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Chapter 2

Neuroinflammation and Neurodegeneration

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Abstract

Pathophysiological processes of neurodegenerative diseases are not clearly defined. However, an important body of evidence points toward the role of various inflammatory processes. The microglial cell is the main representative of the immune system in the central nervous system (CNS). This cell type can sense foreign or harmful pathogens and trigger its own activation and the generation of neuroinflammatory processes through phagocytosis and the release of cytokines, in order to maintain the cellular microenvironment. However, after maintaining a permanent state of activation due to sustained stimulation over time, microglial cells may generate a focus of persistent inflammation that in some cases precedes or enhances the neurodegenerative process. Thus, neuroinflammatory microenvironment becomes toxic and harmful for the neuronal cell, which degenerates and releases various factors that in turn activate the inflammatory response of microglia, potentiating the neurodegenerative cycle. In this chapter, we discuss the evidence on the role of microglial cell activation in neurodegenerative conditions and the association between neuroinflammatory processes and age-related neurological diseases. Finally, we outline how this new approach can help us to find new ways to understand neurodegenerative processes and to orientate the search for new therapies.

Keywords: neuroinflammation, neurodegeneration, Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, microglia, neuroimmunomodulation hypothesis, inflammatory response

1. Introduction

Neurodegeneration is a degenerative process that occurs in the central nervous system (CNS), in which an injury or deleterious condition detonates progressive neuronal death, leading to

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the loss of cognitive and motor functions associated with the CNS. The causes that trigger this neuronal death are still unknown, but clinical evidence demonstrates that age is an important risk factor and that the number of people suffering from dementia and other neurodegenerative conditions will increase as a consequence of increased life expectancies [1]. The main diseases that are defined by neurodegenerative processes are: AD and PD, but this term also includes other conditions such as amyotrophic lateral sclerosis (ALS), multiple sclerosis and products of viral infections. These diseases have an impact not only on the individual suffering from the disease but also on their families, causing social isolation, family misunderstanding, and loss of friendships and social ties [2]. This is an important issue and should be further considered, especially because it is currently estimated that 94% of people living with dementia are cared for at home, generating an important amount of distress and economic burden on their closest relatives. This is particularly true for many low- and middle-income countries, where in many cases patients and caregivers have access only to limited support from the state and health providers.

According to epidemiological data from the "World Alzheimer Report 2015" [3], there are more than 46 million people with dementia worldwide, and it is estimated that this number will increase to 131.5 million by 2050. Moreover, it is also important to consider that this type of disease carries a huge economic impact. Currently, only AD monetarily translates in US $818 million per year globally and is estimated to be billions of dollars by 2018 [3]. This amount will certainly rise significantly if we consider other neurodegenerative diseases mentioned above. The reasons that trigger neurodegenerative processes in these diseases remain unclear, especially considering the many variables that are involved in their development. One of these variables, inflammation, became more relevant in recent years. One example is the evidence that exists today on neurodegeneration induced by viral infections [1, 4], as it involves the interaction of the CNS, environmental factors, and immune response. In parallel there are also studies that link the rising number of mild proinflammatory conditions described with major degenerative diseases of the elderly [5]. Thus, the major pathologies, associated with aging and increased physical frailty, are also associated with changes in body composition, energy imbalance, homeostatic dysregulation, and neurodegeneration. Chronic inflammation is strongly connected to each of these aging phenotypes [6].

The inflammatory response is triggered to fight and control an injury, infection or other stimulus and may involve many cell types. The impact of the response is dependent on the numerous factors secreted by these cells, and they have the ability to self-regulate their response in order to repair tissue damage and to eliminate pathogenic elements. But when the response is prolonged in time, it causes a chronic inflammatory environment that leads to progressive tissue damage [6]. One of the evidences that support the relation between inflammation and increasing age is given by the increase in inflammatory mediators IL-6 and IL-8 and the rise in C-reactive protein in men and women with age, and the fact that these values also increase in obesity and neurodegenerative diseases [7].

In this chapter, we present a complete summary of the neuroinflammatory process and we explain how it relates to the development of features of neurodegeneration and neuronal death as in dementia neuropathology. We describe the neuroinflammatory processes considering

microglial cell as the main cell type involved in the development of the immune response in the CNS. Finally, we link the development of the immune response to long-term development of three of the most characteristic diseases related to neurodegenerative diseases: AD, PD and ALS.

2. Methodology

We performed a detailed assessment of current evidence about main and nascent topics in the area of "Neuroinflammation and Neurodegeneration." Additionally, we focused our search in the three prototypic neurodegenerative diseases, considering classical concepts on neuropathology and incorporating new evidence on the role of neuroinflammatory process.

The focus of this review is to show evidence on common pathological role of neuroinflammatory process and microglial cells in neurodegenerative diseases, proposing a new approach for research of these diseases, in order to give support for the development of innovative therapies.

We performed a systematic search in the main database of National Center for Biotechnology Information Database (PubMed). Key words were: *inflammatory response*, *neuroinflammation*, *neurodegeneration*, *neurodegenerative diseases*, *neuronal death*, *microglial cells*, *microgliosis*, *Parkinson disease*, *Alzheimer disease and Amyotrophic Lateral Sclerosis*.

3. Neuroinflammatory processes

Neuroinflammation is defined as the reactive response of CNS against elements that interfere with homeostasis, inside or outside the CNS, and this response is involved in all neurological diseases, including developmental, traumatic, ischemic, metabolic, infectious, toxic, neoplastic, and neurodegenerative diseases. Emerging evidence suggests that inflammation has a causal role in disease pathogenesis, and understanding and controlling interactions between the immune system and the nervous system might be key for the prevention or delay of most late onset CNS diseases.

