Journal of Integrative Neuroscience

J. Integr. Neurosci. **2026**; 25(4): 49765
https://doi.org/10.31083/JIN49765

Review

Astrocytes and Their Role in the Development and Progression of Alzheimer's Disease: Gatekeepers of Neurodegeneration

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Academic Editor: Bettina Platt
Submitted: 6 January 2026 Revised: 23 March 2026 Accepted: 26 March 2026 Published: 22 April 2026

Abstract

Astrocytes are increasingly recognized as central players in the pathogenesis of Alzheimer's disease (AD), exhibiting both neuroprotective and neurotoxic functions, which complicates their role in disease progression. Under physiological conditions, astrocytes support neuronal homeostasis, facilitate synaptic function, and promote the clearance of Amyloid-β (Aβ), thereby contributing to neuroprotection. In the context of AD, however, reactive astrocytes can adopt detrimental phenotypes, releasing pro-inflammatory cytokines, generating oxidative stress, and disrupting neuronal networks, thereby exacerbating neurodegeneration. Consequently, the shift from a protective to a neurotoxic phenotype may not only drive neuronal loss but also accelerate AD progression. The dual roles of astrocytes and the dynamic changes in their functions—protecting neurons under normal conditions while promoting pathology when dysregulated—underscore their complex contribution to AD pathophysiology. Elucidating the mechanisms underlying astrocyte-mediated neuroprotection and neurotoxicity is essential for developing targeted therapeutic strategies aimed at modulating astrocyte activity to slow or prevent disease progression. This review aims to present and critically discuss recent advances and ongoing controversies concerning the involvement of astrocytes in AD.

Keywords:
Alzheimer's disease; Amyloid-β; astrocytes; astrogliosis; calcium dyshomeostasis; PI3K/Akt; JAK/STAT; NF-κB; Nrf2; neuroinflammation

1. Introduction

Alzheimer's disease (AD) is the most common form of dementia, accounting for at least two-thirds of cases in individuals over the age of 65. It is a slowly progressive neurodegenerative disorder that affects memory, cognition, and behavior, and is characterized by confusion, communication difficulties, and personality changes. Although the symptoms of AD have been extensively studied, there is currently no cure to halt or reverse its progression. However, certain medications are available that may help slow the course of the disease [1].

AD is a multifactorial neurodegenerative condition resulting from a combination of factors, including protein aggregation, chronic neuroinflammation, and neuronal loss. Although our understanding of AD pathogenesis remains incomplete, several hallmark pathological features have been identified—namely, extracellular neuritic plaques and intracellular neurofibrillary tangles. These are composed of accumulated Amyloid-β (Aβ) and hyperphosphorylated tau protein, respectively [2]. Amyloid plaques accumulate in the extracellular space between neurons, disrupting synaptic communication, whereas neurofibrillary tangles form within neurons and contribute to their degeneration. Together, these pathological processes lead to progressive neuronal loss and cognitive decline. In addition, activation of inflammatory pathways and immune responses is commonly observed in the brains of individuals with AD [3].

In recent years, increasing attention has been directed toward the role of glial cells in both normal brain function and neurodegenerative diseases [4–6]. In this context, the present review focuses on the contribution of astrocytes to AD pathogenesis and progression, summarizing recent advances and outlining key priorities for future research.

2. Basic Characteristics of Astrocytes

Astrocytes are the most abundant glial cells in the adult human brain, with numbers estimated between 40 and 130 billion, resulting in a glia-to-neuron ratio of approximately 1:1 [7]. They play essential roles in neuronal development, activity, and homeostasis, emphasizing the importance of glia–neuron interactions [8]. First named for their star-like shape by Mihály Lenhossék in 1895 [9], astrocytes are structurally and functionally diverse, supporting central nervous system (CNS) function throughout life. They regulate synapses, neurotransmitters, ion and water balance, and maintain the extracellular matrix, while also contributing to metabolic support, synapse formation, and synaptic pruning [6,10]. Additionally, astrocytes are critical for the blood–brain barrier (BBB), neuroprotection, waste clearance, and neurogenesis, acting alongside microglia as a frontline defense [11].

Under CNS injury or disease, astrocytes become reactive, undergoing morphological, transcriptional, and func-

tional changes in a process called astrogliosis. Reactive astrocytes can adopt distinct phenotypes, including A1 pro-inflammatory, potentially neurotoxic cells, and A2 neuroprotective cells that support repair. The role of astrocytes varies across pathological contexts, and morphology alone does not always indicate function [12–14]. According to current perspectives, reactive astrocytes should not be classified solely within simplified frameworks such as neurotoxic versus neuroprotective or A1 versus A2 states. Instead, a more comprehensive approach that integrates multiple molecular and functional parameters, along with their impact on pathological hallmarks in relevant models, is preferred [12]. The goal is to move beyond rigid categorization and to identify the key variables that drive distinct reactive astrocyte states, phenotypes, and functions within specific pathological contexts. Achieving this requires the use of multidimensional datasets and co-clustering approaches to accurately define the diversity and distinctiveness of astrocyte phenotypes. Consequently, future classification systems should incorporate a range of criteria, including transcriptomic and proteomic profiles, morphological characteristics, and specific cellular functions.

3. Astrocytes in Pathological Brain Conditions

Astrocytes play a fundamental role in maintaining CNS homeostasis by supporting key physiological processes, including neurotransmitter clearance, energy metabolism, ion buffering, and immunomodulation. Disruption of these functions is thought to occur progressively during aging and disease progression, thereby amplifying other pathological mechanisms in the brain. Under adverse conditions, astrocytes can adopt pathological phenotypes characterized by distinct morphological and molecular alterations. Neurodegenerative processes are commonly associated with dysregulated astrocyte reactivity, astrogliosis, functional impairment, and, in some cases, the induction of cellular senescence or cell death. One of the earliest astrocyte-driven mechanisms contributing to neurodegeneration involves changes in the astrocytic secretome. Astrocytes release a wide range of cytokines, chemokines, and interleukins that can amplify inflammatory signaling through multiple pathways, including autocrine activation, stimulation of microglia, and recruitment of peripheral immune cells [11]. Persistent activation of these pathways promotes a chronic inflammatory environment that ultimately leads to neuronal dysfunction, neurotoxicity, and cell death. Under pathological conditions, astrocytes not only lose their supportive roles but may actively contribute to disease progression through the secretion of toxic mediators, including pro-inflammatory cytokines and neurotoxic lipids [15]. Although altered astrocyte reactivity, functional impairment, and cytotoxicity often occur concurrently, the precise mechanistic relationships among these processes remain incompletely understood.

