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REVIEW ARTICLE

Alzheimer's Disease: New Concepts on the Role of Autoimmunity and NLRP3 Inflammasome in the Pathogenesis of the Disease

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Abstract: Alzheimer's disease (AD), recognized as the most common neurodegenerative disorder, is clinically characterized by the presence of extracellular beta-amyloid (Aβ) plaques and by intracellular neurofibrillary tau tangles, accompanied by glial activation and neuroinflammation. Increasing evidence suggests that self-misfolded proteins stimulate an immune response mediated by glial cells, inducing the release of inflammatory mediators and the recruitment of peripheral macrophages into the brain, which in turn aggravate AD pathology.

The present review aims to update the current knowledge on the role of autoimmunity and neuroinflammation in the pathogenesis of the disease, indicating a new target for therapeutic intervention. We mainly focused on the NLRP3 microglial inflammasome as a critical factor in stimulating innate immune responses, thus sustaining chronic inflammation. Additionally, we discussed the involvement of the NLRP3 inflammasome in the gut-brain axis. Direct targeting of the NLRP3 inflammasome and the associated receptors could be a potential pharmacological strategy since its inhibition would selectively reduce AD neuroinflammation.

Keywords: Alzheimer's disease, autoimmunity, neuroinflammation, microglial NLRP3 inflammasome, microbiota-gut-inflammasome-brain-axis, therapeutic targets.

1. INTRODUCTION

Alzheimer's disease (AD), one of the most common neurodegenerative diseases, is clinically characterized by memory loss and by a progressive decline of cognitive functions from mild cognitive impairment (MCI) to the entire defeat of language and the aptitude to be self-sufficient [1].

Over a century ago, the German psychiatrist Alois Alzheimer described the symptoms of this pathology and identified both insoluble plaques and neurofibrillary tangles as hallmarks of the disease [2]. Alzheimer also noticed a copious number of cells near the neurons in the brain, now known to be microglia, thus predicting neuroinflammation as a characteristic of AD.

As of 2020, AD is a diffused condition among the general population, especially among the elderly. AD is clinically characterized by the presence of extracellular beta-amyloid plaques and by intracellular neurofibrillary tau tangles. The involvement of the immune system in the pathogenesis of AD is widely accepted; however, increasing evidence is accumulating on active crosstalk between autoimmunity and neuroinflammatory processes.

This review updates the existing knowledge regarding autoimmunity and neuroinflammation in the pathogenesis of AD, focusing on the role of the NLRP3 inflammasome as a critical factor in stimulating innate immune responses, with emphasis on microglial receptors that trigger the generation of inflammatory mediators through inflammasome, indicating a new target for potential therapeutic intervention.

2. EPIDEMIOLOGY

AD represents about 70% of dementia cases and affects nearly 40 million people worldwide, with a predicted increase of 60% by 2030 [3]. Advanced age represents the most substantial risk factor for AD, and the significant increase in life expectancy indicates AD as a critical topic for public health. Unfortunately, no efficacious therapy exists for AD as of 2020. Up to now, the exclusive approved symptomatic treatment implies the use of cholinesterase inhibitors, which are able to significantly improve cognitive decline observed in AD patients. Increasing evidence suggests gender-related differences regarding brain atrophy, biomark-

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ers and degree of cognitive functions decline, indicating female gender as an important aspect for AD patient stratification [4]. As recently described, at the prodromal stages of AD, despite both men and women presenting equivalent hippocampal atrophy, women seem to be more protected compared to men in terms of cognitive performances [5]. However, in the advanced phase of the disease, women exhibit a sharper cognitive decline and higher rates of brain atrophy [6].

3. ETIOPATHOGENESIS

The hallmarks of AD are the intra-neuronal fibrillary tangles constituted of altered phosphorylated and truncated portions of the tau protein and the presence of the abnormal deposition of extracellular insoluble plaques composed of neurotoxic beta-amyloid (Aβ) peptides, deriving from the proteolytic processing of the amyloid precursor protein (APP) [7]. Following the amyloidogenic pathway, sequential cleavage of APP by β-secretase (also known as BACE) and γ-secretase generates Aβ peptides [8,9].

Numerous data supporting the amyloid hypothesis indicate Aβ as the culprit of the selective neurodegeneration seen in AD [7]. Neuroimaging and biomarker studies support this hypothesis, establishing that amyloid alterations anticipate tau pathology, and no mutations in the gene encoding tau protein (MAPT) are associated with AD, even if they induce tauopathies [9].

3.1. The Genetic Theory

Pathological mutations in APP, PS1 or PS2 can be congenital in familial forms of AD [10,11] characterized by an early-onset and quick progression of the disease. The pathogenic mechanisms that determine the sporadic AD, which arises in 10–30% of the population aged over 65, are not fully understood.

Nevertheless, several other gene variants that induce an increased risk in the development of this pathology have been identified, and these variants have been established as involved in AD pathophysiology mechanisms such as lipid transport and autophagy [12].

APOE4 protein, which is processed into neurotoxic fragments [13] and regulates brain Aβ clearance [14], represents the main genetic risk factor for sporadic AD. Indeed, epidemiological studies indicate that APOE4 homozygotes have a lifetime risk for AD of more than 50%, as compared to 20–30% for APOE3 and APOE4 heterozygotes [15].

3.2. The Autoimmune Theory

Numerous evidence support the role of the innate immune system in AD etiopathogenesis [11,16-18]. It has been shown that an increased risk of developing AD can be related to some rare genetic variants of the gene encoding the triggering receptor expressed on myeloid cells 2 (TREM2) [19] or of the CD33 gene [20].

