Chapter 4

Neuroimmune Dynamics in Alzheimer's Disease Progression

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Additional information is available at the end of the chapter

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disease, the most common cause of dementia in senile population. According to the World Health Organization, AD represents around 12% of people over 65 worldwide. Due to its etiological agents, neurofibrillary tangles (NFT) and amyloid plaques (AP), several attempts to explain the genesis and progression of AD have been proposed. Pathological variants of tau protein, are the main precursor for AD onset, with a molecular mechanism based on neuroinflammatory processes in the context of the neuroimmunomodulation theory. Microglial cells play preponderant roles in innate immunity and are the main source of proinflammatory factors in the central nervous system (CNS), the links between microglia and neurons are the main focus on AD pathogenesis. Depending on these factors, either a neuroprotective or a proinflammatory effect could be triggered. In AD, a persistently active microglial condition generates neuronal damage and death, causing the release of pathological tau toward the extracellular environment. This causes the activation of microglia, **promoting a feedback mechanism** and generating a continuous cellular damage. After activation of microglia, generation of NF-kB occurs, thus promoting the expression and release of proinflammatory cytokines. As a consequence, short-lived cytotoxic factors, such as O2, NO and other reactive oxygen species, are released. In normal physiological conditions, tau's kinases play a role in regulating normal tau functions in neurons. Glycogen synthase kinase 3-beta (GSK3β)-mediated tau phosphorylation promotes N-methyl-D aspartate receptor (NMDAr)-mediated long-term depression. The increase of proinflammatory cytokines during AD by microglia leads to an increase in kinase expression and activity of cyclin-dependent kinase 5 (Cdk-5) and GSK3-β. On the other hand, TNF-α and IL-8 increase expression and activity of Cdk5, whereas IL-1β hyperactivates GSK3-β, leading to tau hyperphosphorylation and impairing its normal function. Tau hyperphosphorylation results in microtubule destabilization, impaired axonal transport, NMDAr-mediated neurotoxicity, synaptic dysfunction and cell death. Finally, the previously summarized mechanisms could explain the onset and progression of AD, opening a new projection to

focus research on therapeutic agents that could modulate the interactions between tau and microglial cells. The neuroimmunomodulation mechanism has been the conceptual framework for the search of therapeutic approaches for AD and other neurodegenerative disorders.

Keywords: Alzheimer's disease, natural compounds, molecular networks, molecular functions, prevalent neurological disorders, neuroimmunomodulation, inflammation

1. Introduction

1.1. Alzheimer's disease

Alzheimer's disease (AD) is the most common type of brain dementia in senile population (over 60 years old) [1], which gradually affects learning and memory, displaying a prevalence and impact in constant expansion according to the World Health Organization (WHO). This expansive and epidemic behavior is concerning medical and public health opinion focusing efforts on its prevention and treatment. On its biological context, two main etiological effectors have been reported: (i) NFT, composed by accumulation of the hyperphosphorylated protein tau, inside the neuron, and assembled in oligomerical structures denominated paired helical filaments (PHF) [2–5] (ii) Senile plaques, composed by deposits of the amyloid-β (Aβ) peptide of 39–42 aminoacidic residues, generated by the proteolytic excision of the amyloid precursor protein (APP) by the enzymes β and γ secretases, in the extracellular space, both promoting loss of synaptic processes and neuronal death [1, 6]. Among the novel clinical studies to control progression of this pathology, new strategies are being implemented to prevent this brain impairment based on dietary changes and nutritional supplements, functional foods and nutraceuticals. We proposed earlier that the onset of AD is a consequence of the response of microglial cells to "damage signals" or tau oligomers, which triggers a neuroinflammatory response, promoting the misfolding of the cytoskeleton structure [4, 7, 8]. Innovative treatments are essential to improve the life quality of affected subjects. Pharmaceutical industry has failed to developed new drugs of efficacy to control it. In this context, major attention has been given to nutraceuticals and novel bioactive compounds, such as the Andean Compound, obtained from areas in the north of Chilean mountains [9, 10]. We hope that this compound be effective in order to control the disease or serve as a coadjuvant for an effective treatment. Intensive work toward elucidation of the molecular mechanisms involved in the action of these compounds is being carried out. In addition, an advanced second phase clinical trial is actually being developed.

1.2. Neuroinflammation and neurological diseases

Neuroinflammation is defined as the response of the CNS against exogenous and/or endogenous agents, which can interfere with the normal homeostatic processes in the cell. This inflammatory response is usually triggered from a secondary signaling cascade after a trauma or infection. Nevertheless, this mechanism has been characterized as one of the central axis

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during the progression in neurodegeneration. Probably, during this secondary response, there will be an important loss of neurons, in contrast with the first damage [11]. The previous effect is also involved in every neurological disease, including developmental pathologies, traumatic, ischemic, metabolic, infectious, toxic ones, neoplasic and neurodegenerative disorders. Inflammation plays one of the main roles in triggering a number of different neuropathologies, such as AD, Parkinson's or amyotrophic lateral sclerosis, among others [12]. In AD, a continuously active inflammatory condition could promote neural damage, consequently, neuronal cells death, which as a consequence induce the release of pathological forms of the protein tau into the extracellular environment. Since it has been reported that certain tau oligomers are able to activate microglial cells, they subsequently trigger a positive feedback mechanism, generating a constant damage to cells [7, 13, 14]. Moreover, an overexpression of inflammatory mediators has been reported in the vicinity of Aβ and the paired helical filaments (PHF) in AD, which, at the meantime, are associated with highly affected zones in the pathology [15].