The wide variety of cellular and molecular mechanisms of neuroinflammation, probably the same in aging and chronic metabolic diseases such as hypertension, diabetes, depression, dementia or traumatic brain injury, are currently considered as silent contributors to neuroinflammation [1]. In addition to these chronic diseases, another major risk factor that causes tissue destruction in CNS is stroke and atherosclerosis. This disease of brain arteries is characterized by vascular inflammation caused by monocyte infiltration in the injured vessel wall and increased interleukin (IL)-6 triggering significant damage in the area of the lesion [8]. Considering the current poor quality of life in many cities and unhealthy eating habits, we must know that this can lead to a number of disorders and diseases such as cardiovascular disease, stroke, hypertension, insulin resistance, and metabolic syndrome. Thus, lipid hormones, cytokines, and adipokines play an important role in inflammatory metabolic diseases

through induction of adverse regulatory responses [1]. In other way, the chronic activation of proinflammatory signals in aging CNS may contribute to an increased vulnerability to neuropsychiatric disorders [9]. For example, the group of Dr. Ouchi linked obesity and inflammation, and they demonstrated that the inflammatory state was associated with a higher concentration of proinflammatory markers including IL-6, CRP, and adipokines [10]. All these proinflammatory markers are correlated positively with symptoms of depression and anxiety, and in agreement with those findings, metabolic diseases such as obesity, hypertension, and even senescence are prevalent risk factors for depression, cognitive dysfunction, and dementia [1] favoring the neurodegenerative process. On the other hand, the mechanism linking inflammation and depression involves oxidative stress and elevated levels of proinflammatory cytokines IL-6 and IL-8 among other factors. For example, major depressive disorder, a serious psychiatric illness, is associated with increased levels of peripheral inflammatory markers and to mortality due to depression and suicide [11, 12]. Therefore, inflammatory markers, identified in neurodegenerative diseases including psychiatric disorders, are related to increased processes of neuronal death.

It is important to consider that some biological mechanisms involved in neuroinflammatory processes, such as the participation of complement cascade and microglial cells in responses of pruning synapses, also occur in healthy brain development [13].

On the other hand, the inflammatory response in the CNS is also linked to various processes such as aging, systemic infection, metabolic syndrome, and intrinsic CNS disease. Activation of the immune system in the CNS may compromise the generation of neurotrophic factors and the secretion of cytotoxic factors from the microglial cell. In line with the hypothesis that proinflammatory molecules such as the IL-1β family of cytokines and factors that simulate Toll-like receptors (TLRs) can impair the clearance function of microglia, there are some findings showing that disrupting IRAK4, an essential kinase downstream of TLRs and receptors for IL-1β cytokines, shifts microglial cells from a proinflammatory phenotype toward an anti-inflammatory phenotype [14].

The main agent involved in neuroinflammation is the microglial cell, but other factors that are also present in the inflammatory response should be considered. In animal models of AD, it has been demonstrated in areas associated with amyloid plaques, infiltration of mononuclear cells into the CNS as part of an innate immune response, but the role and the participation of these cells is not very clear yet [15]. Evidence from a mouse model of AD showed that peripheral mononuclear phagocytes have an important role to reduce the buildup of amyloid-beta plaques, which improve local inflammatory response [16].

The astroglial cells are also involved in the inflammatory response. Astrocytes respond to all forms of CNS insults through a process referred to as reactive astrogliosis. This response is a complex, multistage and pathology-specific reaction. On the other hand, the response of astrocytes is generally aimed for neuroprotection and recovery of injured neural tissue [17]. Emerging evidence of sustained inflammatory response in the CNS supports the major contribution of microglia and astrocytes in the progression of a wide variety of diseases, suggesting an important role as effectors of neuroinflammation in neuronal dysfunction and death. Other cell types including neurons, astrocytes, endothelial cells, etc., also express

receptors for cytokines and other inflammatory mediators and can be activated by these signals and participate in the coordinated inflammatory response in the brain.

3.1. Microglia and neuroinflammation

Microglia is widely distributed throughout the brain and spinal cord but mainly in the hippocampus and the substantia nigra [18]. These cells are approximately 5–20% of the total population of glial cells in the CNS and are considered the representatives of the immune system in the central nervous system, since they have the ability to perform phagocytosis, release cytotoxic factors, and behave as antigen presenting cells [19, 20]. These cells are derived from macrophages produced by hematopoiesis in the primitive yolk sac [21], and they migrate to the developing neural tube, where they give rise to microglia [22].

This cellular type represents the major cellular component of the innate immune system of the brain. In normal conditions, microglia protects the brain environment by initiating a quick response to changes and effectively modulates inflammation.

Numerous signs that threaten homeostasis of the CNS, such as structures and/or residues from bacteria, viruses, and fungi; abnormal endogenous proteins; complement factors; antibodies; cytokines and chemokines, among others, are sensed by the microglia and consequently induce their activation [18]. Thus, there are two major functional aspects of the microglial cell: immune defense and maintenance of the CNS. Microglial cells function as immune cells acting as sentinels, detecting the first signs of invasion of pathogens or tissue damage. Furthermore, under inflammatory conditions produced by an active immune response, the microglia should moderate potential damage to the tissues that support, help to repair, and remodel CNS [22].

Microglial cells mediate immune and inflammatory responses in the CNS. These cells become functionally polarized to execute specific effector programs and thus, express specific functional reaction programs in response to diverse microenvironmental signals. Microglia have two functional states of polarization: one of them is phenotypically polarized to develop a classical proinflammatory or an alternative phenotype is anti-inflammatory and prohealing [23]. Thus, diverse pro- and anti-inflammatory cytokines, and others stimulus, can polarize microglia toward distinct functional phenotypes.

Microglial cells are characterized by the expression of distinct cell surface receptors and also by the release of numerous soluble factors. Activated cells with inflammatory phenotype are characterized by upregulation of CD16 Fc receptors, CD32, CD64, CD86, IL-1β, IL-6, IL-12, IL-23, tumor necrosis factor (TNF)-α, inducible nitric oxide synthase (iNOS), and chemokine, whereas microglial cells with anti-inflammatory phenotype display the upregulation of arginase (Arg)-1, mannose receptor (CD206), insulin-like growth factor (IGF)-1, triggering receptor expressed on myeloid cells 2 (TREM2), chitinase 3-like 3 (Ym-1), among others [23]. All these factors contribute to microglia activation that leads to further production of cytokines and other inflammatory mediators, which may contribute to the apoptotic cell death of neurons in multiple neurodegenerative diseases.

