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Review article

# Astrogliosis: An integral player in the pathogenesis of Alzheimer's disease

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ABSTRACT

Alzheimer's disease is the main cause of dementia in the elderly and begins with a subtle decline in episodic memory followed by a more general decline in overall cognitive abilities. Though the exact trigger for this cascade of events remains unknown the presence of the misfolded amyloid-beta protein triggers reactive gliosis, a prominent neuropathological feature in the brains of Alzheimer's patients. The cytoskeletal and morphological changes of astrogliosis are its evident features, while changes in oxidative stress defense, cholesterol metabolism, and gene transcription programs are less manifest. However, these latter molecular changes may underlie a disruption in homeostatic regulation that keeps the brain environment balanced. Astrocytes in Alzheimer's disease show changes in glutamate and GABA signaling and recycling, potassium buffering, and in cholinergic, purinergic, and calcium signaling. Ultimately the dysregulation of homeostasis maintained by astrocytes can have grave consequences for the stability of microcircuits within key brain regions. Specifically, altered inhibition influenced by astrocytes can lead to local circuit imbalance with farther reaching consequences for the functioning of larger neuronal networks. Healthy astrocytes have a role in maintaining and modulating normal neuronal communication, synaptic physiology and energy metabolism, astrogliosis interferes with these functions. This review considers the molecular and functional changes occurring during astrogliosis in Alzheimer's disease, and proposes that astrocytes are key players in the development of dementia.


**Contents**



*Abbreviations:* AD, Alzheimer's disease; Aβ, amyloid-beta; APP, amyloid precursor protein; GABA, gamma-aminobutyric acid; GFAP, glial fibrillary acidic protein; IF, intermediate filament; VIM, vimentin; TNFα, tumor necrosis factor α; BBB, blood brain barrier; EC, entorhinal cortex; ECM, extracellular matrix; GLT-1, glutamate transporter-1; SR-BI, scavenger receptor class B member 1; ApoE, Apolipoprotein E; ApoE4, Apolipoprotein E ε4; LDLR, low-density lipoprotein recepto; LRP1, low-density lipoprotein receptor-related protein 1; BACE1, β-secretase; AICD, APPintracellular domain; ALS, amyotrophic lateral sclerosis; JAK/STAT3, Janus kinase/signal transducer and activator of transcription 3; NFAT, nuclear factor of activated T cell; GSH, glutathione; Nrf2, nuclear factor erythroid 2-related factor 2; TGFβ, transforming growth factor beta; ABCA1, ATP-binding cassette transporter; CEBPD, CCAAT/enhancer-binding protein delta; EAAT1,EAAT2, Excitatory Amino Acid transporter-1 and -2; GLAST, Glutamate aspartate transporter; ACh, acetylcholine; BCHE, butyrylcholinesterase; $PrP^{c}$, cellular prion protein; α7nAChRs, α7 nicotinic acetylcholine receptors; mGluR5, metabotropic glutamate receptor 5; CAA, cerebral amyloid angiopathy; CLU, clusterin; PICALM, Phosphatidylinositol-Binding Clathrin Assembly Protein; TREM2, Triggering Receptor Expressed on Myeloid Cells 2; ATP, adenosine triphosphate; PEA-15, phophoprotein enriched in astrocytes 15; MHC, major histocompatibility complex; HSPB8-BAG3, heat shock protein 8-BCL2-associated athanogene 3; SAP-C1q, serum amyloid P-complement component 1 q subcomponent; CaMKII, $Ca^{2+}$/calmodulin-dependent protein kinase II; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor.

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## 1. Astrocytes: active players in physiology and pathology

More than a century ago, Santiago Ramón Y Cajal and Camillo Golgi proposed astrocytes as functional in a capacity beyond simple structural support (García-Marín et al., 2007; Kettenmann and Verkhratsky, 2008). Their innovative thinking only truly began to take hold within the past several decades and the classical view of astrocytes as simply passive support cells to neuronal function began to change. Astrocytes are now considered an intricate element in the information processing microcircuit because of their calcium dynamics, and respond to specific neuronal signals that can in turn modulate synaptic function (Araque et al., 2014, 1998; Di Castro et al., 2011; Fellin et al., 2004; Khakh and McCarthy, 2015; Navarrete et al., 2012; Perea and Araque, 2007; Rossi, 2015; Rusakov, 2015). These highly specialized and multifunctional glial cells express metabotropic and ionotropic membrane receptors allowing them to sense neuronal activity. They also express transporters for glutamate, gamma-aminobutyric acid (GABA), and glycine. As the major provider of glutamine to neurons and crucial players in the spatial regulation of extracellular potassium, astrocytes are highly relevant to neuronal excitability (Halassa and Haydon, 2010; Kofuji and Newman, 2004). From the past two decades of research it is clear that not a single feature of astrocytes facilitates their role as modulators of synaptic transmission, but the interplay of structural, anatomical, and functional characteristics allows them to exert their influence on neuronal signaling. Astrocytes bring unique forms of molecular, morphological, and functional plasticity to the information processing microcircuit. In brain diseases, including Alzheimer's disease (AD), molecular and cellular features of astrocytes distinctly change. This process is known as astrogliosis. The consequences of this change for astrocyte function and the connected neuronal networks are just becoming clear.

## 2. Astrocytes in Alzheimer's disease

### 2.1. Introduction

Alzheimer's disease (AD) is the main cause of dementia in elderly and one of the most economically burdensome health conditions in our society. At the clinical level, a subtle decline in episodic memory is followed by a more general decline in overall cognitive abilities (Querfurth and LaFerla, 2010) beginning with an inability to recall the recent past, followed by loss of long-term memories, personality changes, and loss of other cognitive functions including language and attention. Histopathologically, the disease is characterized by amyloid-beta (Aβ) aggregates forming extracellular deposits (plaques) in the brain, and by the presence of abnormally phosphorylated tau developing intracellular neuronal tangles. The Aβ plaques are surrounded by a sphere of reactive astrocytes and activated microglia. The role of these activated glial cells is a topic of great scientific interest as, on the one hand, glial activation has been considered as an endogenous defensive mechanism against plaque deposition, while on the other hand, the persistent activation and associated inflammation may also contribute to the progression of AD.

Over the last decades, the identification of several causal genetic mutations in a small patient subset has revealed detailed information on molecular pathways involved in AD. Unfortunately, this has not yet led to a breakthrough in AD therapy, which is expected as the vast majority of AD patients (>95%) do not suffer from a monogenic form of AD. In these patients additional risk factors, such as age, Apolipoprotein E (ApoE) genotype and vascular changes are involved (Bettens et al., 2013). Although AD is commonly seen as a neuronal disease, a complex interaction between the different cell types in the brain exists. It is therefore conceivable that a pathological change in this interaction is responsible for the cognitive decline. Interestingly, several of the causal and risk factor genes for AD – amyloid precursor protein (APP), presenilin-1, presenilin-2, ApoE, clusterin (CLU), Phosphatidylinositol-Binding Clathrin Assembly Protein (PICALM), Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) – are not only expressed by neurons but also, if not predominantly, by astrocytes (Orre et al., 2014a). Corroborating the idea that astrocytes are important players in AD pathogenesis.

### 2.2. A brief overview of the physiological functions of astrocytes

Under physiological conditions astrocytes play many roles in the brain and their highly branched morphology and intimate contact with neurons make them highly conducive to maintaining a milieu that is balanced and favorable for proper neuronal