Additionally, AD is characterized by the appearance of autoantibodies against a variety of molecules, some of which are specifically linked to the pathology, such as Aβ and tau, thus helping to identify blood-derived diagnostic/prognostic AD biomarkers [21,22].

The most studied autoantibodies modified in the serum of AD patients are those against Aβ.

Antibodies against oligomeric Aβ decline in advancing AD patients, contributing to controlling plaque burden [23-25]. The protective role of these antibodies supports the active (stimulation of anti-Aβ antibodies production) and passive amyloid immunotherapy (direct administration of these antibodies) as a potential therapeutic approach for AD [26-28].

In addition to autoantibodies against Aβ and tau, numerous autoantibodies related to inflammation, such as antibodies against microglia and astrocytes, have been detected in the blood of AD patients, suggesting inflammatory processes as a fundamental aspect of AD pathophysiology. [22,29]. Epidemiological and clinical lines of evidence have confirmed a relationship between autoimmunity and inflammation related to AD. Indeed, it has been established that a subgroup of genes involved in immune-mediated diseases with increased risk of inflammation, such as Crohn's disease, ulcerative colitis, rheumatoid arthritis, and type 1 diabetes is also associated with increased risk for AD [30].

To support this evidence, it has been demonstrated that patients affected by autoimmune diseases chronically treated with non-steroidal anti-inflammatory drugs (NSAIDs) have a lower incidence of AD [31]. Converging lines of evidence suggest an active involvement of neuroinflammatory processes in the pathogenesis of AD.

Inflammation in the brain, also caused by impaired functioning of the innate immune system, does not always comprise the classic hallmarks of inflammation, but somewhat shows infiltration of leukocytes or monocytes into the CNS, increased blood-brain barrier permeability, edema and gliosis.

Reactive astrogliosis is demonstrated by the presence, in the blood of AD patients, of autoantibodies against selective proteins produced by astrocytes, such as glial fibrillary acidic protein (GFAP) [32,33] and S100b [34], a protein that at high levels induces neuronal apoptosis [35]. Specifically, analyzing different stages of AD, levels of S100b antibodies show a relationship parallel to the Aβ25-35 trend, in correlation with the transformation of benign amyloid deposits into neuritic plaques [36].

Furthermore, immunocompetent microglia play a key role in AD, as established by the presence of antimicroglia antibodies not only in the blood, but also in CSF of AD patients, thus demonstrating the involvement of dysregulation of microglial function in AD pathogenesis [37].

3.3. The Neuroinflammation Theory

The inflammatory processes related to AD have been widely established in disease development [38]. The immune response through the brain's resident macrophage (microglia), worsening both amyloid and tau pathology, represents a key aspect in the investigation of AD. Indeed, it has been established that systemic inflammation, due to sustained microglial activation, represents a risk factor for AD development, appearing before the onset of cognitive decline [39].

3.3.1. The Role of Microglia

Microglia have turned out to be fundamental to the relationship between inflammation and neurodegeneration. In a healthy brain, microglia are in an inactive state, characterized by highly ramified cell processes. Immunological challenge or tissue injury leads to their activation, inducing a reduction in branch number and an increase in cell soma volume, identified by the expression of immune-related molecules and migration to the source of damage [38,40,41]. Microglia exist in two different phenotypes, the M2 form and the aggressive M1 form, that produce pro-inflammatory cytokines [42]. In AD, depending on the severity and the stage of the disease, the M1 phenotype is the predominant microglial form, promoting Aβ accumulation and neurotoxicity [43], thus suggesting that polarizing microglia to its good phenotype could represent a therapeutic opportunity [44].

The role of microglia around plaques has been highlighted in both AD animal models and post-mortem human brains, indicating that activation of these cells is accompanied by specific alterations of normal housekeeping genes with the purpose of attempting to defend the brain [41,45].

However, while activated microglia migrate to the plaques and phagocytes Aβ in an early phase, with time and pathology progression, they become inactive to clean extracellular Aβ [43,46]. Indeed, protracted activation of the immune response induces a reactive microgliosis with a persistent secretion of pro-inflammatory molecules and the recruitment of peripheral macrophages into the brain, which in turn aggravate AD pathology [43,47-49].

In recent years, many authors have emphasized the role of inflammasome as a link between the immune system and AD inflammation.

3.3.2. The Role Of Inflammasomes

Inflammasomes are multiprotein complexes that can stimulate innate immune responses, thus commencing inflammation, releasing activated inflammatory molecules such as interleukin (IL) IL-1β and IL-18, remaining continuously activated during the disease development and progression [50-53].

The key function of these cytosolic multiprotein complexes present not only in microglia [54], but also in immune cells and astrocytes [55], is stimulating the innate immune responses by recognizing injury signals, to control the activity of caspase-1 and the activation of interleukins [56].

Bacteria, viruses and fungi, toxins, aggregates such as Aβ and danger-associated molecular patterns (DAMPs) such as ATP, could activate inflammasome complexes [51].

Inflammasomes, essential for processing the inactive proforms of IL-1β and IL-18 into their mature active forms, are organized in three components: 1) a receptorial component, acting as a danger sensor; 2) an adaptor protein named apoptosis-associated speck-like protein (ASC) containing a caspase recruitment domain, and 3) a proteolytic effector consisting of procaspase-1.

