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Function and therapeutic value of astrocytes in neurological diseases

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Abstract

Astrocytes are abundant glial cells in the central nervous system (CNS) that perform diverse functions in health and disease. Astrocyte dysfunction is found in numerous diseases, including multiple sclerosis, Alzheimer disease, Parkinson disease, Huntington disease and neuropsychiatric disorders. Astrocytes regulate glutamate and ion homeostasis, cholesterol and sphingolipid metabolism and respond to environmental factors, all of which have been implicated in neurological diseases. Astrocytes also exhibit significant heterogeneity, driven by developmental programmes and stimulus-specific cellular responses controlled by CNS location, cell–cell interactions and other mechanisms. In this Review, we highlight general mechanisms of astrocyte regulation and their potential as therapeutic targets, including drugs that alter astrocyte metabolism, and therapies that target transporters and receptors on astrocytes. Emerging ideas, such as engineered probiotics and glia-to-neuron conversion therapies, are also discussed. We further propose a concise nomenclature for astrocyte subsets that we use to highlight the roles of astrocytes and specific subsets in neurological diseases.

Multiple different populations of resident non-neuronal cells, known as glial cells, have important roles in central nervous system (CNS) development, function and disease. Types of glial cell include oligodendrocytes, microglia and astrocytes[1]. Among these, astrocytes are the most numerous[2].

Astrocytes were first described in the nineteenth century by Rudolf Virchow[3]. A decade later, Camillo Golgi visualized the morphology of astrocytes using the silver chromate staining technique, advancing the notion that glial cells act as a 'glue' of the brain[4]. Astrocytes were soon classified into two basic morphological subtypes: protoplasmic and fibrous[5,6]. Protoplasmic astrocytes are typically seen in the grey matter, and fibrous astrocytes are prevalent among the white matter of the CNS. Santiago Ramón y Cajal

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Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

The authors declare no competing interests.

adopted these subtypes and further revealed the diverse morphology of astrocytes in the human cerebellum, shedding new light on their potential heterogeneity[7].

Recent developments in high-throughput single-cell RNA sequencing (scRNA-seq)[8–13], spatial transcriptomic methods[9,12,14] and techniques for the study of astrocyte cell–cell interactions[15] have provided a unique understanding of astrocyte heterogeneity and its relevance in health and disease. It is now appreciated that astrocytes comprise multiple subsets with diverse and potentially opposing roles in disease based on location, gene expression or function[8,9,14,16] (BOX 1). For example, neocortical protoplasmic astrocytes display morphological heterogeneity dependent on cortical layers[17], a finding that has been refined at the molecular level by scRNA-seq and spatial reconstruction analysis[14]. Moreover, by responding to signals in their microenvironment, astrocytes have the potential to promote or arrest inflammation and neurodegeneration, having active roles in multiple neurological diseases including multiple sclerosis (MS)[8,9,15,18–28], Alzheimer disease (AD)[10,29,30], Parkinson disease (PD)[31,32], Huntington disease (HD)[33–38] and behavioural neuropsychiatric disorders[38–42] (BOXES 2,3). In this Review, we discuss recent insights into the central roles of astrocytes, their subsets and regulation, in neurological and psychiatric disorders, and their potential as targets for therapeutic intervention.

Astrocytes in homeostasis

Astrocytes are derived from neural progenitor cells (NPCs) in the subventricular zone (SVZ) and migrate along radial glia processes to populate all areas of the CNS[43,44]. Mature astrocytes participate in key processes relevant to CNS homeostasis including neurotransmitter recycling, ionic balance, modulation of synaptogenesis and synaptic transmission, and maintenance of the blood–brain barrier (BBB)[45–47]. Indeed, astrocytes are also one of the major components of the BBB, as astrocytic end-feet processes form a thin barrier that surrounds endothelial cells, pericytes and the basal lamina, which is called the glia limitans[46–50]. Interestingly, although the BBB surrounds most blood vessels in the brain, separating the CNS from the peripheral blood circulation, more than 97% of astrocytes contact the blood supply[51], suggesting that astrocytes may respond to molecules produced by peripheral cells, such as the cytokines produced by circulating immune cells.

