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REVIEW

Targeting neuroinflammation in Alzheimer's disease

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Abstract: Almost 47 million people suffer from dementia worldwide, with an estimated new case diagnosed every 3.2 seconds. Alzheimer's disease (AD) accounts for approximately 60%–80% of all dementia cases. Given this evidence, it is clear dementia represents one of the greatest global public health challenges. Currently used drugs alleviate the symptoms of AD but do not treat the underlying causes of dementia. Hence, a worldwide quest is under way to find new treatments to stop, slow, or even prevent AD. Besides the classic targets of the oldest therapies, represented by cholinergic and glutamatergic systems, β-amyloid (Aβ) plaques, and tau tangles, new therapeutic approaches have other targets. One of the newest and most promising strategies is the control of reactive gliosis, a multicellular response to brain injury. This phenomenon occurs as a consequence of a persistent glial activation, which leads to cellular dysfunctions and neuroinflammation. Reactive gliosis is now considered a key abnormality in the AD brain. It has been demonstrated that reactive astrocytes surround both Aβ plaques and tau tangles. In this condition, glial cells lose some of their homeostatic functions and acquire a proinflammatory phenotype amplifying neuronal damage. So, molecules that are able to restore their physiological functions and control the neuroinflammatory process offer new therapeutic opportunities for this devastating disease. In this review, we describe the role of neuroinflammation in the AD pathogenesis and progression and then provide an overview of the recent research with the aim of developing new therapies to treat this disorder.

Keywords: reactive gliosis, astrocyte, microglia, Alzheimer's disease

Introduction

Dementia is a chronic condition characterized by a progressive cognitive impairment that leads to functional disability.[1] In 2015, it was estimated that approximately 47 million people worldwide were affected by dementia, and this number is expected to increase, reaching 131.5 million by 2050.[2] As such, it represents a veritable public health challenge. Alzheimer's disease (AD), a pathology first described by Alois Alzheimer in 1907,[3] is the most frequent cause of dementia in elderly. Knowledge about the etiology and pathogenesis of the disease is continuously updated,[4] but there are still limitations in diagnostic capability[5] and in the discovery of pharmacological treatments that would be able to stop or better prevent the disease. At present, AD is incurable. Despite the huge amount of preclinical and clinical investigation, medications currently used provide only a modest symptomatic relief to a subset of patients and do not treat the underlying causes of this disease. The reasons for this failure are probably due to the scant knowledge of the cellular and molecular mechanisms implicated in AD pathogenesis and of the approved therapies that coarsely affect both

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cholinergic and glutamatergic neurotransmission. Conversely, many of the new drugs in development aim to modify the disease process itself by impacting one or more of the many wide-ranging brain changes caused by AD. These changes offer potential targets for new drugs to stop or slow down the disease progression. It is now well recognized that AD is a multifactorial disorder. It is pathologically characterized by widespread oxidative stress, mitochondrial damage, glutamate excitotoxicity, neuroinflammation, neurofibrillary tangle (NFT) formation, and β-amyloid (Aβ) deposition creating senile plaques (SPs).[6] These latter are constituted by Aβ peptide, and their genesis is followed by intracellular deposition of NFTs,[7] as a consequence of tau protein hyperphosphorylation. The results are synaptic and neuronal dysfunction and loss.[8] Over the years, it has been demonstrated that other factors play an important role in the pathogenesis and progression of AD. Among them, the key role of neuroinflammation has been affirmed.[9]

Physiologically, the inflammatory process is aimed at controlling injuries through several mechanisms to repair tissues.[10] However, an increasing amount of literature confirms its role in the pathogenesis and exacerbation of AD.[11–14] Inflammation acts to remove both the initial cause of the infliction and to eliminate the destroyed tissues and dead cells resulting from the original injury.