Based on the receptor structure, sensors can be classified into two types: nucleotide-binding oligomerization domain-like receptors (NOD-like receptors; NLRs) and absent in melanoma 2 receptors (AIM2-like receptors; ALRs) [52].

The most broadly studied classes of inflammasomes are represented by the inflammasome-forming NLRs, including NLRP1, NLRP3, NLRC4, NLRC5, NLRP6, NLRP7 and NLRP12, followed by the non-NLR inflammasome, known as AIM2 [57].

Although the NLRP3 is the most characterized inflammasome subtype in AD, the roles of NLRP1, NLRC4 and AIM2 inflammasomes have been established in experimental AD models.

Indeed, by silencing the Nlrp1 gene, significantly upregulated in APP/PS1 mice cerebral tissues, a reduced neuronal pyroptosis and a rescue of cognitive impairments were observed [58]. The role of NLRC4 inflammasome has been also highlighted in cultured primary astrocytes able to produce cytokines, causing AD-like changes in primary co-cultured neurons. By down-regulating NLRC4 inflammasome in astrocytes, and consequently decreasing IL-1β secretion, reduced production of Aβ was observed in primary neurons [59].

Finally, the involvement of AIM2 inflammasome has been demonstrated in transgenic 5xFAD mice: Aim2 knockout reduced Aβ deposition and microglial activation, without a beneficial effect on spatial memory or cytokine expression [60].

3.3.3. The Role of the NLRP3 Microglial Inflammasome

As previously reported, the main inflammasome involved in the pathogenesis and progression of AD is the NLRP3 (NOD-like receptor protein 3) inflammasome composed of NLRP3 protein as a danger sensor receptor [61].

In AD, local factors such as aggregated Aβ or molecules produced during systemic neuroinflammation, for instance, the cytokines IL-1β and IL-18, concur to stimulate the inflammasome NLRP3.

NLRP3 activation is regulated by two steps. In the first step, the activation of the Nuclear Factor κB (NF-κB)-mediated pathway induces an increase of NLRP3 inflammasome-related proteins, among which the precursors of IL-1β and IL-18 (proIL-1β and proIL-18).

The second step is characterized by the NLPR3 oligomerization, followed by the assemblage of the NLRP3 protein, the adaptor ASC, and procaspase-1 to constitute the NLRP3 inflammasome complex, finally activating caspase-1, which proteolytically triggers IL-1β and IL-18 and promotes pyroptotic cell death [51,61-62].

The ability of Aβ to activate the NLRP3 inflammasome is mediated by receptors present on the surface of microglial cells. Among these receptors, the most relevant in inducing the microglial inflammatory phenotype and the release of inflammatory molecules are the Toll-like receptors (TLR) and the purinergic ionotropic receptors.

The Toll-like receptor 4 (TLR4) can directly bind Aβ and activate intracellular signaling, leading to the translocation of the NFκB into the nucleus and the transcription of several pro-inflammatory molecules [63,64]. The dangerous role of

TLR4 receptor in AD has been established by epidemiological studies indicating that rare genetic variants of the gene encoding the TLR4 receptor, with a reduction of function, can be related to a decrease of susceptibility to late-onset AD, independent of the APOE ε4 status [65].

Another relevant microglial receptor capable of activating the NLRP3 inflammasome is the purinergic P2X7 ion channel receptor (P2X7R) for ATP and adenosine 5′ diphosphate (ADP) [66], confirmed to exert a pivotal role in neuroinflammation and in neuron-glia interactions [67,68].

In physiological conditions, the microglial low-affinity P2X7R needs high concentrations of ATP for activation. However, during pathological neuroinflammatory conditions, like that observed in AD, this receptor is over-expressed and can be activated by ATP released by degenerating neurons [69-71]. It is worth noting that P2X7R up-regulation was observed in microglia obtained from both AD patients and Aβ treated rats [72].

In AD, it has been established that soluble or fibrillar Aβ triggers the activation of the NLRP3 inflammasome and the release of inflammatory molecules *via* P2X7R activation [73,74]. Aβ seems to act both indirectly, by increasing ATP release followed by P2X7R activation, and directly, by stimulating the large conductance P2X7 pore, a protein (pannexin-1) separated from the receptor and functioning as a hemichannel [75].

As shown in Fig. (**1**), P2X7-mediated activation of NLPR3, combined with the K^+ and Cl^- efflux [76], syner-