For these characteristics, microglia is considered the resident immune cells in the brain that are sensitive to even minor disturbances in homeostasis of the central nervous system (CNS)

and become readily activated during most neuropathological conditions, including PD and AD [24].

But, which are the determinants that define whether the inflammatory response from microglial cells will result in a protective or neurodegenerative effect?

An important consideration, among other things, is the timing of the disease in which microglial activity begins. For example, in the case of AD, an increase in microglial activation at early stages has been observed [25]. This could be an indication that the microglia initially tries to eliminate harmful elements involved in disease such as amyloid-beta plaques. Thus, to assess whether microglial response is harmful or has a protective effect, we must distinguish between chronic and acute stimulation. An acute injury can cause oxidative and nitrosative stress, but it is usually short lived and unlikely to be detrimental to long-term neuronal survival. Therefore, it is believed that acute neuroinflammatory response is usually beneficial to the CNS, tends to minimize damage, and helps to repair damaged tissue. Moreover, microglial cells are capable of removing glutamate, a well-known neurotoxic substance that acts at NMDA receptors from neurons and can lead to neuronal death. In the case of AD, importance of glutamate and associated microglial function has been evidenced by the therapeutic effect of the drug memantine (an antagonist of NMDA receptors) that improves cognitive ability and everyday life functions in AD patients [26].

Oppositely, chronic microglia stimulation would trigger a chronic neuroinflammatory response, which is almost always harmful and damaging to nerve tissue. Thus, if neuroinflammation has beneficial or deleterious results in the brain, it depends primarily on the length of the inflammatory response given by the microglial cell. For example, in the initial phases of AD, the progressive deposition of amyloid-beta plaques could provide chronic stimulation for microglial cells [27]. The release of pathogenic tau protein (hyperphosphorylated and self-aggregated) from dying neurons would also cause a constant activation of microglia [28]. As for the relationship of the proinflammatory cytokine IL-1 and the anti-inflammatory cytokine IL-10, levels of IL-1 raises drastically in the serum of AD patients, giving these patients a defined proinflammatory long-term profile, indicating a chronic CNS neuroinflammatory state [29]. In addition, the loss of neurons that characterizes AD further contributes to the generation of waste that is liberated from degenerating neurons and maintains microglia indefinitely in a state of long-term activation. These data indicate that, in AD, inflammation may be more chronic and therefore contribute to disease progression [27].

It is important to consider that microglia can be stimulated with environmental toxins, or with endogenous proteins too, and in this way, the cell can enter an overactivated state and release reactive oxygen species (ROS) and also reactive nitrogen species (RNS), which cause environmental toxicity for surrounding neurons [30]. This information is of great interest because overactivated microglia can be detected using imaging techniques, and therefore this knowledge offers an opportunity for an early diagnosis, and eventually in the future, this could be a target for the development of targeted anti-inflammatory therapies that lead to diminish the progression of a disease or may support existing therapies.

Thus, chronic inflammation is characterized by the long-standing activation of microglia, produced by chronic stimuli, trauma, and even pathological aggregates of neuronal proteins such as tau and beta-amyloid. These stimuli induce sustained release of inflammatory mediators, leading to an increase in oxidative and nitrosative stress, which perpetuates the inflammatory cycle, causing a permanent and detrimental inflammatory state.

3.2. Astrocytes and neuroinflammation

These type of cells are the most abundant and heterogeneous type of glial cells in the CNS. Their morphology can change depending on their developmental stage, subtype, and localization [31]. For example, astrocytes of the gray matter are the protoplasmic ones; they exhibit short branches, whereas the fibrous astrocytes, present in the white matter, exhibit long unbranched processes [32].

The astrocytes are supportive for neuronal cell components in neural tissue and, as well as microglia, also respond to all forms of insults to the CNS through a process known as reactive astrogliosis, and this process is a reliable and sensitive marker of diseased tissue. These cells, which are responsible for a wide variety of complex and essential functions in healthy CNS, for example, are involved in primary roles in synaptic transmission and information processing by neural circuits [17], and they can contribute to synaptogenesis and dynamically modulate information processing and signal transmission, regulate neural and synaptic plasticity, and provide trophic and metabolic support for neurons [33, 34].

In effect, astrocytes are involved in very important processes such as controlling the environment by regulating pH, ion homeostasis, blood flow, and modulating oxidative stress [31], and they are also responsible for a massive number of homeostatic tasks in the CNS [35]. With all these capacities, astrocytes, together with microglia, act as the main effectors of the neuroinflammatory response. After suffering an injury, or detecting a damage signal, astrocytes rapidly act in response to pathology and undergo important changes in their morphology and functioning [17], as occurs with microglial cells. Thus the objective of the response is to control and to remove the brain insult, but this response may also have deleterious consequences. In fact, reactive gliosis is a self-perpetuating process, which, at the end, exacerbates the injury and, on the other hand, represents a nonphysiologic state in which astrocytes lose their helpful properties [31].

The mechanisms leading to the activation of these cells are actually unclear, and many factors that are involved in neurodegenerative diseases can trigger the response of these cells. In AD, for example, it has been demonstrated that the presence of amyloid activates astrocytes. As microglial cells, astrocytes also can phagocytose and degrade amyloid-beta, and to bring this capacity, astrocytes and microglia are activated through TLRs and RAGE receptors, thus causing local inflammation [36]. When the response of astrocytes is activated, they change their morphology and increase significantly the expression of the glial fibrillary acidic protein (GFAP), a recognized marker of astrocyte reactivity [37]. All these changes cause a disturbance of normal activities in astrocytes, which are essential for normal neuronal function.

Activation of astrocytes, internally, involves the activation of transcription factor NF-κB, which controls secretions of chemokine and adhesion molecules, and thus favors peripheral lymphocyte infiltration and increases inflammatory response, which leads to neurodegeneration [36]. It has been shown that blockage of NF-κB transcriptional activity in astrocytes can extensively reduce inflammation, thus suggesting that inhibition of NF-κB in astrocytes may be regarded as a potential therapy for diseases such as AD [38].

