-1389

[18] Vassar R, Kovacs DM, Yan R, Wong PC. The beta-secretase enzyme BACE in health and Alzheimer's disease: Regulation, cell biology, function, and therapeutic potential. The Journal of Neuroscience. 2009;**29**(41):12787-12794

[19] Nunan J, Williamson NA, Hill AF, Sernee MF, Masters CL, Small DH. Proteasome-mediated degradation of the C-terminus of the Alzheimer's disease beta-amyloid protein precursor: Effect of C-terminal truncation on production of beta-amyloid protein. Journal of Neuroscience Research. 2003;**74**(3):378-385

[20] Luo Y, Bolon B, Kahn S, Bennett BD, Babu-Khan S, Denis P, et al. Mice deficient in BACE1, the Alzheimer's beta-secretase, have normal phenotype and abolished beta-amyloid generation. Nature Neuroscience. 2001;**4**:231-232

[21] Lazarov Lazarov O, Marr RA. Neurogenesis and Alzheimer's disease: At the crossroads. Experimental Neurology. 2010;**223**(2):267-281

[22] Sisodia SS, St George-Hyslop PH. Gamma-secretase, notch, Abeta and Alzheimer's disease: Where do the presenilins fit in? Nature Reviews. Neuroscience. 2002;**3**(4):281-290

[23] Kim BH, Kim JS, Kim JL, Kim YS, Yang TG, Lee MY. Determination of the neutron fluency spectra in the neutron therapy room of KIRAMS. Radiation Protection Dosimetry. 2007;**126**:384-389

[24] Zhang S, Iwata K, Lachenmann MJ, Peng JW, Li S, Stimson ER, et al. The Alzheimer's peptide a beta adopts a collapsed coil structure in water. Journal of Structural Biology. 2000;**130**(2):130-141

[25] Sgourakis NG, Yan Y, McCallum S, Wang C, Garcia AE. The Alzheimer's peptides Aβ40 and 42 adopt distinct conformations in water: A combined MD / NMR study. Journal of Molecular Biology. 2007;**368**(5):1448-1457

[26] Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, et al. Neuroinflammation in Alzheimer's disease. Lancet Neurology. 2015;**14**(4):388-405

[27] Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurology. 2010;**9**:119-128

[28] Frost GR, Li YM. The role of astrocytes in amyloid production and Alzheimer's disease. Open Biology. 2017;**7**:170228

[29] Figley CR, Stroman PW. The role(s) of astrocytes and astrocyte activity in neurometabolism, neurovascular coupling, and the production of functional neuroimaging signals. The European Journal of Neuroscience. 2011;**33**(4):577-588

[30] Aguirre-Rueda D, Guerra-Ojeda S, Aldasoro M, Iradi A, Obrador E, Ortega A, et al. Astrocytes protect neurons from Aβ1-42 peptide-induced neurotoxicity increasing TFAM and PGC-1 and decreasing PPAR-γ and SIRT-1. International Journal of Medical Sciences. 2015;**12**:48-56

[31] Aguirre-Rueda D, Guerra-Ojeda S, Aldasoro M, Iradi A, Obrador E, Mauricio MD, et al. WIN 55,212-2, agonist of cannabinoid receptors, prevents amyloid β1-42 effects on astrocytes in primary culture. PLoS One. 2015b;**10**(4):e0122843

[32] Verkhratsky A, Olabarria M, Noristani HN, Yeh C-Y, Rodriguez JJ. Astrocytes in Alzheimer's

disease. Neurotherapeutics. 2010;**7**:399-412

[33] Hoffman JM, Dikmen S, Temkin N, Bell KR. Development of posttraumatic stress disorder after mild traumatic brain injury. Archives of Physical Medicine and Rehabilitation. 2012;**93**(2):287-292

[34] Farina N, Page TE, Daley S, Brown A, Bowling A, Basset T, et al. Factors associated with the quality of life of family careers of people with dementia: A systematic review. Alzheimer's & Dementia. 2017;**13**(5):572-581

[35] Markesbery WR. The role of oxidative stress in Alzheimer disease. Archives of Neurology. 1999;**56**:1449-1452

[36] Baggiolini M, Clark-Lewis I. Interleukin-8, a chemotactic and inflammatory cytokine. FEBS Letters. 1992;**307**(1):97-101

