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The crucial Role of Neuroinflammation in the consistency and development of Alzheimer's Disease

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I. Introduction:

Dementia is a syndrome characterized by failure of recent memory and otherIntellectual functions that are usually insidious in onset, but steadily progresses. Alzheimer's disease (AD) is the most common dementia, accounting for 60-70% of cases in the elderly [1](Hebert, Scherr et al. 2003). AD affects 20 to30 million individuals worldwide [2](Selkoe 2005). The prevalence of AD increases with age, affecting approximately 1% to 3% of the population round 60 years of life, 3% to 12%of the population between 70 and 80 years, and up to 25% to 35% of the population older than 85 years [3](Walsh and Selkoe 2004). Life expectancy has been constantly increasing in industrialized countries, predicting that the incidence of AD will increase three fold over the next 50 years. The earliest sign of AD is typically an impairment of recent memory function and attention followed by failure of language skills, abstract thinking and judgment and visualspatial orientation. AD gradually progresses to severe dementia and stupor. These defects are accompanied by alterations of personality[4] (Nestor, Scheltens et al. 2004). The earliest symptoms appear as subtle, sporadic deficits in remembering minor events of everyday life, including forgetfulness and difficulties recalling new names or recent conversations, referred to as loss of episodic memory. At a later stage, a profound dementia develops affecting multiple cognitive and behavioral abilities. The patient is unaware of time and place and cannot even identify close family members. These symptoms are frequently accompanied by additional neurological symptoms such as extrapyramidal motor signs, slowed movements and hampered motor coordination. Death occurs, on average, 9 years after the initial clinical diagnosis, usually caused by respiratory complications such as aspiration of pneumonia.

CONCEPT OF NEUROINFLAMMATION IN ALZHEIMER DISEAE:

Inflammatory responses within the brain are mainly carried out by activated microglia and reactive astrocytes. Microglia was first identified as brain phagocytes in 1919. [5] In the normal brain, they are generally ramified in their resting state. In this stage, microglia does not produce any pro inflammatory or reactive oxygen/nitrogen molecules. However, following pathological and/or traumatic insults microglia become activated and assumes an amoeboid morphology and increase in size. In addition, certain receptors are up regulated in activated microglia.[6] [Once activated, microglia phagocytose foreign substances and release pro-inflammatory molecules, such as cytokines that include interleukins (ILs), interferons (INFs),tumor necrosis factors (TNFs), and growth factors that further activate other inflammatory responses and thus potentiate the cycle.[7] The production of cytokines is increased in inflammatory states and they function by regulating the intensity and duration of the immune response. They are produced by bothmicroglia and astrocytes in the CNS.[8] Aβ has been shown to increase expression of several cytokine mRNAs.[9]]Activated microglia are a major source of ROS in the AD brain, further highlighting the potential molecular mechanism by which microglia inadvertently enhance disease progression. [10] .

These clinical features are the result of neuronal death and dysfunction in the cerebral cortex, entorhinal area, hippocampus, ventral striatum and basal forebrain, eventually resulting in severe dementia. Pathologically, the two hallmark findings of the disorder are neurofibrillary tangles and amyloid plaques [11]. Senile plaques, a pathologic hallmark of Alzheimer's disease, are associated with GFAPpositive activated astrocytes [12]. It is reported that in various neuropathological states, the increased GFAP expression corresponds to the severity of astroglial activation[13][14][15][16][17][18] .Concerning astrocytes, recent findings suggest that they play a role in the clearance of the Aβ- peptide and thus in preventing plaque formation [19]. Similarly, this peptide decreases glutamate uptake in cultured astrocytes, thus increasing oxidative stress