Accumulating evidence indicates that several essential astrocytic functions are compromised during both acute inflammation and chronic neurodegeneration. For instance, astrocytes promote synapse formation during development by secreting synaptogenic factors such as SPARC-like protein 1 (SPARCL1), thrombospondins (TSP1 and TSP2), and glypicans (GPC4 and GPC6) [16–18]. However, the expression of these molecules is markedly reduced in neurotoxic reactive astrocytes in both rodent models and human tissue, resulting in a diminished capacity to support synaptogenesis in neuron–astrocyte co-culture systems [19]. These findings underscore how the loss of astrocyte-mediated support directly contributes to synaptic dysfunction in neurodegenerative diseases.

Importantly, astrocyte dysfunction does not occur in isolation but is closely intertwined with neuroinflammatory processes that characterize many CNS disorders. A comprehensive understanding of astrocyte involvement in neurodegeneration therefore requires detailed investigation of their role in inflammatory signaling networks.

3.1 Neuroinflammation and Astrogliosis

Neuroinflammation is a defining feature of many neurodegenerative disorders, including AD, and astrocytes play a central role in this process. Inflammation is typically initiated as a protective response to infection or injury, but in the CNS it can also be triggered by endogenous molecules associated with neurodegenerative pathology, including Aβ, tau, α-synuclein, and mutant huntingtin. Within the CNS, the inflammatory response is primarily mediated by microglia [15] together with infiltrating peripheral immune cells such as T lymphocytes [20]. However, astrocytes act as key downstream effectors that amplify and sustain inflammatory signaling within neural tissue [15,21]. In response to injury or disease, astrocytes undergo a process known as astrogliosis, which involves a transformation into a reactive cellular state.

Astrogliosis represents a complex and highly context-dependent response characterized by several defining features: (1) it encompasses a broad range of molecular, cellular, and functional changes occurring in response to nearly all types of CNS insults; (2) these changes occur along a graded continuum depending on the severity of injury; (3) reactive responses are shaped by diverse signaling pathways and intercellular interactions; and (4) astrocyte reactivity can result in both gain- and loss-of-function effects [22].

The contribution of neuroinflammation and astrogliosis to neurodegeneration remains an area of active debate. While some evidence suggests that these processes arise as secondary responses to protein aggregation, other studies indicate that immune signaling may actively drive disease progression. For example, variants in the *TREM2* gene—which encodes an innate immune receptor highly expressed in microglia—can increase the risk of late-onset AD by two-

to four-fold, comparable to the risk associated with a single apolipoprotein E (*APOE*) ε4 allele [23]. These findings support the idea that innate immune responses participate directly in AD pathogenesis. Astrocytes themselves undergo extensive molecular remodeling during neuroinflammation. In AD, reactive astrocytes show increased expression of glial fibrillary acidic protein (GFAP) and complement component C3, which are widely used markers of astrocyte reactivity associated with a neurotoxic phenotype [19]. These protein changes reflect broader transcriptomic and proteomic alterations, including the downregulation of homeostatic functions such as ion regulation, cholesterol metabolism, glutamate uptake, and synaptic maintenance. At the same time, inflammatory pathways—including JAK-STAT3, NFAT, and NF-κB signaling—become strongly upregulated, promoting the acquisition of toxic astrocyte functions [24].

Astrocyte reactivity is often influenced by microglial activation states. Microglia themselves can be modulated by signals from other CNS cells as well as by systemic factors such as gut microbiome–derived metabolites that activate the aryl hydrocarbon receptor [25]. This highlights the complex, multicellular nature of neuroinflammatory signaling networks. Another important factor shaping astrocyte responses is cellular heterogeneity. Advances in single-cell and single-nucleus sequencing have revealed numerous astrocyte subpopulations that differ in morphology, gene expression, and functional properties. These subtypes can change dynamically during development, aging, and disease, thereby altering the overall composition of the astrocyte population [26]. In AD, pronounced transcriptomic changes in astrocytes occur along the spatiotemporal progression of the disease, reflecting shifts between homeostatic and reactive astrocyte states [27]. Importantly, individual astrocytes may display both protective and detrimental properties depending on environmental signals and the stage of the disease [19]. Recent spatial transcriptomics data mapping glial states and molecular events within plaque–glial niches in human AD brain tissue provide new insights into the cellular and molecular heterogeneity underlying neurodegenerative pathology [28]. Current single-cell sequencing techniques also enable the correlation of transcriptional changes in astrocytes from AD patients with specific clinical indicators [29]. While astrogliosis and inflammatory signaling represent major components of astrocyte pathology, they are accompanied by additional cellular changes that affect astrocyte physiology and survival.

3.2 Astrocyte Functional Impairment, Senescence, and Death

Beyond inflammatory activation, astrocytes in neurodegenerative conditions frequently exhibit profound functional impairments that further compromise neuronal homeostasis. In both AD patients and experimental models, astrocytes show disturbances in key processes such as calcium signaling and glutamate buffering. For instance, astrocytes in AD models display abnormal intracellular Ca^{2+} dynamics characterized by hyperactive signaling patterns that parallel neuronal hyperexcitability observed during disease progression [30]. Elevated astrocytic expression of the Ca^{2+}/calmodulin-dependent phosphatase calcineurin has also been detected in early-stage AD and may contribute to the induction of inflammation-related genes [31]. Additionally, decreased levels of inositol 1,4,5-trisphosphate receptor type 2 have been reported [32,33]. Such remodeling of calcium signaling can impair astrocyte reactivity and disrupt homeostatic support mechanisms [34]. Alterations in glutamate metabolism represent another important pathological feature. Reduced expression of the glutamate transporter EAAT2 and diminished glutamate uptake activity have been reported in the frontal cortex of AD patients [35]. Impaired glutamate transport has also been associated with increased Aβ accumulation [36]. Furthermore, decreased expression of glutamine synthetase in astrocytes during AD progression disrupts the glutamate–glutamine cycle, potentially contributing to synaptic dysfunction and cognitive deficits [37]. These changes may promote excitotoxicity, which is widely recognized as a contributor to neurodegeneration [38].