[37] McGeer PL, McGeer EG. The inflammatory response system of brain: Implications for therapy of Alzheimer and other neurodegenerative diseases. Brain Research. Brain Research Reviews. 1995;**21**:195-218

[38] Griffin WS, Stanley LC, Ling C, White L, MacLeod V, Perrot LJ, et al. Brain interleukin 1 and S-100 immunoreactivity are elevated in Down syndrome and Alzheimer disease. Proceedings of the National Academy of Sciences of the United States of America. 1989;**86**:7611-7615

[39] Licastro F, Grimaldi LME, Bonafe' M, Martina C, Olivieri F, Cavallone L, et al. Interleukin-6 gene alleles affect the risk of Alzheimer's disease and levels of the cytokine in blood and brain. Neurobiology of Aging. 2003;**24**:921-926

[40] Das S, Potter H. Expression of the Alzheimer amyloid-promoting factor antichymotrypsin is induced in human astrocytes by IL-1. Neuron. 1995;**14**:447-456

[41] Dallagnol KMC, Remor AP, da Silva RA, Prediger RD, Latini A, Aguiar AS Jr. Running for REST: Physical activity attenuates neuroinflammation in the hippocampus of aged mice. Brain, Behavior, and Immunity. 2017;**61**:31-35

[42] Hull M, Strauss S, Berger M, Volk B, Bauer J. The participation of interleukin-6, a stress-inducible cytokine, in the pathogenesis of Alzheimer's disease. Behavioural Brain Research. 1996;**78**(I):37-41

[43] Bhaskar K, Konerth M, Kokiko-Cochran ON, Cardona A, Ransohoff RM, Lamb BT. Regulation of tau pathology by the microglial fractalkine receptor. Neuron. 2010;**68**(1):19-31

[44] Maphis N, Xu G, Kokiko-Cochran ON, Jiang S, Cardona A, Ransohoff RM, et al. Reactive microglia drive tau pathology and contribute to the spreading of pathological tau in the brain. Brain. 2015;**138**:1738-1755

[45] Sanchez-Mejias E, Navarro V, Jimenez S, Sanchez-Mico M, Sanchez-Varo R, Nuñez-Diaz C, et al. Soluble phospho-tau from Alzheimer's disease hippocampus drives microglial degeneration. Acta Neuropathologica. 2016;**132**(6):897-916

[46] Yoshiyama Y, Higuchi M, Zhang B, Huang SM, Iwata N, Saido TC, et al. Synapse loss and microglial activation precede tangles in a P301S tauopathy mouse model. Neuron. 2007;**53**(3):337-351

[47] Asai H, Ikezu S, Tsunoda S, Medalla M, Luebke J, Haydar T, et al. Depletion of microglia and inhibition of exosome synthesis halt tau propagation. Nature Neuroscience. 2015;**18**(11):1584-1593

[48] Gorlovoy P, Larionov S, Pham TT, Neumann H. Accumulation of tau induced in neurites by microglial proinflammatory mediators. The FASEB Journal. 2009;**23**(8):2502-2513

[49] Johnson GV, Stoothoff WH. Tau phosphorylation in neuronal cell function and dysfunction. Journal of Cell Science. 2004;**117**(24):5721-5729

[50] Sato C, Barthélemy NR, Mawuenyega KG, Patterson BW, Gordon BA, Jockel-Balsarotti J, et al. Tau kinetics in neurons and the human central nervous system. Neuron. 2018;**98**(4):861-864

[51] Nizynski B, Dzwolak W, Nieznanski K. Amyloidogenesis of tau protein. Protein Science. 2017;**26**(11):2126-2150

[52] De la De la Fuente-Rocha J. Taupatía en la enfermedad de Alzheimer. Medicina Interna de México. 2017;**33**(4):515-521

[53] Metaxas A, Kempf SJ. Neurofibrillary tangles in Alzheimer's disease: Elucidation of the molecular mechanism by immunohistochemistry and tau protein phospho-proteomics. Neural Regeneration Research. 2016;**11**(10):1579-1581

[54] Ohtsubo K, Izumiyama N, Shimada H, Tachikawa T, Nakamura H. Three-dimensional structure of Alzheimer's neurofibrillary tangles of the aged human brain revealed by the quick-freeze, deep-etch and replica method. Acta Neuropathologica. 1990;**79**(5):480-485

