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Review

Impairment of astrocyte homeostasis and lysosomal function in Alzheimer's disease pathogenesis

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ABSTRACT: Physiological functions of astrocytes, the most abundant cell type in the brain, are important in maintaining many central nervous system (CNS) functions. In this review, we summarized astrocytes' normal physiological roles. However, under the pathological conditions of Alzheimer's Disease (AD), astrocytes pause their homeostatic roles to address and contain abnormal changes in AD brains in response to Aβ deposits, neuroinflammation, and neurodegeneration. The chronic perturbation in AD brains causes various populations of astrocytes to permanently forgo their physiological roles throughout different regions of the brain to contain disease progression. This transition leads to reactive astrogliosis, in which astrocytes transform into reactive phenotypes that eventually contribute to pathological severity. The transformations in astrocytes can negatively impact their morphology and mobility, inflammatory response, energy metabolism, and their ability to properly degrade Aβ deposits. We reviewed recent literature exploring the underlying mechanisms on how AD induces astrocyte morphological, transcriptional, and functional changes. Together, these findings reveal that loss of astrocyte homeostatic function and transformations into neurotoxic states contribute to AD pathology throughout each stage of disease progression. Thus, aims to restore astrocyte homeostatic functions by developing astrocyte-specific therapeutic targets to attenuate AD pathology and clinical manifestations are warranted.

Keywords: Aβ uptake, lysosomal degradation, neurodegeneration, pH homeostasis, phagocytosis, reactive astrocytes

1. Introduction

Alzheimer's disease (AD) has long been referred to as a neurodegenerative disease, primarily due to its accelerated brain neuronal death [1-3], and multiple clinical symptoms associated with dementia [2]. In 1906, Drs. Alois Alzheimer and Oscar Fischer initially reported the presence of amyloid beta (Aβ) plaques and buildup of neurofibrillary tangles in post-mortem brain tissues of patients with dementia like clinical symptoms [2]. Aβ plaques are defined as the extracellular aggregates of b-amyloid oligomers which are formed by β-secretase cleavage of the Amyloid precursor protein (APP), while neurofibrillary tangles (NFT) are entanglements of abnormally hyperphosphorylated tau protein that accumulate inside neurons [3]. Resulting from these brain pathologies are many clinical manifestations of AD patients, including memory loss, poor judgement, problem solving challenges, etc. More recent clinical research has also reported non-dementia related cognitive changes, that often lead to character or personality changes, referred to as the HIDA (Hyperactivity-Impulsivity-Irritability-Disinhibition-Aggression-Agitation) domain [4]. The advancement of minimally

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invasive imaging technologies and biochemical testing of blood and cerebral spinal fluid (CSF) samples have significantly widened the window for earlier detection of AD development and severity of progression [5]. fMRI and PET brain imaging techniques using different radioactive tracers, such as Pittsburgh compound B (PiB), have been crucial in detecting Aβ protein oligomerization and protofibril formation [6]. These diagnostic tools are able to assist in differentiating the six different Braak stages of AD [7] Stages I and II are characterized by mild or severe buildup of NFT and neuropil thread which lead to alterations of the trans-entorhinal layer but often present normal cognitive and clinical profiles [7, 8] (Table 1). Stages III and IV are marked by extended pathology to the trans-entorhinal layer and the entorhinal cortex [7] (Table 1). Lastly, stages V and VI are marked by the degeneration of most iso-cortical associated areas, caused by the increasing severity of the NFT accumulation in neurons [7,9,10] (Table 1).

Table 1. AD Diagnostics and Treatments.

Diagnosis	Type	Usage	Benefits	Limitations
Bakk Stage Pathology	I-II (transentorhinal stage): mild to severe alteration of trans-entorhinal layer III-IV (limbic stage) pathology extends to entorhinal cortex and hippocampus V-VI (isocortical stage) majority isocortical areas display severe pathology [9, 10]	Identify AD stage progression through neurofibrillary Tau (NFT) pathology which induces neurodegeneration across the brain	Early detection and insight into AD progression	No distinction in cognitive changes
Biofluid Biomarkers	$A\beta_{42/40}$ ratios, p-tau (231, 181, 217), and GFAP in CSF and Blood Plasma [16, 17, 19, 121]	Detect abnormal levels of disease-associated biomarkers	Early detection and monitor AD prognosis during disease phases	Accessibility in rural communities; invasiveness of CSF collection
Brain Imaging	Functional Magnetic Resonance Imaging (fMRI), Positron Emission Tomography (PET) to detect AD related brain pathologies [6, 8, 12, 125, 145]	Detect Aβ protein-oligomerization and protofibrils, glymphatic changes, white matter hyperintensities, and astrogliosis	Noninvasive, high resolution of brain structures and activity	Expensive form of testing
Therapy	**Type**	**Usage**	**Benefits**	**Adverse Effects**
FDA-Approved Antibodies	Lecanemab: Anti-Aβ human monoclonal antibody [137, 139, 141]	Target removal of premature Aβ soluble protofibril in early AD	Reduced amyloid burden in AD patients brains, CSF and plasma and led to moderately less cognitive decline	Infusion-related reactions, ARIA and cerebral microhemorrhages
	Aducanumab: Anti-Aβ monoclonal antibody [141, 146]	Target highly aggregated, mature Aβ plaques in late AD	Dose- and time-dependent reduction of brain Aβ slowing cognitive decline	ARIA-Edema, urinary and upper respiratory tract infections
	Bepranemab: Anti-tau monoclonal antibody (in FDA Phase 2) [138]	Target extracellular tau aggregation	Passed safety trials and reduced cognitive decline	Therapeutic window has not been optimized, lacks specificity for extra vs intracellular Tau

In addition to neurodegeneration, recent AD research reveals that dysfunction of other brain cells, including astrocytes, microglia, and oligodendrocytes, also play key roles in the development of AD pathogenesis [11]. Specifically, the roles of astrocytes in relation to AD pathology has gained attention due to their significant changes in morphology and function [11]. CSF and blood serum samples from AD patients often display abnormally high concentrations of Aβ, tau protein [12] as well as glial fibrillary acidic protein (GFAP) [13]

biomarkers in early detection of AD development (Table 1). Serum Aβ42/Aβ40, followed by GFAP and p-tau231, showed the largest rate of change at the transition from Aβ- to Aβ+ and from Tau- to Tau+ in AD subjects [14]. Several studies have reported that inclusion of plasma GFAP levels as a biomarker in aged individuals [15] and in APOE4 positive subjects [16] reliably predicted Aβ positive individuals based on PET detection and rose sharply when CSF Aβ became abnormal. However, Periera et al. (2021) reported that GFAP was not a reliable predictor of Tau aggregate pathology [17]. Here, we reviewed recent publications on the physiological functions of astrocytes and how AD development induces astrocytic morphological, transcriptional, and functional changes that further provoke disease development. Together, these findings reveal that loss of astrocyte homeostatic function and transformations into neurotoxic states contribute to AD pathology throughout each stage of disease progression. Thus, aims to restore astrocyte homeostatic functions by developing astrocyte-specific therapeutic targets to attenuate AD pathology and clinical manifestations are warranted.

2. Astrocytes and physiological functions in the CNS

Astrocytes are the most abundant neuroglial cells in the central nervous system (CNS), characterized by their large star-shaped morphology with endfeet associated with cerebral vasculature's blood-brain barrier (BBB) function [18]. Astrocytes execute many functions within the CNS, such as providing trophic support for neurons and modulating synaptic transmission and plasticity [19]. German physician Rudolph Virchow first described neuroglia in 1826 as the connective tissue of the brain, as it embeds many components of the CNS. [18]. Furthermore, depictions of astrocytes' morphology and their placement amongst neurons in the CNS were famously illustrated by Spanish scientist Santiago Ramón y Cajal at the turn of the 19th century [20]. Currently, common methods for detecting astrocytes include probing for GFAP, astrocytes' primary cytoskeleton protein; S100β, a calcium ion-binding peptide; aquaporin 4 (AQP4), a water channel protein localized at the astrocytic endfeet, and excitatory amino acids transporter proteins EAAT-1 and EAAT-2, which help clear excess glutamate from the synaptic cleft [21, 22]. To better study astrocytes *in vivo*, researchers developed transgenic astrocyte-specific Cre mouse lines, such as the Aldh1a1Cre^{ERT2} knock-in line, which revealed five novel astrocyte subtypes with superior morphological capacity [23]. These techniques have been essential for understanding astrocyte heterogeneity and their diverse roles in the CNS.