In addition to functional impairment, astrocytes may undergo cellular senescence, particularly during aging and chronic stress. Senescent astrocytes enter permanent cell-cycle arrest but remain metabolically active and develop a senescence-associated secretory phenotype (SASP). This phenotype promotes chronic inflammation and can negatively influence surrounding neural cells [39]. Accumulation of senescent astrocytes has been increasingly linked to neurodegenerative disease progression [40,41]. Metabolically, senescent astrocytes undergo a shift from glycolytic metabolism to increased oxidative phosphorylation, which reduces lactate supply to neurons [42,43]. This shift is associated with enhanced inflammatory signaling and a transition from neurotrophic to neurotoxic phenotypes. In parallel, several essential astrocytic functions—including glutamate uptake, cholesterol synthesis, and ATP production—are significantly reduced [44–46]. These deficits may contribute to BBB dysfunction, synaptic impairment, decreased Aβ clearance, and neuronal loss. Additionally, senescent astrocytes have been found to contribute to neurotoxicity [47]. A recent study based on single-cell and bulk RNA sequencing suggests that senescence of different cell types in brain, including astrocytes, may contribute to the initiation and development of AD [48]. Importantly, given the role of senescence in protein pathology and disease progression, specifically targeting senescent cells has emerged as a promising therapeutic approach in AD [49].

Astrocytes may undergo cell death under pathological conditions. Both apoptotic and non-apoptotic mechanisms have been reported, including ferroptosis, an iron-dependent form of cell death associated with lipid peroxidation [50,51]. Although astrocyte death can trigger im-

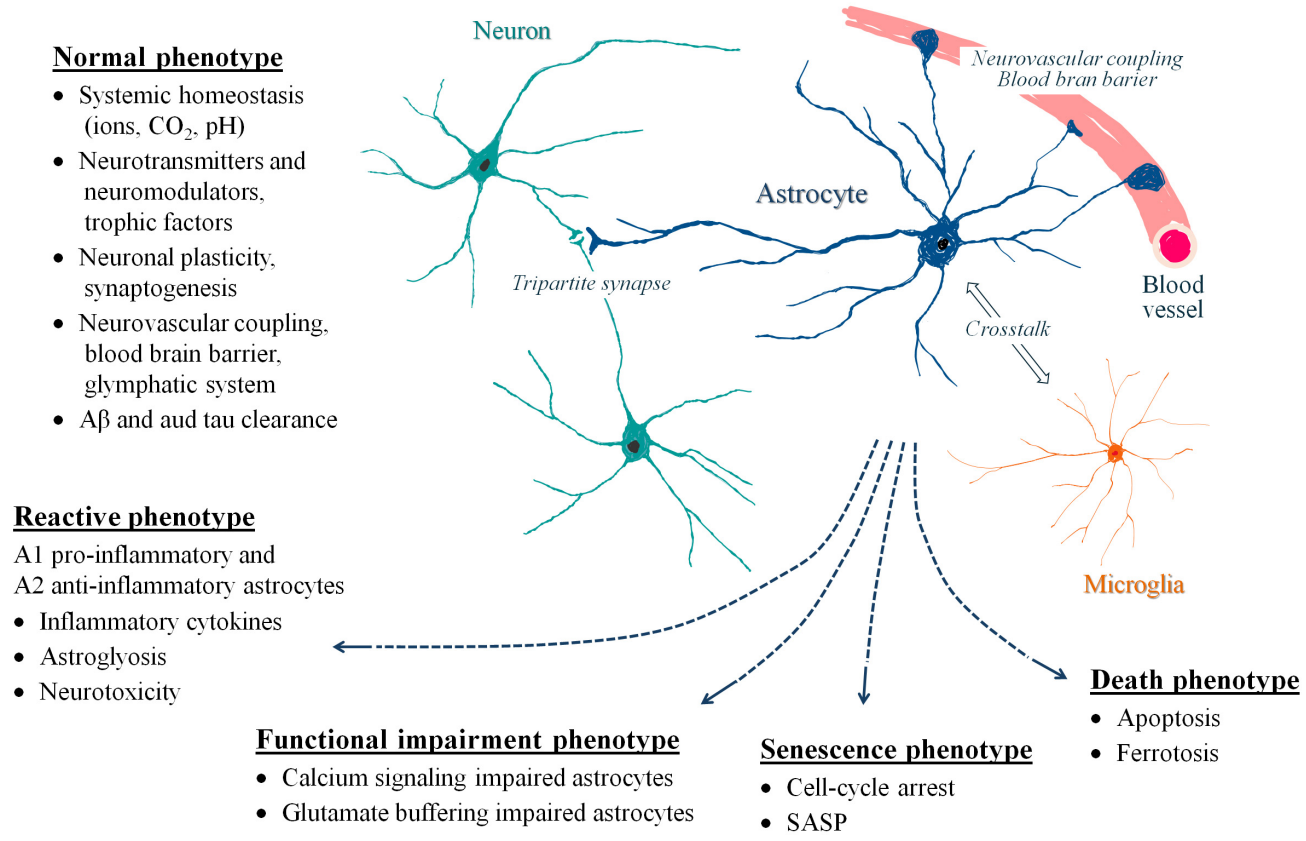

Fig. 1. Schematic overview of characteristic features of normal and pathological astrocyte phenotypes potentially involved in AD pathology. Normal, healthy astrocytes play a crucial role in maintaining CNS homeostasis, including regulation of pH and ion balance (Na^+, K^+, Ca^{2+}), production of trophic factors (BDNF, GDNF, CNTF, NGF), neurotransmitter recycling, modulation of neuronal plasticity, formation and maintenance of the neurovascular unit and the BBB, support of glymphatic function, and clearance of Aβ and tau proteins. Under adverse conditions, distinct pathological astrocyte phenotypes can emerge and contribute to AD pathogenesis. Accumulation of Aβ, oxidative stress, and inflammatory cytokines—depending on their intensity and duration—can alter astrocyte reactivity, promote astrogliosis, impair astrocytic function, or induce cellular senescence and cell death. Pathological astrocyte phenotypes exhibit morphological and molecular alterations, including disrupted Ca^{2+} signaling and intracellular signaling pathways. These changes may contribute to AD progression by impairing Aβ clearance, promoting tau hyperphosphorylation, disrupting glucose metabolism, and inducing neuronal dysfunction. Aβ, amyloid-β; AD, Alzheimer's disease; CNS, central nervous system; BDNF, brain-derived neurotrophic factor; GDNF, glial cell line-derived neurotrophic factor; CNTF, ciliary neurotrophic factor; NGF, nerve growth factor; BBB, blood–brain barrier.

mune responses that promote the clearance of aggregated proteins, chronic cell loss and sustained inflammation may exacerbate neurodegenerative processes [52]. Astrocytic death phenotypes have been observed in the brains of AD patients [50,53].

Taken together, these findings highlight the multifaceted ways in which astrocyte dysfunction contributes to brain pathology. These mechanisms are particularly evident in AD, where astrocytic alterations influence multiple aspects of disease progression. The key features of normal and pathological astrocyte phenotypes potentially involved in AD development are schematically illustrated in Fig. 1.