In fact, inflammation is emerging as the real cause of the associated disease, more than a mere contribution to the exacerbation of tissue damage. Indeed, some studies have revealed that the injection of lipopolysaccharide in transgenic mice induces neuroinflammation, triggering intracellular Aβ deposit and tau phosphorylation.[15,16]

The molecular processes are not necessarily the primary events. The inflammatory machine could also be triggered by traumatic or surgical causes. The microglial priming model suggests that the presymptomatic AD pathology, characterized by low levels of proinflammatory mediators, can act on microglia for long periods of time.[17] Furthermore, stress, inflammation, and infection can operate as secondary triggers, causing changes in these primed cells: they reach an activated state establishing an inflammatory response contributing to AD pathogenesis.[18]

From an immunological point of view, the central nervous system was always seen as a highly protected tissue, exposed to inflammatory phenomena solely in cases of infection or disruption of the blood–brain barrier (BBB). Nowadays, we know that there are several cells expressing pattern recognition receptors able to induce inflammatory signaling pathways.[13] These pattern recognition receptors can recognize molecular signals of microbial molecules, called pathogen-associated molecular patterns, as well as endogenous damage-associated molecular patterns (DAMPs), that typically accumulate in infected tissues. DAMPS are present in diseased brains as misfolded proteins (eg, SPs and NFTs), aggregated peptides, or nucleic acids.[19] It is clear that DAMPs can trigger neuroinflammation by deflecting proinflammatory reactions from their helpful purpose, and this is the reason why our way of viewing neurodegenerative diseases has changed over the years.

The role of the neuroinflammatory process is not exclusively attributable to innate immunity (which in the brain is constituted by microglia), but it is also caused by other brain resident cells that constitute, in one word, macroglia (ie, astrocytes, NG2-positive cells, and oligodendrocytes), as well as endothelial cells and neurons.[20–23]

Hence, it is clear that there are many characters involved in this inflammatory process. Thus, a better knowledge of the mechanisms underlying the role of neuroinflammation in AD can be an excellent starting point for the development of molecules able to counteract it.

The pathophysiology of neuroinflammation and its role in Alzheimer's disease

Even if Aβ deposits can alone induce an inflammatory response that subsequently leads to AD development, it is well established that the neuroinflammatory pathophysiology is more complex and driven by the activation of different brain cells. In particular, growing evidence suggests that this phenomenon is mainly supported by glial cells, which respond quickly to brain injuries, activating a series of repair mechanisms to restore brain physiology. Glial cells are nonexcitable cells of the central nervous system. These cells are a highly heterogeneous population, responsible for many important brain functions.[24] While microglia acts as the first form of immune defense in the brain, astrocytes are an essential neurosupportive cell type. Indeed, astrocytes finely control the environment by regulating pH, ion homeostasis, oxidative stress, and blood flow.[25,26] These cells together with microglia, oligodendrocytes, neurons, pericytes, and endothelial cells constitute the neurovascular unit, responsible for the proper functioning of the BBB.[27] In addition, astrocytes contribute importantly to synaptogenesis and dynamically modulate information processing and signal transmission, regulate neural and synaptic plasticity, and provide trophic and metabolic support to neurons.[28,29] Interestingly, data from animal models and human autopsy revealed that both SPs

and NFTs cause an immune response in the brain and colocalize close to activated glial cells. Astrocyte and microglia acquire a reactive phenotype[20] and rapidly act in response to pathology undergoing important changes in their morphology and functioning.[30,31] Such an activation is fundamentally a protective response aimed at removing injurious stimuli. The neuroprotective action of reactive astrocytes takes place by modulating Aβ-mediated neurotoxicity, degrading, internalizing, and removing Aβ, thus creating a protective barrier that surrounds plaques.[32–34] However, uncontrolled and prolonged activation goes beyond physiological control, and detrimental effects override the beneficial ones. In this condition, glial cells foster neuroinflammatory response, accounting for the synthesis of different cytokines and proinflammatory mediators.[35,36] This condition is called reactive gliosis and is a characteristic event of AD brains (Figure 1). For example, activated microglia reduces Aβ accumulation by increasing its phagocytosis, clearance, and degradation,[37] as well as by secreting factors such as the glia-derived neurotrophic factor, helpful for neuronal survival.[38] Recently, microglia functions aimed at Aβ clearance were attributed to the presence of triggering receptor expressed on myeloid cells 2 (TREM2), a transmembrane receptor;[39,40] indeed not long ago, TREM2 was identified as a risk gene for AD.[41,42] It is reasonable to think that this association between TREM2 and AD is due to the many functions carried out through the activation of different pathways ranging from phagocytosis to encouraging survival and proliferation, and finally promoting secretion of cytokines and chemokines.[43–45]