Astrocytes play a crucial role in maintaining brain health, contrasting from the late 20th century idea that they only served in a passive insulation role within the CNS [19, 24]. Of high importance, astrocytes supply energy and metabolic substrates to active neurons by regulating glucose, lipid, and amino acid metabolism throughout the neuronal environment [25]. Astrocytes can take up and metabolize glucose from the blood through Glucose Transporter 1 (GLUT1) via glycolysis to shuttle lactic acid substrate to neurons as a primary energy for their mitochondria [25]. Astrocytes also act as the main reservoir for glucose storage as glycogen in brain. An alternative source of energy provided to neurons by astrocytes comes from β-oxidation of lipid droplets for fatty acids metabolism when glucose is not as widely available [26]. Furthermore, astrocytes actively remove and metabolize amino acids, specifically, Glutamate and GABA from neuronal synaptic clefts using Glutamine Synthase enzyme to prevent toxic neurotransmission [19, 25] Additionally, astrocytes efficiently regulate ion and neurotransmitter transport, respond to micro-environmental threats, upkeep BBB maintenance, clear glymphatic debris, through which they coordinate synapse formation, modulation, and elimination while communicating with other cells of the CNS [24, 27] (Fig. 1). Considering our extensive knowledge about astrocytes' essential roles in the CNS, it is not surprising that their dysfunction contributes to cognitive decline and the progression of AD pathogenesis [28], emerging as a key focus in AD research.

3. Reactive astrocytes in AD brains

3.1 Diversity of Pathological Astrocyte Activation

In response to neurological disease, injury, infection, and normal aging, astrocytes undergo morphological, transcriptional, and functional transformations in attempt to resolve the presented challenges. Patani and colleagues categorized these astrocytic changes into two domains: dyshomeostatic and cytotoxic, where astrocytes either downregulate/abandon their duties for maintaining the normal homeostatic environment or directly contribute to the neuropathological consequences [29]. For example, in physiological settings, astrocytes localize in tile-like domains that cover the entire brain, and through their numerous fine processes, they interact with other cells and blood vessels within their spatial domains [30]. However, after an acute ischemic stroke, astrocytes attempt to address the hypoxic insult through short term dyshomeostasis by abandoning their normal domains to form a protective glia scar barrier around the infarct and to prevent further neuronal death beyond the peri-infarct area [31] [32]. It has been suggested that to properly address local threats, astrocytes, throughout various brain

areas, undergo a diverse array of dyshomeostatic transformations in a regionally specific manner.

Several regionally specific changes were observed when comparing astrocyte structural, morphological, and transcriptional profiles [27]. Endo and colleagues characterized astrocytes from 13 regions of wild-type adult mouse brains, including the hippocampus, motor cortex, and striatum. Astrocytes from each of the 13 regions generally shared functional roles in maintaining metabolism, cholesterol, and neurotransmitter uptake homeostasis [27]. However, regionally specific phenotypes in the APP/PS1dE9 AD mouse model deviated from their general homeostatic roles, displaying reduced territory size in the cortex and enhanced ion and neurotransmitter uptake in a striatum astrocyte subcluster [27]. Several studies have also shown that neuronal firing and signaling cues influence astrocyte morphological dyshomeostasis, depending on how often these cells interact at the tripartite synapse [33]. The tripartite synapse consists of both pre- and post-synaptic neuronal plasma membranes, ensheathed by an individual astrocyte process at the synaptic cleft [34]. The synapses that are heavily enwrapped by astrocyte processes, tend to be larger and stronger, promoting efficient neuronal communication, a concept known as axon-spine interface [34]. However, not all astrocytes cover, ensheathe, or invade synaptic clefts to the same degree, which results in variability in glutamate uptake and neuronal firing dynamics, diversifying synaptic plasticity across subregions of the brain [35]. At the tripartite synapse, astrocytes function to clear excess glutamate from the synaptic cleft mediated by glutamate transporters. Astrocytes' dynamic morphological and functional states, ranging from homeostatic to reactive to hypertoxic, can structurally influence synaptic development, neuronal transmission, and pruning within tripartite synapses across the brain [33] [36]. Under the hypertoxic state, astrocytes reached maximal hypertrophy and branching and chronic pro-inflammatory molecule release but no longer perform homeostatic functions (Fig. 1). Reactive astrocytes of AD brains displayed decreased expression of glutamate transporter GLT1. Glutamate-mediated toxicity and hyperexcitability are a known component of AD pathology, indicating defective astrocyte-mediated glutamate clearance [37]. Excitotoxicity can lead to neurodegeneration at the synaptic level and more broadly lead to the elimination of glutamatergic neuronal pathways, contributing to learning and memory impairments in AD. Another role of astrocytes at the tripartite synapse involves the release of ATP upon intracellular Ca^{2+} concentration increase after neuronal firing [33, 38]. Reactive astrocytes displayed heightened release of ATP in AD mouse models, resulting from ionotropic purinoceptor P2Y1R overstimulation and Ca^{2+} secretion from the ER, leading to increased vesicular ATP release into the extracellular space and causing suppressed synaptic maturity and short term spatial memory learning deficits [36, 38]. Consequentially, disease-related morphological deficits in astrocytes may contribute to inefficient neuronal communication which can trigger synaptic pruning or elimination and contribute to AD-induced neurodegeneration [37] (Fig. 1).

3.2 Migration Patterns of Astrocytes in AD Brains

As astrocytes mature throughout CNS development, they branch into areas not covered by other astrocytes and maintain discrete territories due to maturation of neuronal dendrites [39, 30]. It was shown that glutamate excitotoxicity decreased branch complexity in reactive astrocytes, but increased branch overlapping and process exploration as neurons were damaged in primary neuron-astrocyte co-cultures [30]. This suggests that neurodegeneration promotes astrocytes to "abandon" their designated posts and attend to brain regions experiencing neuronal death. Lagos-Cabres and colleagues highlighted that astrocytes' exploration and migration are essential for glia scar formation after severe neuronal damage [40], yet more recent literature indicates that astrocyte migration is also crucial in containing and restricting large Aβ plaque deposits from chronic accumulation throughout AD brains [41-43]. The process of preparing astrocytes for collective migration heavily relies on connexin channel proteins which coordinate collective astrocyte communication either physically, through gap junctions (GJs) or through hemi-channel signaling, including small molecule communication throughout the extracellular matrix [40]. Connexin-43 (Cx43) and hemi-channels are primarily involved in reactive astrocyte migration because they enable astrocytes to release cues into the extracellular space for neighboring astrocytes to receive, initiate signaling cascades and act in a synchronous manner [40]. Specifically, these signaling cascades can activate cell polarization, filopodia extension and movement by attaching to extracellular matrix structural proteins [40]. Kotini & Mayor revealed how *in vivo* embryonic Cx43 ablation disrupts astrocyte migration, which resulted in abnormal distribution of astrocytes and defective brain architecture [44]. Overall, the presence of Cx43 enables astrocytes to communicate in unison and move synchronously towards their proper domains and pathological threats [40]. Although astrocytic Cx43 protein is normally localized to plasma membrane hemichannels of astrocyte distal processes, Cx43 protein levels were found to be elevated in cytosolic fractions of cultured astrocytes upon oxygen glucose deprivation [45]. This finding suggested that hypoxic stress promoted

Cx43 internalization for degradation which therefore no longer receive inflammatory cues from neighboring cells, a potential mechanism preventing astrocytic communication and migration toward to the neurological threat [44, 45]. Astrocytes' migration patterns can be both activated and disrupted by neurological insult and pathology and have been mostly studied *in vitro*. Primary astrocytes derived from the human $SOD1^{G93A}$ Amyotrophic Lateral Sclerosis (ALS) mouse model displayed significantly increased reactivity, focal adhesion, and migration in response to inflammatory TNF exposure, suggesting that an inflammatory environment is needed to elevate astrocytes' response to neuronal cues for migration [46]. Lin and colleagues found that treatment of APP/PS1 mouse-derived primary astrocytes with serum amyloid A inhibited migration by disorganizing microtubule and actin networks, which create protrusions used to mobilize astrocytes [47]. On the contrary, exposure to angiotensin receptor blocker Losartan improved migration and increased cell velocity and motility of primary astrocytes derived from adult 3xTg-AD mice [48]. Repeated administration of Losartan in *in vivo* 3xTg-AD mice reduced both soluble and non-soluble Aβ plaque densities, suggesting that Losartan may reduce Aβ load by mobilizing astrocytes to their local threats and promoting phagocytosis [48] (Fig. 1). Although astrocyte migration is an evident first step in responding to general local threats and reducing toxic Aβ accumulation in AD brains, mechanisms exploring specific astrocyte migration dynamics towards Aβ deposits remain understudied. Understanding basic astrocyte mobility dysfunctions will improve our comprehension on the role of astrocytes' mobile response in Aβ pathogenesis throughout AD development.