Chronic metabolic diseases as hypertension, diabetes, clinical depression, dementia or traumatic lesions in the brain are considered as a silent contribution to neuroinflammation [16]. In the same context, other risk factors causing impairment or even death in the CNS tissue are strokes and atherosclerosis. Moreover, during normal aging, there is a natural chronic activation of proinflammatory signals in the same areas, contributing to an even higher vulnerability for neuropsychiatric disorders [17]. Finally, proinflammatory agents, IL-6, IL-8, C-reactive protein and adipokines are correlated with clinical depression and anxiety symptoms [16, 18].

Over activation of the immune response in the CNS compromises the generation of neurotropic factors and releases of cytotoxic agents to the microglial cell [7]. Since the microglia have an important role in the immune system of the brain and it is widely distributed in every region of the CNS, especially in the hippocampal region and the substantia nigra [19], the effect of this positive feedback gives insights of the genesis and progression in neurodegenerative diseases.

1.3. Microglial cells role on neuroinflammation

Microglial cells have an irregular morphology, with an enlarged nucleus and represent between 5 and 20% of the total glial cell population in the CNS. They are able to produce phagocytosis, releasing cytotoxic factors and behaving as antigen presentation cells [20]. These cells are derived from macrophages produced during the hematopoietic processes in the primitive yolk sac [21], migrating to the neural tube during development [22]. Their physiological functions are essential for the control of the normal homeostasis in the CNS, even in altered conditions, such as the presence of disease [15]. They are capable of sensing different damage signals which could represent a possible impairment for the CNS, some of them are: (i) microorganisms, (ii) abnormal endogenous proteins, (iii) complement factors, (iv) antibodies and (v) citoquines, chemoquines, among others. These impairment agents are able to interact with receptors such as toll-like ones (TLR), inducing the cellular activation of the microglia [19, 23]. Under the previous conditions, microglial cells control the expression of

different surface markers, for example, the major histocompatibility complex II (CMH-II) and pattern of molecular recognition receptors (PRRs). After these interactions, the production of proinflammatory cytoquines is triggered, among them: interleukin I beta (IL-1β), interleukin 6 (IL-6), interleukin 8 (IL-8), interleukin 12 (IL-12), interferon gamma (IFN-γ) and the tumor necrosis factor-alpha (TNF-α) [15]. At the same time, there are synthesis and release of cytotoxic factors with a low biological half-life as superoxide radicals (O_2^-), NO and other ROS [24, 25]. During brain development, microglial cells play the specific role in apoptotic cells elimination. In the cerebellum, they regulate phagocytosis of Purkinje neurons after cell death mediated by caspase-3. Therefore, microglia have been implicated with synapse removal during development after birth [26]. Finally, the activation process for these cells will be related to the intensity, context and kind of stimulus generated and, depending on these factors, the microglia could trigger a neuroprotector or neuroinflammatory effect. Precisely, it is the equilibrium between neurotoxicity and neuroprotection, which will determine the microglia functional effect in neurological diseases or/and specific condition [15].

As we said previously, microglial cells mediate the immune response in the CNS. In order to accomplish this task, the microglia will turn into a functional polarized state, being able to carry out a specific effector program. This brain cellular type exhibits two polarized forms: one of them develops the classical proinflammatory response, being the most common phenotype. The alternative form generates an anti-inflammatory effect directed to heal an affected zone by an acute injury [27].

Additionally, microglial cells are characterized by the expression of several receptors in the membrane surface and also, by the release of different soluble factors. The activated cell, with the proinflammatory phenotype, promotes the regulation of Fc receptors as CD16, CD32, CD64, CD86, IL-1b, IL-6, IL-12, IL-23, TNF-α, inducible nitric oxide synthase (iNOS) and chemokines; meanwhile, the alternative anti-inflammatory phenotype regulates positive arginase-1 (Arg-1), the mannose receptor (CD206), insulin growth factor-1 (IGF-1), the triggering receptor expressed in myeloid cells 2 (TREM1), chitinase 3-like 3 (Ym-1), among others. All previous proteins contribute the active microglia in order to produce additional cytokines and inflammatory mediators which could direct the neurons to apoptotic mechanisms in multiple neurodegenerative pathologies [12]. Although microorganisms and their related secreted proteins (LPS among them) are recognized by the Toll receptors family, neurons suffering apoptosis are sensed by different receptor systems, such as asialoglycoproteins, vitronectin and phosphatidylserine mediated ones [28].