4. Astrocyte Involvement in Alzheimer's Disease

Astrocytes play a central role in the pathophysiology of AD, exerting both protective and detrimental effects depending on disease stage and pathological context. Under physiological conditions, they maintain neuronal homeostasis by regulating metabolic pathways, neurotransmitter cycling, ion balance, and the clearance of toxic metabolites. However, chronic exposure to pathological stimuli such as Aβ, oxidative stress, and inflammatory cytokines can drive astrocytes toward maladaptive reactive states that contribute to neurodegeneration [54,55].

Increased amounts of both A1 and A2 astrocytes identified in post-mortem brain tissue from patients with AD suggest the roles for both these phenotypes in the disease

pathogenesis [56]. In the early stages of AD, astrocyte activation may serve protective functions. Reactive astrocytes can enhance Aβ clearance and support neuronal survival [1,57]. With disease progression, however, persistent stimulation promotes the development of chronic inflammatory phenotypes that disrupt neuronal networks and exacerbate neurodegeneration [58,59]. As a result, neuroprotective and neurotoxic astrocyte subtypes may coexist within the same brain regions at similar stages of the disease [60]. Interestingly, astrocytes exhibit diverse morphological responses, including hypertrophy and atrophy depending on disease stage and proximity to amyloid plaques [61]. Nevertheless, the functional implications of these morphological changes remain incompletely understood, although recent findings suggest that morphological features of iPSC-derived astrocytes from AD patients correlate with donor-specific pathophysiological phenotypes [62]. Astrocyte reactivity in AD is strongly influenced by interactions with other glial cells. Microglia-derived signals modulate astrocyte activation, and Aβ-associated astrocyte reactivity across cortical regions appears to depend on the presence of microglial activation [63].

Several molecular mechanisms underlie astrocyte-mediated contributions to AD pathology. Reactive or senescent astrocytes often exhibit altered cytokine secretion and impaired glutamate uptake, increasing the risk of excitotoxic neuronal injury [64,65]. They may also promote tau hyperphosphorylation and impair Aβ clearance, thereby accelerating neurofibrillary tangle formation [66,67]. Astrocytes are key regulators of the glymphatic system, which facilitates the clearance of metabolic waste via aquaporin-4 (AQP4) channels localized in astrocytic endfeet. Disruption of this system impairs the removal of toxic proteins and metabolites, thereby promoting AD pathology [68,69]. Indeed, impaired glymphatic function has been associated with astrocyte activation and synaptic loss in AD [70,71]. In this context, the astrocyte–vascular axis has emerged as an important component of disease progression. Molecules such as vascular endothelial growth factor-C and angiotensin-converting enzyme show stage-specific expression patterns associated with cognitive outcomes, suggesting that astrocytes may act as intermediaries linking AD pathology with vascular dysfunction [72].

Metabolic dysregulation represents another key aspect of astrocyte involvement in AD. Astrocytes play a central role in brain energy metabolism through the astrocyte–neuron lactate shuttle, which supplies neurons with metabolic substrates. Disturbances in cerebral glucose metabolism—commonly observed in AD—may partly result from impaired astrocytic glucose uptake and metabolism [73,74]. Disruption of astrocyte-derived lactate production can compromise neuronal energy supply and synaptic transmission [75,76]. These metabolic deficits likely arise from a combination of astrocytic dysfunction, vascular abnormalities, and impaired glucose transport across the BBB. In addition, growing evidence indicates that astrocytes play a key role in the regulation of fatty acid and cholesterol metabolism, which is disrupted in astrocytes in AD [77]. Alterations in astrocytic lipid metabolism may directly affect neuronal health by disturbing cholesterol homeostasis, promoting neuroinflammation through lipid peroxidation byproducts, and impairing energy metabolism. Furthermore, these metabolic changes may contribute to AD pathophysiology by compromising the astrocyte-mediated clearance of Aβ.

Genetic evidence further supports the involvement of astrocytes in AD. Apolipoprotein E4 (ApoE4), the strongest genetic risk factor for sporadic AD, is predominantly produced by astrocytes in the healthy brain. While astrocyte-derived ApoE regulates Aβ metabolism, ApoE4 can compete with Aβ for binding to lipoprotein receptor-related protein 1 (LRP1), a key mediator of Aβ clearance across the BBB. This competition may impair Aβ removal and promote plaque accumulation [78]. Other AD-associated genes expressed in astrocytes include clusterin (CLU), which plays a role in regulating Aβ metabolism and modulating neuronal function [79].

Despite these pathological mechanisms, astrocytes retain important neuroprotective capacities. They contribute to Aβ elimination through multiple pathways, including the secretion of Aβ-degrading enzymes such as insulin-degrading enzyme, neprilysin, and matrix metalloproteinases [80,81]. Experimental evidence supports this protective role: suppression of astrocyte reactivity in the APPswe/PS1ΔE9 mouse model increases Aβ plaque deposition, indicating that reactive astrocytes help limit Aβ pathology [82]. Additionally, increased secretion of CLU from astrocytes was shown to rescue synaptic deficits and improve Aβ neuropathology in the 5xFAD AD mouse model [83]. Astrocytes also regulate neuronal excitability and neurotransmitter balance. Under pathological conditions, reactive astrocytes may release γ-aminobutyric acid (GABA), which is synthesized by monoamine oxidase-B, thereby reducing neuronal hyperexcitability and inflammatory signaling [9]. Given that GABAergic transmission is reduced in AD, astrocyte-derived GABA may represent a compensatory mechanism that stabilizes neuronal networks. Conversely, astrocytic dysfunction can impair neurotransmitter homeostasis; reduced expression of the glutamate transporter GLT-1 disrupts glutamate clearance and promotes excitotoxicity, contributing to cognitive decline [84].