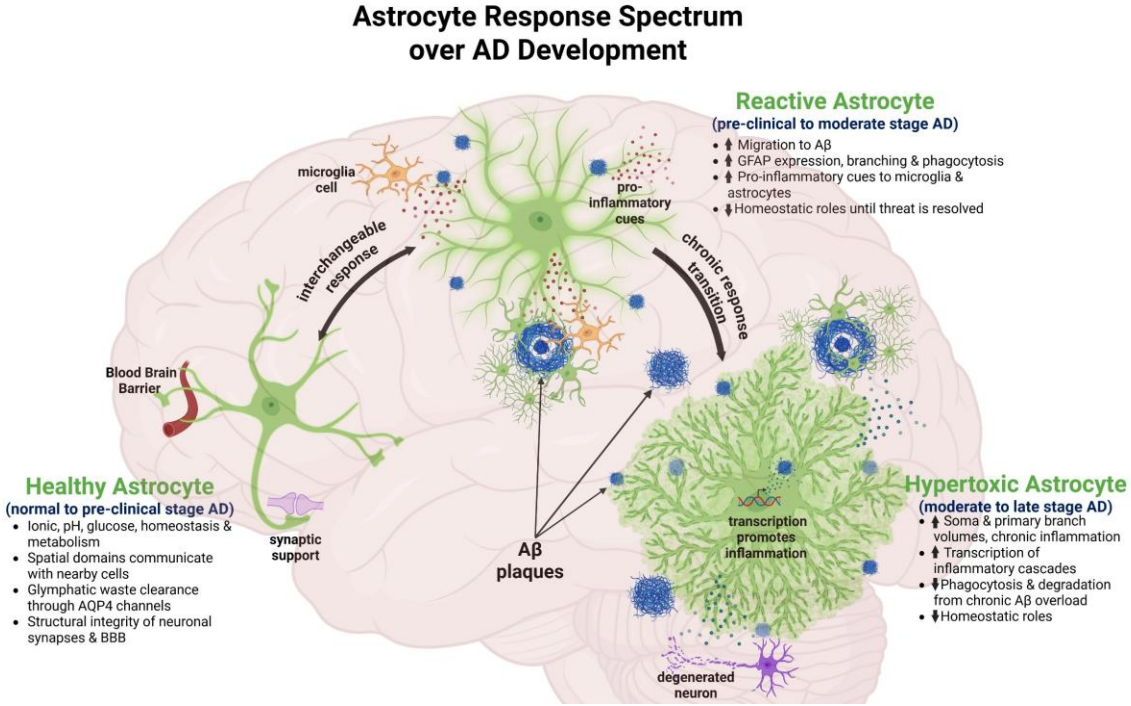

Figure 1. Astrogliosis transformation in AD brain. Healthy Astrocyte: Observed in normal to pre-clinical stages of AD, astrocytes maintain homeostatic functions including maintaining synaptic structures and BBB integrity, and regulating ionic, glucose, and metabolic homeostasis, and conducting waste clearance through the glymphatic system. Reactive Astrocyte: Observed in preclinical to moderate stages of AD, pause homeostatic functions to address Aβ plaque pathology, and increase pro-inflammatory cytokine release, communication with microglia, increased branching, phagocytosis and GFAP expression. Hypertoxic Astrocyte: Reactive astrocytes that have transitioned to a chronically responsive and toxic status. These astrocytes contribute to neuroinflammation amplification by chronic secretion of pro-inflammatory cues and transcription of neuroinflammatory cascades. Highly branched, phagocytic failure due to Aβ overload, leading to plaque buildup and neuronal death [27, 37, 42, 47].

3.3 Astrocyte Morphological Changes in AD Brains

Within the context of AD, astrocytes become more susceptible to cytotoxic changes that ultimately intensify disease progression and severity [49]. Some studies conclude that astrocyte atrophy precedes the more commonly observed hypertrophic astrogliosis throughout AD pathology [50]. However, regardless of the order, it is evident that both phenotypes can contribute to disease progression through various ways [43]. Hypertrophic astrocytes often develop near Aβ, then turn reactive in response to Aβ overload in later phases of AD [43]. These reactive astrocytes are most often identified by a significant increase in GFAP expression with somatic

hypertrophy, highly branched processes, and increased soma and process volumes [51] [17]. We detected $GFAP^+$ reactive astrogliosis in both human AD post-mortem and 8-month-old APP/PS1dE9 mouse cortical and hippocampal tissues, specifically with increased soma volumes and primary branch volumes in 3D reconstructed $GFAP^+$ astrocytes from the post-mortem tissues, and significantly elevated GFAP intensity in close proximity to Aβ plaques in the APP/PS1dE9 mice [52]. However, increased GFAP expression does not reveal the full scope of changes associated with reactive astrogliosis, especially since a decrease in GFAP expression in atrophic astrocytes has also been detected in hippocampal and cortical tissues of AD brains [53]. Other various astrocytic morphological changes have been reported in studies investigating different pathological and protective mechanisms. CSF levels of YKL-40, an indicator of inflammation and glial activation, have been tested as a potential predictive biomarker of AD progression. Rowland et al., found that astrocytes developed from induced pluripotent stem cells (iPSC) derived from early symptomatic AD patients with low levels of the YKL-40 displayed significant process extension, changes in cell roundness and width-to-length ratios upon exposure to exogenous $Aβ_{25-35}$ oligomers, indicating early, possibly protective astrocytic morphological changes during early stages of AD [54]. A different approach in detecting AD progression also revealed that high intensity interval training on a treadmill in streptozotocin-induced sporadic AD like rat models improved Aβ and Tau clearance, reduced GFAP intensity and hypertrophic astrocyte cell volume, and restored AQP4 polarization at the astrocytic endfeet [55]. Moreover, a more pathologic atrophic astrocyte phenotype was reported in 3xTg AD mice, with reduced astrocyte process branching, soma and cell surface volumes in the hippocampus both at 6 months and 18 months of age [56]. Interestingly, around the Aβ plaques in the CA1 region of 12-month-old 3xTg AD mice, astrocytes displayed a significantly hypertrophic morphological phenotype, indicating that astrocyte atrophy and astrogliosis can occur in parallel, both sub regionally and dynamically [56]. Therefore, astrocytic morphological responses have reasonable capability in analyzing disease stage and progression in AD (Fig. 1).

3.4 Aβ Induces Astrocyte Reactivity

Physiologically, Aβ monomers exist at low concentration levels throughout normal brain development to promote general cell homeostasis and neuronal survival [57]. During normal brain aging, Aβ can become toxic when monomer fragments aggregate which can then further develop into toxic oligomers and harmful Aβ plaques [58]. In AD brains, toxic Aβ arises from enzymatic b-secretase (BACE1) cleavage of APP followed by abnormal or mutation-induced transmembrane γ-secretase cleavage of the resulting C99 fragment, producing pathological Aβ isoforms [58]. This abnormal cleavage produces isoforms of various Aβ fragments, including dimers, oligomers, and fibrils of $Aβ_{40}/Aβ_{42}$ peptides, which are most commonly observed as extracellular deposits in AD brain tissues and around brain vasculature, contributing to vascular induced cognitive impairment and dementia (VCID) pathology [57]. Human post-mortem AD brain tissues with the highest accumulation of Aβ are often found in the hippocampus and the prefrontal cortex areas, and also display the earliest and most severe neuronal loss throughout the course of the disease [59, 8, 58]. Lana et al. discovered that in early stages of the TgCRND8 AD mouse model at 2 months of age, non-reactive astrocytic changes were detected when no Aβ was present [60], however, astrocytes shifted to a significant hypertrophic morphology in the TgCRND8 AD mouse at 6 to 12 months of age due to an increased presence of Aβ peptides. Astrocytes displayed increased contact and encircling of smaller amyloid plaques but specifically expressed elevated GFAP near larger plaques, insinuating that the size of the plaque can influence how reactive astrocytes morphologically respond to their presence [60]. In the hemizygous TgF344 AD rats expressing Designer Receptors Exclusively Activated by Designer Drugs (DREADDS) to trigger hyperactive firing activity in dopaminergic striatal neurons, significantly increased density of $GFAP^+$ reactive astrocytes covered and ensheathed Aβ plaques in hippocampal regions, demonstrating that astrocytes' response to Aβ burden can be heightened by pathological neuronal hyperactivity [61](Fig. 1). In their review, Tsering et al. explored a subset of Aβ plaques known as *neuritic* plaques identified by their recruitment of swollen neurites into their core, and compared the preferential clustering morphologies between astrocytes and microglia around these neuritic plaques in different brain regions [62]. They reported $GFAP^+$ astrocytes preferentially clustered around neuritic plaques in both frontal cortex and hippocampus of human post-mortem AD brains, with a tendency to cluster outside or around the outer layer of the neuritic plaque, rather than penetrating the dense plaque as microglia do [63]. These studies reveal diversity in the astrocytic responses to Aβ pathology within subregions of the brain and their morphological responses to Aβ can differ due to the size or content of the plaque and can be influenced by the activity of other cell types (Fig. 1). These various morphological dynamics can associate with either astrocytic protective or reactive responses in specific brain regions. Additional studies connecting Aβ-induced astrocyte morphology dynamics to other AD pathological

hallmarks, such as neuronal firing dysfunction or neuroinflammation, are warranted [29].