[55] Sheng H, Laskowitz DT, Mackensen GB, Kudo M, Pearlstein RD, Warner DS. Apolipoprotein E deficiency worsens outcome from global cerebral ischemia in the mouse. Stroke. 1999;**30**(5):1118-1124

[56] Jiang T, Zhang YD, Gao Q, Ou Z, Gong PY, Shi JQ, et al. TREM2 ameliorates neuronal tau pathology through suppression of microglial inflammatory response. Inflammation. 2018;**41**(3):811-823

[57] Marin I, Kipnis J. Learning and memory ... and the immune system. Learning & Memory. 2013;**20**(10):601-606

[58] Kitazawa M, Oddo S, Yamasaki TR, Green KN, LaFerla FM. Lipopolysaccharide-induced inflammation exacerbates tau pathology by a cyclin-dependent kinase 5-mediated pathway in a transgenic model of Alzheimer's disease. The Journal of Neuroscience. 2005;**25**(39):8843-8853

[59] Kitazawa M, Trinh DN, LaFerla FM. Inflammation induces tau pathology in inclusion body myositis model via glycogen synthase kinase-3beta. Annals of Neurology. 2008;**64**(1):15-24

[60] Noble W, Garwood C, Stephenson J, Kinsey AM, Hanger DP, Anderton BH. Minocycline reduces the development of abnormal tau species in models of Alzheimer's disease. The FASEB Journal. 2009;**23**(3):739-750

[61] Hunt JB Jr, Nash KR, Placides D, Moran P, Selenica ML, Abuqalbeen F, et al. Sustained arginase 1 expression modulates pathological tau deposits in a mouse model of tauopathy. The Journal of Neuroscience. 2015;**35**(44):14842-14860

[62] Roe AD, Staup MA, Serrats J, Sawchenko PE, Rissman RA. Lipopolysaccharide-induced tau phosphorylation and kinase activity—Modulation, but not mediation, by corticotropin-releasing factor receptors. The European Journal of Neuroscience. 2011;**34**(3):448-456

[63] Harrison JK, Barber CM, Lynch KR. cDNA cloning of a G-protein-coupled receptor expressed in rat spinal cord and

brain related to chemokine receptors. Neuroscience Letters. 1994;**169**:85-89

[64] Gautier EL, Shay T, Miller J, Greter M, Jakubzick C, Ivanov S, et al. Gene-expression profiles and transcriptional regulatory pathways that underlie the identity and diversity of mouse tissue macrophages. Nature Immunology. 2012;**13**:1118-1128

[65] Lee DC, Rizer J, Selenica ML, Reid P, Kraft C, Johnson A, et al. LPS-induced inflammation exacerbates phospho-tau pathology in rTg4510 mice. Journal of Neuroinflammation. 2010;**7**:56

[66] Kitazawa M, Cheng D, Tsukamoto MR, Koike MA, Wes PD, Vasilevko V, et al. Blocking IL-1 signaling rescues cognition, attenuates tau pathology, and restores neuronal beta-catenin pathway function in an Alzheimer's disease model. Journal of Immunology. 2011;**187**(12):6539-6549

[67] Sy M, Kitazawa M, Medeiros R, Whitman L, Cheng D, Lane TE, et al. Inflammation induced by infection potentiates tau pathological features in transgenic mice. The American Journal of Pathology. 2011;**178**(6):2811-2822

[68] Piras A, Collin L, Gruninger F, Graff C, Ronnback A. Autophagic and lysosomal defects in human tauopathies: Analysis of post-mortem brain from patients with familial Alzheimer disease, corticobasal degeneration and progressive supranuclear palsy. Acta Neuropathologica Communications. 2016;**4**:22

[69] Ghosh S, Wu MD, Shaftel SS, Kyrkanides S, LaFerla FM, Olschowka JA, et al. Sustained interleukin-1beta overexpression exacerbates tau pathology despite reduced amyloid burden in an Alzheimer's mouse model. The Journal of Neuroscience. 2013;**33**(11):5053-5064

[70] Mrak RE, Sheng JG, Griffin WS. Correlation of astrocytic S100 beta expression with dystrophic neurites in amyloid plaques of Alzheimer's disease. Journal of Neuropathology and Experimental Neurology. 1996;**55**:273-279