With this background, it is possible to say that activated astrocytes are able to cause neurodegeneration; moreover, when activated astrocytes express inflammation-associated factors, such as the peptide S100β, they represent a key factor for neuroinflammation. S100β is exclusively produced by astrocytes and, under physiological conditions, it is a neurotrophin responsible for survival, development, and function of neurons [39]. In neurodegenerative diseases such as AD and PD, among others, and also in subjects with severe brain trauma, the peptide S100β is overexpressed, and its levels correlate with the progression of the pathology [36, 40].

Another evidence linking astroglial activation with the development of neurodegenerative processes is proton resonance spectroscopy. Through this technique consistent evidence of significant increase of myoinositol (characteristic marker of astroglial cells) in neurodegenerative diseases has been obtained. This has been observed both in brains of patients with mild cognitive impairment (MCI) and AD patients, and according to some studies, it has been reported to correlate with progression of pathology [36, 41, 42].

4. Neuroinflammation in Alzheimer disease

AD is a neurodegenerative disease that affects more than 20 million people worldwide and is characterized by a progressive deterioration of cognitive functions, particularly memory [43].

Currently, it is the most common cause of dementia in older adults and accounts for 50–60% of cases [44]. This disease usually begins after 65 years of age with a gradual increase in oblivion accompanied with other cognitive impairments, such as problems with calculations, visuospatial orientation, and language [45, 46]. This disease is defined as a multifactorial disorder in which genetic and environmental factors combine, but that is mostly of sporadic origin; It is estimated that only 2–10% of cases are hereditary [47, 48]. However, experts agree that the development of AD would be the result of multiple converging factors in the same case with multiple pathophysiological mechanisms explaining the cognitive impairment that causes this disease.

AD is a neurodegenerative disorder, characterized by the formation of two types of protein aggregates in the brain: senile plaques and neurofibrillary tangles (NFTs) consisting of amyloid-beta and altered tau, respectively [49]. At present, it is also considered that astroglial and microglial activation is characteristic of the disease, which in interaction with abnormal protein aggregates ultimately leads to dysfunction and neuronal death [50]. Histological evidence suggests that NFTs formed by self-aggregation of hyperphosphorylated tau protein

forming paired helical filaments (PHFs) are pathognomonic for the disease; the pathology of tau is directly correlated to clinical deterioration [48, 49]. There are numerous and diverse factors such as head injuries, high fat intake, B vitamin deficiency, recurrent infections, alterations in cholesterol homeostasis, obesity and poor eating habits, among others that are able to increase the risk of developing the disorder [1, 51–55]. However, none of these risk factors seems to act as the real cause of the disease, although all are involved in its development [56].

Furthermore, and looking for a common event in the existing hypotheses, neuroinflammation in the CNS appears as a key event in the pathophysiology of AD. Based on this, promising targets for AD treatment have emerged by regulating neuroinflammation and cross-talk mechanisms between microglia and neurons [57–59].

In this context, it becomes interesting to identify the levels of neuroinflammation and microglial activation, leading to the permanent release of cytokines, which have neurotoxic effects and are involved in the progression of this pathophysiological process [60].

In the case of AD, there is evidence to correlate high expression of inflammatory mediators in the vicinity of deposits of amyloid-beta peptide and neurofibrillary tangles, which in turn are associated with the development of neurodegeneration, exemplifying the relationship between neuroinflammation, neurodegeneration, and cell types involved [58].

As explained above, neuroinflammation is a key event in the development of AD, as it involves the different triggers of the disease. Based on this, it has been suggested that the use of anti-inflammatory drugs could be beneficial and could delay the onset or progression of AD. To continue, we must at least mention the role of the cyclooxygenase (COX) enzyme. COX is an enzyme that exhibits two catalytic activities: an activity of bis-oxygenase (catalyzes the formation of prostaglandins G_2 (PG) from arachidonic acid) and its second peroxidase activity (reduced PG G_2 to PG H_2) [61]. COX in its peroxidase activity also produces free radicals, which are partly used for the same enzyme [61]. With this information, the possible mechanism of NSAIDs in neurodegenerative diseases such as AD would be based on their inhibitory effect on brain COX. COX-1 and COX-2 enzymes are expressed in the CNS, but COX-2 plays a unique role in the brain compared to the periphery: COX-2 is expressed constitutively only in the brain, while elsewhere expression is activation dependent [27]. Although expression of this enzyme is related primarily to neurons, authors have already shown expression in astrocytes and microglia [62]. It has also been demonstrated that COX-inhibiting NSAIDs reduce microglial activation and, on the other hand, neuronal stress processes, such as ischemia and excitotoxicity, are associated with strong upregulation of neuronal COX-2 expression. This suggests that COX-2 is involved in neurotoxic mechanisms and could be an effective target for treatment [27].

NSAIDs have another non-COX-dependent mechanism that can decrease the inflammatory response through direct activation of the peroxisome proliferator-activated receptor gamma (PPARy), a nuclear transcription factor, which acts to suppress the expression of a broad range of proinflammatory genes [63], even in the microglial cell. NSAIDs act as PPARy agonists and bind to it directly giving a start to its transcriptional activity, thus inhibiting the expression of

proinflammatory cytokines such as IL-6 and TNF-α secreted by microglia and astrocytes, avoiding proinflammatory activity of these cells [27, 64].

In clinical studies, comparative analyzes were performed in the brains of cognitively normal patients chronically using NSAIDs over age versus those not using NSAIDs that revealed no changes in the appearance of senile plaques, but there was a threefold decrease in the number of activated microglia in the brains of chronic users of NSAIDs [65]. AD patients who used NSAIDs compared with another group of patients who did not use NSAIDs showed a significantly slower progression of disease [66]. These findings are correlated with the above and suggest that the protection provided by the chronic use of NSAIDs in AD patients may be derived at least partially from the attenuation of microglial activation [58].