3.5 Inflammation and Astrocyte Reactivity

Astrocytes and microglia are the brain's primary cells tasked with responding to neuroinflammatory threats. In AD brains, both accumulated toxic Aβ and hyper-phosphorylated Tau-induced NFTs lead to neuroinflammation [29]. In response to these threats, reactive astrocytes secrete pro-inflammatory cytokines, which have been detected in the serum of AD patients in high levels [64, 65]. Proinflammatory cytokines can activate various inflammatory responses and cell death pathways, including pyroptosis [66] and subsequent release of pro-inflammatory factors such as interleukins, IL-1β and IL-18 through the pores of the plasma membrane [66]. $A\beta_{42}$ exposure in astrocyte cultures induced pyroptosis and elevated the secretion of TNF-α, IL-1α, IL-1β, and IL-18, which also caused damage to nearby vascular endothelial cells in astrocyte-endothelial cell co-cultures [67]. However, siRNA-induced knockdown of the pore-forming protein gasdermin D (GSDMD), activated by pro-inflammatory caspases 1 and 11, significantly reduced astrocyte secretion of pro-inflammatory cytokines (IL-1β, and IL-18 levels) in astrocyte cultures. shRNA-mediated GSDMD knockdown in APP/PS1dE9 mice significantly reduced neuroinflammation in hippocampal tissues as well as aortic tissue lesions [67]. Moreover, many inflammatory cytokines and chemokines released from astrocytes occur in response to back-and-forth communication from nearby microglia through extracellular vesicles (EVs) [68]. Crivelli et al. reported that upon $A\beta_{1\text{-}42}$ peptide exposure, primary microglia released pro-inflammatory cytokines IL-1α, TNF-α and C1q, which induced the secretion of ceramide containing EVs from reactive astrocytes, causing mitochondrial damage in surrounding neurons and neuronal death [69]. These studies indicate that in responses to Aβ deposits, astrocytes amplified neuroinflammation in the microenvironment in part by alerting other inflammatory cells in the CNS.

Astrocytes' physiological role in maintaining ionic homeostasis and redox balance makes them susceptible to increased oxidative stress in AD pathogenesis. Thioredoxin-interacting protein (TXNIP) has been identified as a key regulator in oxidative stress as it inhibits antioxidative function of the antioxidant Thioredoxin in the cytosol and mitochondria, eventually leading to apoptosis [70]. TXNIP protein levels were upregulated in $GFAP^+$ astrocytes from AD post-mortem cortical tissues and in APP/PS1 mice [71]. By significantly increasing NF-κB phosphorylation levels, TXNIP overexpression in primary human astrocytes increased the production of pro-inflammatory markers IL-6, CXCL10, CXCL11 and lipocalin-2 (LCN2) along with CD147, and migration inhibitory factor (MIF) which was shown to induce mitochondrial oxidative stress and ATP reduction in human astrocytes [71]. Secretion of pro-inflammatory LCN2 glycoprotein was found upregulated not only in AD brain astrocytes, but also in astrocytes in brain tumor microenvironment [72]. Secretion of LCN2 was also detected in reactive astrocytes of an acute ischemic stroke mouse model and contributed to neuronal death [31]. Hence, astrocyte reactivity and neuroinflammation are intertwined pathological events in multiple brain diseases.

3.6 Changes of Glucose and Lipid Metabolism Homeostasis in AD Astrocytes

Other important astrocyte functions include maintaining glucose and lipid metabolic homeostasis, which are important energy sources for highly active and energy consuming neurons [73,25]. Astrocytes uptake glucose from the blood through the glucose transporter (GLUT1) and convert it to L-lactate, the primary energy source for surrounding neurons [25]. Alternatively, astrocytes may transfer fatty acids from neurons utilizing the ApoE protein, and store them as lipid droplets as an energy reserve for neurons [73]. When astrocyte metabolic activities are disrupted, neuronal activity is negatively impacted in various neurodegenerative diseases [25, 74]. Dysregulated glucose metabolism is implicated in AD brain pathologies, which has been attributed to astrocytic dysfunction [37]. Both *in vivo* and *ex vivo* models of lipopolysaccharide (LPS)-induced neuroinflammation displayed elevated glucose uptake and lactate release (raising serum and CSF levels of astrocyte marker, S100β), increased S100β secretion in hippocampal slices, impaired astrocytic glutamate uptake, and neurotoxicity [75]. Another study measured the association between both plasma and CSF GFAP levels, as well as glucose consumption throughout the entire brain and subregions of AD human subject brains [76]. When plasma GFAP levels were increased, PET glucose measurements, using glucose analog fluorodeoxyglucose marker (^{18}F) FDG, showed increased global brain glucose consumption, however, increased CSF GFAP levels were associated with high glucose consumption only in the temporal and superior temporal lobes [76]. These findings first implied that higher astrocytic reactivity is related to significantly higher glucose consumption, and secondly, that plasma GFAP may be an earlier and more reliable biomarker for early AD pathology than CSF GFAP [76]. Lipid metabolic dyshomeostasis has also been found in AD brains [77]. Because lipid metabolism produces glycerol which can also enter the glycolytic pathway, this makes

astrocytic metabolic dysfunction even more important [37]. Aware of the pathological astrocytic metabolic shift in AD, Mi and colleagues developed an astrocyte specific mitochondrial oxidative phosphorylation deficient mouse model ($Tfam^{AKO}$) in assessing its impact on brain lipid homeostasis, and they observed lipid droplets specifically localized to astrocytes, and found increased fatty acid lipid levels in the hippocampus and cortex, accompanied by neurodegeneration and memory recognition deficits, which they found comparable results in the actual 5xFAD AD mouse model [78]. Lipid accumulation within astrocytes and microglial cells in AD brains is harmful because it interrupts their phagocytic function and can also trigger their proinflammatory responses, which are both already perturbed by extracellular Aβ pathology [79]. As these cells shift to address both lipid accumulation and Aβ buildup, their normal homeostatic roles are not efficiently met, negatively impacting neuronal glucose metabolism, indirectly promoting neuronal death. Taken together, these studies suggest that astrocytes contribute to AD pathology when they can no longer meet their metabolic demands. Many of these changes occur at the transcriptional level before functional deficits are observed, next, we summarize astrocyte transcription transformations in the AD context.

4. Transcriptional changes in reactive astrocytes of AD brain

Single cell RNA sequencing (scRNAseq) or single nuclei RNA sequencing (snRNAseq) has provided a powerful technique for understanding the state of astrocyte function in human AD brain tissues [80], revealing how astrocytes from AD brains differ from those in non-disease brains [81]. ScRNAseq analysis of the dorsolateral pre-frontal cortex brains from fifteen human subjects with normal, pathological aging, or AD brains detected four distinct astrocyte clusters [82]. Among 196 dysregulated genes in the AD astrocytes, 144 genes were downregulated, 52 genes upregulated, and 17 of the 144 downregulated genes were transcription factors [82]. Specifically, the protein coding gene ERBB4 and the transcription factor NFIA were downregulated in AD reactive astrocytes [82]. In assessing transcriptome changes in the postmortem prefrontal cortex samples from AD (late onset) and age-matched controls [81], there were 450 unique downregulated differentially expressed genes (DEGs) and 1,084 unique upregulated DEGs. AD astrocytes downregulated vascular endothelial growth factor A (VEGFA), which may be involved in the breakdown of the blood brain barrier in AD brains [81]. In contrast, AD astrocytes upregulated several transcripts, such as HPSE2, SLC39A11, PFKP, NEAT1, RANBP3L, PLPP1, and PLCG2 [81]. Specifically, the gene HPSE2 acts as a competitive inhibitor of HPSE which is an enzyme that breaks down heparan sulfate, a component of the extracellular matrix. Elevation of HPSE2 leads to increased Aβ accumulation and the expansion of plaques in the AD brain [81]. Qian and colleagues integrated several multi-omics datasets to create a single-cell transcriptomic dataset of human brains and found that upregulation of stress and inflammatory genes were present in AD brains [83]. These included heat shock protein (HSPB1, HSP1A1, and HSPBB) and cellular stress genes (e.g., GFAP, UBC, FOS, and JUN) [83]. Astrocyte snRNAseq data of AD patient entorhinal cortex also revealed reduction in genes primarily involved in pre- and post-synapse and synaptic membrane cellular components in addition to genes involved in glutamate receptor, neurotransmitter receptor activities and cell-cell adhesion molecules [84]. Lau et al. found loss in astrocyte neuroprotective functions of prefrontal cortical tissues from AD patients, specifically identifying several subpopulations of astrocytes displaying either upregulated stress response genes (CRYAB, GFAP and LINGO1) or down regulated genes (SLC1A2 and GLUL) [85]. SnRNAseq data from Braak staged I and II AD patient frontal cortex regions showed distinctly altered transcriptional networks, displaying the upregulation of HIF1A, SOX2, NRF1, and RB1 genes involving extracellular signaling transcription in astrocytes [86]. Considering that astrocytes are the source of ApoE protein production and APOE (ε4 variant, APOE4) is highly associated with AD risk [87], Celis and colleagues reported the differences in APOE4 gene expression and accessibility between AD brain autopsies samples with European versus African ancestry [88]. Increased chromatin accessibility at the APOE4 promoter area was observed in those with European ancestry, contributing to higher risk of AD development. Astrocytes displayed the highest amount APOE gene expression amongst all cell types between the two ancestries and gene ontology (GO) data sets [88]. European ancestry astrocyte subclusters revealed specific changes in cholesterol metabolism, synaptic and axonal transport and astrocytic process projections [88]. These findings emphasize transcriptional networks and gene expression differences specifically in AD astrocytes, warranting their direct contributions to AD pathology and symptomology.