Recent reports have demonstrated that after the microglial cells are activated, they overexpress several receptors and ligands belonging to the main chemokines families (CC, CXC and CX3C). Some of these are also expressed in astrocytes, which suggest that chemokines may serve as communication signals between them and microglia. It has been proposed that CX3CR1 and its ligand, fractaline (CX3CL1), which are expressed in neurons too, play a paramount role in neuronal signaling with the microglial cells [29]. There are diverse factors regulating the phagocytic activity of microglial cells, one of them is the chloride intracellular channel (CLIC1). The pharmacological inhibition of this channel or its negative regulation of its expression at transcriptional level, by an interference RNA, alters the normal phagocytic

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activity of the microglia. On the other hand, it has been reported that the ciliary neurotrophic factor (CNTF) promotes the phagocytosis in a way mediated by Ca^{2+} [30]. In conclusion, microglial cells can receive stimulus by environmental agents or endogenous proteins, which triggers an over activated state, releasing proinflammatory factors, ROS, reactive nitrogen species (RNS) and, evoking toxicity in the vicinity of neuronal population [31].

1.4. Astrocytes and their role in neuroinflammation

Another cellular type implicated with neuroinflammation is the astrocyte, which is the most widely and heterogeneously distributed glial class cell in the CNS. Their morphology can change depending on the development, sub-type and localization of the CNS [32]. This kind of cells has been considered as the support in the brain; nowadays, it is known that they display several functions in the CNS and that they are seriously implicated with neurodegenerative diseases. Astrocytes do not generate action potentials, although are excitable cells with the properties of communication with themselves or with neurons. Their activation is mediated by inner and/or external signals, sending specific messages to their neighbor cells. This process is called "gliotransmission" [33]. During the astrocyte/cells communication, there is a transitory increase in the intracellular calcium concentration. These variations are responsible for this cross-talking, and they occur in two different ways: (i) as intrinsic oscillations resulting after the release of intracellular calcium (spontaneous excitability) and (ii) induced by neurotransmitters. In the last case, neurons release ATP or glutamate [34], activating protein G receptors, driving to the increase of inositol trisphosphate, which will direct the calcium release from the endoplasmatic reticulum to the extracellular space [35]. Some other gliotransmitters are D-serine, a co-agonist, as glutamate, for the NMDA receptor (Panatier et al., 2006), growth factors and cytokines, which promote stronger and long-term effects over synapses, polyunsaturated fatty acids and steroids as estradiol and progesterone and other neuroactive metabolites with affinity to $GABA_A$ receptors [36].

As the microglia, astrocytes are reactive to endogenous and/or exogenous injuries affecting the CNS, by a process called astrogliosis. This phenomenon triggers molecular, cellular and functional changes in cells, as a response to damage and CNS diseases. The undergone changes in astrocytes will be different according to the injury severity and will be regulated in order to modify the astrocytic activity, gaining or losing functionality, which could have an effect over circundante cells [37]. There are three severity levels: (i) mild to moderate, (ii) severe diffuse and (iii) severe reactive with compact glial scar. The first one increases the glial fibrillary acidic protein (GFAP) expression in astrocytes and triggers hypertrophy in the cell body and their astrocytic processes. The second does the same but the astrocyte processes are more pronunciated, and there is an astrocyte overlap with a proliferation increase. These changes are able to conduct a long-term tissue reorganization. Finally, on the third case, there is formation of a glial scar preventing the axonal regeneration and cellular migration, but at the same time, protecting the tissue from infectious or proinflammatory agents [38–41]. After astrocytes activation, the transcription factor NF-κB, which controls chemokines and adhesion molecules, is also overactivated, promoting the periferic lymphocytes infiltration and the improvement in the inflammatory response, which could lead to neurodegeneration. It has been demonstrated that blocking the transcriptional function of

NF-κB in astrocytes severely reduce the inflammation, which suggest that the inhibition of NF-κB in astrocytes could be a potential therapy for brain pathologies, such as AD [42]. Astrocytes also protect the CNS by glutamate hijack which could be potentially cytotoxic [43], glutathione (GSH) release in order to counteract the oxidative stress [44], Aβ peptide degradation (Koistinaho et al., 2004), blood-brain barrier reconstitution [38], synaptogenesis promotion and dynamic modulation of synaptic transmission and neural plasticity, enhancing the metabolic trafficking [45].

Another evidence linking the astroglial activation with the development of neurodegenerative processes makes allusion to the nuclear magnetic resonance spectroscopy, because this technique has allowed the discovery of consistent evidence related with a significant raise of myoinositol (characteristic marker of astroglial cells) in neurodegenerative diseases. This has been observed in the brains of patients with mild cognitive impairment (MCI) and patients with AD, and according to some studies, this raise is correlated with the progression of this pathology [12].