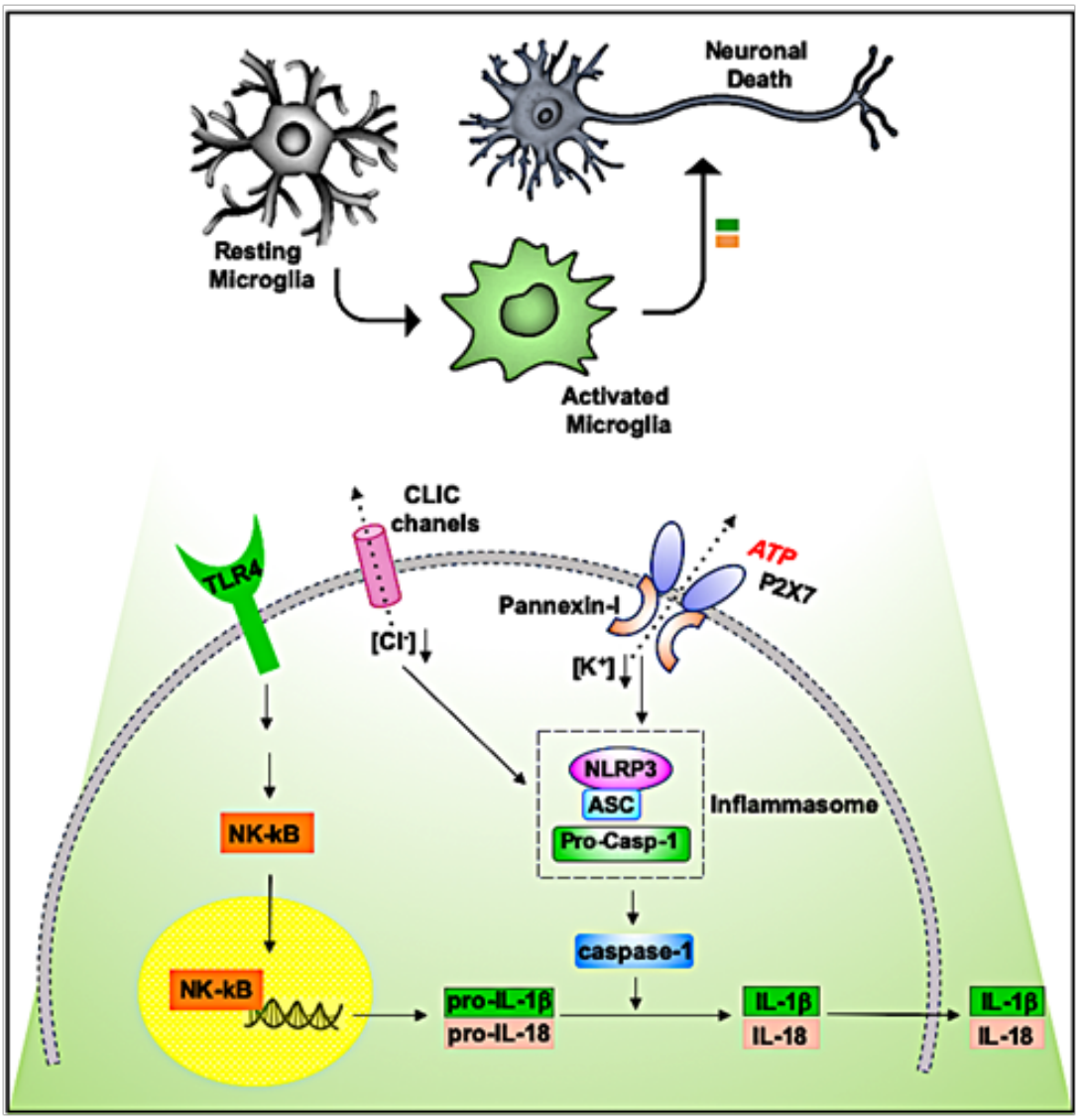

Fig. (1). Schematic illustration indicating the role of the microglial NLRP3 inflammasome in Alzheimer's disease. Soluble or fibrillar Aβ triggers the activation of NLRP3 inflammasome *via* TLR4- NF-κB pathway or P2X7 receptor. The NLRP3 inflammasome assembly also requires K^+ and Cl^- efflux. NLRP3 inflammasome activation induces increased synthesis of pro-IL-1β and pro-IL-18 and activates caspase-1. The proteolytic caspase-1 processes the inactive IL pro-forms into their mature pro-inflammatory active forms. Once secreted, IL-1β and IL-18 promote the pyroptotic death of neurons. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 1. Summary of the current evidence about the role of the NLRP3 inflammasome in the brains of AD patients and animal models.

Model	Involvement of NLRP3 Complex in AD Pathology	Refs.
AD patients	Increase of NLRP3 and of caspase-1mRNA levels	[77]
	Increased expression of NLRP3, ASC, caspase-1, and caspase-5 and the cytokines IL-1β and IL-18	[78]
	Polymorphisms of the Nlrp3 and of the CARD8 gene associated with AD risk	[79, 80]
	NLRP3 (NALP3) inflammasome activation by Aβ in microglial cells	[81]
AD animal models	Reduced Aβ deposition, attenuated spatial memory impairment by Nlrp3 inflammasome ablation in APP/PS1 mice	[77, 82]
	Reduced Aβ deposit and improved cognitive functions by anti-ASC antibody in APPSwePSEN1dE9 mice	[83]
	NLRP3 activation mediates Aβ-induced tau pathology in Tau22 mice	[84]

gizes with TLR4-mediated transcription to promote the inflammation pathway.

The harmful role exerted by the NLRP3 inflammasome complex in AD has been demonstrated in both AD clinical and preclinical studies, in agreement with the hypothesis that the activation of the NLRP3 inflammasome induced by Aβ can improve AD progression, by mediating a damaging chronic inflammatory tissue response (Table **1**).

Various studies have recognized that the NLRP3 inflammasome plays a critical role in AD human pathology. An increase of mRNA levels of the NLRP3 and of caspase-1 has been demonstrated in the brains of AD patients [77], as well as higher expression of NLRP3, ASC, caspase-1, and caspase-5, and the cytokines IL-1β and IL-18 have been identified in severe and mild AD patients' brains and monocytes [78].

Genetic evidence indicates that selected polymorphisms in the Nlrp3 gene in the late-onset AD brain could be associated with the risk of developing AD [79]. Moreover, it has been shown that the p.C10X polymorphism of the CARD8 gene, coding for a protein able to reduce NLRP3 activity by suppressing NF-kappaB, predisposes people to AD by increasing NF-kappaB activity and amplifying inflammatory process [80].