Moreover, one unique study aimed to model cellular dynamics of the aging brain based on transcriptomic data from clinical cohorts and proposed a cellular dynamic trajectory leading to AD [89]. In their proposed chain-of-events analysis, relating different glial and neuronal cell subpopulation to specific stages of the AD cascade, they found that one astrocyte subpopulation (Ast.10) heavily mediated the “strong tau-cognitive decline” association, suggesting that reactive astrocytes might serve to

determine whether cognitive decline will be either tau-dependent or -independent [89]. Astrocyte homeostatic functions have been related to certain aspects of AD pathology and groups of astrocytes have been identified as responsible for metabolism homeostasis and linked to AD dysfunction, consisting of metabolism-associated genes (e.g., CLU, GLUG, GJA1, APOE, and MT3) [83]. Two of these genes are familiar AD-risk genes (APOE, and CLU) and play an important role in AD pathogenesis through metabolic interactions with surrounding neurons [83]. Another group of astrocytes studied in AD brains were enriched in metabolic genes associated with glutamate uptake and metabolism (SLC1A2/EAAT2/GLT-1, SLC1A3/EAAT1/GLAST-1, GLUL), which are two main functions that astrocytes execute at the tripartite synapse [82]. Due to the heterogenous nature of astrocytes, understanding how these specific astrocyte groups change when subjected to various neurodegenerative and AD pathologies [83] is needed to evaluate which subpopulations of astrocytes should be targeted as a potential treatment for AD. There are more recent studies in identifying different AD profiles [90] and predicting AD progression through transcriptomic astrocyte profiles [91]. Both studies provide further detailed discussions on using astrocytic AD profiles to investigate potential mechanisms underlying disease protection.

SnRNAseq comparison of transcriptomic profiles of astrocytes and microglia from post-mortem AD brains revealed the most positively associated transcripts from AD astrocytes, were involved in metal ion homeostasis, protein structure, inflammatory process pathways [92]. Increased expression of AD risk genes CLU and IQCK was observed in association with Aβ plaque and pTau pathology in specific astrocyte subclusters [92]. Microglia, on the other hand, showed upregulation of APOE, alongside TREM2 and other inflammatory genes in association with pTau and Aβ in AD post-mortem pathologies [92]. Another study used snRNAseq data to identify shared and unique molecular networks in disease-associated microglia (DAM) and disease-associated astrocytes (DAA) from AD patient entorhinal cortex and superior frontal gyrus. The DAA networks displayed several enriched genes, including NFKB1, MAPK1, HSP90AA, JUN and IL17 signaling, as well as the antigen processing and presentation immune pathways [93]. However, enriched genes that overlapped in DAM and DAA molecular networks, specifically derived from AD mouse model datasets, included APOE, CD9, CD63, and CDST genes [93].

5. Astrocytic lysosomal dysfunction and Aβ accumulation in AD brains

5.1 Astrocytic Phagocytosis in AD Brains

An important subset of homeostatic astrocyte functions involves ensheathing, phagocytosing, and degrading harmful misfolded materials within the neuronal environment [94, 95] (Fig. 2). Mammalian cells utilize several mechanisms to capture and degrade unwanted material either from inside or outside of the cell, each with the aim of maintaining proper cellular homeostasis. Autophagy is specifically responsible for recognizing and degrading either misfolded proteins and old organelles from within the cell, while endocytosis and phagocytosis are responsible for bringing in smaller and larger extracellular materials, respectively, to be used by the cell or for degradation [96, 97].

In AD brains, the presence of toxic Aβ activates some astrocytic protective functions but negatively impacts other astrocyte homeostatic functions, including the regulation of synaptic loss and efficient phagocytosis [41]. Many studies report astrocytes' involvement in eliminating Aβ burden. As astrocytes detect Ab, astrocytes first surround plaques by morphologically shifting their processes to extend around the surface of Aβ aggregate plaques [60] (Fig. 2). After signaling the microenvironment of the present threat, astrocytes transform into a phagocytic state to engulf and effectively degrade Aβ plaques, utilizing various mechanisms and pathways to alleviate further neuronal damage [98] [99]. Overexpressing enzymatic protein peroxiredoxin 6 (PRDX6) in 10 month-old APP/PS1 mice led to astrocyte-specific encircling and penetration of Aβ plaques, along with the promotion of improved plaque degradation, while PRDX6 knockout in APP/PS1 mice decreased astrocytic activation around Aβ, resulting in greater Aβ burden [42]. Potentially linked to deficient Aβ clearance, APOE4 is a primary genetic risk factor for late-onset AD [58] [100] [101]. In APOE4 knockout primary mouse astrocytes, little to no reduction in Aβ burden was observed. In contrast, wildtype astrocytes effectively reduced $A\beta_{40}$ and $A\beta_{42}$ levels by 69 and 52%, respectively [98]. As BACE1 exists as one of the secretase enzymes responsible for cleaving and forming Aβ monomers and inducing reactive astrogliosis, Zhou et al. manipulated BACE1 expressions to investigate its effects on Aβ clearance [102]. BACE1 null primary astrocytes displayed significantly enhanced Aβ uptake and less overall Aβ deposition was detected in cortical regions in astrocyte-specific $BACE1^{KO}$;5xFAD AD mouse models [102]. Moreover, a new tool for plaque clearing treatments was recently developed by forming magnetic plaques from $A\beta_{42}$ oligomers using superparamagnetic iron oxide nanoparticles (SPION) [103]. Using SPION stirring treatment, Sabu and colleagues found that astrocytes receiving this stirring treatment reduced

astrogliosis stimulation, upregulated EAAT-2 expression and improved astrocyte phagocytosis [103]. Each of these examples present mechanisms that have led to efficient uptake of Aβ, but what remains to be understood is which preferential pathways astrocytes choose to efficiently degrade unwanted Aβ plaques, or when are dysregulated due to the overarching pathology of AD.

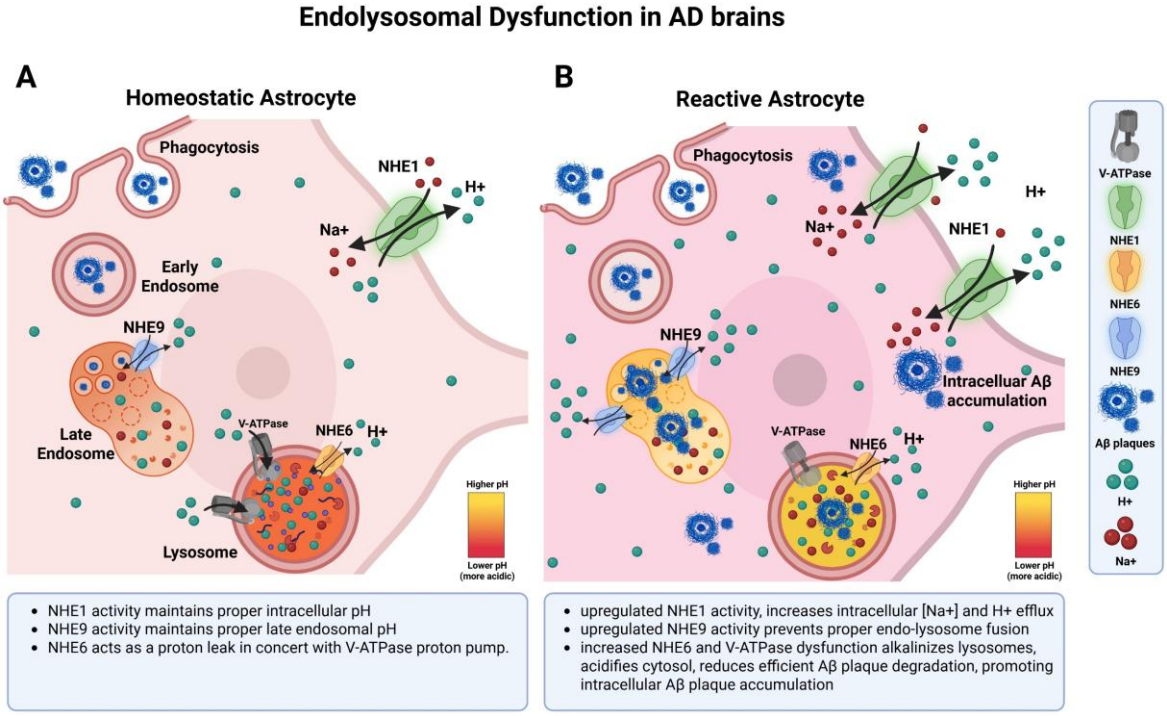

Figure 2. Endolysosomal Dysfunction in AD brains. (A) In a homeostatic astrocyte state, NHE1 activity at the plasma membrane maintains proper intracellular pH, NHE9 activity maintains proper late endosomal pH, and NHE6 acts as proton leak to regulate lysosomal acidification in concert with the V-ATPase proton pump. **(B)** In pathological conditions such as AD, reactive astrocytes can display upregulated NHE1 activity increasing intracellular Na+ concentration and H+ efflux, upregulated NHE9 activity which prevents proper endosome-lysosome fusion, and increased NHE6 activity alongside V-ATPase dysfunction, could acidify the cytosol and alkalinize lysosomes, reducing efficient Aβ plaque degradation, causing intracellular Aβ accumulation [51, 88, 90, 100, 103, 109].