It has been possible to associate neurodegenerative diseases of the CNS with neuroinflammatory events based on the appearance of high levels of proinflammatory cytoquines during disease progression, like in AD, Parkinson's disease, Huntington's disease, multiple sclerosis, amyotrophic lateral sclerosis and others [13]. For all of these diseases, neuropathological and neuroradiological studies have been carried out, providing evidence that neuroinflammatory responses could appear before the loss of neuronal cells. In this issue, robust evidence has been obtained about the role of certain cytokines in the direct activation of the cell cascade leading to neurodegeneration and AD. In world population terms, AD is the most common form of dementia and it generally affects people older than 65 years old. The anomalous tau structures, PHF and NFT, cause a loss of synaptic function ending in neuronal death [46]. This neurodegeneration process is automatically amplified when the tau aggregates are released to the extranuclear medium. At the meantime, in AD, an increase of the microglial activity in the first stages of the disease has been observed, which could be indicative of the microglia attempts to eliminate the noxious elements involved in AD such as the Aβ plaques. In later stages, when the microglial cells are chronically exposed to injuries, they could lead to a chronic neuroinflammatory response, which is almost always harmful to the nervous tissue. Thus, the progressive deposition of Aβ [47] and the liberation of pathogenic tau protein to the extracellular medium could trigger a constant microglia activation [13]. Also, the neuronal loss, characteristic to this disease, contributes even more to the generation of residues that are liberated by these degenerating neurons, which could keep the microglia in a long term activation condition. Thus, the activated glial cells respond with an overproduction of proinflammatory cytokines like TNF-α, IL-1β and IL-6, which are considerably increased in AD. In conclusion, neuroinflammation is a fundamental stage in the development of this disease, because it implicates different etiological factors for AD.

1.5. Alzheimer disease and synapse

In AD, degradation can be located in several sections of the brain, such as the entorhinal cortex, amygdala, cerebral cortex, forebrain and hippocampus, among others [48, 49]. Furthermore,

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there is evidence of serious changes in glutamatergic neurons present in certain sections of the hippocampus, as well as frontal, temporal and parietal cortexes. These areas of the brain are essential for the generation of new memories and for learning processes, which is a major function compromised in this disease [50, 51].

The glutamatergic system works by transforming electric neural impulses with chemical stimuli, which allows for control of glutamate neurotransmitter in the synapse process. In the presynaptic neuron, vesicular transporters VGLUT1 and VGLUT2 are in charge of maintaining glutamate in the vesicle [52] for its release on the synaptic cleft following a depolarization, where the neurotransmitter interacts with the glutamatergic receptors in the postsynaptic membrane [53–55]. Two families of these receptors are present in the neural membrane, the iGluR (ionotropic) and mGluR (metabotropic). The first group can be divided in three classes: NMDA, which are permeable for Ca^{2+} ions, the AMPA (***α*-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid**) and the kainite, which are permeable for Na^{+} and K^{+} ions. On the other hand, there are eight metabotropic glutamate receptors associated with G-Protein, which are then divided in three more groups [55]. Contrary to the ionotropic receptors, which are primarily found in the postsynaptic membrane for rapid modulation of excitatory impulses, metabotropic receptors are found in several membrane compartments on glial and neural cells [56]. Functionally, it has been suggested that group 1 of these receptors mediates inhibitory effects on a presynaptic level, group 2 would be activated in the presence of the released glutamate and group 3 would serve as autoreceptors [56, 57].

In a synaptic context, plasticity regulation is negatively affected by the Aβ peptide. Previous experiments show that soluble oligomers of the peptide are capable of blocking the long-term potentiation (LTP) generation in the hippocampus, establishing in electrophysiological terms the relation of this compound with memory and learning processes [58–61]. At a molecular level, previous reports support the effect of AD on components that play roles in the glutamatergic synapse. Lee et al. experiments in 2004 detected a non-regulated overexpression of the metabotropic receptor 2 (Group 2) in patients with Alzheimer's disease, which through ERK (extracellular signal-regulated kinases) receptors affect the abnormal hyperphosphorylation of tau protein observed in the disease. Through the same methods, mRNA levels of AMPA receptor subunits were measured, and thus, their differential expression in the hippocampus of *postmortem* brains with the disease was evaluated [62]. In a different point of view, Shao et al. in 2011 [63] utilized two transgenic mice models (5XFAD and JNPL3) to observe, at different periods of time, a correlation between the development of the disease and the decrease of PSD-95 protein on excitatory synapses, where AD is mediated by Aβ deposition or hyperphosphorylated tau protein. PSD-95 protein has a structural role within the postsynaptic density (or PSD), where it interacts with a complex of scaffolding proteins, along which are NMDA ionotropic receptors that participate in synaptic transmission. The postsynaptic density is considered an organized structure with mainly glutamatergic receptors associated along with other signaling proteins and cytoskeleton elements, which work together with scaffold proteins in the postsynaptic membrane [63, 64]. Specifically, it has also been indicated that PSD-related gene products could be impaired during this pathology [65]. On that regard, reports also show that the expression of several genes involved in PSD, including genes of

glutamate receptors, varies on different stages during growth, which would imply its relation to synapse development [66]. Finally, since there is evidence of the role of pro inflammatory microglial agents in synaptic impairment, an overview of their possible molecular effects on synapses is paramount in the study of new treatments.