Even astrocytes play an important role in the maintenance of the cerebral homeostasis. These cells are responsible for the proper functioning of the BBB, provide nutrients to neurons, preserve the extracellular ion balance, and remove and degrade Aβ.[46] However, glial functions are deeply altered whenever tissue physiology is not restored. In these circumstances, the inability to counteract Aβ and NFTs accumulation constantly stimulates the machinery needed to remove debris; in this way, astrocytes actively support inflammation.[47,48]

Several studies demonstrated that their action becomes relevant from early stages of the pathogenic process, turning to a cycle independent from Aβ presence, neural dysfunction, cell death, and disease progression.[49–51] The resulting chronic inflammation is due to the release of proinflammatory molecules that act not only in an autocrine manner, allowing the perpetuation of the reactive gliosis, but also in a paracrine one, the main cause of the neuronal death that increases the pathological damage.[52,53] Neuronal death is determined by the release of not only inflammatory mediators, but also of reactive oxygen species, nitric oxide (NO), proteolytic enzymes, complement factors, and/or excitatory aminoacids.[54] At the molecular level, the release of these mediators affects neuron–glia crosstalk, influencing redox enzyme sensors, receptors, and transcription factors.[55]

In physiological conditions, microglia protects the brain from pathogens, and, together with macroglia, helps maintain homeostasis of the tissue. In AD, all these cells became more reactive and change their morphology surrounding SPs.[56]

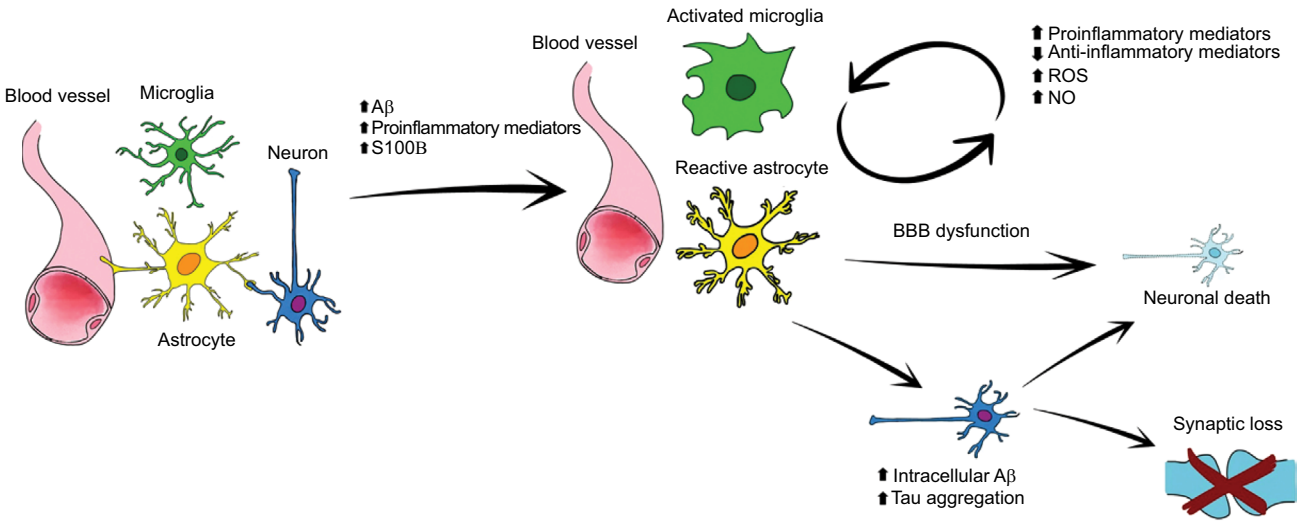

Figure 1 Schematic representation of glial activation.
Notes: As a result of brain damage (eg, brain trauma, ischemia, Aβ accumulation, NFTs, etc) microglia and astrocytes acquire a so-called reactive phenotype losing their physiological functions. Morphofunctional changes, loss of three-dimensional network, and neurovascular unit alterations contribute to cause a homeostatic imbalance. Moreover, after activation, these cells produce a wide range of cytokines and proinflammatory mediators, leading to chronic inflammation. Even if the initial intent of these modifications is reparative, such long-lasting and uncontrolled activation causes further neurodegeneration.
Abbreviations: ROS, reactive oxygen species, NO, nitric oxide; Aβ, β-.amyloid; NFTs, neurofibrillary tangles; BBB, blood–brain barrier.