5.2 Changes of Astrocytic Lysosomal Degradation in AD Brains

A critical step following astrocytes' phagocytosis of Aβ plaques is their efficacy in degrading unwanted materials. As stated before, astrocytes utilize many pathways to efficiently degrade toxic debris from the microenvironment for maintaining brain health [104]. AD pathogenesis disrupts many of these pathways and directly impacts available degradation pathways that astrocytes would normally rely on to eliminate cellular debris. Astrocytes' role in proper Aβ degradation is heavily influenced by cellular pH homeostasis [104]. Disruption of astrocytic pH homeostasis has direct consequences on proper endolysosomal degradative functions [105] (Fig. 2).

Cellular degradation pathways consist of a form of vesicle formation (autophagosome, phagosome, clathrin-coated vesicle) derived from the cellular membrane to enclose the cargo followed by a transition into the endolysosomal pathway which specifically functions to sort, escort and properly degrade unwanted cargo [106]. The endolysosomal pathway is initiated at the early endosome (pH ~6.0-6.5), which sorts and escorts cargo for recycling and other cellular use. If the cargo is intended to be degraded, then it transitions into the late endosome, which holds a lower pH (pH ~5.5), lysosomal enzymes, and lipid degrading acids to prepare for its final destination into the lysosome [97] (Fig. 2). Once cargo in the late endosome fuses with the lysosome, the unwanted debris and material are finally degraded by a plethora of hydrolytic, lipase and other acidic enzymes housed within the highly acidic lumen of the lysosome (pH 4.5-5.5) [97, 107] (Fig. 2).

Lysosomes are heavily involved in regulating cell homeostasis, development, and aging, which is why their degradation function is critical for the health of the neuronal microenvironment [108]. Depending on the type of cellular threat, lysosomes will respond to the primary demands of the specific cell based on intra-and

extracellular cues, and by either up- or down regulating translation and expression of their membrane protein, substrates and enzymatic content [107]. Lysosomes rely on the vacuolar ATPase (V-ATPase) to actively pump protons into the lysosomal luminal space against their concentration gradient to activate pH-sensitive enzymes, maintaining a physiological lysosomal lumen pH of 4.5-5.5 [107, 108] (Fig. 2). The three types of proteolytic hydrolases contained in lysosomal lumen include papain-like cysteine proteases, pepsin-related aspartyl proteases, and asparaginyl endopeptidase. These highly acidic lysosomes are continuously used and replenished to effectively degrade many of the neurodegenerative disease hallmark misfolded proteins, such as alpha-synuclein, TDP-43, huntingtin, tau, and Aβ [104, 108], but there are instances where lysosomes fail to meet the demand. In the context of aging, Sun and colleagues reported several morphological and functional age-associated changes in lysosomes, including shorter tubular morphology, failure to increase in their mean and total volumes, and decreased acidity, motility and degradation activity in aged sea-elegans [109]. Several AD specific research studies investigating Aβ effects in endolysosomal pH have reported various reactive astrocyte-associated lysosomal dysfunctions. Using pH sensitive dyes and endo-lysosomal markers, Prasad et al. found defective endolysosomal Aβ trafficking and clearance in combination with increased lysosomal pH but decreased endosomal pH in astrocytes from APOE4 mutant AD models [110] (Fig. 2). Several mechanisms have been suggested involving dysregulated lysosomal and endosomal pH in AD brain astrocytes, including faulty, hyperactive, and mutated proton exchangers and V-ATPase pumps [110].

5.3 Astrocytic Lysosomal pH Dysregulation in AD Brains

A recent review on astrocyte pH regulation emphasized the roles of Na^+/H^+ Exchangers (NHEs) in maintaining pH throughout the cells [111]. This family of NHEs, with 11 isoforms, are cation proton antiporters and part of the larger Solute Carrier Transporters (SLC9A) gene family, which are transcribed throughout the soft tissues of the body [112], [113]. The C terminus of an SLC9A transcribed protein is variable amongst the isoforms and helps dictate their function and phosphorylation targets. In general, NHEs form dimers which consist of 11-12 transmembrane domains with pH sensors and a funnel to serve as the antiporter domain [112]. NHE1, the most well studied isoform, is highly abundant in the plasma membranes of most cell types and helps regulate intracellular pH and cell volume, but NHE2 is specifically present in the gastrointestinal organs' brush borders, while NHE3 is mostly present in the plasma membrane and helps reabsorb Na^+ in the small intestine and renal tubules and loop of Henle [113]. NHE4 helps to control ammonium excretion and is present in many organs like the stomach, kidney and salivary glands - especially in epithelial cells' basolateral membranes [112]. NHE5 is present mostly in neurons' plasma membranes and endosomes. NHE6, 7 and 9 are localized to specific organelles and are hypothesized to regulate their individual pHs [114]. NHE8 is shorter than the other NHE proteins in structure, important for kidney pH regulation and Na^+ reabsorption, and typically located in the Golgi Apparatus [115]. Many of these proteins are linked to diseases and symptoms observed in experiments conducted in mice [112] NHE6 is specifically expressed throughout the endolysosomal pathway, suggesting a crucial role for NHEs in maintaining proper lysosomal and broader cytosolic pH balance [110] [111] (Fig. 2).

The AD associated presenilin-1 (PSEN1) mutations have been implicated in subunit V0α1 reduction, which disrupts the proper formation of the V-ATPase pump (Fig. 2), causing a leaky lysosome, which no longer maintains proper acidic lysosomal pH to degrade unwanted phagocytosed material [116]. Prasad's study indicated the role of NHE6 in directly maintaining lysosomal pH in Apoe4 astrocytes [110]. They detected endolysosomal hyperacidification in APOE4 astrocytes, likely resulted from a 45% reduction in NHE6, which pumps H^+ out of the lysosomal lumen in exchange for Na^+, working as a H^+ leak for the V-ATPase pump [110] (Fig. 2). NHE9 is localized to early and late endosomes, regulating luminal pH by transporting protons out in exchange for Na^+ or K^+ [112]. Shamroukh et al. observed significant NHE9 colocalization with early endosomal marker Rab5, rather than late endosomal marker Rab7 in the context of bactericidal activity of macrophages, and further found that overexpression of NHE9 in bacteria-exposed macrophages limited the acidification of the maturing endo-phagosome [117]. NHE9 can also indirectly influence proper lysosomal degradation due to its disruption of the acidification of the endo-lysosomal pathway, caused abnormal diffusive motion of the phagosome, which prevented its transport to the perinuclear cellular region to fuse with the lysosome [117]. A different study revealed that NHE9 overexpression promoted a more progenitor-like transcriptome in a glioblastoma line, characterized by significantly lower GFAP and mature oligodendrocyte O4 transcripts [118]. This cellular stemness was attributed to the alkalinization of endosomal pH by NHE9 overexpression [118]. Although NHE9 has not been studied in the AD context, exploring its roles on the clearance of Aβ is warranted, especially in trafficking unwanted material to the lysosome [119]. We recently

reported NHE1 upregulation in reactive astrocytes in the hippocampal tissues of AD post-mortem brain and APP/PS1dE9 mouse brain, especially around Aβ plaques [52]. Overstimulation of NHE1 localized at the plasma membrane can indirectly impact lysosomal acidification and function due to NHE1-mediated H^+ extrusion and cytosolic alkalinization, which results in less available protons for V-ATPase to pump into lysosomes against their concentration gradient (Fig. 2). We reported that pharmacological inhibition of NHE1 with Cariporide (HOE642) reduced diffused Aβ plaque density in 8-month-old APP/PS1dE9 mice [52], suggesting NHE1's hyperactivity may indirectly affect lysosomal degradation due to its interference with the lysosomal lumen pH balance (Fig. 2). As several endo-lysosomal impairments occur at early stages of AD progression [116], targeted protein degradation in the endo-lysosomal pathways should be further investigated [97].

When investigating APOE4 effects on lysosomal function in neurons, similar to astrocytic cells, both endosome and lysosomal pH measurements using Lysotracker staining and the Oregon Green pH probes, respectively, indicated significant lysosomal alkalization in ApoE4 expressing neuron cells, and Magic Red Cathepsin B dye measurements indicated impaired lysosomal degradation [120]. In the TauP301S AD mouse model with tau pathology, Dejanovic et al. discovered that astrocytes preferred excitatory over inhibitory synapse for phagocytosis, reflected by a significant increase in excitatory presynaptic marker Homer1 puncta in hippocampal $LAMP1^+$ lysosomes [121]. Efficient degradation of misfolded proteins, defective organelles and debris allows for cells to make room for newly translated proteins in the cell. Furthermore, while autophagy regulates the removal of unwanted cytosolic materials, mitophagy specifically controls the elimination of defective mitochondria within the cell. In AD brains, mitochondrial dysfunction was associated with the APP and PS1 mutations, specifically presenting as abnormal fusion of mitochondria-carrying autophagosome with lysosomes [122]. As lysosomes are found defective in the AD context, they cannot maintain the correct pH to activate or degrade mitochondria specific proteases within the autophagosome, resulting in the accumulation of non-active autophagosomes throughout the cell, awaiting proper degradation, further interrupting cellular homeostasis [87, 122].