Emerging evidence suggests that in AD the initial pro-inflammatory stimulus may arise from stressed or damaged neurons. This primary insult can then initiate a secondary inflammatory cascade mediated by complex intercellular interactions between astrocytes and microglia, ultimately driving disease progression [60,85]. Astrocyte reactivity may gradually shift toward neurotoxic phenotypes characterized by a transcriptional profile that impairs synaptic support and promotes neuronal death [19]. A central driver of astrocyte subtype switching during AD progression is

Aβ pathology, which acts as an early and sustained trigger of glial activation. Accumulating Aβ aggregates stimulate astrocytes through pattern recognition receptors, including Toll-like receptors and receptor for advanced glycation end products (RAGE), initiating intracellular signaling cascades such as NF-κB and Janus kinase/signal transducer and activator of transcription (JAK/STAT3). These pathways promote transcriptional reprogramming toward reactive states characterized by altered cytokine production, impaired synaptic support, and complement activation [60,86]. Another major determinant is oxidative and metabolic stress, which increases with disease progression. Mitochondrial dysfunction and elevated ROS production impair astrocytic energy metabolism and redox balance [87]. This metabolic shift reduces the capacity of astrocytes to sustain neuronal support while enhancing inflammatory signaling and susceptibility to neurotoxic conversion [88]. Concurrently, impaired lactate shuttle and glutamate clearance exacerbate neuronal vulnerability and synaptic failure. Aging may also act as a permissive and priming factor for astrocyte subtype transitions as aging astrocytes exhibit baseline upregulation of inflammatory pathways, reduced proteostasis, and diminished stress resilience. This primed state lowers the threshold for conversion into reactive phenotypes upon exposure to Aβ, cytokines, or vascular damage, thereby accelerating AD-related astrocytic dysfunction [12,89]. Reactive astrocytes can also acquire features of cellular senescence, releasing SASP factors that promote Aβ accumulation and tau hyperphosphorylation [90,91]. Reactive astrocytes apparently represent a heterogeneous population with both neuroprotective and neurotoxic properties [54,55]. In this context, network-based integration of RNA-seq and ATAC-seq datasets offers significant potential to elucidate the functional specialization of astrocyte subtypes in AD pathogenesis [92].

Overall, astrocytes exhibit complex and context-dependent roles in AD. While they can protect neuronal networks by maintaining metabolic and synaptic homeostasis and facilitating protein clearance, persistent activation and dysfunction may transform them into contributors to neurodegeneration. This duality is particularly evident in AD, where astrocytes transition from initially protective to progressively detrimental states in response to sustained pathological stress. Understanding the molecular pathways that regulate astrocyte subtype transitions is essential for developing therapeutic strategies targeting their function in AD. In particular, signaling mechanisms such as astrocytic calcium dynamics and the JAK/STAT, PI3K/Akt, NF-κB, and nuclear factor erythroid 2–related factor 2 (Nrf2) pathways have emerged as key regulators of astrocyte behavior under pathological conditions (Fig. 2).

4.1 The Role of Calcium Dyshomeostasis

Calcium dyshomeostasis is a common feature of many neurodegenerative diseases, including AD [93]. Dysregulated calcium signaling often arises early in disease progression and contributes to pathological alterations in neuronal synaptic activity [94,95]. In particular, oligomeric Aβ peptides can induce astrocytic calcium hyperactivity during the early stages of AD, promoting glutamatergic hyperexcitability in neighboring neurons [96]. These findings suggest that abnormal astrocytic calcium signaling represents an early event linking astrocyte dysfunction to neuronal injury. Under physiological conditions, astrocytes exhibit dynamic intracellular calcium signaling that regulates neurotransmitter uptake, gliotransmitter release, neural circuit activity, and neurovascular coupling [6,97]. Astrocytic Ca^{2+} is primarily stored in the endoplasmic reticulum (ER) and released through inositol 1,4,5-trisphosphate receptors (IP_3Rs), particularly IP_3R2, which mediates calcium-dependent gliotransmission [98]. In addition, calcium can enter astrocytes through plasma membrane channels, including AMPA and NMDA receptors, transient receptor potential (TRP) channels, and voltage-gated calcium channels. These tightly regulated calcium transients enable astrocytes to respond to diverse extracellular signals, including neurotransmitters, inflammatory mediators, and metabolic cues [98,99].

Although the mechanisms underlying astrocytic dysfunction in AD are not fully understood, disruption of Ca^{2+} signaling is considered a key contributing factor. Aβ interferes with gliotransmission by exacerbating astrocytic calcium signaling, leading to sustained intracellular Ca^{2+} elevations and abnormal oscillatory activity following chronic exposure to Aβ peptides and inflammatory cytokines [93, 96]. Aβ-induced Ca^{2+} dysregulation is therefore regarded as a central mechanism of astrocyte activation. Chronic calcium dysregulation has several downstream consequences. Sustained Ca^{2+} elevations impair mitochondrial function and increase oxidative stress through excessive production of ROS, ultimately contributing to neuronal dysfunction and neurodegeneration [100,101]. Moreover, elevated Ca^{2+} signaling promotes the production of Aβ and hyperphosphorylated tau, thereby amplifying pathological processes [102]. Astrocytic Ca^{2+} signals also regulate the release of gliotransmitters such as glutamate, GABA, D-serine, and ATP, which modulate synaptic activity and plasticity [98]. In AD models, however, these processes become dysregulated. For example, aberrant purinergic signaling mediated by metabotropic P2Y1 receptors can drive persistent astrocytic self-activation and calcium hyperactivity [24]. Excessive Ca^{2+}-dependent release of glutamate and D-serine enhances neuronal excitability, while ATP released from astrocytes activates microglial P2Y receptors, promoting neuroinflammation through cytokine production [103,104]. Additional astrocyte-derived mediators, including tumor necrosis factor-α (TNF-α) and prostaglandins, may further amplify these calcium-dependent signaling cascades [105].

Disrupted astrocytic calcium signaling also affects neurovascular regulation and neuronal network activity.