1.6. Physiological function of cytokine-regulated tau kinases

In neurons, there are several kinases that phosphorylates tau protein under physiological conditions and during AD, being Cdk5, GSK3-β, C-Jun-N-terminal kinase (JNK) regulated by cytokines released by astrocytes and glia. Cdk5 is a proline-directed serine threonine kinase, this is, phosphorylate serine and threonine residues, particularly serine 202 (Ser202) and threonine 205 (Thr205) residues of tau protein, also found in PHFs. Cdk5 activity is regulated by p35 and p39, which has a short mid-life and phosphorylates Cdk5 at its T-loop, and translocates to cellular membrane. This activation and translocation of Cdk5 have important biological roles in cortex layer formation, neurite outgrowth, migration and differentiation of neurons, synapse formation and cognitive processes. Cdk5 also regulates mitochondrial morphology and cell survival to stress [67–69]. GSK3-β is also a serine threonine, which phosphorylates tau at threonine 221 (thr221), and its kinase activity is upregulated by phosphorylation of tyrosine 216 (Tyr216) and tyrosine 279 (Tyr279) residues; meanwhile, Akt-mediated phosphorylation of Ser9 and Ser21 residues inactivates its activity. GSK3-β regulates memory processes by induction of LTD and inhibition of LTP, being these effects reversed by GSK3-β inactivation by insulin and Wnt. Also, GSK3-β promotes assembly of actin to form filaments and of tubulin, leading to microtubule formation, thus regulating the reorganization of synaptic architecture [70–72]. Finally, JNK phosphorylates tau at serine 396 (Ser396) and threonine 221 (Thr221). This kinase has three isoforms that participate in brain development, immune modulation, induction of LTP, neurite formation and JNK3 in particular induces cell death by apoptosis [67].

1.7. Physiological function of cytokine-releasing cells: microglia and astrocytes

Microglia are the principal component of innate immune response in the brain, and the first line of defense of central nervous system from pathogen aggressions. Microglia phagocytes pathogens, and releases proinflammatory cytokines, ROS and RNS to eradicate infections. Microglia also participate in neurogenesis by the release of brain-derived neurotrophic factor (BDNF), and in remodeling of brain tissue during embryonic development and in adult brain by inducing apoptosis mediated by release of cytokines (TNF-α, IL-1β), neurotrophic factors (NGF) and NO, and subsequently phagocytizing apoptotic neurons, thus allowing the maturation of surviving cells and posterior memory and learning processes. Additionally, microglia play a paramount role in synaptic plasticity, regulating presynaptic and postsynaptic processes according to their fuction [73]. Astrocytes are antigen presenting cells (APC) of brain where their functions are scaffolding and guidance of developing neurons, formation of synapses and promoting of phagocytosis of synapses by microglia, by inducing the expression of complement system that tags synapses for their elimination by microglia. Also, regulates the diameter of brain vessels, the blood flow to neurons in relation with synaptic activity

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and synaptic interstitial fluid homeostasis. Astrocytes also participate and regulate synaptic activity by releasing vesicles that uptake neurotransmitters of synaptic interspace for their posterior recycling and releasing neurotransmitters, as we said previously [74].

1.8. Dysfunction of astrocytes, microglia and tau kinases hyperactivation by proinflammatory cytokines in AD

During AD, Aβ oligomers are, on first instance, uptaken and degraded by microglia, apparently in an attempt to maintain neuronal environment homeostasis and functionality during early stages of disease. Aβ is able to induce the expression of complement system and microglia activation at two levels: activating CR1 transmembrane receptor, which initiates the activation cascade of complement system, associated to cytokines and ROS release. On the other hand, Aβ also induces its own phagocytosis by activating Fc receptor and C3 factor of complement system, being the last one capable of activating microglia and induce microglial-mediated free radicals release. Proinflammatory molecule C5 is downstream of activation cascade and binds CD88 receptor, inducing the release of IL-1Beta and IL-6, two proinflammatory cytokines [75]. Also, fibrillar Aβ binds to CD14 coreceptor of Toll-like receptor 4 (TLR4), which recruits and transport TLR4 to lipid rafts, followed by recruitment of coreceptor of myeloid differentiation factor 2 (MID-2) which bind to CD14/TLR4 heterodimer to form a heterotrimer CD14/TLR4/MID-2, that is phagocytized by the cell to cytoplasm. Thus, TLR4 binds to the myeloid differentiation primary response protein 88 (MyD88) and recruits IL-1 receptor-associated kinase (IRAK4) which in turn dissociates from MyD88 and binds to and activates tumor necrosis factor associated receptor factor 6 (TRAF6) forming the complex 1. The later dissociates from TLR4 and forms complex 2 by recruiting of transforming growth factor alpha-related kinase (TAK-1) and TAK-1 binding protein (TAB), then IRAK4 phosphorylates TAK-1 which in turn phosphorylates and activates the inhibitor of kappa beta kinases complex which phosphorylates kappa beta inhibitor of NF (Ikβ). This targets to degradation by proteasome, and releasing NF-κB for its translocation to the nucleus where binds to its NF transcription factor promoter in DNA, leading to expression of coding genes of IL-1β, IL-6 and TNF-α proinflammatory cytokines [76, 77]. This signaling pathway is also activated by binding of Aβ to TLR-2, but this receptor does not need a coreceptor for signal transduction [77].