Various authors have established that theNLRP3 inflammasome seems to exert a detrimental role in AD animal models too. *In vitro* studies using primary mouse microglial cells treated with fibrillar Aβ have established the activation of the NLRP3 (NALP3) inflammasome, leading to stimulation of caspase-1 and release of IL-1β [81].

In vivo studies using the transgenic APP/PS1 mouse model of AD showed that the Nlrp3 inflammasome ablation skewed microglial cells to an M2 phenotype and reduced Aβ deposition, attenuating spatial memory impairment [76].

These results were confirmed by Dempsey *et al*., [82] in the same experimental model, demonstrating that inhibition of the NLRP3 inflammasome by MCC950/CRID3 was able to promote Aβ clearance and to ameliorate cognitive functions of APP/PS1 mice.

Moreover, in transgenic APPSwePSEN1dE9 mice, intrahippocampal injection of prion-like ASC specks, produced by microglia in response to NLRP3 activation, significantly increased Aβ pathology, while co-application of an anti-ASC antibody reduced Aβ deposit and improved cognitive functions [83].

Additionally, it has been recently assessed that NLRP3 activity represents an essential component in the Aβ-tau cascade, since intracerebral injection of fibrillar Aβ induced tau pathology in an NLRP3-dependent manner in Tau22 mice [84].

Recently, it has been established that the NLRP3 inflammasome-signaling pathway is a key mediator of damaging effects of microglial activation during systemic inflammation, since it has been demonstrated that NLP3 knockout mice are resistant to microglial changes induced by inflammation [85].

The above-mentioned results show that the inhibition of NLRP3 inflammasome and related receptors could represent a therapeutic target as an AD modifying agent.

3.3.4. NLRP3 Inflammasome and the Gut-brain Axis

The gut microbiota is a complex and active population of microorganisms that colonize the intestinal tract, exerting a striking influence on the host during both health and disease [86].

A bidirectional communication system between the intestinal tract and the central nervous system (CNS)—the gut-brain axis—has highlighted the involvement of gut microbiota into the complex biology of AD, establishing a link between peripheral inflammation and dementia [87].

During aging, or in the presence of central neurodegenerative diseases, changes in gut microbiota, referred to as dysbiosis, can contribute to gastrointestinal dysfunctions, modifying the intestinal epithelial barrier and endorsing enteric neurogenic/inflammatory responses. Not only the intestinal barrier but also the blood-brain barrier have turned out to be significantly more permeable, allowing potential neurotoxic factors generated by microbiome, such as inflammatory cytokines, to penetrate the CNS, consecutively contributing to neuroinflammation and neurodegenerative processes [88-90].

Alteration of gut microbiota composition, with a shift towards a pro-inflammatory profile and the occurrence of enteric inflammation, has been observed in AD patients [91-

93]. In AD animal models, it has been confirmed that microbiota directly contributes to the development of cerebral Aβ amyloidosis [94, 95].

Recently, NLRP3 inflammasome activation has been established to exert a key role in the interplay between the intestinal tract and the CNS, formerly referred to as microbiota-gut-inflammasome-brain-axis, as extensively reviewed by Pellegrini *et al*. [96].

In AD, the 'pro-inflammatory' dysbiosis most likely induces the activation of the NLRP3 inflammasome in immune/inflammatory cells, contributing to the modification of both the intestinal epithelial and the blood-brain barrier, amplifying not only the peripheral, but also the central neurogenic/immune-inflammatory responses [93].

Moreover, gut microbiota in AD patients has been shown to produce amyloid peptides which, escaping from the gastrointestinal tract and accumulating in the brain through the gut-brain ascending pathways, might play a role in the production of proinflammatory cytokines, possibly by NLRP3 activation [97,98].

Further evidence of the relationship between NLRP3 inflammasome and gut microbiota has recently been established by Shen *et al*., [99]. These authors demonstrated that the transplant of gut microbiota from AD patients into APP/PS1 mice increased the expression levels of intestinal NLRP3 and of inflammatory factors in peripheral blood, worsening the cognitive impairment of the mice.

Furthermore, since the communication between the two systems is bidirectional, central NLRP3 activation and consequent release of inflammatory mediators could contribute to worsening enteric neuroimmune/inflammatory responses *via* brain-gut descending pathways.

Taken together, this evidence shows that inhibition of NLRP3 inflammasome could be directed against both central and peripheral inflammation, exerting a multidirectional therapeutic potential.

4. CLINICAL ASPECTS

The clinical progression of AD is divided into three phases ranging from a preclinical state, showing amyloid depositions and neurodegeneration without clinical impairments, an MCI state with initial cognitive decline, and a final stage characterized by dementia. These clinical criteria were implemented by the individuation of several biomarkers and neurodegenerative hallmarks [100].

The progression of symptoms meets the criteria of non-amnestic AD presentation including language, visuospatial, and executive dysfunction features and of amnestic AD, the larger part of the disease [101]. AD patients show a preferential degradation of cognitive over motor and sensory networks, which are not included in normal aging changes [102]. The prevalent symptoms during the preclinical or early stages of AD include anxiety, depressive symptoms, and apathy. The progression to later-stage psychiatric symptoms, such as impaired judgment, disorientation/confusion, agitation and other typical neuropsychiatric symptoms, such as hallucinations, might go unrecognized until clinical diagnosis. The first step of AD clinical evaluation is the recognition of selected early warning symptoms as widely described by the Alzheimer's Association [103,104].