and and activation of mitogen-activated protein kinase cascades [20][21]. High levels of pro-inflammatory cytokines such as interleukin 1β interleukin 6 and TNFα, mostly produced by reactive astrocytes, are detected in the brain of AD subjects, so the consequences of this phenomenon are unclear, also because pro-inflammatory cytokines have varied effects depending on the biological context[11]. A previous study indicated that activated astrocytes were closely associated with amyloid plaques in the molecular layer of the cerebral cortex [22]. Astrocytes might be activated by human amyloid-β(Aβ) [23]. indicating a correlation between this protein and subsequent alterations in astrocyte function. Astrocytes also accumulate neuron-derived amyloid material resulting from local neurodegeneration. Once substantial accumulation of this debris occurs, the astrocytes themselves might undergo cell death, resulting in the formation of GFAP+ amyloid plaques [12]. In vitro analyses also indicate that treatment of astrocytes with Aβ results in an increase in calcium-wave signaling between these cells [24]. In cells expressing the familial AD presenilin 1 (PSEN1) mutation, calcium oscillations in astrocytes were found to occur at lower ATP and glutamate concentrations than in wild-type astrocytes [25]. These data support a model in which calcium signaling between astrocytes is altered by the disease process, which might, in ways that are not fully understood, contribute to dysfunction or death of neurons.

Role of Astrocytes in Alzheimer's Disease:

Histopathological features of AD include large extracellularsenile plaques (SPs) composed of the amyloid-b (Ab) plaguesand neurofibrillary tangles, which [28]areintracellularinclusions of hyperphosphorylated tau protein in selectiveregions of the brain (Koistinaho et al. 2004; Nagele et al.2003).[28] Ab is a peptide of 42 amino acid residues producedby the selective proteolytic cleavage of transmembrane amyloidprecursor proteins (APP) by b- and g-secretases (Haassand Selkoe 1993). Ab can directly induce [29]neuronal cytotoxicity,but the relevance of such toxicity to the disease is controversial(Pimplikar 2009; Yankner, Duffy, and Kirschner 1990[28]).Morphological characterization of GFAP-positive astroglialcells performed on AD mouse model at different ages showedan age-dependent reduction in GFAP expression (Rodrıguezet al. 2009). These authors suggested that in an AD transgenic,reactive hypertrophic astrocytes surround the neuritic plaques whereas astroglial cells in other brain regions undergo atrophy,which may account for early changes in synaptic plasticity and cognitive impairments inherent to AD. In the AD human tissue,prominent astrogliosis occurs in the cells surrounding amyloid plaques, and these activated astrocytes accumulatelargeamounts of Ab42, which are derived from neuronal debris andassociated withplaques (Nagele et al. 2003)[30]. Moreover,astrocytes from patients with dementia show significantly decreased complexity compared to the healthy brain(Senitz,Reichenbach, and Smith 1995).[29]It is widely recognized that age is the most important risk factor for AD and that the innate immune system plays a role in the development of neurodegeneration. Very little information is available on how aging affects the innate immune system. However, thereare clear indications that the development of AD is due to age-related changes that modulate innate immunity. It is interesting that Aβ and other proteins found in the senile plaques of AD patients are potent activators of the innate immune response because chronic stimulation of the innate immune system may lead to alterations of astrocytes. When the brain is injured, astrocytes are believed to react by putting down glial scar tissue as part of the healing process. Recently, it has been shown that astrocytes themselves actively contribute to the inflammatory response ([31]Farina, Aloisi et al. 2007).It has been shown that the neurotransmitter glutamate is released in neuroinflammatory conditions and to some degree under normal circumstances, which on the long term isproved to be toxic to neurons. The neuroprotective action of astrocytes has also been attributed to their capacity to take up the neurotransmitter glutamate, convert it to glutamine, and recycle it to neurons [32]

Astrocytes ,Astrogliosis and neurological disorders:

Astrocytes are an essential neurosupportive cell type in brain. support, nourish and protect neurons. Their well-known interactions with neurons include secretion and recycling of transmitters, ion homeostasis, regulation ofenergy metabolism, synaptic remodeling, and modulation of oxidative stress. Tiling the entire brain in contiguous, orderly fashion, each single gray matter astrocyte has been estimated to envelope as many as 100,000 synapses[26]. As such, perturbation of the many neurosupportive astrocyte functions can have extremely deleterious consequences for the CNS) (1). Moreover, like microglia, astrocytes respond quickly to pathology with changes in their morphology, antigenicity, and function, and, like microglia, these reactive states havebeen increasingly recognized as a continuum with potentially beneficial and destructive consequences (reviewed in Sofroniew and Vinters 2010)Astrocytes are known to be important for Aβ clearance and degradation, for providing trophic support to neurons, and for forming a protective barrier between Aβ

deposits and neurons [27]. Thepresenceoflarge numbers of astrocytes associated with Aβ deposits in AD suggests that these lesions generate chemotactic molecules that mediate astrocyte recruitment. Under certain conditions related to chronic stress, how ever, the role of astrocytes may not be beneficial. A report suggests that astrocytes could also be a source forAβ,because they overexpress β-secretase of APP (BACE1) in response to

chronic stress [27]. In vitro and in vivo experiments suggest though that inflammatory active astrocytes do not generate significant amounts of these molecules Astrocytes and microglia respond to central nervous system (CNS) injury with changes in morphology, proliferation, migration and expression of inflammatory regulators. This phenomenon is known as reactive gliosis. Astrocytes respond to all forms of CNS insults through a process referred to as reactive astrogliosis.