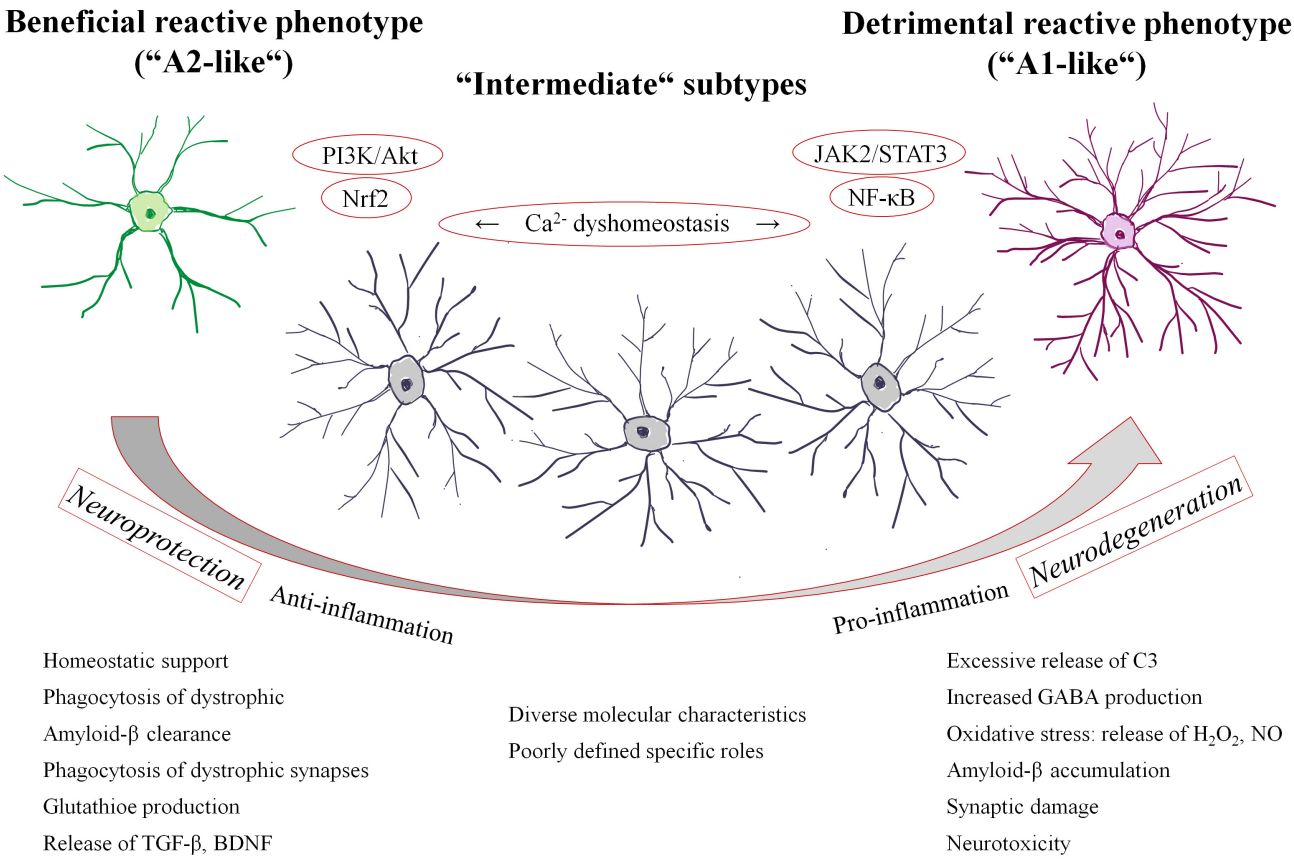

Fig. 2. A simplified schematic illustrating the dual roles of reactive astrocytes in AD and the regulation of their phenotypic states. Astrocyte polarization is governed by a balance of intracellular signaling pathways, in which JAK/STAT3 and NF-κB drive detrimental A1-like states, whereas PI3K/Akt and Nrf2 promote protective A2-like phenotypes; aberrant intracellular Ca^{2+} signaling represents a common hallmark of astrocyte reactivity. Beyond the classical A1 and A2 phenotypes, multiple distinct astrocyte subtypes have been identified based on transcriptomic profiling of the AD brain, although their functional characterization remains incomplete. JAK/STAT3, Janus kinase/signal transducer and activator of transcription 3; NF-κB, nuclear factor-kappa-B; PI3K/Akt, phosphoinositide 3-kinase/Akt; Nrf2, nuclear factor erythroid 2–related factor 2.

Under normal conditions, astrocytic Ca^{2+} transients trigger the release of vasoactive molecules that regulate local cerebral blood flow [106]. Impairment of this mechanism contributes to neurovascular dysfunction in AD. Indeed, astrovascular decoupling observed in AD mouse models has been associated with altered astrocytic calcium signaling and reduced astrocyte functional connectivity [107]. Reactive astrocytes in amyloid models also exhibit abnormal Ca^{2+} dynamics that disrupt communication between astrocytic endfeet and cerebral arterioles, potentially contributing to the cerebral hypometabolism characteristic of AD [108]. Importantly, normalization of astrocytic calcium signaling has been shown to reduce neuronal network hyperactivity and improve cognitive performance in β-amyloidopathy models [33,109].

Calcium dysregulation further contributes to neuronal excitotoxicity by disrupting glutamate homeostasis. Under physiological conditions, astrocytes remove synaptic glutamate through excitatory amino acid transporters and convert it to glutamine via glutamine synthase. The Wnt/β-catenin pathway promotes the expression of these proteins; however, reduced β-catenin signaling in AD impairs glutamate uptake, leading to synaptic glutamate accumulation, calcium overload, mitochondrial dysfunction, and neuronal death [110]. Similarly, astrocytic metabotropic glutamate receptor 5 (mGluR5) signaling influences AD progression. Increased receptor activity accelerates Aβ pathology, whereas its downregulation alleviates Aβ accumulation and cognitive deficits in AD mouse models [111]. Notably, brain-derived neurotrophic factor (BDNF) has recently been shown to prevent Aβ-induced upregulation of astrocytic mGluR5, thereby limiting pathological Ca^{2+} transients [112].

4.2 The JAK/STAT Pathway

Another critical signaling mechanism implicated in AD is the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, particularly the JAK2/STAT3 axis, which plays a central role in regulating neuroinflammation and astrocyte reactivity. Activation of

JAK2/STAT3 signaling promotes astrocyte and microglial activation and stimulates the release of pro-inflammatory cytokines, thereby contributing to the inflammatory environment characteristic of AD [113]. Increased STAT3 activity has been associated with Aβ accumulation, synaptic dysfunction, and cognitive decline, whereas inhibition of this pathway can attenuate cognitive deficits and slow disease progression [109,114].

The JAK/STAT pathway is a key mediator of astrocyte reactivity in several neurodegenerative disorders, including AD, Huntington's disease, and Parkinson's disease [115]. Activation of STAT3 regulates multiple aspects of astrocyte behavior, including morphological remodeling, migration, proliferation, and the expression of reactive markers such as GFAP, as well as the secretion of inflammatory cytokines. Through these mechanisms, STAT3 acts as a master regulator that drives the formation of distinct reactive astrocyte phenotypes. Experimental studies further demonstrate that activation of the JAK2/STAT3 axis induces reactive astrocyte formation in AD models, whereas SOCS3, an endogenous inhibitor of JAK/STAT signaling, functions as a negative regulator that restrains astrocyte reactivity [86]. Manipulation of this pathway has revealed important functional consequences in experimental models. In the APP/PS1ΔE9 mouse model of β-amyloidopathy, selective inhibition of JAK2/STAT3 signaling reduced astrocyte reactivity and improved amyloid plaque burden, spatial memory, and electrophysiological performance [114]. However, similar interventions in the 3 $\times$ Tg AD model failed to significantly affect plaque load or cognitive impairment [116]. These findings highlight the complexity of STAT3-mediated signaling and suggest that the therapeutic effects of targeting this pathway may depend on disease stage, model system, and the specific astrocyte subpopulations involved.