The passage of molecules and cells across the BBB is modulated by multiple cell types, including astrocytes[50,52,53]. Astrocytes produce the protein sonic hedgehog (SHH), which promotes anti-inflammatory signalling and contributes to the formation and maintenance of the BBB[46,54]. Similarly, apolipoprotein E3 (APOE3), produced by astrocytes, suppresses signalling via a cascade involving peptidyl-prolyl *cis-trans* isomerase A (also known as cyclophilin A (CYPA)), nuclear factor-κB (NF-κB) and metalloproteinase 9 (MMP9) in pericytes; APOE3 counteracts APOE4-associated BBB breakdown[55]. Conversely, astrocyte-derived vascular endothelial growth factor (VEGF), a potent angiogenic factor, promotes CNS inflammation by increasing BBB permeability and enhancing immune cell extravasation[56,57]. Thus, astrocytes regulate the formation, maintenance and permeability of the BBB, which is commonly disrupted in neurological diseases.

Astrocytes also have intimate roles in the regulation of synaptic function through their participation in tripartite synapses, regulating synaptic formation, transmission and plasticity[39,58–60]. Indeed, although astrocytes were traditionally considered to merely provide trophic and structural support for neurons, it is now clear that astrocytes engage in extensive crosstalk with neurons through multiple mechanisms involving ion channels, neurotransmitters and metabolites[61–65]. For example, extracellular K^+ levels are crucial for the control of neuronal responses[66,67]. Astrocytes express K^+ channels, which clear K^+ ions from the extracellular environment and modulate the membrane potential and excitability of neurons. Conversely, downregulation of astrocyte inwardly rectifying K^+ channel (K_{ir}) expression results in increased extracellular K^+ levels and neuronal hyperexcitability, a mechanism that is linked to neuronal dysfunction in HD[33,34] and PD[68,69]. These findings highlight astrocyte roles in CNS homeostasis and neurodegeneration.

Tripartite synapses

Bidirectional interactions established by astrocytes with pre- and post-synaptic nerve terminals.

Astrocytes also regulate ionic tone by recycling neurotransmitters. The high-affinity glutamate transporters excitatory amino acid transporter 1 (EAAT1, also known as GLAST) and EAAT2 (also known as GLT1) take up the neurotransmitter glutamate from the synaptic cleft for recycling[70,71]. The dysfunction of astrocyte glutamate transporters leads to excessive glutamate release from neurons, promoting neuronal death by excitotoxicity[72], a process that has long been associated with the pathogenesis of neurodegenerative diseases[73–77]. Indeed, the pro-inflammatory cytokine tumour necrosis factor (TNF) boosts glutamate production[78], which in turn triggers excitotoxicity and Ca^{2+} signalling. Ca^{2+} elevation in astrocytes releases glutamate, ATP and γ-aminobutyric acid (GABA)[79–84]. Moreover, excessive GABA and ATP release by reactive astrocytes has been linked to disease pathogenesis in AD models[85,86].

Excitotoxicity

Neuronal dysfunction and death caused by the accumulation of excess neurotransmitters, primarily glutamate, in synapses.

Finally, high extracellular K^+, glutamate uptake and intracellular Ca^{2+} waves trigger lactate release from astrocytes. Astrocyte-produced lactate is used by neurons to fuel their energetic needs[87,88]. Dysfunctional astrocyte–neuron metabolic interactions are a key feature of several neurodegenerative diseases including PD[89], AD[90], HD[36,91,92], MS[93] and amyotrophic lateral sclerosis (ALS)[94]. Overall, these observations highlight the importance of astrocytes in the control of synaptic plasticity and CNS physiology.

Reactive astrogliosis

Pathogenic processes that target the CNS (for example, inflammation, neurodegeneration or trauma-induced injuries) are usually associated with astrogliosis, an astrocyte response

characterized by functional, morphological and molecular remodelling[22,95,96]. Reactive astrocytes are highly heterogeneous and contribute to the pathology of neurodegenerative and neuropsychiatric diseases, but also to CNS repair. Several markers are commonly used to monitor astrocyte reactivity, but the functional investigation of molecularly defined astrocyte subtypes is still in its infancy[95]. The application of high-throughput sequencing techniques, including scRNA-seq and spatial transcriptomics, has enabled the identification of reactive astrocyte subsets and novel pathways involved in their regulation[9,14,22].