[71] Cho SH, Chen JA, Sayed F, Ward ME, Gao F, Nguyen TA, et al. SIRT1 deficiency in microglia contributes to cognitive decline in aging and neurodegeneration via epigenetic regulation of IL-1beta. The Journal of Neuroscience. 2015;**35**(2):807-818

[72] Liu Z, Condello C, Schain A, Harb R, Grutzendler J. CX3CR1 in microglia regulates brain amyloid deposition through selective protofibrillar amyloidbeta phagocytosis. The Journal of Neuroscience. 2010;**30**(50):17091-17101

[73] Lee S, Xu G, Jay TR, Bhatta S, Kim KW, Jung S, et al. Opposing effects of membrane-anchored CX3CL1 on amyloid and tau pathologies via the p38 MAPK pathway. The Journal of Neuroscience. 2014;**34**(37):12538-12546

[74] Petkau TL, Leavitt BR. Progranulin in neurodegenerative disease. Trends in Neurosciences. 2014;**37**(7):388-398

[75] Takahashi H, Klein ZA, Bhagat SM, Kaufman AC, Kostylev MA, Ikezu T, et al. Opposing effects of progranulin deficiency on amyloid and tau pathologies via microglial TYROBP network. Acta Neuropathologica. 2017;**133**(5):785-807

[76] Nelson PT, Alafuzoff I, Bigio EH, Bouras C, Braak H, Cairns NJ, et al. Correlation of Alzheimer disease neuropathologic changes with cognitive status: A review of the literature. Journal of Neuropathology and Experimental Neurology. 2012;**71**(5):362-381

[77] Zamanian JL, Xu L, Foo LC, Nouri N, Zhou L, Giffard RG, et al.

Genomic analysis of reactive astrogliosis. Journal of Neuroscience. 2012;**32**:6391-6410

[78] Livne-Bar I, Wei J, Liu HH, Alqawlaq S, Won GJ, Tuccitto A, et al. Astrocytederived lipoxins A4 and B4 promote neuroprotection from acute and chronic injury. The Journal of Clinical Investigation. 2017;**127**(12):4403-4414

[79] Vainchtein ID, Chin G, Cho FS, Kelley KW, Miller JG, Chien EC, et al. Astrocyte-derived interleukin-33 promotes microglial synapse engulfment and neural circuit development. Science. 2018;**359**(6381):1269-1273

[80] Sheng JG, Mrak RE, Griffin WST. Microglial interleukin-I-alpha expression in brain regions in Alzheimer's disease—Correlation with neuritic plaque distribution. Neuropathology and Applied Neurobiology. 1995;**21**(4):290-301

[81] Habbas S, Santello M, Becker D, Stubbe H, Zappia G, Liaudet N, et al. Neuroinflammatory TNFalpha impairs memory via astrocyte signaling. Cell. 2015;**163**(7):1730-1741

[82] Anderson MA, Burda JE, Ren Y, Ao Y, O'Shea TM, Kawaguchi R, et al. Astrocyte scar formation aids central nervous system axon regeneration. Nature. 2016;**532**(7598):195-200

[83] Liddelow SA, Barres BA. Reactive astrocytes: Production, function, and therapeutic potential. Immunity. 2017;**46**(6):957-967

[84] Laird FM, Cai H, Savonenko AV, Farah MH, He K, Melnikova T, et al. BACE1, a major determinant of selective vulnerability of the brain to amyloid-b amyloidogenesis, is essential for cognitive, emotional, and synaptic functions. The Journal of Neuroscience. 2005;**25**: 11693-11709

[85] Blasko I, Veerhuis R, Stampfer-Kountchev M, Saurwein-Teissl M, Eikelenboom P, Grubeck-Loebenstein B. Costimulatory effects of interferon-g and interleukin-1b or tumor necrosis factor a on the synthesis of Ab1-40 and Ab1-42 by human astrocytes. Neurobiology of Disease. 2000;**7**:682-689

[86] Jin SM, Cho HJ, Kim YW, Hwang JY, Mook-Jung I. Ab-induced Ca2þ influx regulates astrocytic BACE1 expression via calcineurin/NFAT4 signals. Biochemical and Biophysical Research Communications. 2012;**425**:649-655

[87] Leuba G, Wernli G, Vernay A, Kraftsik R, Mohajeri MH, Saini KD. Neuronal and nonneuronal quantitative BACE immunocytochemical expression in the entorhinohippocampal and frontal regions in Alzheimer's disease. Dementia and Geriatric Cognitive Disorders. 2005;**19**:171-183