Research on Alzheimer's disease (AD) focuses mainly on neuronal death and synaptic impairment induced by β-Amyloid peptide (Aβ), events at least partially mediated by astrocyte and microglia activation. Astrogliosis is an early pathological manifestation of Alzheimer's disease and might represent a response to the accumulation of amyloid and or the increasing number of degenerating synapses and neurons40.Astrogliosis is characterized by increased expression of the astrocyte marker glial fibrillary acidic protein(GFAP), and it occurs mainly around amyloid deposits both in the brain parenchyma and the cerebral microvasculature40,41.Migration of astrocytes to amyloid plaques, as shown by in vitro studies, is promoted by the chemokines CCL2 and CCL3, which are released by activated microglial cells that surround the plaque42.Astrocytes that are recruited to amyloid-β plaques have the potential to both mediate neurotoxicity and participate in the clearance of amyloid-β. In brain sections from patients with Alzheimer's disease, activated astrocytes,as well nasactivated microglial cells, contain amyloid-βfragments43. Mouse astrocytes plated on amyloid—rich brain sections from APP-transgenic mice reduce the overall amyloid levels in these sections44. AD Astrocytes are the most abundant non-neuronal cells in the CNS, constituting about 20–50% of the human brain volume, much higher than microglia[33]. Astrocytes have multiple functions, such as regulation of extracellular ions and energy reserves, clearance and metabolism of neurotransmitters, and facilitating the maintenance of normal neuronal functions in the CNS(Dong and Benveniste, 2001; Rossi and Volterra, 2009[34]). Astrocytes can be activated by numerous factors, including pathogens, lipopolysaccharide, oxidative stress ,free saturated fatty acids (Liu et al., 2013a) as well as A _ (Jana andPahan, 2010)[35]. The activation of astrocytes is believed to last longerthan that of microglia, enabling a prolong engagement of astrocytesin the neuroinflammatory response [36](Li et al., 2011).Reactive astrocytes as opposed to quiescent astrocytes, can pro-duce cytokines such as interleukins, TNF _ and interferon _ (IFN- _),etc. (Liu et al., 2013a). They can also generate low amount of A _, inaddition to neurons, the major producer of A _ (Blasko et al., 2000; Liet al., 2011)[37]. Cytokines, IFN- _ along with TNF _ or IL-1 _, have beendemonstrated to induce the generation of A _ in primary human astrocytes and astrocytoma cells [33]Proinflammatory molecules secreted by reactive astrocytes can elevate the expression of secretases in neurons to enhance the production ofA _ (Tang, 2009; Yu et al., 2009b)[37], and activate microglia to further produce inflammatory factors (Otth et al., 2002)[37]

Chemokines and cytokines:

The cytokines are a family of hormones –like proteins or glycoproteins that regulation the immunity ,inflammation ,and hematopoiesis.the major classes of cytokines are the interferon(IFNS),interleukins(IL),tumor nercosis factor (TNF),transforming growth factors(TGFs)and colony stimulating factors(CSFS).

Chemokines are a family of small pro- inflammatory chemotactic cytokines proteins that participate in inflammatory cell recruitment .the chemokines are released by different cells in response in injury and they function by attracting leucocytes to sites of inflammation where they induce cell activation . both cytokines and chemokines have been showed in elevated in AD brains (tuppo and Arias,2005)[40].Among them ,extensively studied in relation with AD onset or progression were mainly :pro-inflammatory cytokines interleukins -1 alpha and beta (IL-1α,IL-1β),tumor nercosis factor alpha (TNFα),interleukin-6(IL-6),and transforming growth factor beta (TGF-β), together with chemokines IL-8,monocyte chemoattractant proteins -1(MCP-1) and macrophage inflammatory protein-1(MIP-1α,MIP-1β) (mark et al ,1995 ,McGeer and McGeer ,2003;Cacquevel et al,2005)