5.4 Other Aβ Clearance Systems

Microglia work in conjunction with astrocytes to eliminate Aβ from the AD brain [68]. Microglia, known as the brain's resident immune cells, are often considered the primary phagocytic and inflammatory cells of the brain [68]. Similarly to astrocytes, they survey the brain's microenvironment for potential pathological threats and alert other brain cells of growing threats via small molecule signaling. Several studies have indicated microglia's role in attenuating AD Aβ and other pathologies. Clustering of $CD68^+$ phagocytic microglia was detected around neuritic Aβ plaques in hippocampal regions from AD post-mortem brain tissues [63]. 5xFAD mice containing inactivated fatty acid amide hydrolase (FAAH) ($5xFAD/FAAH^{-/-}$) displayed a significant increase in the percentage of phagocytic microglia, compared to regular 5xFAD mouse due to increased levels of immune regulating protein TREM2 [123]. Imploring flow cytometry and pH-sensitive fluorescent Aβ methods to study phagocytosis, Prakash et al. discovered that in *in situ* slices of rat hippocampus, of all the $Aβ^{pH}$ taken up by glia cells, around 60% was phagocytosed by microglia while 40% was internalized by astrocytes, suggesting that microglia uptake dominates over astrocytes [124]. However, a $PSEN1^{KI/KI}$ AD mouse model, deficient in phosphorylated Presenilin 1 at serine 367, displayed accumulation of intracellular Aβ and the inability for Aβ degradation, attributing PS1 malfunction to phago-lysosome dysregulation in microglial cells [125]. These results suggest that while microglia, often designated as the primary phagocytic cell in the brain, are heavily involved in Aβ degradation and yet still susceptible to lysosome-related dysfunctions.

Another mechanism for cerebral Aβ clearance involves the CNS's adaptation of the peripheral lymphatic system called the glymphatic system, in which glia cells regulate waste clearance [126]. The glymphatic system is comprised of the perivascular space (PVS), in which astrocytes link the para-arterial and para-venous spaces mediated by arterial pulsations, to transport important nutrients from the blood to the brain tissue as well as draining unwanted brain solutes through the CSF in the brain parenchyma [126]. The glymphatic system heavily utilizes AQP4 channels located at the endfeet of perivascular astrocytes to efficiently shuttle CSF bulk flow, interstitial fluid and clear waste throughout the brain, therefore, astrocyte dysfunction can indirectly impact efficient Aβ plaque clearance and later cognitive function in the AD developing brain [127, 128]. CSF production and circulation rates are reported to be significantly reduced in AD patients, negatively impacting Aβ clearance, resulting in accumulated Aβ in the brain parenchyma [127, 129]. Moreover, as individuals age, the efficacy of the glymphatic system decreases [19, 127]. Focusing on assessing glymphatic water diffusion dysfunction on Aβ clearance, new human imaging studies detected a reduced perivascular space index, a measurement of perivascular clearance, and its correlation with impaired cognitive function in Aβ

positive AD patients [130], accelerated $A\beta_{42}$ PET burden, brain atrophy and cognitive decline [131] and positive deposition of cortical [^{11}C] Pittsburgh compound B (PiB) [132]. These approaches are non-invasive and therefore favorable tools since images can be collected directly from patients at different stages of disease progression. These new studies shed light on the clinical relevance of glymphatic dysfunction in predicting AD development and monitoring Aβ pathology and should therefore be given continuous attention alongside astrocytic AQP4 channels which have considerable influence on the glymphatic system.

Table 2. Efficacy of Experimental AD Therapies on Changes of Astrogliosis.

Main Target	AD Subjects	Outcomes	References
FDA-approved anti-Aβ antibody Lecanemab	Phase 3 clinical trial sub-study of early AD patients (MCI or mild dementia with positive PET Aβ or CSF)	↓ $A\beta_{1-40}$, $A\beta_{1-42}$, p-tau181, and neurogranin in CSF, ↓ Aβ 42/40 ratio, p-tau181, GFAP and NFL in plasma	van Dyck et al.[147]
KL-VS variant of KLOTHO aging suppressor gene protective in AD risk patients	CSF profiles observed in aged cognitively normal patients with KL-VS variant heterozygosity for KLOTHO aging suppressor gene	↓inflammatory, synaptic dysfunction, and neurodegenerative markers IL-6, S100β, Ng and α-synuclein in CSF, ↓ GFAP, TREM2 and YKL-40 biomarker levels	Driscoll et al. [152] ; Jarchow et al. [153]
Selective deletion of astrocytic STAT3 in APP mice	Inducible deletion of astrocytic-STAT3 and STAT3 inhibitor SH-4-54 in APP/PS1 mice starting at 6 weeks of age	↓ soluble Aβ plaque accumulation, neuroinflammation, ↑ Aβ phagocytosis by microglia and spatial learning at 8 months of age	Reichenbach et al. [143]
Reducing astrocytic inflammation with GLP-1 receptor agonists	APP/PS1 mice treated with DA4-JC dual agonists or GLP-1/GIP/glucagon triple agonists at 6 months of age	↑ spatial memory, synaptogenesis and neurogenesis, ↓ Aβ burden, proinflammatory cytokine levels, neuroinflammation, and activated glia levels in a dose-dependent manner for DA4-JC	Diz-Chaves et al. [139]; Maskery et al. [138]; Tai et al. [136]
Reducing glia inflammation, cognitive decline, and brain pathology with DMSP	Antioxidant compound dimethylsulfoniopropionate (DMSP) in 3xTg mice at 4 months of age	↓ S100β expression in astrocytes in both hippocampal and cortical regions, cognitive decline, and Aβ brain pathology	Sun et al. [142]
Blocking NHE1 protein in APP mice	APP/PS1dE9 mice treated with pharmacological NHE1 inhibitor HOE642 at 4 months of age	↓ hyperactive locomotor activity and cortical Aβ plaque density by 7 months	Collier et al. [50]
Targeting astrogliosis with Pantethine in 5xFAD cell cultures	5xFAD mouse-derived primary neonatal cortical astrocyte cultures treated with Pantethine	↓ astrocyte reactivity, inflammatory Il-1β and human APP mRNA expression, ↑ ATP and energetic metabolite availability and improved enzymatic activity	Van Gijsel-Bonnello et al. [140] ; Baranger et al. [141]
JBPOS0101 treatment in 5xFAD mice	JBPOS0101 phenyl carbamate compound injected in 5xFAD female mice at 5 months of age	↓ memory impairments and brain pathology via regulating astrocyte activation leading to neurotoxicity	Jeong et al. [144]
Raddeanin A treatment in 3xTg mice	Raddeanin A, a triterpenoid compound, administered oral treatment in 3xTg mice at 4 months of age	↑ neuronal structure patterning in cortical and hippocampal brain regions, ↓ spatial and learning memory deficits, Aβ accumulation, and pathological GFAP, Bax/Bcl2 protein levels	Liu MH et al. [146]
BACE1 deletion in 5xFAD astrocytes	Astrocytic BACE1 deletion in 5xFAD mouse at 2 months: single-cell transcriptome and primary astrocyte cultures	↑ Clusterin and Cxcl14 gene expression and insulin signaling pathway genes, ↑ astrocytic Aβ uptake and degradation in culture	Zhou et al. [101]