This is possible because of the presence of proinflammatory receptors on their surface. Microglia is able to identify and bind Aβ oligomers and fibrils and the amyloid precursor protein (APP)[57] through a large number of receptors, including scavenger receptor class A type 1, MARCO, scavenger receptor class B member 1, CD36, and the receptor for advanced glycation end product,[58,59] G protein-coupled receptors formyl peptide receptor 2 [60] and chemokine-like receptor 1,[61] toll-like receptors (TLRs) TLR2,[62] TLR4, and the CD14 coreceptor, and α6β1 integrin.[63] The outcome of the bond between Aβ and these receptors is the production of inflammatory mediators such as cytokines (interleukin [IL]-1α, IL-1β, IL-6, IL-8, IL-12, IL-18, and IL-23, interferon (IFN)-γ, tumor necrosis factor [TNF]-α, and granulocyte-macrophage colony-stimulating factor [GM-CSF]),[64,65] chemokines (monocyte chemotactic protein 1 (MCP1), MCP-113, fractalkine),[66,67] chemoattractant proteins, prostaglandins, complement factors, thromboxanes, pentraxins, NO, reactive oxygen species, leukotrienes, proteases, protease inhibitors, adhesion molecules (interaction between CD40-CD40 ligand CD40L),[68] coagulation factors, and C-reactive protein, most of which are detectable in AD animal and/or in the brain or cerebrospinal fluid of AD patients.[25,69,70] However, glial cells are also capable of producing some regulatory cytokines, such as IL-10 and transforming growth factor-β (TGF-β), but in AD their release is modified, exacerbating the disease.[71–73] Among anti-inflammatory factors, we also recall the cluster of differentiation-200 (CD200) regulated by the anti-inflammatory IL-4 and expressed by neurons, T- and B-cells, whose receptor is expressed by glia. Both AD patients and mouse models show an age-related or Aβ-induced CD200 reduction.[74–76]

Upstream of cytokines production is the activation of the nuclear factor-kappa B (NF-κB) pathway,[77] and the subsequent activation of mitogen-activated protein kinase (MAPK) pathways, whose proinflammatory gene expression is Aβ dependent.[78] Extracellular signal-regulated protein kinases (ERKs), stress-activated protein kinases c-Jun NH2-terminal kinase (JNK), and p38 constitute the set of MAPKs whose action is exerted both in the cytoplasm and in the nucleus, thereby phosphorylating transcription factors. For example, p38 can contribute to neuroinflammation by inducing TNF-α gene transcription, which increases the activator protein-1 (AP-1) activity,[79] besides being directly responsible for tau phosphorylation.[80]

In turn, proinflammatory mediators increase the activity and the products of amyloidogenic pathway, especially $A\beta_{(1-42)}$. For instance, the γ-secretase cell-based assays showed that TNF-α, IL-1β, and IFN-γ cause the initiation of APP cleavage through the MAPK pathway,[81] and a more recent study demonstrated that NF-κB signaling, activated by TNF-α, results in an increased Aβ synthesis driven by the β-secretase (BACE-1) transcription.[82]

To the vicious circle driven by cytokines and MAPKs,[83,84] the resulting activation of the complement cascade has to be added,[85] as well as the induction of proinflammatory enzymes, such as cyclooxygenase-2 (COX-2)[86] and the inducible nitric oxide synthase (iNOS).[87] Induction of these enzymes may also be linked to the excessive release of S100B (ββ form of the S100), a neurotrophin expressed by activated astrocytes,[88] which is able to induce NF-κB activation,[89] as well as encourage tauopathy.[23] Two more proinflammatory proteins, implicated in the pathophysiology of AD, belong to the S100 family: S100A9 and S100A12. These proteins, produced by activated microglia and macrophages, are increased in AD brain and are responsible for protein complex formation.[90,91] S100A9 is present within SPs and Aβ deposits surrounding blood vessels, and it is also abundant in tissues neighboring Aβ deposits, confirming that increased S100A9 levels can stimulate peptides aggregation and deposition.[92]