Reactive astrocytes are now considered active players in CNS inflammation. Indeed, reactive astrocytes express a wide variety of receptors including pattern recognition receptors and cytokine receptors. Consequently, astrocytes can respond via the production of immunoregulatory molecules that may promote or limit inflammation in response to multiple cues in the CNS microenvironment[97–99]. In addition, newly proliferated astrocytes form a ‘glial scar’, which was initially viewed as a physical CNS barrier that interferes with axonal regrowth[96,100]. However, recent studies have shown that some reactive astrocytes produce molecules that support axon regeneration, such as neurotrophin-3 and brain-derived neurotrophic factor, and thus promote recovery from severe spinal cord injury (SCI)[101,102]. Additional reactive astrocyte subsets release a broad range of pro-inflammatory molecules that support immune cell invasion into the CNS[25,50]. These findings highlight the functional heterogeneity of reactive astrocytes in the context of neuroinflammation and CNS injury. Identifying the molecular mechanisms that control astrocyte subsets and function is likely to pave the way for novel therapies for neurological disorders.

Reactive astrocyte signals and pathways

Multiple signalling pathways and transcription factors modulate astrocyte responses in the context of neurodegenerative diseases, including STAT3, NFAT and NF-κB. The transcription factor NF-κB is a central regulator of inflammation and neurodegeneration[103,104]. In astrocytes, NF-κB signalling is triggered by pro-inflammatory mediators such as cytokines (TNF, IL-1β and IL-17)[26,105], reactive oxygen species (ROS)[106], Toll-like receptor (TLR) agonists[107] and environmental factors[26]. Conversely, the downregulation of NF-κB in astrocytes has been linked to decreased CNS inflammation or injury in multiple contexts including SCI[108], optic neuritis[109] and experimental autoimmune encephalomyelitis (EAE, a model of multiple sclerosis)[110–112], suggesting a pathogenic role for NF-κB-driven transcriptional modules in astrocytes. Of note, microbial metabolites have been shown to regulate astrocyte pathogenic functions in EAE by suppressing NF-κB signalling via suppressor of cytokine signalling 2 (SOCS2)[21]. NF-κB activation is also detected in preclinical models of Alzheimer disease (AD)[113,114] and Huntington disease (HD)[115]. Protein misfolding and aggregation (that is, β-amyloid in AD, and misfolded mutant huntingtin (mHTT) in HD) triggers NF-κB activation in astrocytes, upregulating pro-inflammatory molecules during neurodegeneration.

The JAK–STAT3 pathway is a ubiquitous signalling system with newly identified roles in the control of reactive astrocytes[116,117]. Early studies reported that STAT3 is expressed in the brain and contributes to CNS development during astrogliogenesis[118,119]. In acute CNS injury, it is well established that the JAK–STAT3 pathway controls astrocyte reactivity and

glial scar formation[120,121]. Recent studies revealed the importance of JAK–STAT3 signalling in reactive astrocytes, and thus its potential as a therapeutic target in CNS neurodegenerative diseases including MS, AD and HD[116,122–125]. For example, phosphorylated (activated) STAT3 has been observed in astrocytes in the white matter adjacent to active MS lesions and in EAE mice[124,125]. Moreover, conditional expression of a dominant mutant of the gene encoding IL-6 receptor subunit-β, a potent JAK activator in astrocytes, significantly increases EAE severity[123]. Furthermore, JAK–STAT3 signalling is activated in astrocytes in preclinical models of AD and HD[116]. Selective overexpression of suppressor of cytokine signalling 3 (SOCS3) in astrocytes suppresses JAK–STAT3 signalling, resulting in reduced astrocyte and microglia activation in the context of neurodegenerative disease models including those of AD and HD[116]. Interestingly, in the HD model, SOCS3 overexpression also increased mutant huntingtin (mHTT) aggregates, a hallmark of HD pathogenesis. Consistent with these findings, the conditional deletion of STAT3 in astrocytes is associated with fewer amyloid-β (Aβ) plaques, and milder deficits in spatial learning and memory, in the APP/PS1 model of AD[122]. However, most evidence supports a pro-inflammatory role for STAT3 signalling in reactive astrocytes. Indeed, the cell-specific inactivation of STAT3 in astrocytes decreases amyloid-β (Aβ) plaques and improves spatial learning in the amyloid precursor protein/presenilin 1 (APP/PS1) model of AD. This effect is recapitulated by the administration of a STAT3 inhibitor[122]. Thus, JAK–STAT3 signalling in astrocytes has important roles in both the aggravation and the alleviation of neurodegeneration.