6.0 Targeting reactive astrocyte in AD therapeutics

6.1 Experimental Therapies Targeting Astrocytes in AD

The three most prominent regions primarily affected in AD brains are the hippocampus, pre-frontal cortex and amygdala [59] [133], meaning that these regions have selective pathological vulnerability [94]. The hippocampus region, for example, is impacted the earliest in AD pathogenesis, indicated by its severe atrophy and

contribution to dementia symptoms observed over AD progression [134]. Throughout these various regions, reactive astrocytes contribute to overall AD disease pathology and neurotoxicity, which have been further discussed in depth in recent reviews [95, 135] [136]. Several experimental studies have found that manipulating reactive astrocytes' homeostatic compensation can have neuroprotective effects in AD brains. Glucagon-like peptide 1 (GLP-1) receptors (GLP-1R) are expressed across several brain regions including the hippocampus, cerebral cortex and hypothalamus, and their agonists exert their anti-inflammatory effects on astrocytes through the cAMP/PKA signaling pathway, which specifically promotes neuronal health by reducing mitochondrial stress signaling molecules [137, 138] and reducing TNF-alpha and IL-1B proinflammatory cytokine production in astrocytes and microglia [139, 140]. The activity of PKA can also promote neurotransmitter release, long-term potentiation and support synaptic plasticity, collectively making GLP-1R a considerable target for attenuating cognitive decline in AD [140]. GLP-1R agonists, Liraglutide and DA4-JC, have proven to have anti-inflammatory effects due to its ability to lessen astrocyte reactivity and Aβ plaque load in AD mouse models [137, 139, 140] (Table 2). Furthermore, targeting primary astrocytes from the 5xFAD mouse model via administration of pantethine, a hypolipidemic and hypo-cholesterolemic agent, which was previously found to alleviate metabolic dysfunction and immune responses [141], reduced AD-related changes, including astrogliosis, Aβ plaque load, and the upregulation of inflammatory and phagocytosis genes [142]. The antioxidant and neuroprotective compound, Dimethyl-sulfoniopropionate (DMSP) attenuated cognitive decline, brain pathology, and glial inflammation in the 3xTg AD mouse model, specifically displaying reduced S100β expression levels in astrocytes in both hippocampus and cortex [143] (Table 2). Additionally, the inhibition of astrocytic-STAT3, a transcription factor known to induce astrogliosis, not only decreased Aβ plaque burden but also attenuated spatial learning deficits by modulating neuronal network imbalance observed in the APP/PS1 mice [144] (Table 2). The JBPOS0101, phenyl carbamate compound, was approved for Phase 2 clinical trials in epilepsy, successfully ameliorated multiple memory impairments and brain pathologies in the 5xFAD mouse model by specifically regulating astrocytic activation-associated neurotoxicity and learning and memory neuronal networks [145] (Table 2). Virtual screenings of small-molecule drugs targeting human leukocyte antigen (HLA)-C (HLA-C) and HLA-DRB1, revealed that the Dfo compound perfectly embedded itself in the predictive active pocket of HLA-C/B2M residues, after displaying high correlation with highly upregulated inflammatory cytokines secreted from glia cells in 6-month old APP/PS1 mice, emphasizing the contributions of inflammation in early stages of AD development [146]. Moreover, Oral administration of the triterpenoid, Raddeanin A, decreased pathological GFAP, and Bax/Bcl2 apoptotic protein levels and improved neuronal structure and patterning in 3xTg AD mouse cortical and hippocampal brain regions while also attenuating spatial and learning memory deficits and Aβ accumulation in the whole brain [147]. In our recent report, targeting reactive astrocyte pH dysfunction by blocking NHE1 protein hyperactivity with pharmacological NHE1 inhibitor HOE642 in APP/PS1dE9 mice attenuated astrogliosis, hyperactive locomotor activity and hippocampal and cortical Aβ plaque density, which we hypothesize to occur through an astrocytic pH homeostasis pathway [52] (Table 2). For future studies, there is an unmet need to develop AD therapeutic strategies in inhibiting astrocyte transformations into pathological culprits in AD pathogenesis.

6.2 Clinical AD Therapies in Restoring Astrocyte Function and Aβ Load

No current AD intervention therapies have completely halted disease progression or reversed the damage, but several treatments for attenuating AD pathology and clinical symptoms are being investigated. One of them is Lecanemab, an FDA-approved anti-Aβ antibody, for the treatment of early AD [148]. In the recent clinical trial, Lecanemab reduced amyloid markers in early AD and showed moderately less decline in measures of cognition and function. The usage of astrocytic GFAP as a plasma biomarker for AD-related diagnostics has become more common and reliable in clinical settings, alongside blood-based p-tau (231, 181) and Aβ42/40 ratio immunoassays [17]. The correlation of reactive astrogliosis with tau and amyloid pathologies, however, is still heavily influenced by the collection method of samples (blood plasma, CSF, Aβ PET detection, etc.). Significantly increased plasma GFAP levels were highly associated with Aβ brain pathology on the PET scan. In contrast, decreased plasma GFAP levels in AD subjects were observed in a phase 3 clinical trial of amyloid-removal therapy (Lecanemab) [149](Table 2). There were some adverse effects of Lecanemab, mainly about infusion related reactions [150]. Although the pathological post-translational modifications to Tau can trigger astrocyte activation, current Tau targeting therapies, including Bepranemab, have not reported changes in plasma GFAP levels or effects on gliosis in clinical trials [151]. Salvado and colleagues, however, found the combination of pTau and Aβ42 to be the best predictors of cognitive decline in MCI patients from 3 large longitudinal cohorts, by analyzing

combinations of other CSF biomarkers including GFAP, YKL-40, S100β [152]. A different study sought to determine whether the presence of KL-VS variants in the KLOTHO aging suppressor gene was advantageous to AD risk patients than multiple CSF biomarkers of neurodegeneration [153]. It was reported that YKL-40 biomarker levels were reduced in KL-VS heterozygotes, compared to non-carriers, which was associated with decreased inflammatory, synaptic, and neurodegenerative CSF markers (IL-6, S100β, Ng, and α-Syn, GFAP, TREM2), suggesting aging may influence more broader AD related biomarker profiles in AD risk patients [153]. When peak oxygen consumption was included as an additional variable analysis to indicate cardiorespiratory fitness levels, older KL-VS heterozygotes who displayed better fitness levels revealed lower CSF levels of YKL-40, sTREM2, Ng, and pTau, supporting the idea that AD develops on account of multiple factors such as age and cardiovascular health [154]. Another trial investigating the efficacy of a the 2021 FDA approved AD drug Aducanumab, a medication that targets mature Aβ plaques, found that it caused a dose-and time-dependent reduction in pathophysiological markers of AD as well as cognitive decline [155, 156] (Table 1). A study evaluating Deferiprone, which reduces the amount of iron in the body and commonly used to treat inherited blood disorders, decreased brain iron accumulation but accelerated cognitive deterioration, leading to brain volume loss in the frontal brain of AD patients[157]. A clinical trial investigating repetitive Transcranial Magnetic Stimulation (rTMS) in treating AD reported that patients in the rTMS group showed significant cognitive improvement for up to two months post-treatment with rTMS [158]. Lastly, as acetylcholinesterase inhibitor drugs have gained attention in AD and MCI treatment, since the transmitter levels are shown to decrease in AD, several meta-analysis studies have summarized the efficacy and safety of these drugs on reducing hippocampal atrophy by donepezil at 10mg dosage, whole brain atrophy in APOE4 carriers by galantamine[159], and various cognitive improvement in AD patients by donepezil, galantamine and rivastigmine [160]. Though not all targeting astrocytes, many of these new clinical trials continue to assess the cognitive effect of the treatment, which is rightfully warranted, but they lack further investigation on how these drugs impact AD brain pathogenesis (including reactive astrocyte and Aβ plaques pathologies throughout AD progression).

7. Limitation of Experimental AD Models

While many findings in this review have been drawn from commonly used AD mouse models including the APP/PS1, 3xTG, 5xFAD models, as well as relevant cell cultures, they have limitations for not presenting all aspects of AD's complexity and pathologies. For example, AD mouse models cannot fully recapitulate the aging progression aspect of AD due to their short life span, therefore most mouse studies actually model early onset AD instead of the sporadic late onset AD. Additionally, AD is often a disease of mixed pathologies including Aβ, Tau, vascular impairments and/or presence of Alpha-synuclein Lewy bodies and TDP-43 [161] yet, the commonly used APP/PS1 model only develops Aβ pathology without Tauopathy [162]. While the 3xTG model presents both Aβ and neurofibrillary Tau tangle pathologies, there are pathological inconsistencies across studies, and sexually dimorphic disease trajectories have been observed in this model[163]. Sharma and colleagues' review on AD models also noted the differences between the human and mouse glia cells and their contributions to neuroinflammation in AD [164]. Developing AD mouse models utilizing CRISPR genomic editing can recapitulate more specific AD features, such as encompassing risk variants like APOE4 and TREM2 for sporadic late-onset AD [165]. The availability of more genetic manipulating technologies for mice and human derived cellular models will move AD research in a more clinically relevant and translational direction.

8. Conclusions

Physiological functions of astrocytes are important in maintaining a wide spectrum of CNS functions. In response to Aβ deposits, neuroinflammation, and neurodegeneration in AD pathology, astrocytes pause their homeostatic roles to address and contain these abnormal changes. However, the chronic perturbation in AD brains causes various populations of astrocytes to permanently forgo their physiological roles to contain disease progression throughout different regions of the brain. This transition leads to reactive astrogliosis, in which astrocytes transform into reactive phenotypes that eventually contribute to pathological severity. The accumulation of Aβ causes several downstream transformations in astrocytes that negatively impact their morphological structures and mobility, inflammatory response, energy metabolism, and their ability to properly degrade these deposits. The endo-lysosomal pathway and phagocytic clearance in reactive astrocytes is severely impaired in several models of AD, which attributed to impairment of V-ATPase and dysregulation of other pH regulatory proteins, presenting them as plausible therapeutic targets to efficiently handle Aβ overload in AD. While new clinical trials aim to prevent disease progression in AD patients with early symptomatic and pathologic markers, efforts are warranted to develop

interventions focused on restoring early astrocyte dysfunction in prodromic phases of the AD pathogenesis.

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