Astrocytes, as well as microglia, uptake Aβ, since transplanted astrocytes in hippocampal cells of mice, carrying the Swedish mutation of amyloid precursor protein (APPSwe) together with a mutation of presenilin 1 (Psen), were able to internalize Aβ oligomers deposition characteristic of these mice [78]. The phagocytosis of Aβ is mediated by CD36, CD47 and RAGE receptors present in cellular membrane, which subsequently activates astrocytes, promotes their proliferation, and induces the activation of NF-κB signaling pathway. These receptors have affinity for this molecular hallmark of AD and promote its degradation by astrocytic lysosomes [79–83]. Unlike microglia, astrocytes do not need to be activated for its Aβ clearance ability that depends on the apolipoprotein E (ApoE)-induced formation of cell aggregates around Aβ deposits, since astrocytes of mouse lacking the ApoE gene were unable to aggregate around AP [84]. Another response of astrocytes to Aβ oligomers is the increase of expression of glutamate transporters GLT and GLAST whose physiological function is to prevent excitotoxicity and promote the survival of mouse [85]. Since Aβ is able to trigger

excitotoxicity by the hyperactivation of NMDAr, the augment of expression of astrocytic glutamate transporters in the presence of Aβ could be a mechanism to counteract this effect [86].

During AD progression, astrogliosis and microgliosis appear before the formation of NFT and AP [87]. The exposition of astrocytes to Aβ oligomers triggers their activation, revealed by a change in astrocytic morphology from stellate to a swelling morphology with more processes than inactive astrocytes. The previous effect induces cellular aggregation around Aβ oligomers and also triggers calcium influx into astrocytes, activating the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. The subsequent release of ROS and activation of IL-6 induce APP processing and a major Aβ production, together with the induction of Cdk5-p35-mediated tau hyperphosphorylation at Ser203 and Thr205 [88, 89]. Another astrocytic response to Aβ oligomers is the activation of GSK3-β which in turn activates NMDAr present in membrane of these cells, triggering CREB binding protein mediated (CPB) translocation of NF-κB transcription factor from cytoplasm to nucleus, where it binds to its promoter and induces the expression of proinflammatory cytokines like IL-1β and TNF-α [90–92]. IL-1β and IL-6 will contribute with the processing of APP and subsequent Aβ overproduction. IL-6 and IL-1 beta trigger a positive feedback that increases Aβ and proinflammatory cytokine overproduction [88]. IL-1β is able to trigger chronic activation of NF-κB signaling pathway by binding to type 1 IL-1 receptor (IL-1R1), which recruits IL-1 receptor accessory protein (IL-1RAcP)—a co-receptor for signal transduction—forming a trimer that later recruits and assembles MyD88 and IRAK4. This last one phosphorylated by itself and induced to phosphorylate IRAK1 and IRAK2, subsequently recruits TRAF6 which in turn bind to E2 ligase complex, thus promoting ubiquitination of TAK-1 and its binding with TRAF6 and mitogen-activated protein kinase kinase kinase (MAPKKK), forming a complex which activates NF-κB signaling pathway by phosphorylation of its inhibitor Ikβ, with subsequent activation of JNK and COX-2 expression [93]. Furthermore, IL-1β induces the cleavage of tau at Asp421 in neurons by the exacerbation of caspase 3 activation, together with the hyperphosphorylation of tau in Ser199, Thr221, Ser396 and Ser413 due to induction of GSK3-β activation that reduces the production of anti-inflammatory cytokine IL-10, known to inhibit NF-κB pathway [88, 94–96]. TNF-α expression activates NF-κB and c-Jun kinase signaling pathways, inducing cell proliferation and migration [88]. Both IL-1β and TNF-α bind to its respective receptors IL-1R and TNFR, respectively, and lead to MAP kinase kinases 3 and 6-mediated activation of p38-mitogen-activated-protein-kinase (p38 MAPK) by dual phosphorylation of Thr and Tyr residues in its kinase activation loop, leading to p38 MAPK hyperphosphorylation of tau at residue 356 and, to a reduction of synaptophysin expression, thus affecting synaptic activity [97]. These two cytokines also induce phospholipase A-mediated production of arachidonic acid (AA), together with the NF-κB-mediated expression of cyclooxygenase 2 gene (COX-2) which dioxygenates AA to produce prostaglandins (PG's) like PGE2, whose binding to its EP3 receptor leads to a reduction of adenylyl cyclase monophosphate (cAMP) activity and, to subsequent reduction of LTP [94, 98–100]. On the other hand, IL-18 release promotes BACE and Ps1 mediated APP processing, caspase-1, mediated IL-1β activation and, tau hyperphosphorylation, mediated by activation of Cdk-5/p35 [89, 101]. Finally, IL-6 induces JAK/STAT and MAPK signaling pathways, triggering Cdk5/P35 deregulation and subsequent tau hyperphosphorylation at Ser202 and Thr205 [102].

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Microglia, as the same as astrocytes, are activated by Aβ, turning its morphology from a cell with a soma and processes to an ameboid active form [73], and its activation leads to the expression of cytokines by astrocytes in AD, thus activated astrocytes and glia act together in Aβ overproduction, tau cleavage and its hyperphosphorylation. Both, **hyperphosphorylation and caspase cleavage of tau are early events of AD that make this protein more prone to aggregate**, disassembling from microtubules, impairing microtubule stabilization, axonal transport and vesicle release. This leads to synaptic dysfunction, axonal degeneration and formation of tau oligomers, PHF and NFTs and finally to cell death [103–106]. Also, it has been demonstrated that tau oligomers are able to activate astrocytes and glia, triggering its uptake by these cells [107].