Despite all these favorable results, we cannot overlook the fact that clinical trials of NSAIDs for patients with cognitive impairment and AD did not show clear results, and the observed effects vary depending on the cognitive instrument that is used. For example, the results indicate that the NSAID naproxen reduced cognitive decline in some patients but caused acceleration in cognitive decline in other patients. Conversely, celecoxib (another NSAID) appears to have similar, but attenuated effects in AD patients [67]. Therefore, it is still premature to make clinical recommendations, despite the positive results. However, positive findings open new avenues of research with significant clinical potential in order to develop an effective treatment for AD and other diseases with neuroinflammatory components.

On the other hand, as a result of the lack of efficacy of current treatments for AD, and based on the positive results obtained in patients taking anti-inflammatory drugs, a new possibility has opened up the study of the association of inflammatory processes and pathophysiology of AD.

A new form of prevention against the neuroinflammatory process, and thus also an interesting way to prevent neurodegenerative brain damage, is based on changes in diet and the consumption of nutritional supplements, functional foods, and nutraceuticals.

An interesting example of such food supplements is a new naturally occurring compound with high concentrations of antioxidants and anti-inflammatory properties called Andean Compound (initially called as Shilajit Andino). The Andean Compound is a very complex mixture of humic substances, generated by the decomposition of ancient plant material; it is originated as an endemic natural product of the Andes Mountains. Its main active principle is fulvic acid [68]. According to studies by Cornejo et al., fulvic acid is able to block tau self-aggregation affecting the length and morphology of PHFs generated *in vitro*, projecting as a good support for the treatment of AD. Also, after exposure of preformed tau fibrils to fulvic acid, a decrease in the length of PHFs can be detected [69]. So, this compound emerge as a novel nutraceutical with potential uses against neurodegenerative brain disorders [69].

The formation of tangles has been identified as a key and convergent event among many of the factors involved in the neurodegenerative process. Our multidisciplinary research group is currently working on a new nutraceutical containing Andean Compound plus B vitamins (B6, B9, and B12 vitamins) named Brain-Up 10®. Patients who have participated in a pilot clinical trial showed a trend toward lower cognitive impairment, a reduction in neuropsy-

chological symptoms, and less distress for the caregiver. The appearance of new compounds that can open the way to new treatments becomes a necessity. In this search, compounds such as Andean Compound, which, because of their natural origin and the lack of adverse effects, appears as a promising therapy against neurodegenerative diseases, can give strong evidence that their effects are mediated by disruption of the inflammatory response and self-aggregation of the tau protein [58].

5. ALS: neuroinflammation and neurodegeneration

ALS is another neurodegenerative disease whose hallmark is a combination of degeneration of upper motor neurons in the brain stem and motor cortex and lower motor neuron death from spinal cord. This causes progressive muscle atrophy and paralysis, leading to death of the patient 3–5 years after the diagnosis. Although there are some variations, it is considered a late-onset disease, because visible symptoms appear around 55–60 years, including weakness in hands or legs, speech difficulties, and dysphagia [70]. The global incidence of ALS is 2–3 per 100,000 people, affecting more men than women [71]. The primary mechanism of disease still remains unknown, although there is evidence of calcium deregulation, mitochondrial damage, RNA alterations, protein misfolding and aggregation, ROS imbalance, and inflammation, among others [72, 73].

There are two subtypes of ALS: sporadic (sALS) that represents between 90 and 95% of total cases and familial ALS (fALS) that represents the remaining percentage (10–5%). It has been reported that fALS can be triggered by mutations in more than 24 different genes, associated with very diverse cellular functions. Superoxide dismutase 1 (SOD1) has been the most characterized gene, accounting for ~20% of total of fALS cases with more than 150 different mutations associated with the disease [74, 75]. Transactive response DNA binding protein 43 (TDP-43) is another remarkable gene in the disease, affecting both fALS and sALS [76, 77]. This protein is also linked with the development of frontotemporal dementia (FTD), both diseases sharing the deposition of TDP-43. This protein was identified as a major component of the ubiquitinated neuronal cytoplasmic inclusions deposited in cortical neurons in FTD and in upper and lower motor neurons in ALS, coinciding with an overlap in clinical development of FTD with ALS. This kind of overlapping syndrome may be expected since both diseases affect neurons in frontal cortex [78, 79]. In recent years, there are many reports of hexanucleotide repeat expansions in the chromosome 9 open reading frame 72 gene (C9ORF72) that has also been associated with FTD and ALS, being present in around 30% of familial cases [80].

Recent evidence suggests that motor neuron degeneration in ALS is not an autonomous process; instead it includes astrocyte and microglia participation as discussed below. The observation that nonneuronal cells contribute to neuron death in transgenic model of mice carrying $SOD1^{G37R}$ mutation, was broadly supported by different groups that saw the same effect on *in vitro* studies observing that astrocytes from human ALS patients and transgenic $SOD1^{MUT}$ mice induce motor neuron death [81–84]. In addition to astrocytes, an active contribution of microglia expressing $SOD1^{MUT}$ was evidenced in motor neuron degeneration

[85] and recently was demonstrated that microglia rather than astrocytes induce neuronal death through NF-κB, major regulator of inflammation in $SOD1^{G93A}$ mouse model [86].