[88] Orre M, Kamphuis W, Osborn LM, Jansen AHP, Kooijman L, Bossers K, et al. Isolation of glia from Alzheimer's mice reveals inflammation and dysfunction. Neurobiology of Aging. 2014;**35**:2746-2760

[89] Zhao J, O'Connor T, Vassar R. The contribution of activated astrocytes to Ab production: Implications for Alzheimer's disease pathogenesis. Journal of Neuroinflammation. 2011;**8**:150

[90] Colton CA, Mott RT, Sharpe H, Xu Q, Van Nostrand WE, Vitek MP. Expression profiles for macrophage alternative activation genes in AD and in mouse models of AD. Journal of Neuroinflammation. 2006;**3**:27

[91] Jekabsone A, Mander PK, Tickler A, Sharpe M, Brown GC. Fibrillar beta-amyloid peptide Abeta1-40 activates microglial proliferation via stimulating TNFalpha release and H_2O_2 derived from NADPH oxidase: A cell culture

study. Journal of Neuroinflammation. 2006;**3**:24

[92] Morgan D. Modulation of microglial activation state following passive immunization in amyloid depositing transgenic mice. Neurochemistry International. 2006;**49**:190-194

[93] Malik M, Parikh I, Vasquez JB, Smith C, Tai L, Bu G, et al. Genetics ignite focus on microglial inflammation in Alzheimer's disease. Molecular Neurodegeneration. 2015;**10**:52

[94] Painter MM, Atagi Y, Liu C-C, Rademakers R, Xu H, Fryer JD, et al. TREM2 in CNS homeostasis and neurodegenerative disease. Molecular Neurodegeneration. 2015;**10**:43

[95] Wunderlich P, Glebov K, Kemmerling N, Tien NT, Neumann H, Walter J, et al. Sequential proteolytic processing of the triggering receptor expressed on myeloid cells-2 (TREM2) protein by ectodomain shedding and g-secretase-dependent intramembranous cleavage. The Journal of Biological Chemistry. 2013;**288**:33027-33036

[96] Beach TG, Mcgeer EG. Lamina-specific arrangement of astrocytic gliosis and senile plaques in Alzheimer's disease visual cortex. Brain Research. 1988;**463**:357-361

[97] Sofroniew MV, Vinters HV. Astrocytes: Biology and pathology. Acta Neuropathologica. 2010;**119**:7-35

[98] Huang P, Wang ZY, Tuo Y. The research progression of S100beta as a neurochemistry maker. Fa Yi Xue Za Zhi. 2005;**21**(2):149-151

[99] Daginakatte GC, Gadzinski A, Emnett RJ, Stark JL, Gonzales ER, Yan P, et al. Expression profiling identifies a molecular signature of reactive astrocytes stimulated by cyclic AMP or proinflammatory cytokines. Experimental Neurology. 2008;**210**:261-267

[100] Olabarria M, Noristani HN, Verkhratsky A, Rodríguez JJ. Concomitant astroglial atrophy and astrogliosis in a triple transgenic animal model of Alzheimer's disease. Glia. 2010;**58**:831-838

[101] Sofroniew MV. Molecular dissection of reactive astrogliosis and glial scar formation. Trends in Neurosciences. 2009;**32**:638-647

[102] Bignami A, Eng LF, Dahl D, Uyeda CT. Localization of the glial fibrillary acidic protein in astrocytes by immunofluorescence. Brain Research. 1972;**43**(2):429-435

[103] Carter SF, Schöll M, Almkvist O, Wall A, Engler H, Långström B, et al. Evidence for astrocytosis in prodromal Alzheimer disease provided by ^{11}C-deuterium-L-deprenyl: A multitracer PET paradigm combining ^{11}C-Pittsburgh compound B and ^{18}F-FDG. Journal of Nuclear Medicine. 2012;**53**(1):37-46

[104] Heneka MT, Sastre M, Dumitrescu-Ozimek L, Dewachter I, Walter J, Klockgether T, et al. Focal glial activation coincides with increased BACE1 activation and precedes amyloid plaque deposition in APP[V717I] transgenic mice. Journal of Neuroinflammation. 2005;**2**:22