Although STAT3 regulates many reactive astrocyte states following inflammatory insults [117], recent single-cell and single-nucleus RNA sequencing studies have identified astrocyte subpopulations that appear to be independent of STAT3 signaling [118,119]. Alternative regulators of astrocyte reactivity include the chromatin remodeler SMARCA4 [120] and microRNAs such as *miR-146a*, *miR-145*, and *miR-125b* [121]. While these microRNAs may not directly initiate the transcription of reactive genes, they likely stabilize reactive transcriptional programs and contribute to the sustained transition from physiological to reactive astrocyte states [122]. These observations suggest that neuroprotective and neurotoxic astrocyte phenotypes may coexist within the same cellular populations, reflecting the complex regulatory networks that govern astrocyte responses during neurodegeneration.

4.3 PI3K/Akt, NF-κB and Nrf2 Signaling Pathways

The PI3K/Akt pathway, which is upstream of NF-κB and Nrf2, also plays an important role in astrocyte-mediated processes in AD. Positive effects associated with reduced astrocyte activation have been observed in APP/PS1 Alzheimer's model mice following PI3K/Akt signaling activation [123]. Activation of this pathway has also been reported to promote autophagy, thereby attenuating glial cell activation-induced inflammatory responses in this model [124]. In primary rat astrocytes, PI3K/Akt activation has been shown to inhibit Aβ aggregation [125]. Furthermore, activation of this pathway counteracted A1/A2 astrocytic alterations induced by microglia-conditioned medium and reversed the transition to the neurotoxic A1 phenotype in primary mouse astrocytes [126]. However, other studies suggest that overactivation of astrocytes and microglia through the PI3K/Akt/mTOR pathway can promote pathological neuroinflammatory responses, and that inhibition of this pathway may therefore exert beneficial effects [127]. Similarly, activation of the PI3K/Akt/GSK-3β pathway has been reported to promote amyloid accumulation and tau phosphorylation [128]. Aβ itself can activate PI3K/Akt signaling in astrocytes, contributing to the development of reactive astrocytes [129]. Likewise, activation of PI3K/Akt by extracellular filamentous tau has been shown to facilitate the secretion of complement component C3 and promote pro-inflammatory astrogliosis [130]. Taken together, these findings suggest that the role of PI3K/Akt signaling in AD is context-dependent and requires further investigation.

The NF-κB signaling pathway is another major regulator of astrocyte-mediated inflammation. Overactivation of NF-κB has been observed in both animal models and human AD brains and is associated with increased Aβ production and inflammatory responses [131]. Aβ oligomers can induce NF-κB activation in astrocytes through upregulation of TNF-α and COX-2, leading to astrogliosis and inflammatory signaling. Importantly, ApoE4—the major genetic risk factor for late-onset sporadic AD—has been shown to drive inflammatory responses in human astrocytes via NF-κB activation [132]. Although inhibition of NF-κB signaling has been reported to attenuate disease progression in several animal models of neuroinflammation, its precise role in astrocyte reactivity remains controversial. For example, it has been demonstrated in an APP23 AD model that NF-κB activation resulted in pronounced astrogliosis and neuroinflammation [133]. Surprisingly, this response also promoted microglia-mediated Aβ clearance and reduced the size and number of amyloid plaques. In contrast, another study using rat hippocampal astrocytes treated with Aβ_{1-42} peptides reported detrimental effects of NF-κB-driven neuroinflammation [134]. Interestingly, miRNA-146a-5p has been shown to activate NF-κB signaling without increasing pro-inflammatory cytokine production, suggesting an anti-inflammatory role through a negative feedback loop within the NF-κB pathway [134]. These conflicting findings highlight the complexity of NF-κB signaling and indicate that further research is needed to clarify the downstream mechanisms linking astrocytic NF-κB activity, Aβ deposition, and cognitive impairment.

Several studies have demonstrated that Nrf2 plays a key role in regulating redox homeostasis and exerts anti-inflammatory effects in various neurodegenerative disorders [135]. The importance of astrocytes in this context is underscored by findings showing that astrocyte-specific activation of Nrf2 is sufficient to attenuate disease progression in multiple experimental models, including AD [136]. Consistently, Nrf2 deficiency promotes the activation of reactive astrocytes in brain tissue from 5xFAD mice, whereas Nrf2 upregulation suppresses the induction of reactive astrocyte gene expression by inhibiting the recruitment of the NF-κB subunit p65 [137]. Overall, enhanced Nrf2 signaling appears to drive astrocytes toward a neuroprotective phenotype [138].

4.4 Some Unanswered Questions, Model Limitations, and Translational Gaps

To better understand the functional changes in astrocytes that may contribute to the initiation and progression of inflammatory responses and neurodegenerative diseases, several important questions still need to be addressed. Different neurodegenerative conditions appear to affect distinct anatomical regions of the brain. In AD, pathology initially targets the hippocampus and entorhinal cortex, before later spreading to the neocortex [139]. This suggests that certain brain regions may be inherently more vulnerable to internal pathological changes, external toxic insults, or natural processes such as those occurring during aging [140]. Aging—one of the major risk factors for neurodegenerative diseases—has been shown to influence astrocytic immune responses and other key functions [141]. However, further research is needed to determine whether astrocyte heterogeneity and region-specific dysregulation actively contribute to the neurodegenerative process. It is therefore essential to investigate whether astrocytic changes vary depending on brain region or proximity to pathological features. For instance, it would be of interest to determine whether the reduction in glutamate transporter currents and other neurosuppressive functions observed in the AD brain occurs predominantly in astrocytes located near Aβ plaques.

It is also important to examine the role of astrocytes in disrupting the signaling pathways between neurons, astrocytes, and blood vessels that underlie neurovascular coupling. Furthermore, identifying which astrocytic alterations have the greatest impact on cognitive performance is essential for pinpointing the astrocyte phenotypes that should be targeted by future therapies. However, these questions may be overly simplistic, as multiple functional disturbances can contribute to circuit dysfunction, synapse loss, or neuronal death. In addition, the stage of the disease may critically determine whether a given therapeutic intervention will be effective.