IL-1 is expressed in many cell types including macrophages,monocytes and neurtrophils, and in the CNS IL-1 can be releasedfrom astrocytes, microglia and neurons (Dinarello, 2010)[46]. IL-1induces diverse signaling which are cell type specific (Srinivasanet al., 2004), for example, in glial cells IL-1activates NFB (nuclearfactor kappa B) signaling to upregulate cytokine production. In contrast, in neurons IL-1 activates the MAPK-p38 signaling cascade toincrease the secreted APP fragment cleaved by BACE1 to enhance the ability to form A(Salminen et al., 2008; Srinivasan et al., 2004;Sun et al., 2003)[47]. IL-1 plays a key role in the onset and development ofdiverse diseases, including neurodegenerative diseases such as AD(Dinarello, 2010). The IL-1 gene and eight other interleukin 1 family genes form a cytokine gene cluster on chromosome 2 (Webbet al., 1986). Elevated IL-1 has been observed in the serum, cere-brospinal fluid and brain of patients with AD as well as otherdementia (Blum-Degen et al., 1995; Cacabelos et al., 1991; Deniz-Naranjo et al., 2008[37]). Elevated levels also have been reported inthe cerebrospinal fluid and brain parenchyma of both humans androdents shortly after traumatic brain injury, the latter is an indepen-dent risk factor for AD (Emmanouilidou et al., 2011; Shaftel et al.,2008; Yamasaki et al., 1995)[37]. IL-1 can activate other cell types,in particular astrocytes and microglia, to further induce cytokinerelease (e.g. IL-1, IL-6 and IL-18), as well as inducible nitric oxide

synthase activity to produce the free radical NO, leading to neuro-toxicity (Rossi and Bianchini, 1996; Rubio-Perez and Morillas-Ruiz,2012). IL-1 secreted from astrocytes has been shown to enhancethe [33][48]production of APP and Afrom the neurons [40]). Additionally, IL-1 hasbeen found to increase the release of S100B from an astrogliomacell line and the plaque-associated activated astrocytes in the pri-mary cortex that promote neuronal APP synthesis (Li et al., 2011;Liu et al., 2005). Injecting IL-1 into the cerebral hemisphere
upregulates the levels of APP and amyloidogenesis ([46]Furthermore, several studies demonstrate that IL-1 can inducethe phosphorylation of the tau protein and mediate the formationof neurofibrillary tangles through the MAPK-p38 pathway [49]). Blocking IL-1 signaling in thebrain of an AD mouse model is able to alter the inflammatory responses.

Interleukin-1:

Interleukin-1 was first described in 1972 as a lymphocyte activating factor[38] and later was shown to exert a variety of effects including induction of inflammation, body temperature increase, proliferation of T and B cells, induction of acute phase proteins and prostaglandins and regulation of hematopoesis. Its activities are not restricted to the immune system. Interleukin-1 is also involved in the regulation of blood calcium levels, stimulation of proliferation of various cells, regulation of blood pressure or modulation of sleep. However, IL-1 represents one of the most important mediators of the inflammatory response that induces a cascade of proinflammatory effector molecules [39].

Interleukin-1 (IL-1) has been implicated in a number of neurodegenerative conditions and is generally believed to have neurotoxic actions, although the mechanisms of these effects are unclear (Lucas et al, 2006[40]. There are two molecular forms (ILla and IL- IB), that is secreted by microglia and astrocytes. IL- 1 produced by activated microglia may trigger production of other cytokines, such as IL-6, TNF-a by astrocytes and other cells.