[105] Jo S, Yarishkin O, Hwang YJ, Chun YE, Park M, Woo DH, et al. GABA from reactive astrocytes impairs memory in mouse models of Alzheimer's disease. Nature Medicine. 2014;**20**(8):886-896

[106] Chun H, An H, Lim J, Woo J, Lee J, Ryu H, et al. Astrocytic proBDNF and tonic GABA distinguish active versus reactive astrocytes in hippocampus. Experimental Neurobiology. 2018;**27**(3):155-170

[107] Oberheim NA, Takano T, Han X, He W, Lin JH, Wang F, et al. Uniquely hominid features of adult human astrocytes. The Journal of Neuroscience. 2009;**29**:3276-3287

[108] Jorda A, Cauli O, Santonja JM, Aldasoro M, Aldasoro C, Obrador E, et al. Changes in chemokines and chemokine receptors expression in a mouse model of Alzheimer's disease. International Journal of Biological Sciences. 2019;**15**:453-463

[109] Valles SL, Dolz-Gaiton P, Gambini J, Borras C, Lloret A, Pallardo FV, et al. Estradiol or genistein prevent Alzheimer's disease-associated inflammation correlating with an increase PPAR gamma expression in cultured astrocytes. Brain Research. 2010;**1312**:138-144

[110] Bardehle S, Krüger M, Buggenthin F, Schwausch J, Ninkovic J, Clevers H, et al. Live imaging of astrocyte responses to acute injury reveals selective juxtavascular proliferation. Nature Neuroscience. 2013;**16**(5):580-586

[111] Constam DB, Philipp J, Malipiero U V, ten Dijke P, Schachner M, Fontana A. Differential expression of transforming growth factor-beta 1, – beta 2, and -beta 3 by glioblastoma cells, astrocytes, and microglia. Journal of Immunology 1992;**148**:1404-1410.

[112] Hu J, Akama KT, Krafft GA, Chromy BA, Van Eldik LJ. Amyloid-b peptide activates cultured astrocytes: Morphological alterations, cytokine induction and nitric oxide release. Brain Research. 1998;**785**:195-206

[113] Johnstone M, Gearing AJ, Miller KM. A central role for astrocytes in the inflammatory response to beta-amyloid; chemokines, cytokines and reactive oxygen species are produced. Journal of Neuroimmunology. 1999;**93**:182-193

[114] Huberman M, Shalit F, Roth-Deri I, Gutman B, Brodie C, Kott E, et al. Correlation of cytokine secretion by mononuclear cells of Alzheimer patients and their disease stage. Journal of Neuroimmunology. 1994;**52**:147-152

[115] De Simone R, Levi G, Aloisi F. Interferon g gene expression in rat central nervous system glial cells. Cytokine. 1998;**10**:418-422

[116] Fultz MJ, Barber SA, Dieffenbach CW, Vogel SN. Induction of IFN-gamma in macrophages by lipopolysaccharide. International Immunology. 1993;**5**:1383-1392

[117] Tarkowski E, Blennow K, Wallin A, Tarkowski A. Intracerebral production of tumor necrosis factor-alpha, a local neuroprotective agent, in Alzheimer disease and vascular dementia. Journal of Clinical Immunology. 1999;**19**:223-230

[118] Tan J, Town T, Crawford F, Mori T, DelleDonne A, Crescentini R, et al. Role of CD40 ligand in amyloidosis in transgenic Alzheimer's mice. Nature Neuroscience. 2002;**5**:1288-1293

[119] Ershler WB, Keller ET. Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. Annual Review of Medicine. 2000;**51**:245-270

[120] Galimberti D, Venturelli E, Fenoglio C, Guidi I, Villa C, Bergamaschini L, et al. Intrathecal levels of IL-6, IL-11 and LIF in Alzheimer's disease and frontotemporal lobar degeneration. Journal of Neurology. 2008;**255**:539-544

[121] Licastro F, Pedrini S, Caputo L, Annoni G, Davis LJ, Ferri C, et al. Increased plasma levels of interleukin-1, interleukin-6 and a- 1-antichymotrypsin in patients with Alzheimer's disease: Peripheral inflammation or signals from the brain? Journal of Neuroimmunology. 2000;**103**:97-102

[122] Shibata N, Ohnuma T, Takahashi T, Baba H, Ishizuka T, Ohtsuka M, et al. Effect of IL-6 polymorphism on risk of Alzheimer disease: Genotype–phenotype association study in Japanese cases. American Journal of Medical Genetics. 2002;**114**:436-439