Astrocyte functional heterogeneity under different pathological conditions is closely linked to dysregulated intracellular signaling pathways, including Ca^{2+} dynamics, JAK/STAT, PI3K/Akt, NF-κB, and Nrf2 signaling, which collectively regulate inflammation, metabolism, and cellular stress responses. In AD, astrocytic signaling is characterized by a shift from PI3K/Akt- and Nrf2-supported protective states toward JAK/STAT- and NF-κB-driven inflammatory reactivity, accompanied by disrupted Ca^{2+} signaling. From a translational perspective, the most promising therapeutic strategy is not single-pathway inhibition but rather coordinated reprogramming of astrocyte states, aimed at enhancing metabolic and antioxidant support while limiting chronic inflammatory activation.

Translational gaps and limitations between rodent models and human studies should also be considered. Rodent astrocytes differ from their human counterparts in morphology, gene expression, and functional complexity; human astrocytes are larger and exhibit greater structural and transcriptional diversity [142,143]. Another limitation is the incomplete representation of AD pathology in experimental models. Most transgenic mouse models rely on amyloid precursor protein overexpression and primarily reproduce Aβ plaque deposition, while failing to capture the full spectrum of tau pathology, neuronal loss, and age-related processes characteristic of human disease [144]. Astrocyte reactivity observed in these systems—often simplified into binary "neurotoxic" versus "neuroprotective" states—does not adequately reflect the diversity of astrocyte states identified in human brains [60]. Consequently, therapeutic targets identified in animal models often fail to translate into clinical efficacy.

Astrocyte heterogeneity itself represents a critical translational barrier. Single-cell and single-nucleus transcriptomic studies have identified multiple astrocyte subpopulations with distinct molecular signatures that vary across brain regions and disease stages [145]. As discussed above, in AD, disease-associated astrocytes exhibit context-dependent phenotypes that may exert both protective and detrimental effects. This functional duality complicates therapeutic strategies, as indiscriminate modulation of astrocytes could disrupt essential homeostatic functions, including neurotransmitter recycling and ion balance. Temporal dynamics further complicate translation. Astrocytes may initially contribute to amyloid clearance and synaptic support but later acquire pro-inflammatory and neurotoxic properties as disease progresses [12].

The lack of robust and specific biomarkers of astrocyte function in living patients represents another major gap. While GFAP levels in cerebrospinal fluid and plasma show promise as indicators of astrocyte reactivity, they lack specificity for distinct functional states and do not capture the full complexity of astrocyte responses [146]. This limitation hampers patient stratification and the assessment of target engagement in clinical trials. Astrocytes also operate within a tightly interconnected cellular network involving neurons, microglia, and vascular cells. For example, microglia-derived cytokines can induce specific reactive astrocyte phenotypes, underscoring the importance of

intercellular signaling in disease progression [19]. Consequently, targeting astrocytes in isolation may be insufficient, and combinatorial or systems-level therapeutic approaches may be required. An additional complication arises from the difficulty of identifying the optimal therapeutic window in human patients, due to the long preclinical phase of AD and the limited tools available for monitoring astrocyte activity *in vivo*.

5. Conclusion and Future Directions

Astrocytes are critical regulators of CNS homeostasis, far beyond their traditional role as support cells. They maintain neuronal function through metabolic regulation, ion signaling, synaptic modulation, clearance of toxic molecules, and contributions to the blood–brain barrier. In response to physiological stress or pathological insults, astrocytes undergo functional and morphological changes that enable them to modulate immune signaling, preserve tissue integrity, and limit neuronal damage.

A hallmark of AD is astrogliosis, characterized by structural remodeling and altered gene expression. While initially protective, excessive or prolonged astrocyte reactivity can become detrimental, amplifying neuroinflammation, promoting neuronal apoptosis, and facilitating Aβ accumulation. These observations suggest a tipping point at which astrocyte-mediated neuroprotection shifts toward neurotoxicity. Importantly, astrocyte reactivity is highly heterogeneous, varying with the type of insult and CNS region. Transcriptomic and single-cell analyses reveal diverse reactive states, some neuroprotective and others neurotoxic. However, functional characterization of many subpopulations remains incomplete, leaving open questions about how astrocyte responses are conserved or differ across disease contexts. Moreover, astrocytes interact extensively with other glial cells, particularly microglia and oligodendrocytes, within disease-associated microenvironments, influencing both inflammatory signaling and disease progression.

The heterogeneity and intercellular crosstalk of astrocytes position them as promising therapeutic targets in AD. Effective strategies are likely to be combinatorial, enhancing neuronal resilience while modulating astrocyte reactivity. Interventions could prevent the emergence of harmful reactive phenotypes, promote clearance of toxic proteins, restore glutamate homeostasis, support glymphatic function, and optimize astrocytic metabolic capacity. Emerging technologies—spatial transcriptomics, single-cell sequencing, and chromatin accessibility profiling—are beginning to reveal the transcriptional and epigenetic programs underlying astrocyte heterogeneity and plasticity. When integrated with physiologically relevant models, including organoids, organotypic slices, and *in vivo* imaging, these insights offer the potential to translate mechanistic understanding into targeted interventions. Ultimately, mapping astrocyte state transitions and intercellular interactions will be essential for developing precision therapies that harness their full therapeutic potential in AD.

Importantly, it cannot be ruled out that neurotoxic and neuroprotective functional changes, driven by distinct transcription factors, may occur simultaneously within the same astrocyte. From a therapeutic standpoint, strategies aimed at enhancing adaptive and protective astrocytic responses while concurrently inhibiting pathways that promote neurodegeneration or functional neglect could shift the balance of astrocyte sub-states. Such an approach may result in reactive astrocytes exerting a net disease-modifying and potentially neuroprotective effect. This implies the necessity of developing strategies that selectively modulate specific astrocyte functions in a stage-dependent manner, as certain astrocytic activities may be beneficial during early disease stages but become detrimental as pathology progresses. For instance, during the early inflammatory phase of AD—when neuronal stress pathways are first activated—the temporary removal of compromised neurons from active circuits might help preserve overall network stability and provide time for neuronal recovery. In this context, transient suppression of astrocytic synaptic maintenance functions could be advantageous. Conversely, in later stages of AD, when synapse density is already severely compromised due to excessive microglial pruning, the preservation and support of remaining synapses by astrocytes becomes critically important. These complex and dynamic shifts suggest that broadly targeting astrocyte reactivity may not yield therapeutic benefit. Instead, focusing on defined astrocyte substates or isolating specific functional pathways may offer more precise and effective therapeutic opportunities.

Author Contributions

IS conceived the project, conducted the analysis of previous studies, and wrote the preliminary draft. ZB performed the literature search and revised the manuscript. JN contributed to the study the conception, the design of the content framework, and the preparation of the final manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research was supported by the Czech Grant Foundation (grant no. 23-07184S).

Conflicts of Interest

The authors declare no conflicts of interest.

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