5.1. Inflammation and neuroimmunomodulation: microglial signs

A lot of evidence, from animal models as well as patients from familial and sporadic cases, has been observed related to microglia involvement in ALS pathogenesis. In the last time, the microglia role in ALS went from being considered as a consequence of the pathogenic process to being considered as a key factor in the progress of disease, existing two different stages associated to opposite functions of microglia: first in a protective mode in early stages of disease and a later stage with neurotoxic participation [87]. In lumbar spinal cord from 11 weeks old (disease onset) $SOD1^{G93A}$ mice, microglial cells show an M2 phenotype and improve motor neuron survival, while microglia from end stage $SOD1^{G93A}$ mice display an M1 phenotype producing motor neuron death [88, 89]. Anti-inflammatory profile in ALS is documented by release of cytokines such as interleukin 4 (IL-4) and neurotrophic factors such as insulin-like growth factor 1 (IGF-1) and significantly increased expression in microglia from spinal cord of presymptomatic $SOD1^{G93A}$ mice [90]. Recently, through a technique that allows the *in vivo* following of activated microglia in $SOD1^{G93A}$ and $SOD1^{G37R}$ ALS mice, the overexpression of IL-10, an important regulator that would control the anti-inflammatory profile in the presymptomatic stage of disease, was demonstrated [91]. On the other hand, proinflammatory phenotype in ALS is evidenced by the increased expression of interleukin-1 beta (IL-1β) and tumor necrosis factor α (TNF-α) in spinal cord of $SOD1^{G93A}$ of advanced stages of disease [92–94]. Another consequence of neuroinflammatory process is ROS release and, in microglia from spinal cord of $SOD1^{G93A}$ mice, is that genes of enzymes that regulate the nitric oxide production, Arg1 and iNOS, are upregulated [95] contributing with more evidence to support the neuroinflammatory theory for ALS pathogenesis. Moreover, astrocytes from ALS murine models including $SOD1^{G37R}$ and $SOD1^{G93A}$ have shown an increase in the expression of proinflammatory genes too, as diverse interleukins (IL-1β; IL-18), prostaglandin E_2, interferon gamma (interferon-γ), and TNF-α, among others, which could also potentiate the activation of microglia, participating in a vicious circle [96–98].

Meanwhile, in ALS patients, microgliosis also has been seen in the ventral horn of spinal cord, together with T cells near to corticospinal tract, in CSF, and in other regions of central nervous system at autopsy [99]. In addition to that, through a new technology used in other neurodegenerative diseases, such as AD or Huntington disease, which utilizes a specific ligand for positron emission tomography (PET) that detects only activated microglia, *in vivo* microgliosis was observed in diverse areas of the brain such as motor and dorsolateral prefrontal cortex and thalamus, in a heterogeneous population of ALS patients, existing a correlation between the intensity of microgliosis and disease progression [100–102].

In AD, it has been demonstrated that after neuronal death, aggregated tau can induce microglial activation and generate a neuroinflammatory cascade resulting in the expression of damage signals [28], surging the possibility that in ALS, SOD1 and TDP43 aggregates (hallmark of disease) could have a similar effect on inflammatory process. However, recent evidence shows that, in fact, inflammatory process through LPS and TNF-α stimulation

induces the formation of TDP43 aggregates and its mislocalization in a motor neuron cellular model and primary culture of microglia and astrocytes from hTDP43^{A315T} transgenic model, as in spinal cord from the same mice [103], presenting new data to this possible vicious cycle between neuroinflammation and aggregates in the disease.

5.2. Other microglial evidence

Other possible link between microglia, neuroinflammation and ALS corresponds to hemichannels. The communication between glial cells mainly occurs through gap junctions (GJ) [104]. These are intercellular channels that connect the cytoplasmic compartment of neighboring cells, allowing the pass of ions and small molecules up to 1000 Da [105, 106]. Every GJ is composed of two hemichannels, and each hemichannel is formed by six subunit proteins called connexins [107, 108]. In general, hemichannels are closed in physiologic states; however under pathologic conditions, they present a higher activity and opening, which could be triggered by metabolic inhibition, inflammatory mediators, or connexin mutations [109, 110]. In addition to that, it has been proposed that in pathologic environments, activated microglia is capable of releasing proinflammatory molecules that increment the opening of hemichannels, reducing the communication between astrocytes; depriving neurons of protective role of glia and reduce the neuronal viability [109]. Otherwise, different inflammatory treatments such as TNF-α and interferon-γ enhance connexin-43 (Cx43) expression in activated microglia, establishing a possible mechanism of activation after inflammatory stimulus in ALS [104].

In AD, it has been observed that exposition of amyloid-beta peptide increases the activity of hemichannels in astrocytes, microglia, and neurons and that hemichannel blockers prevent death of hippocampal neurons [111, 112]. It was also demonstrated that a hemichannel blocker, capable of crossing the blood-brain barrier, INI-0602, alleviates AD symptoms in a transgenic model of disease [112].

In ALS, although there are few antecedents about hemichannels and the disease, the same publication shows that SOD1^{G93A} transgenic mice treated with the INI-0602 blocker incremented the life span in comparison to the nontreated group, preventing axonal lost and diminishing the atrophy and improving muscular size [112].

6. Neuroinflammation in Parkinson disease

PD is the second most prevalent neurodegenerative disease after AD. These diseases are prototypic examples of the clinical manifestations of pathological brain aging and are characterized by cognitive deterioration—the first—and movement disorder—the latter. About 3% of the population over 65 years old will develop PD and these patients will be affected by a combination of movement disorders -i.e. parkinsonian sindrome- cognitive and neuropsychiatric symptoms, and autonomic function impairment [113]. Neuropathological studies on AD, ALS and PD brains have demonstrated the presence of protein aggregates that have been considered as a central part of neurodegenerative process.

In PD there is a specific damage to neurons in substantia nigra pars compacta in midbrain. Degeneration of nigrostriatal connections is responsible for motor, cognitive, and psychiatric symptoms.

There is a complex interaction between genetic susceptibility and external factors that determines damage to dopaminergic neurons of the substantia nigra that is responsible for PD development.

Increased permeability of blood-brain barrier and neurovascular dysfunction has been linked to the risk of PD as has been suggested by positron emission tomography (PET) and neuropathology studies. This may be related to increased leakage of systemic inflammatory molecules into the midbrain, activation of microglia, and death of dopaminergic neurons [114]. The role of systemic inflammatory response in PD is supported by increased activation of peripheral lymphocytes and increased levels of serum cytokines—that is, TNF-α, IL-2, IL-6, and regulated on activation, normal T cell expressed and secreted (RANTES) protein in PD patients [114].

A role of adaptive immune response is also supported by increase of MHC II in ventral midbrain astrocytes and microglia as an inflammatory response to MPTP in a murine PD model [115]. On the other hand, MHC II null mice showed less MPTP-induced neuronal death, reduced invasion of astrocytes and microglia, and no elevation in IFN-γ and TNF-α [115].