It has been demonstrated that age-related senescence of astrocytes and microglia with aging diminish their Aβ phagocytic capability and that the exposure to increasing concentrations of a neurotoxic compound reduces glial capability to protect neurons from damage. This may lead to progressive Aβ accumulation and subsequent inflammation in brain tissue during AD. This, in turn, triggers a chronic inflammatory environment mediated by astrocytes and glia, changing their initial neuroprotective response to neurodegeneration mediated by proinflammatory cytokines which, induces AP formation and accumulation of NFTs. This effect results in activation of signaling pathways that activates the expression and release of proinflammatory cytokines, in a vicious circle that finally leads to synaptic dysfunction, neurodegeneration and cell death [108, 109].

1.9. Proposed new targets and therapies for AD in the neuroimmunemodulation context

On the same autoneuroimmune context, several new targets attempt to control Alzheimer's disease by modulation of the inflammatory signals (**Table 1**), among them, some are based on inhibitors of acetylcholinesterase like rivastigmine to improve cholinergic synapses which are severely diminished in AD, and inhibitors of N-methyl-D-aspartate receptor, which are hyperactivated in AD and exerts excitotoxicity, however these drugs only delay the progress of disease [110]. As mentioned above, neuroinflammation is an early event of AD, even earlier than NFT and Aβ plaques formation, which makes the modulation of inflammation an attractive target for development of new drugs for treatment and prevention of AD. One alternative is non-steroidal anti-inflammatories (NSAID's)—such as ibuprofen, paracetamol, aspirin and sulindac—commonly used for treatment of other illness whose symptoms are inflammation (e.g., infections, headache), which appear to reduce the risk of AD onset in patients who were in treatment for a long period [111]. One of the mechanisms of action that has been proposed to explain the preventive capability of AD of these drugs is the inhibition of NF-κB signaling pathway by inhibiting the phosphorylation IκBα subunit of inhibitor of kappa beta kinases complex, thus impairing NF-κB release for its translocation to the nucleus and so the induction of expression of proinflammatory cytokines [46]. Another mechanism consists of inhibition of enzymatic activity of cyclooxygenases, preventing the production of prostaglandins [112]. NSAIDs also activate the peroxisome proliferator-activated receptor gamma (PPARγ) signaling pathway which induces expression of anti-inflammatory substances, and direct Aβ processing and reduction of its release, impairing the formation of plaques. These anti-inflammatory drugs also act

Drug/Active agent	Mechanism	Reference
Rivastigmine	Inhibition of AchE	[110]
Memantine	Inhibition of NMDAr	
Non-steroidal anti-inflammatories	Inhibition of NF-κB signaling pathway	[112]
	Inhibition of cyclooxygenase enzymatic activity	
	Activation of PPARγ receptor	
Cannabinoids	Impairment of aperture of ion channels of astrocytes	[115]
	Inhibits tau hyperphosphorylation and inflammation	[119]
Quercetin	Reduction of levels of IL-6 and TNF-α	[120]
Apigenin	Reduction of expression of COX and iNOS	[118]
Curcumin	Reduction of the expression of COX-2, iNOS	
	Impairment of IL-6, NF-κB and MAPK signaling pathways	
Magnesium	Inhibits GSK3-β	[121]
Lithium	Inhibits GSK3-β	[122]
Dihydropyridines	Reduce all type of tau levels	[123]
Nobiletin	Reduce tau hyperphosphorylation and oxidative stress	[124]
Brain–Up10®	Reduces tau aggregation and increases neuritogenesis	[9]

Table 1. Drugs or active compounds for neuroimmunomodulation therapies.

inhibiting microglial and astroglial activation, thus impairing NFT and AP formation mediated by chronic inflammation induced by these cells [113]. However, these drugs does not work in patients who are already suffering of AD with cognitive impairment, and thus for the effective use of NSAID's, there is necessary an early diagnosis, when inflammatory process is in course but prior to inflammation-induced formation of NFT and Aβ plaque deposition [108]. Another approach is the use of biological active molecules of polyunsaturated fatty acids as agonists of PPARγ transcription factor, which inhibits the expression of proinflammatory cytokines and turn response of immune cells to anti-inflammatory [114]. Another challenge to overcome for these approaches is tissue specificity, since these compounds inhibit signaling pathways which are ubiquitously expressed, which means that their use as therapy for AD would be detrimental for immune response against pathogens aggressions. A recent study targets ionic hemichannels