Studies report that tau hyperphosphorylation is directly affected by inflammatory mediators, including the cyclin-dependent kinase 5 (CDK5):[93] IL-6 stimulates neuronal protein p35, which in turn is responsible for the kinase activation that can act on tau.[94] CDK5 is not the only kinase related to neuroinflammation. Recently, the role of protein kinase 2 (CK2, former casein kinase II) has been described. In fact, CK2 immunopositive astrocytes have been found to be associated with amyloid deposits in AD brains, suggesting its involvement in the neuroinflammatory response.[95]

Inflammatory mediators, in particular cytokines, are also responsible for increased BBB permeabilization driven by chemokines, allowing leukocyte penetration in the brain.[96,97] This is possible because of altering the resistance of tight junctions, upregulation of cytokines expression, and COX-2 transcription in endothelial cells.[98] For example, IL-6, IL-10, IL-13, and prostaglandins stimulated by lipopolysaccharide may increase the influx of Aβ across the BBB, besides upregulating APP processing in the brain.[99,100]

Another mechanism underlying the pathogenic process led by neuroinflammation is the blockage of neurogenesis, which is inhibited by some proinflammatory cytokines such as IL-6, TNF-α, and IL-18, responsible for neural progenitor cells death, and inhibition of their differentiation.[101] Interestingly, these cells are located in the subgranular layer of the dentate gyrus of the hippocampus, in the subventricular zone

of the lateral ventricles, and amygdala – areas mainly affected by AD and cognitive impairment.[102]

One of the still poorly explored mechanisms that might govern the relationship between AD and neuroinflammation, but definitely is in charge of the neurodegenerative processes, involves the glycogen synthase kinase-3 (constitutively active serine/threonine protein kinase) pathway.[103] This idea comes from the observation of the results obtained by blocking this kinase, which causes an increase of the anti-inflammatory IL-10 and a decrease of proinflammatory cytokines as a consequence of TLRs stimulation and NO production.[104–106]

The salient events reported in this paragraph are summarized in Figure 2.

Neuroinflammatory targets in Alzheimer's disease

Because of the knowledge acquired so far and the failure of so many antiamyloid trials, scientific interest has shifted to other features of neurodegeneration including neuroinflammation.[107]

Evidence mentioned in "The Pathophysiology of Neuroinflammation and Its Role in Alzheimer's Disease" section shows how neuroinflammation is driven by a large number of events apparently different but strongly dependent one on the other.[108] For this reason, it is difficult to identify the best target upon which to act. Recently, much work has been done, but much more research still needs to be done.

It is now clear that the AD neurodegenerative process is also orchestrated by proinflammatory cytokines and their receptors, which therefore become promising targets on which to focus by means of different approaches. Blocking gene expression of cytokines, releasing or binding their receptors, or better regulating the functioning of cells implicated in the neuroinflammation are definitely strategies still in exploration.[109] The possibility of of reducing tau kinase activity and oligomeric and fibrillary Aβ accumulation by neutralizing