In 2013, the term "neurocognitive disorder" was introduced by the American Psychiatric Association in Diagnostic and Statistical Manual of Mental Disorders, DSM-5, enlarging the definition of mild cognitive disorder to MCI and major cognitive disorder to dementia, as AD. [105].

5. DIAGNOSIS

AD syndrome can be accurately diagnosed by the integration of individual history, clinical examination, and selected laboratory tests and neuroimaging.

The diagnosis of dementia is defined when a patient presents a chronic and progressive loss of memory and a deficit in at least one other cognitive function such as object knowledge, praxis, language or executive function, that interferes with the capacity to perform daily routine activities. Clinical diagnosis of possible or probable AD can be performed with an accuracy higher than 80% at its earliest stages [106].

Moreover, among the cognitive screening tools, the Mini-Mental State Examination (MMSE), as indicated by Folstein, *et al*, is the most widely used method for grading the cognitive state of AD patients [107].

Patients who are suspected of suffering from AD undergo additional investigations such as blood tests, lumbar puncture (research of beta and tau proteins), genetic tests and different radiologic investigations. Since the presence of β-amyloid plaques and neurofibrillary tau deposits are specific hallmarks of AD, the diagnosis of AD can be made by the presence of specific biomarkers in cerebrospinal fluid (CSF), grouped into those relative to Aβ (A), pathological tau (T) and neurodegeneration/neuronal injury (N) [108].

An AD diagnosis could be made if both A and B biomarkers are altered in CSF (reduced Aβ42 or the Aβ42/Aβ40 ratio and increased total and phosphorylated tau).

Additionally, positron emission tomography (PET) using specific ligands for Aβ (Pittsburgh compound B) and for tau (flortaucipir) is valid *in vivo* substitute for the detection of Aβ deposits and of pathologic tau tangles [109,110]. Magnetic resonance imaging (MRI), detecting brain atrophy is a neuroimaging technique routinely used for AD diagnosis, however, alone it is not specific since it only detects the neurodegeneration within (but not limited to) AD-affected regions, indicating a decrease of cognitive functions that may also be of another origin [111].

Fig. (**2a**) shows that PET from AD patients positive for CSF biomarkers and neurodegeneration (A+T+(N)+) is characterized by cerebral atrophy accompanied by both abnormal Aβ and phospho-tau. On the other hand, as shown in Fig. (**2b**), brain atrophy not correlated to biomarkers (A+T−(N)−) and Aβ and phospho-tau PET abnormalities support non-Alzheimer's pathologic changes.

6. TREATMENT

The available therapies for AD are unable to stop or reverse the progressive neurodegeneration but can only provi-