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of astrocytes by using cannabinoids to impair the aperture of astrocytic hemichannels triggered by proinflammatory cytokines released upon Aβ stimulation, thus impairing the activation of astrocytes, the release of more proinflammatory cytokines and cell death [115]. Also, the use of stem cells has been proposed as treatment of AD, since administration of mesenchymal stem cells reduces plaque formation, promotes Aβ degradation and reduces levels of proinflammatory cytokines, thus reducing microglial proliferation and general neuroinflammation, and so did the treatment with soluble factors, which means that stem cells could release anti-inflammatory cytokines, and more interesting, when these cells are injected intravenously, they migrate to brain [116]. A disadvantage of this approach is the invasiveness of this possible treatment. Lately, efforts have been made to find natural compounds for effective and non-invasive treatment against AD, like quercetin, which is a flavonoid is able to reduce astrocyte activation, thus reducing neuroinflammation and improving learning and memory in SAMP8 accelerated senescence mice which were treated with an oral formulation of quercetin nanoencapsulated in zein nanoparticles [117]. Another flavonoid compound with AD treatment potential is apigenin, which can be found, between other sources, in flowers of chamomile and grapefruit. This compound is able to inhibit microglia-mediated release of IL-6 and TNF-α, the prostaglandin and NO production by inhibiting COX-2 and iNOS enzymatic activities, respectively, and also inhibits the NF-κB signaling pathway [118]. However, the most promising natural compound for anti-inflammatory treatment of AD is a compound called curcumin, a polyphenol isolated from rhizomes of curcuma which reduces the expression of COX-2 and iNOS, impairs IL-6, NF-κB and MAPK signaling pathways, reduces astroglial activation and also prevents and reverts tau aggregation *in vitro*, which could mean that this compound could be used in AD patients with cognitive impairment, if it demonstrates that also have these effects in animal models and human, so more studies have to be made, not only for this compound but also to find or develop new natural or synthetic anti-inflammatory and anti-aggregant compounds to treat AD [118].

2. Conclusion

Alzheimer's disease cases are growing faster every year, not even in senile population, yet also with early onset cases. We have studied different issues related with the beginning and progression of neurodegenerative pathologies. Since in a biological context, the neuroimmuneinflammatory response theory could be the new focus for possible treatments, the research efforts to follow-up should be focused in the control of neuroinflammatory processes.

Microglia seem to be the main brain cells in the pathological pathway of damage signals in the neuronal population of neurodegenerative diseases. The positive feedback cycle, between microglia and neurons, is started by tau oligomers released in the extracellular space after neuron degeneration, triggering the microglia activation (**Figure 1**). Different clinical trials on pharmacological agents attempted to stop the progress of AD or revert its consequences, but only a few ones, are promising. On the other hand, natural compounds have received special attention, because of their benefits in neuritogenesis or possible applications to control the progression of the inflammatory process in AD. Such is the case of "Andean Compound," which we present as an alternative treatment for this pathology (**Figure 1**).

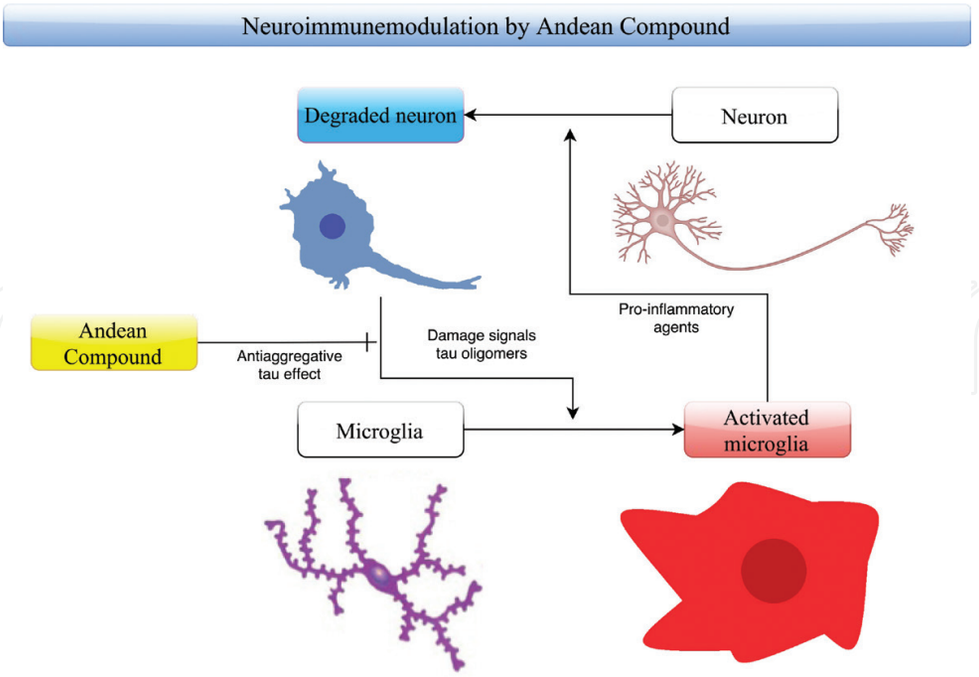

Figure 1. Model of neuroinflammation and neurodegeneration cycle modulated by the "Andean Compound." Non-activated microglial cells are susceptible to different damage signals as aggregated forms of the tau protein, leading to its activation. After activation, several pro-inflammatory agents are release into the extracellular media, being able to promote neuronal damage and degeneration. While neurons are degraded, different tau forms are released, causing a positive feedback in this neurodegenerative pro-inflammatory cycle, triggering the onset and progression of pathologies such as AD. The Andean Compound displays and anti-aggregation effect on tau oligomers, diminishing damage signals and, at the same time, it promotes neuritogenesis processes, featuring itself as an excellent target for the treatment of AD.

We encourage researchers to set their aim in new neuroprotective and anti-neuroinflammatory drugs or nutraceuticals, projecting the answers for neurodegenerative diseases on the basis of the neuroimmunemodulation theory, as the most valuable and useful tools for AD treatment.

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