Furthermore, IL-1 induces astrocytes and neurons to produce more B-amyloid which leads to deposition of amyloid fibrils (Griffin et al, 1995, Nilsson et al, 1998)[40]. Through various pathways, IL- 1 causes neuronal death, which activates more micrglia, which in tum releases more IL-1 in a self-sustaining and self-amplifying fashion.Interleukin-6 (IL-6) is a multifunctional cytokine that stimulates the acute-phase reaction, which enhances the innate immune system and protects against tissue damage. IL-6 is synthetised by microglia, astrocytes, neuronal and endothelial cells. In certain condition, IL-6 may have inflammatory or immunosuppressive effects (Ferencik et al, 200 1).[41] IL-6 seems to act as a secondary process amplifying the inflammatory response initiatedby IL- IB (Lee et al, 1993)[42]. Elevated levels of IL-6 mRNA were demonstrated in the entorhinal cortex and the superior temporal gyrus of AD patients (Ge and Lahiri, 2002, Lahiri et al, 2003)[43]

II. Aβ& TAU hyperphosphoraylation:

Beside this IL-1 is direct toxic to neurons and is responsible for hyperphosphorylation of Tau. Neurofibrillary changes, in the form of neuritic plaques, neuropil threads, and neurofibrillary tangles, are key histological features of AD. Tau is one of the microtubule-associated proteins that stabilizes growing axons necessary for the development and growth of neurites. However, in AD, for unknown reasons, tau becomes excessively phosphorylated and appears in pairedhelical filaments, dystrophic neurites, andneurofibrillary tangles. [50] This neurofibrillary pathology suggests a loss of axonal integrity and an eventual decline in connectivity and synapses, a consistent correlate of dementia in AD. [51][50]

The IL-1 super family members includes IL-1α, IL-1β,and IL-1 receptor antagonist (IL-1RA). Both IL-1α and IL-1βare proinflammatory cytokines involved in the inflammation and immune defense against infection. They could be produced by several kinds of cells, including astrocytes. It has been reported that the level of IL-1βwas elevated in the serum and cerebrospinal fluid (CSF) of patients suffering from AD and other forms of dementia][52][53][54]. In astrocytes of the cortex and hippocampus, IL-1β level was dramatically increased by Aβ [55]. The IL-1β could then be released and bind to IL-1 receptors on the membrane of astrocytes to further induce IL-1secretion. Moreover, IL-1secreted by astrocytes could also stimulate neurons to increase the c production of APP and neurotoxic Aβ][56][57][55][53][57] .The tissue levels of APP were significantly elevated when IL-1 was injected into the cerebral hemisphere [64]. This feedback loop of IL-1βsecretion resulted in an elevation of Aβ□ production which, as mentioned above,is important in the progression of chronic neuroinflammation andactivation of astrocytes in AD patients.In addition to the vicious feedback loop, the effect of IL-1βon promoting neuronal degeneration and astrogliosis has been verified by clinical and experimental studies [58][57].The IL-1βinduced activation of mitogen-activated proteinkinase (MAPK)-p38 in neurons has been implicated in the hyperphosphorylation of tau protein, a major component of NFT in AD brain[58][59][60]. This notion was supported byreports that IL-1is markedly overexpressed at the neuroinflammatorysites and promotes MAPK-p38 generation in theAD brain [60][61][62]. IL-1□□ has also been revealed to induce theAβ-treated astrocytes to undergo astrogliosis by binding toIL-1βreceptors on their membrane][59][63]. The upregulationof IL-1in the activated astrocytes around the senile plaquescontributes not

only to neuroinflammation, but also to theproduction of neurotoxic free radicals through a synthesispartially mediated by the expression of inducible nitric oxidesynthase (iNOS) [71]. The expression of iNOS might haveresulted from the initial induction by IL-1α as IL-1RA which could inhibit nitrite accumulation.[64] Likewise, alphaphenyl-N-tert-butyl nitrone, a nitrone-based free radicaltrapper, significantly suppressed the activation of MAPKp38by IL-1αin rat astrocytes in primary culture as well asdecreased the amount of the IL-1-induced ROS produced inmitochondrial respiration [64] These observations confirmedthat IL-1αexpressed by the activated astrocytes leadsto nitric oxide (NO) accumulation around the Aβplaques inAD brain.[64][65] Thus, the studies indicated a possible additional proinflammatory role of IL-1β in the progression of neuronal degeneration, since it could have up regulated the expression of iNOS in Aβ-activated astrocytes.