[123] Luedecking EK, DeKosky ST, Mehdi H, Ganguli M, Kamboh MI. Analysis of genetic polymorphisms in the transforming growth factorbeta1 gene and the risk of Alzheimer's disease. Human Genetics. 2000;**106**:565-569

[124] Chao CC, Hu S, Frey WH, Ala TA, Tourtellotte WW, Peterson PK, et al. Transforming growth factor beta in Alzheimer's disease. Clinical and Diagnostic Laboratory Immunology. 1994;**1**:109-110

[125] van der Wal EA, Go'mez-Pinilla F, Cotman CW. Transforming growth factor-beta 1 is in plaques in Alzheimer and Down pathologies. Neuroreport. 1993;**4**:69-72

[126] Golde TE, Estus S, Usiak M, Younkin LH, Younkin SG. Expression of beta amyloid protein precursor mRNAs: Recognition of a novel alternatively spliced form and quantitation in Alzheimer's disease using PCR. Neuron. 1990;**4**:253-267

[127] Peress NS, Perillo E. Differential expression of TGF-beta 1, 2 and 3 isotypes in Alzheimer's disease: A comparative immunohistochemical study with cerebral infarction, aged human and mouse control brains. Journal of Neuropathology and Experimental Neurology. 1995;**54**:802-811

[128] Wyss-Coray T, Borrow P, Brooker MJ, Mucke L. Astroglial overproduction of TGF-beta 1 enhances inflammatory central nervous system disease in transgenic mice. Journal of Neuroimmunology. 1997;**77**:45-50

[129] Wyss-Coray T, Lin C, Yan F, Yu G-Q, Rohde M, McConlogue L, et al. TGF-b1 promotes microglial amyloid-b clearance and reduces plaque burden in transgenic mice. Nature Medicine. 2001;**7**:612-618

[130] LeBlanc AC, Papadopoulos M, Be'lair C, Chu W, Crosato M, Powell J, et al. Processing of amyloid precursor protein in human primary neuron and astrocyte cultures. Journal of Neurochemistry. 1997;**68**:1183-1190

[131] Brugg B, Dubreuil YL, Huber G, Wollman EE, Delhaye-Bouchaud N, Mariani J. Inflammatory processes induce beta-amyloid precursor protein changes in mouse brain. Proceedings of the National Academy of Sciences of the United States of America. 1995;**92**:3032-3035

[132] Goldgaber D, Harris HW, Hla T, Maciag T, Donnelly RJ, Jacobsen JS, et al. Interleukin 1 regulates synthesis of amyloid betaprotein precursor mRNA in human endothelial cells. Proceedings of the National Academy of Sciences of the United States of America. 1989;**86**:7606-7610

[133] Heinrich PC, Castell JV, Andus T. Interleukin-6 and the acute phase response. The Biochemical Journal. 1990;**265**:621-636

[134] Raucher D. Tumor targeting peptides: Novel therapeutic strategies in glioblastoma. Current Opinion in Pharmacology. 2019;**47**:14-19

[135] Friedmann-Morvinski D, Bushong EA, Ke E, Soda Y, Marumoto T, Singer O, et al. Dedifferentiation of neurons and astrocytes by oncogenes can induce gliomas in mice. Science. 2012;**338**(6110):1080-1084

[136] Valles S, Sancho-Tello M, Miñana R, Climent E, Renau-Piqueras J, Guerri C. Glial fibrillary acidic protein expression in rat brain and in radial glia

culture is delayed by prenatal ethanol exposure. Journal of Neurochemistry. 1996;**67**:2425-2433

[137] Sancho-Tello M, Vallés S, Montoliu C, Renau-Piqueras J, Guerri C. Developmental pattern of GFAP and vimentin gene expression in rat brain and in radial glial cultures. Glia. 1995;**15**:157-166

[138] Kuramoto K, Yamamoto M, Suzuki S, Sanomachi T, Togashi K, Seino S, et al. AS602801, an anti-cancer stem cell drug candidate, suppresses gap-junction communication between lung cancer stem cells and astrocytes. Anticancer Research. 2018;**38**:5093-5099

[139] Belanger M, Allaman I, Magistretti PJ. Brain energy metabolism: Focus on astrocyte-neuron metabolic cooperation. Cell Metabolism. 2011;**14**:724-738