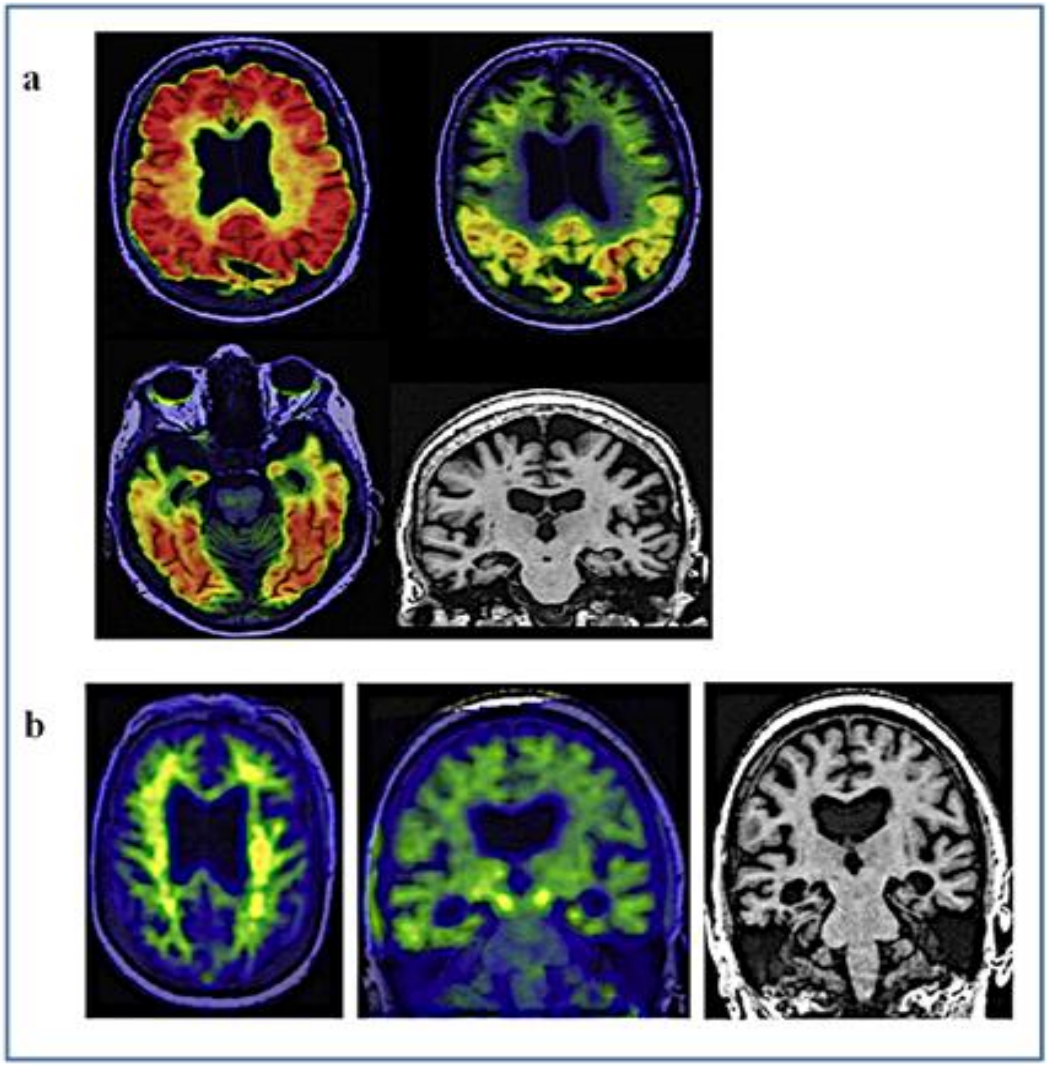

Fig. (2). a. Alzheimer's disease with dementia. PET imaging of a woman with multidomain dementia. Abnormal amyloid PET with Pittsburgh compound B (top left), tau PET with flortaucipir (top right and bottom left), and atrophy on MRI (bottom right). Biomarker profile A+T+(N)+. (From Jack *et al*., 2018 [108]). **b**. Non-Alzheimer's pathologic change with dementia. PET imaging of a woman with progressive amnestic dementia. Imaging reveals a normal amyloid PET (Pittsburgh compound B, left), normal tau PET with flortaucipir (middle), and severe medial temporal atrophy on MRI (right). The biomarker profile [A−T−(N)+] suggests the patient has non-Alzheimer's pathologic change. Hippocampal sclerosis was confirmed at autopsy. (From Jack *et al*., 2018 [108]). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

sionally alleviate the symptoms of the disease. Until now, the United States Food and Drug Administration (FDA) has only approved five drugs for AD symptomatic treatment, including the acetylcholinesterase inhibitors (AChEIs) tacrine (discontinued in the USA in 2013 for its side effects), rivastigmine, galantamine and donepezil, and the glutamate receptor antagonist memantine.

The use of AChEIs, by increasing intracerebral ACh concentration, recovers cognitive deficits and behavior of mild, moderate, and severe stages of AD, mainly during the first year of treatment [112-115].

Memantine, the antagonist of the glutamate N-Methyl-D-aspartate (NMDA) receptor is used to alleviate the symptoms only in moderate and severe stages of AD, being ineffective in mild AD [116,117].

No other drugs have been approved by the FDA since 2003, even though many clinical trials have been carried out [118-119].

The greater part of these studies has been directed against the amyloid-related mechanisms, testing drugs able to reduce Aβ production, such as gamma-secretase inhibitors, BACE inhibitors or alpha-secretase activators, or agents directly inhibiting Aβ aggregation [120].

Considering the role of the immune system in AD pathogenesis, a lot of immunomodulatory therapeutic strategies against amyloid have been extensively tested, with the aim of stimulating the innate immunity and inducing Aβ clearance [121,122].

While active immunization, producing antibodies by using immunogenic Aβ peptides, is accompanied by severe

side effects such as sterile encephalitis [123,124], passive immunization with antibodies against Aβ is characterized by lesser side effects and seems promising, especially if treatment is started in the early stages of the disease.

Several ongoing clinical trials using monoclonal antibodies or immunoglobulins (IgG) anti-Aβ are in phase II and III [125]. Among these, a clinical trial employing aducanumab, a natural human monoclonal antibody that selectively targets aggregated Aβ, showed promising brain Aβ reduction and slowing down of cognitive decline in patients with prodromal or mild AD [126-128].

In the past decades, starting from the inflammatory hypothesis of AD, several studies in both transgenic AD animal models and AD patients demonstrated that NSAIDs can reduce AD pathology [129,130]. Numerous clinical trials using NSAIDs among which indometacin, rofecoxib, naproxen or aspirin were used, showed no significant benefit to people with symptomatic AD [131-135].

The failure of these clinical trials could be related to the fact that most of the patients recruited were in an advanced and irreversible neurodegenerative stage and were not subjected to a long term follow up. Indeed, it has been proposed that NSAIDs could exert a beneficial effect if administered before the clinical diagnosis of AD, which can precede the onset of dementia by a decade [136]. Confirming this hypothesis, clinical trials with naproxen or celecoxib treatment extended to 2 or 3 years reduced AD neurodegeneration in asymptomatic subjects [137].

The high rate of failure of drug development in AD strongly requires new treatment targets and the detection of predictive biomarkers that could provide insight into the impact of new therapies.

As described above, activated microglia stimulate the NLRP3 inflammasome, leading to increased activity of caspase-1 and the release of inflammatory interleukins (IL-1β and IL-18) which play a crucial role in the development of AD neuroinflammation. For this reason, NLRP3 inflammasome and its effectors appear as an attractive target for therapeutic intervention.

Numerous preclinical studies directed against the microglial NLRP3 inflammasome were carried out both *in vitro* and *in vivo*, in AD animal models, using different natural and synthetic drugs able to hamper the NLRP3 activation [138].

Among the studies performed *in vitro*, cultured microglial cells activated by Aβ have been used as a model of NLRP3/caspase-1 inflammasome pathway stimulation. Using this system, natural compounds such as Pterostilbene, Edaravone and Benzyl isothiocyanate have been demonstrated to exert a significant inhibitory activity [139-141]. Similar results were obtained in cultured macrophages stimulated by Aβ, as demonstrated by the ability of Stavudine, a natural nucleoside reverse transcriptase inhibitor, to hamper the assembly of the NLRP3 inflammasome [142].