Since astrocytes constitute near half of central nervous system cells and they may perform a function as immunocompetent cells producing a variety of cytokines. Aquaporin-4 (AQP4) is upregulated in astrocytes in several inflammatory conditions including PD. Sun et al. have described that AQP4 knockout mice treated with MPTP showed increased basal and inducible expression of NF-κB and increased gliosis and they propose that AQP4 may modulate neuroinflammation via regulating release of proinflammatory cytokines and ATP by astrocytes which in turn further activates microglia [116].

There are some features that explain localized damage in substantia nigra pars compacta (SNpc); neurons in the area are particularly susceptible to oxidative damage as they operate under high oxidant conditions due to reduced levels of the anti-oxidant glutathione and increased iron content. On the other hand, there is a high density of microglia cells that mediates neuroinflammatory processes [114]. Oxidative stress induces the generation of ROS by microglia that become activated. DJ-1, the product of PARK 7 gene, is a gene associated with hereditary PD, works as a repressor of phosphatase and tensin homolog (PTEN)—a tumor suppressor gene—and has important functions in cellular antioxidant response. Since loss-of-function mutations of DJ-1 have been associated with PD, Meiser et al. described that loss of DJ-1 impairs antioxidant response and induces weak constitutive microglia activation in mouse microglia [117].

Microglia may become activated by a wide variety of damage signals that include toxins, pathogens, endogenous proteins or products generated by dying neurons. The constitutive expression of proinflammatory cytokines IL-1β, TNF-α, IL-2, IL-6, and IFN-γ has been demonstrated in PD patients in postmortem brain analyses as well as in serum and cerebrospinal fluid *in vivo* [114].

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Activation of microglia by dying neurons may result in a vicious circle of neuroinflammation and neurodegeneration [114]. Some of these substances liberated by degenerating neurons include α-synuclein aggregates, neuromelanin, adenosine triphosphate (ATP), and matrix metalloproteinase-3 (MMP-3) [114].

Microglia can get activated by pathologically altered forms of α-synuclein in PD, but also in other synucleinopathies such as dementia with Lewy bodies and multiple systems atrophy. Microglia activation gives raise to a balance between clearance of α-synuclein by phagocytosis via TLR4 microglia and neuronal dysfunction and neurodegeneration via oxidative stress and proinflammatory cytokine production by microglia [113].

7. Substances that inhibit microglial activation and neuroinflammation are protective in neurodegenerative diseases

Many different substances that prevent the triggering of inflammation in neurons have been used against AD, PD and ALS on primary cell cultures, mice models, and humans.

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a natural polyphenolic compound with antioxidant properties capable of penetrating the blood-brain barrier efficiently [118–120].

Regarding AD, it has been shown that resveratrol inhibits amyloid-beta aggregation *in vitro* [121] and that has neuroprotective properties in cell cultures and animal models [122, 123]. Moreover, a recent clinical study showed that resveratrol was safe and well tolerated in individuals with mild to moderate Alzheimer disease, and although some biomarker levels were altered, a larger research to determine whether resveratrol may be beneficial for AD patients is necessary [124].

In murine models of ALS, resveratrol ameliorated motor neuron loss and degeneration, delayed disease symptoms onset, improved locomotion impairment, and extended the lifespan in the $SOD1^{G93A}$ mice [125], and importantly, it was found that resveratrol administration reduces microglial immunoreactivity in the $SOD1^{G93A}$ mice spinal cord [125]. It has been amply described that one of the mechanisms by which resveratrol promotes neuroprotection is increasing Sirt1 activity, whose increase and activation were demonstrated in motor neuron from spinal cord of $SOD1^{G93A}$ mice [125], showing a crucial role of the antioxidant in the prevention of the neuroinflammation in the disease, specifically through the microglial activation and not astroglial activation. This is in concordance with another evidence that showed that despite that resveratrol was capable of preventing slowly the ROS increase, it could not improve motor neuron survival in a rat primary spinal cord culture after exposition to astrocyte conditioned media from transgenic $SOD1^{G93A}$ [126].

In PD resveratrol participation is still being studied, but it seems to have a protective effect against dopamine-induced cytotoxicity and certain toxins and can also attenuate the inflammatory response in activated microglia [127, 128].

In spite of the neuroprotective properties that characterize resveratrol, it has the drawback of its low bioavailability in the body, so there have been some important efforts to develop analogs with better bioavailability [121].

Another example of natural neuroprotective substances is curcumin. It is also a phenolic compound extracted from perennial herb *Curcuma longa* (turmeric), characterized for its anti-inflammatory and antioxidant properties [129, 130]. It is mainly known for helping to improve impaired cognitive functions in AD [131]. Among its properties, curcumin inhibits microglial proliferation and differentiation [132] and reduces the inflammation inhibiting amyloid-beta-induced expression of specific proteins in monocyte cells, decreasing the transcription of inflammatory cytokines, among others [133].

In transgenic AD mice tg2576, curcumin significantly reduced the levels of amyloid-beta and plaque burden in comparison to not treated tg2576 mice [134]. Finally, a preparation with a high bioavailability of curcumin called "*Longvida*" showed significant improvements in working memory and mood after 4 weeks treatment in a randomized, double-blind, placebo-controlled in a cohort of healthy, elderly subjects [135].

In ALS, in a motor neuron-like cellular model from TDP-43^{MUT}, curcumin abolished the excitability previously induced by the mutation, through the inhibition of the oxidative stress and mitochondrial dysfunction [136].

In another example, Riluzole [2-amino-6-(trifluoromethoxy) benzothiazole], which is the only approved disease-modifying drug for ALS, exhibited protective skills in different neurodegenerative alterations and disorders. It acts as a sodium channel blocker and protects neurons against glutamatergic toxic effects [137, 138] and its anti-inflammatory effects have been demonstrated. In ALS, Riluzole prevents hyperexcitability and motor neuron death in ventral spinal cord cell culture [82], it prolongs survival and delays muscle strength deterioration in a mice model of motor neuropathy (similar motor symptoms to ALS) [139], and it preserves motor neuron function in a transgenic model of ALS [140] but just extends the lifespan by a couple of months in patients [141].