[140] Liou GY, Storz P. Reactive oxygen species in cancer. Free Radical Research. 2010;**44**:479-496

[141] Gebicki JM. Oxidative stress, free radicals and protein peroxides. Archives of Biochemistry and Biophysics. 2016;**595**:33-39

[142] Chen Y, Vartiainen NE, Ying W, Chan PH, Koistinaho J, Swanson RA. Astrocytes protect neurons from nitric oxide toxicity by a glutathione-dependent mechanism. Journal of Neurochemistry. 2001;**77**:1601-1610

[143] Fujita T, Tozaki-Saitoh H, Inoue K. P2Y1 receptor signaling enhances neuroprotection by astrocytes against oxidative stress via IL-6 release in hippocampal cultures. Glia. 2009;**57**:244-257

[144] Dringen R, Kussmaul L, Gutterer JM, Hirrlinger J, Hamprecht B. The glutathione system of peroxide detoxification is less efficient in neurons than in astrocytes. Journal of Neurochemistry. 1999;**73**:S106-S106

[145] Huang J, Philbert MA. Distribution of glutathione and glutathione-related enzyme systems in mitochondria and cytosol of cultured cerebellar astrocytes and granule cells. Brain Research. 1995;**680**:16-22

[146] Makar TK, Nedergaard M, Preuss A, Gelbard AS, Perumal AS, Cooper AJ, et al. Ascorbate, glutathione, glutathione disulfide, and enzymes of glutathione metabolism in cultures of chick astrocytes and neurons: Evidence that astrocytes play an important role in antioxidative processes in the brain. Journal of Neurochemistry. 1994;**62**:45-53

[147] Lachapelle MY, Drouin G. Inactivation dates of the human and guinea pig vitamin C genes. Genetica. 2011;**139**:199-207

[148] Covarrubias-Pinto A, Acuña AI, Beltrán FA, Torres-Díaz L, Castro MA. Old things new view: Ascorbic acid protects the brain in neurodegenerative disorders. International Journal of Molecular Sciences. 2015;**16**(12):28194-28217

[149] Castro MA, Beltrán FA, Brauchi S, Concha II. A metabolic switch in brain: Glucose and lactate metabolism modulation by ascorbic acid. Journal of Neurochemistry. 2009;**110**(2):423-440

[150] Persson T, Popescu BO, Cedazo-Minguez A. Oxidative stress in Alzheimer's disease: Why did antioxidant therapy fail? Oxidative Medicine and Cellular Longevity. 2014;**2014**:427318

[151] Allaman I, Gavillet M, Belanger M, Laroche T, Viertl D, Lashuel HA, et al. Amyloid-beta aggregates cause alterations of astrocytic metabolic phenotype: Impact on neuronal

viability. The Journal of Neuroscience. 2010;**30**:3326-3338

[152] Haydon PG. Astrocytes and the modulation of sleep. Current Opinion in Neurobiology. 2017;**44**:28-33

[153] Delekate A, Fuchtemeier M, Schumacher T, Ulbrich C, Foddis M, Petzold GC. Metabotropic P2Y1 receptor signalling mediates astrocytic hyperactivity in vivo in an Alzheimer's disease mouse model. Nature Communications. 2014;**5**:5422

[154] Rossi D, Brambilla L, Valori CF, Crugnola A, Giaccone G, Capobianco R, et al. Defective tumornecrosis factor-alpha-dependent control of astrocyte glutamate release in atransgenic mouse model of Alzheimer disease. The Journal of Biological Chemistry. 2005;**280**:42088-42096

[155] Talantova M, Sanz-Blasco S, Zhang X, Xia P, Akhtar MW, Okamoto S, et al. Abeta induces astrocytic glutamate release, extrasynaptic NMDA receptor activation, and synaptic loss. Proceedings of the National Academy of Sciences of the United States of America. 2013;**110**:E2518-E2527

[156] Valles SL, Borrás C, Gambini J, Furriol J, Ortega A, Sastre J, et al. Oestradiol or genistein rescues neurons from amyloid beta-induced cell death by inhibiting activation of p38. Aging Cell. 2008;**7**:112-118

[157] Liu B, Teschemacher AG, Kasparov S. Neuroprotective potential of astroglia. Journal of Neuroscience Research. 2017;**95**:2126-2139