Calcineurin (also known as protein phosphatase 3) is a serine/threonine-protein phosphatase that is abundant in the healthy brain[126]. Elevated intracellular Ca^{2+} levels activate calcineurin, which binds to and dephosphorylates NFAT, triggering NFAT nuclear translocation and transcriptional activation[127]. Hyperactivation of calcineurin–NFAT signalling in astrocytes is associated with CNS injury and neurological diseases[128–132]. For instance, calcineurin-expressing reactive astrocytes are present in patients with AD and the APP/PS1 mouse model of AD[128]. Similarly, NFAT activation is elevated in acute brain injury[129,130], and in neurodegenerative diseases such as AD[131] and PD[132]. Further support for the contribution of calcineurin–NFAT signalling to neuroinflammation was provided by studies based on the intracerebroventricular injection or astrocyte-specific overexpression of VIVIT, an inhibitory peptide that blocks calcineurin–NFAT signalling and ameliorates AD symptoms while reducing astrocyte and microglia activation in preclinical models[133,134]. Moreover, in a model of traumatic brain injury, selective blockade of calcineurin–NFAT signalling in astrocytes increases synaptic functional recovery[130]. Enhanced intracellular Ca^{2+} waves in astrocytes can also trigger the release of γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain. Increased GABA uptake by neurons impairs memory and synaptic plasticity, contributing to AD pathology[85]. Of note, JAK–STAT and calcineurin–NFAT signalling pathways have been shown to crosstalk in other cell types[135–138], suggesting that interactions between these two pathways may fulfil important roles in fine-tuning astrocyte responses in neuroinflammation and synaptic plasticity.

Astrocytes in multiple sclerosis

MS is a chronic inflammatory neurological disease thought to be driven, at least during its initial phases, by an autoimmune response to myelin[139] (BOX 2). The clinical course

of MS has multiple phases. Initially, approximately 85% of patients with MS present with relapsing–remitting multiple sclerosis (RRMS). Following this stage, a significant proportion of patients with RRMS develop secondary progressive multiple sclerosis (SPMS), characterized by the progressive and irreversible accumulation of neurological disability, with limited response to available therapies[140]. Evidence for a role of astrocytes in MS pathology was first provided in the nineteenth century, when Jean-Marie Charcot identified astrocytes as key components of MS lesions[141]. Studies in the EAE model further revealed diverse roles of astrocytes in CNS inflammation (FIG. 1). In the acute EAE B6 mouse model, the depletion of reactive astrocytes increases disease severity and CNS inflammation[142–144]. In contrast, selective depletion of reactive astrocytes during the chronic progressive phase in the NOD mouse EAE model ameliorates disease pathogenesis, limiting the recruitment and activation of microglia and monocytes[19]. These seemingly opposing roles of astrocytes highlight their functional heterogeneity in MS.

Relapsing–remitting mutiple sclerosis

(RRMs). The most common phenotype of multiple sclerosis, which is characterized by relapses followed by periods of partial or complete recovery. Most patients with RRMs will eventually develop secondary progressive multiple sclerosis.

Secondary progressive multiple sclerosis

(SPMS). A phase of multiple sclerosis characterized by the progressive, irreversible accumulation of neurological disability, which shows limited response to available therapies.

Novel approaches enabled the identification of specific astrocyte subsets associated with MS pathology. Liddelow et al.[145] identified a subset of neurotoxic reactive astrocytes abundant in multiple neurodegenerative diseases, including MS, and characterized by complement component 3 (C3) expression. In addition, we recently identified a subset of astrocytes, driven by the small MAF bZIP transcription factor (MAFG) and granulocyte–macrophage colony-stimulating factor (GM-CSF) signalling[9], that promotes inflammation and neurodegeneration in EAE and MS. We also identified a subset of anti-inflammatory astrocytes that express the lysosome-associated membrane glycoprotein 1 (LAMP1; also known as CD107a) and tumour necrosis factor-related apoptosis-inducing ligand (TRAIL, also known as TNFSF10). These $LAMP1^{+}TRAIL^{+}$ astrocytes limit EAE pathogenesis by inducing T cell apoptosis via TRAIL–death receptor 5 (DR5) signalling[8].

CNS inflammation in MS is typically initiated by BBB dysfunction and peripheral immune cell invasion, triggering the activation of astrocytes in response to pro-inflammatory cytokines and pathogen-associated molecular patterns (PAMPs)[22,25,146]. Indeed, reactive astrocytes produce a broad range of chemokines that attract leukocytes into perivascular spaces and the CNS parenchyma. Astrocyte-derived C-C motif chemokine 2 (CCL2) controls the onset and progression of EAE by promoting the accumulation of monocytes and T cells into the CNS[26,147,148]. Of note, a recent study reported that astrocytes also control

the phenotype of CNS-infiltrating mononuclear phagocytes[149]. In addition, astrocyte-produced C-X-C motif chemokine 10 (CXCL10) promotes CNS infiltration by $CD4^+$ T cells[150]. Finally, astrocytes show increased expression of CXCL12, a chemoattractant involved in the recruitment of monocytes, T cells, B cells and plasma cells, in active and chronic MS lesions[151]. Taken together, these findings suggest key roles for astrocytes during the initiation of neuroinflammation.