Beside this IL-1α is direct toxic to neurons and is responsible for hyperphosphorylation of Tau. Neurofibrillary changes, in the form of neuritic plaques, neuropil threads, andneurofibrillary tangles, are key histological features of AD.Tau is one of the microtubule-associated proteins that stabilizes growing axons necessary for the development andgrowth of neurites. However, in AD, for unknown reasons,tau becomes excessively phosphorylated and appears impaired helical filaments, dystrophic neurites, andneurofibrillary tangles. [66][67] Thisneurofibrillary pathologysuggests a loss of axonal integrity and an eventual decline inconnectivity andsynapses, a consistent correlate of dementiain AD.[68] Activated microglia increase tau phosphorylation and decrease steady-state levels of synaptophysin through release of IL-1 these IL-1-induced changes occur before significant neuronal cell loss associated with microglial neurotoxicity is detectable and the effects of IL-1 on tau and synaptophysin are mediated, at least in part, through activation of p38-MAPK. [69] Activation of p38MAPK is involved in neuronal responses to various stresses[70][71] and this kinase is closelyrelated to hyperphosphorylated tau protein in AD. [72]Three possibilities have been proposed on the basis of the neuropathology: (1) loss of synapses is a nonspecificconsequence of global neurodegenerative changes thatinclude neuronal loss; [73] (2) loss of synapses results fromthe direct neurotoxicity of amyloid β-peptide (Aβ)][74] and (3)loss of synapses results from cytoskeletal changes causedeither actively by tau aggregates or passively by loss of tau function. [75][76]]IL-1 promotes neuronal production of β-amyloid precursor protein and its derivatives [77] and IL-1- Mediated pro inflammatory sequel could damage neuronal connectivity via mechanisms beyond neurotoxic effects of Aβ production.

Presently Aβ is one of the main therapeutic targets. In fact, immunization with Aβ was successful at removing Aβ from the brain. Imaging studies in AD patients showed that immunization with Aβ decreased amyloid plaques in the brain; however, this had no effect on cognition[78]. In mouse models, immunization has cleared small deposits anddiffuses Aβ surrounding fibrillar cores[79].

The induction of tau phosphorylation by IL- in vitro [80] and in vivo[81] indicates that IL1 might potentially contribute to the reorganization of the cytoskeleton, interrupt normal microtubule assembly and axon stabilization, and eventually result in loss of synaptic proteins and synapses. This is supported by the observations in AD that a loss of synaptophysin is observed in tangle-bearing neurons[82] and that activated microglia correlate with neurofibrillary pathology, [83] including intracellular tau pathology. [84]The overexpression of IL-1 observed in Alzheimer's disease could potentially contribute directly to the neuronal dysfunction and loss seminal to the disease. With regard to direct toxicity, elevating concentrations of IL-1 in vitro are toxic to neuronal explants cultures.[85]

Palmitoylethanolamide as anti inflammatory molecule :

Palmitoylethanolamide (PEA), the naturally occurring amide of palmitic acid and ethanolamine, reduces pain and inflammation through a mechanism dependent on PPAR-α activation., we identify the nuclear receptor peroxisome proliferator-activated receptor-α (PPAR-α) as the molecular target responsible for the anti-inflammatory properties of PEA. P astroglial cells may provide a valuable therapeutic target for the treatment of AD. any compound able to modulate astrocyte activation might be considered as a novel drug of potential therapeutic relevance [86]. Among these molecules, palmitoylethanolamide (PEA) has attracted much attention for its proven anti-inflammatory and neuroprotective properties, as observed in many neuropathological conditions, mainly in the peripheral nervous system[87].PEA is abundant in the CNS and it is visible produced by glial cells[88]. And PEA is able to blunt Aβ-induced astrocyte activation and to exert a marked protective effect on neurons. These findings highlight new pharmacological properties of PEA and suggest that this compound may provide an effective strategy for AD.[89]

III. Conclusion and perspective:

Astrocytes play a critical role in normal function of the mammalian nervous system Astrocytes And a significant role in neurodegenerative diseases and coordinates many of the initial and subsequent responses of astrocytes to injury Astroglial cells are specifically involved in various neurological diseases, Astrocytes regulate synaptic transmission and plasticity, protect neurons against toxic compounds, and support

metabolically to ensure their optimal functioning. , they support neurons. By providing growth factors and cytokines chemokines and IL-1α Astrocytes are involved in all types of neurodegenerative processes, and display prominent remodeling in the AD; early dystrophic changes in astroglia can represent an important step in initiation and progression of Alzheimer's disease. Targeting of astroglia may provide a new principle for treatment of AD at the early stages of the disease.

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