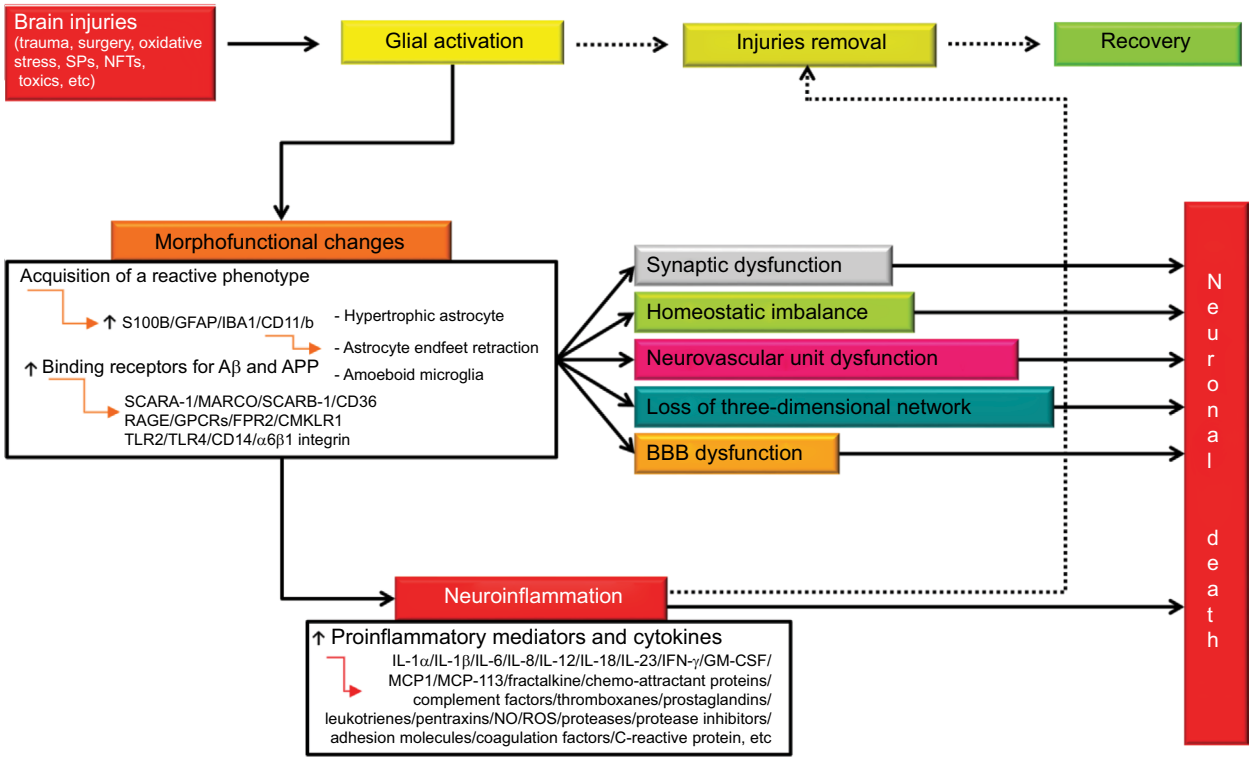

Figure 2 Integrated pathways between glial activation, neuroinflammation, and neuronal death after brain injury.

Notes: Whenever a brain injury occurs, glial activation takes place with the aim of removing injurious stimuli. To this aim, activated cells undergo a series of morphofunctional changes and acquire a reactive phenotype. Activation causes, among other things, glial hypertrophy, astrocyte endfeet retraction, and gain of amoeboid microglial structure. These changes, if not stopped, can induce synaptic dysfunction, homeostatic imbalance, neurovascular unit dysfunction, loss of three-dimensional network, and BBB dysfunction. In addition, reactive microglia and astrocytes release a wide range of proinflammatory mediators aimed at removing the primary injury. The occurrence of a reactive state is very probably a protective response. However, uncontrolled and prolonged activation goes beyond physiological control, and detrimental effects override the beneficial ones. Solid arrows indicate complete pathways. Dashed arrows indicate pathways that that occur partially or do not.

Abbreviations: BBB, blood–brain barrier; Aβ, β-amyloid; NFTs, neurofibrillary tangles; SCARA-1, scavenger receptor class A Type 1; SCARB-1, scavenger receptor class B member 1; RAGE, receptor for advanced glycation end product; GPCRs, G protein-coupled receptors; FPR2, formyl peptide receptor 2; CMKLR1, chemokine-like receptor 1; TLRs, toll-like receptors; IL, interleukin; IFN-γ, interferon-γ; GM-CSF, granulocyte-macrophage colony-stimulating factor; NO, nitric oxide; ROS, reactive oxygen species; SPs, senile plaques; IBA1, ionized calcium-binding adapter molecule 1; CD, cluster of differentiation.

IL-1β or TNF-α/TNF-α receptor through antibodies has been demonstrated in murine models of AD.[64,110–113] In this context, the role of molecules with anti-inflammatory properties (such as minocycline) that are able to decrease astrocyte release of proinflammatory cytokines and reduce both tau and amyloid pathogenesis,[114] as well as improve AD behavioral symptoms, is not less important.[115]

Interestingly, both in vitro and in vivo studies have shown that pharmacological inhibition of COX-2 and inducible NO synthase has positive outcomes.[38,116–120]

Lastly, in AD models it was observed that it is possible to obtain satisfactory results by modulating kinases that are not only directly related to tau hyperphosphorylation but also to neuroinflammation. One example is the modulation of glycogen synthase kinase-3β. Experimental studies have shown that it is possible to exert anti-inflammatory effect by inhibiting this enzyme, giving us another potential therapeutic target to consider.[87,88,121]