Other natural compounds with inhibitory activity against the NLRP3 inflammasome, including Artemisinin and Dihydromyricetin, have been tested in AD animal models. Artemisinin, when intraperitoneally injected in APPswe/PS1dE9 mice, exerted protective effects on AD pathology, suppressing NF-κB activity and NLRP3 inflammasome stimulation and decreasing neuritic plaque burden [143]. Similarly, intraperitoneal treatment of Dihydromyricetin in APP/PS1 mice has been demonstrated to exert an inhibitory effect against the expression of NLRP3 inflammasome components and against memory and cognition deficits [144].

Different groups have synthesized and tested several rationally designed NLRP3 inflammasome inhibitors in AD transgenic animals, demonstrating their potential pharmacological activity [145]. Indeed, it has been shown that chronic treatment of TgCRND8 mice with the NLRP3 inflammasome inhibitor JC-124 was able to inhibit the caspase-1 cleavage and to reduce Aβ deposition and microglial activation [146].

Moreover, treatment with the small molecule NLRP3 inflammasome inhibitor MCC950 has demonstrated an inhibitory neuroinflammatory activity in APP/PS1 mice, reducing inflammasome, microglial activation and Aβ accumulation and improving cognitive functions in mice [82].

Interestingly, MCC950 has also revealed a peripheral anti-inflammatory activity, attenuating colonic inflammation in spontaneous colitis mice, inhibiting IL-1β production and restoring the integrity of the intestinal barrier [147].

Considering the role exerted by NLRP3 inflammasome activation in the microbiota-gut-inflammasome-brain-axis, the beneficial effects of such an NLRP3 inflammasome inhibitor can be exerted dually and synergistically in both AD and chronic peripheral inflammation.

Recently, promising studies were performed using NSAIDs of the fenamate class, demonstrated to be inhibitors of the NLRP3 inflammasome independently of their cyclooxygenase (COX) activity, acting through the inhibition of volume-regulated ion channels (VRACs). In AD transgenic and not transgenic animal models, fenamate treatment completely restored memory deficits and neuroinflammation, in terms of microglial activation and IL-1β expression [148].

Directly aiming at microglial NLRP3 inflammasome could represent a new therapeutic strategy for AD since compounds directed against this target can not only act at both central and peripheral levels, but are also associated with reduced systemic effects with respect to targeting downstream effectors of NLRP3 inflammasome activation.

Indeed, interfering with the downstream effectors caspase-1 or NF-kB signaling or with the interleukins production and their release or with their parent receptors could exert negative systemic effects, as a consequence of the ubiquitous distribution and relevance of these elements in many physiological CNS functions.

As an example, since IL-1 plays a key role in synapses formation and cognitive processes [149-151], inhibition of IL-1 signaling could even leave cognitive impairment unchanged. Numerous compounds able to inhibit the NF-kB signaling pathway demonstrated, *in vitro* and *in vivo* experimental models, the ability to reduce the release of inflammatory mediators [138].

However, NF-kB is implicated in hippocampal synaptic plasticity [152] and targeting this ubiquitary transduction

pathway could exert controversial effects, rendering this approach futile too.

Among the receptors involved in the microglial NLRP3 inflammasome activation, a promising target is represented by the P2X7 receptor, that has been shown as up-regulated in the microglia of both AD patients and Aβ treated rats [72], as confirmed by preclinical studies indicating that P2X7R antagonists can represent novel therapeutic targets for the treatment of AD [153].

Antagonism of P2X7R could represent a selective drug strategy since this physiologically low-affinity receptor is pathologically overexpressed and activated by ATP released by degenerating neurons in AD.

As recently reviewed, new brain penetrating P2X7R antagonists have been synthesized and tested for different CNS disorders in both animal models and human pathologies, highlighting the clinical interest for the application of these compounds in AD [138].

CONCLUSION

The multifactorial etiology of AD pathogenesis represents the most likely reason for the recurring failure of pharmacologically active drugs against the disorder. Right now, the most promising strategy seems to be a combination therapy, targeting different factors at the same time. Besides pharmacotherapy, an early intervention is required, before the irreversible deposition of Aβ plaques and the onset of the typical AD symptoms.

Indeed, it is worth noting that APP processing and Aβ deposition represent an early event in AD, as supported by data indicating that Aβ biomarkers can precede the appearance and progression of cognitive deficit and conversion to AD dementia by 5 to 10 years [154].

Much evidence supports neuroinflammation, coordinated by neurons, glial cells, and immune components, as a contributing cause of neurodegeneration, leading to the clinical symptoms typical of AD.

In the pathogenesis of AD, activation of the microglial NLRP3 inflammasome represents an emerging factor contributing to disease progression. Direct targeting of the NLRP3 inflammasome seems to be a good-looking pharmacological strategy since its inhibition would selectively reduce neuroinflammation, leaving physiological microglial functions unaffected.

Moreover, taking into account the interplay between inflammation in the intestinal tract and the CNS, formerly referred to as microbiota-gut-inflammasome-brain-axis, NLRP3 modifying drugs can also antagonize the peripheral inflammation.

A growing body of evidence suggests that microglial inflammasome could be activated during the asymptomatic phase and that drugs able to interfere with such a system could represent a helpful therapeutic tool in the early and mild stages of the disease.

Indeed, further efforts are needed by future research to focus on identifying additional specific receptor antagonists and, hopefully, starting clinical trials with existing candidate drugs able to target assembly and activation of the inflammasome.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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