In AD, due to a previous work indicating that the amyloid-beta peptide significantly alters the expression of glutamatergic transporter (GLUT1), which leads to increase of synaptic glutamate levels [142], it has been proposed that Riluzole could have potential benefits in the treatment of the disease. Nowadays, there is a phase 2 clinical trial in curse to test cognitive functional changes in mild AD patients [143].

In PD, Riluzole has shown neuroprotective properties reducing GFAP levels in the lesioned striatum in a rodent model [144].

At this point there is an important body of evidence that supports that neuroimmunomodulation/neuroinflammation has an active and potent role in many neurodegenerative diseases. Our three examples (AD, PD and ALS) show that instead of having different and specific targets, all of them share common pathways and participants that lead to activation of microglia and release of inflammatory factors that contribute to neuron death.

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8. Conclusion

The increase in life expectancy and the associated increase in the elderly population have led to a rise in cases of age-associated diseases; thus neurodegenerative diseases, such as AD, ALS and PD, are transformed into global issues and hot points for research and development of new drugs, especially considering the lack of effective treatment. In fact, most of the currently existing treatments, which are designed on the basis of symptom control, are only palliative.

In this chapter, we have delivered some of the evidence linking the development of inflammatory responses in the central nervous system with neuroinflammatory processes, present in the three very characteristic neurodegenerative conditions such as AD, PD and ALS. As we have mentioned an approach that considers similarities in pathophysiologic aspects of these diseases in spite of the very different clinical spectrum of each of them. This integrative approach is a new alternative road to the study of these diseases. Thus, the elements that define prolonged neuroinflammatory processes in time could be important elements to be considered in the early stage and even during pre-clinical asymptomatic stages of disease. In this context,

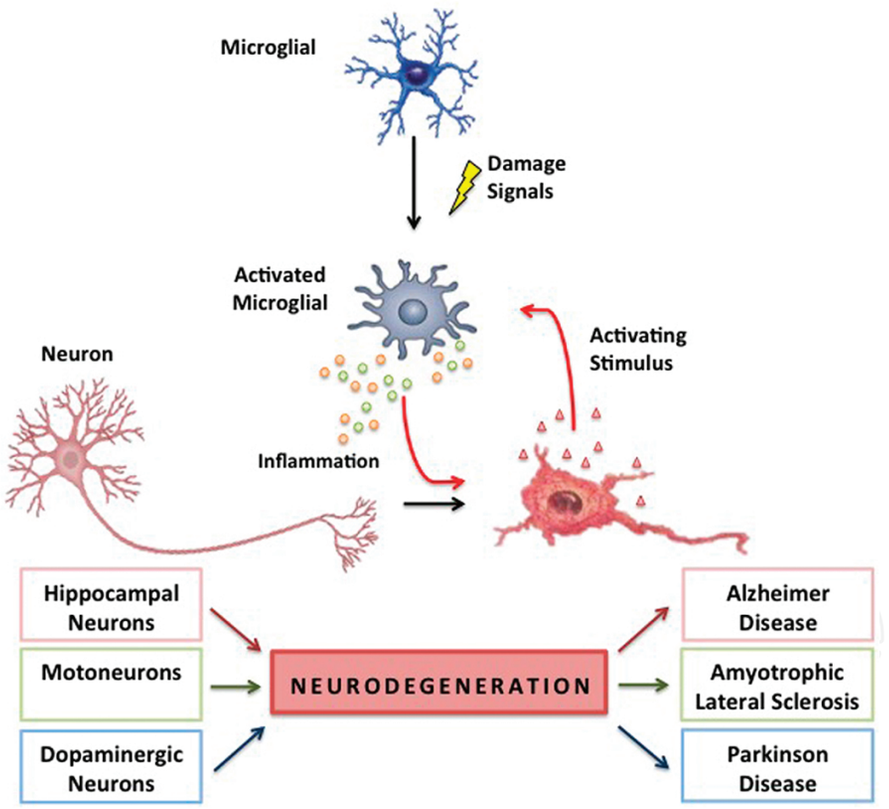


Figure 1. Model of neuroinflammation and neurodegeneration cycle. The microglial cell at rest is sensitive to different factors or signs of damage that lead to its activation. When these damage signals are maintained in time, the result is an altered response of activated microglial cells. This means that there will be a constant release of cytotoxic factors (mainly proinflammatory cytokines and ROS) that promote neuronal damage and/or lead to neurodegenerative processes. Hippocampal neurons, motor neurons, and dopaminergic neurons are susceptible to the action of overactive microglia, favoring neurodegeneration, which will trigger or will promote the development of AD, ALS and PD, respectively. In this model, once neurons degenerate, they release substances into the extra-cellular environment that are recognized by the microglia and act as a further sign of damage, promoting a neurodegenerative cycle.

the neuroimmunomodulation hypothesis [48, 58, 145–147] appears as a very plausible explanation for neurodegenerative stereotypical pathogenic process as well as a guide in the search for new therapeutic and new effective disease-modifying treatments.

We have also shown that microglial cell has an important role in the neuroinflammation and how this cell is linked with the neurodegenerative processes in these three diseases (**Figure 1**). That is, alterations in hippocampal neurons in AD, in motor neurons in ALS, and in dopaminergic neurons of substantia nigra in the PD are linked directly to the inflammatory response of the surrounding altered microglial cells, promoting the neurodegenerative process.

Another evidence of the effect and the importance of this negative neuroinflammatory-neurodegenerative cycle in the development of these diseases is the experimental response obtained after using compounds with anti-inflammatory properties in AD and ALS [131, 136], turning scientific interest in the development of future treatments that act on abnormal inflammatory response of microglial cell, so that might disrupt the neurodegenerative cycle.

Finally, it is of great interest to search for compounds that have fewer adverse effects and at the same time have a preventive action. In this context, the finding of anti-inflammatory and antioxidant properties in natural compounds opens new research possibilities, projecting a possible neuroprotective and anti-neuroinflammatory effects, which based on control of key elements of neuroimmunomodulation hypothesis could be a new tool for the treatment of these diseases.

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