Currently available products and products in research and development focusing on neuroinflammatory targets

In the past decades, several epidemiological and clinical studies were carried out to demonstrate the neuroprotective potential of several nonsteroidal anti-inflammatory drugs.[122,123] After the pioneering work with indometacin demonstrated the ability to restore cognitive functions in the enrolled subjects, many other clinical trials have shown only unsatisfactory results.[124–127] Since the failure of trials with classical nonsteroidal anti-inflammatory drugs, scientists tested COX-2-selective compounds effects. Once again, results were disappointing.[128,129] Evidence from a clinical trial with naproxen suggests its ability to reduce tau and Aβ levels in cerebrospinal fluid and plasma.[130] AD is a multifactorial disease and the inflammatory outcome, driven by glial activation, depends on the context and on the stage of the pathology. For these reasons, an ideal anti-inflammatory compound should be able to control the detrimental effects and, at the same time, preserve the physiological glial activation.

An alternative and recent therapeutic approach is represented by nutraceuticals (eg, curcumin, apigenin, docosahexaenoic acid, resveratrol, and n-3 fatty acids).[131–134] Despite encouraging preclinical results, the success rate in humans has been very low.[135]

Complex results were obtained after vaccinating AD patients against Aβ and NFTs. A large number of studies have been done in this field, and promising data were obtained in preclinical models. Unfortunately, these encouraging findings were not replicated in clinical trials, and promising vaccines were stopped because of adverse effects such as meningoencephalitis.[136] Some of these studies revealed that immunization halts glial activation.[137] By the physiological importance of this phenomenon, this is probably why the immunization has caused severe adverse reactions.

Presently, several competing hypotheses (especially related to time of intervention) may help explain the failure of translating preclinical studies into the clinical ones, but so far there is no way to confirm which of these explanations is correct.

Future research direction

The pathogenic role of neuroinflammation in AD is now well recognized and accepted. Nevertheless, the underlying mechanisms have not been sufficiently elucidated. Several factors contribute to this failure. First of all, there is a lack of adequate preclinical models that best mimic the disease and, in particular, the processes of glial activation and neuroinflammation. Then, another important factor is the comprehension of the role of each cellular component in the inflammatory process, for example, the identification of cell-specific biomarkers. Indeed, specifically clarifying changes in both immune system and inflammatory machinery would make available different pathways for pharmacological manipulations aimed at delaying the onset and/or the progression of the disease. Finally, it is important to define the inflammatory stages to correlate each phase to AD progression and to clarify which processes are protective and which ones are detrimental.

The achievement of these goals will allow scientists to practice many other experimental approaches. The hope is to get satisfactory results from clinical studies with compounds that have been successful in vitro, ex vivo, and/or in vivo experiments, such as the administration of molecules like acetylpuerarin,[138] edaravone,[139] palmitoylethanolamide,[38] *N*-[2-(4-hydroxyphenyl)ethyl]-2-(2,5-dimethoxyphenyl)-3-(3-methoxy-4-hydroxyphenyl) acrylamide (compound FLZ),[140] oleuropeinaglycone,[141] oridonin,[142] protocatechuic acid,[143] resveratrol,[110] rutin,[144] or immunotherapies[145,146] and vaccinations.[147]

Conclusion

Growing evidence confirms that neuroinflammation, finely orchestrated by neuronal, glial, and immune components, is a contributing cause of Aβ aggregation, tau hyperphosphorylation, and neuronal damage and death. The resulting production of cytokines and proinflammatory molecules has

initially a neuroprotective role, but subsequently becomes the cause of further neurodegeneration.

Unfortunately, because of the lack of appropriate animal models, we still lack a complete understanding of the relationship between inflammatory process stages and AD progression. This could explain, at least in part, the unsuccessful results of clinical trials performed with anti-inflammatory molecules whose efficacy was significantly proven in preclinical investigations.

Therefore, future experimental studies must intensively investigate the intricate paths of the neuroinflammatory process and define the best time to control it. In this way, it will be possible to achieve more focused and functional therapeutic strategies in the hope of not only alleviating but also modifying AD progression.

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Disclosure

The authors report no conflicts of interest in this work.

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