Multiple studies have further established the crosstalk between astrocytes and other cells in the CNS as a major regulatory mechanism in MS pathogenesis[139]. We recently described microglia–astrocyte interactions, mediated by semaphorin4D–plexinB1/2 and ephrinB3–EPHB3, that promote CNS inflammation[15]. Reactive astrocytes also control CNS-infiltrating T cells via the expression of pro-apoptotic molecules such as FASL and TRAIL[8,152].

Conversely, astrocyte responses are regulated by T cells. IL-10 produced by regulatory T cells limits astrocyte activation and reduces neuroinflammation[18]. In addition, signalling triggered by GM-CSF, an important cytokine for the pathogenic activity of T cells in EAE and MS[153–155], promotes the differentiation of MAFG-driven pathogenic astrocytes, which have a decreased ability to support the metabolic needs of neurons and limit oxidative stress, and simultaneously activates transcriptional programmes that promote CNS inflammation and neurodegeneration[9,156]. GM-CSF signalling also limits astrocyte anti-inflammatory functions by downregulating TRAIL expression, suggesting an important role for this cytokine in regulating the balance between pro- and anti-inflammatory astrocyte subsets in MS and other neurological diseases[8].

Environmental factors.

Multiple environmental factors have been recently linked to astrocytes in MS pathology (FIG. 1). Importantly, astrocytes express the ligand-activated transcription factor aryl hydrocarbon receptor (AHR), which acts as a sensor for a wide range of small molecules provided by the environment, the diet, metabolic intermediates and the commensal microbiota[157,158]. Selective deletion of AHR in astrocytes worsens EAE, concomitant with increased expression of chemokines (CCL2, CCL20 and CXCL10) and other pro-inflammatory mediators (IL-6, IL-12, IL-23, GM-CSF and nitric oxide (NO)) in the brain[21]. Microbial metabolites of dietary tryptophan are an important physiological source of AHR agonists[159]. Indeed, some tryptophan metabolites controlled by the intestinal microbiome cross the BBB and inhibit EAE pathogenesis by suppressing astrocyte pathogenic activities; this novel gut–brain axis (GBA) provides a means through which the gut flora regulates astrocyte responses and CNS inflammation. These anti-inflammatory effects of AHR activation in astrocytes are mediated by the suppression of NF-κB signalling via SOCS2 (REF.[21]). A similar mechanism operates in microglia, where AHR limits NF-κB activation and also the expression of VEGFB, while increasing TGFα expression. Microglial TGFα interacts with the epidermal growth factor receptor (EGFR, also known as ERBB1), which is expressed on astrocytes, to limit their pathogenicity. In contrast, microglial VEGFB activates FLT1 signalling in astrocytes, which boosts the expression of pro-inflammatory transcriptional programmes that increase CNS pathology[20]. Collectively, these findings

illustrate a novel mechanism by which microbial metabolites control the intrinsic pathogenic activities of microglia and astrocytes as well as their communication.

Gut–brain axis

(GBA). Bidirectional communication between the gut microbiota and the brain.

Environmental chemicals that gain access to the CNS also have the potential to modulate astrocyte responses in CNS inflammation. By using bioinformatics, we integrated data from genomics, perturbation studies in zebrafish, mouse models and tissue samples from people with MS to evaluate the effects of common chemicals on astrocytes and identify environmental factors that modulate CNS pathology, as well as novel regulatory mechanisms and potential targets for their therapeutic modulation[26]. This novel platform established that the herbicide linuron boosts astrocyte pathogenic activities. Linuron boosts unfolded protein response (UPR) signalling by increasing sigma receptor 1 (SIGMAR1)-driven activation of inositol-requiring enzyme 1α (IRE1α) and X-box binding protein 1 (XBP1). Notably, the UPR is a highly conserved cellular stress response that aims to restore endoplasmic reticulum (ER) and protein homeostasis, and has been linked to several neurodegenerative diseases[160–162]. Indeed, IRE1α–XBP1 activation is detected in MS brain lesions, and the selective knock-down of *Xbp1* or *Ern1* (coding for IRE1α) in astrocytes ameliorates CNS pathology in EAE[26]. Moreover, a recent study reported the pathogenic role of UPR activation in astrocytes during prion-induced neurodegeneration[163]. Taken together, these findings suggest that SIGMAR1–IRE1α–XPB1 signalling is a common component of astrocyte pathogenic responses in neurological diseases.

Sphingolipid metabolism.

Sphingolipids are a class of lipids that are major components of the myelin sheath. Abnormal sphingolipid metabolism has been linked to MS pathology[164]. Indeed, sphingosine 1-phosphate (S1P) signalling is an important target in existing therapies for MS, and is associated with the control of CNS infiltration by peripheral immune cells[165]. In addition, the expression of S1P receptors ($S1P_1$ and $S1P_3$) in astrocytes is upregulated in demyelinating and chronic MS lesions. Selective knock-down of S1P signalling in astrocytes reduces EAE severity, demyelination and axonal loss[166]. Furthermore, S1P receptor modulation by fingolimod (FTY720), an approved therapy for MS, suppresses astrocyte pathogenic activities and ameliorates disease progression and neurodegeneration in the NOD EAE model of MS[167], which recapitulates features of SPMS, supporting a role for S1P signalling in astrocytes in MS progression (FIG. 1).

The astrocyte–neuron lactate shuttle supports neuron metabolism[87,88]. Interestingly, sphingolipid metabolism has been recently shown to control the metabolic support of neurons by astrocytes. Levels of the ceramide-derived sphingolipid lactosylceramide (LacCer) and the enzyme β1,4-galactosyltransferase 6 (B4GALT6), which catalyses LacCer synthesis, are upregulated in the NOD EAE model and in brain samples from individuals with MS. LacCer promotes the expression of pro-inflammatory transcriptional programmes in astrocytes, and B4GALT6 inactivation in astrocytes ameliorates EAE[19]. Further

investigations combining proteomic, metabolomic, transcriptomic and gene perturbation studies established that LacCer activates the cytosolic phospholipase A2 (cPLA2) and the mitochondrial antiviral signalling protein (MAVS). LacCer-activated cPLA2–MAVS signalling boosts NF-κB-driven pro-inflammatory transcriptional programmes in astrocytes that contribute to EAE and MS pathogenesis. In resting astrocytes, MAVS interacts with hexokinase 2 (HK2) to promote lactate production by glycolysis[168]. However, LacCer-induced cPLA2–MAVS interactions decrease HK2–MAVS interactions, HK2 enzymatic activity and astrocyte lactate production[93]. These findings identify cPLA2–MAVS–NF-κB signalling as a novel immunometabolic pathway that regulates astrocyte-driven CNS inflammation and neurodegeneration (FIG. 1).

Astrocyte–neuron lactate shuttle

Mechanism by which lactate released by astrocytes from glycolysis is used as a metabolic substrate for neurons under normal physiological conditions.

DNA methylation.

DNA methylation is one of the best-studied epigenetic modifications in mammals. This process is controlled by DNA methyltransferases (DNMTs), which catalyse the transfer of methyl groups to DNA through a reaction that uses the methyl donor *S*-adenosyl methionine (SAM)[169]. DNA methylation represses gene expression by impairing the interactions of DNA elements with protein complexes involved in the regulation of gene transcription[170]. Changes in DNA methylation have been linked to MS pathogenesis[171]. For example, altered DNA methylation is detected in multiple immune cell types and CNS-resident cells in patients with MS[172,173]. Although the study of DNA methylation in astrocytes was initially focused on CNS development, recent studies highlighted the importance of DNA methylation in the control of pathogenic astrocyte activities[9,174,175].

High-throughput scRNA-seq in combination with astrocyte-specific Ribotag RNA profiling identified a novel pathogenic astrocyte subset that is expanded in EAE and MS and features decreased expression of the transcription factor NRF2 and increased expression of MAFG. MAFG has dual roles in controlling NRF2 signalling, and NRF2 is a master regulator of antioxidant transcriptional responses. By forming heterodimers with NRF2, MAFG participates in NRF2-driven gene expression. However, MAFG homodimers are more abundant in CNS inflammation, and compete for MAFG–NRF2 responsive elements to suppress NRF2 signalling[176]. MAFG binding to its DNA responsive elements recruits the co-factor MAT2α, an enzyme that converts methionine into SAM. Together with the BACH1 and BACH2 co-factors that recruit DNA methyltransferases, MAFG–MAT2α–BACH complexes promote DNA methylation. Thus, increased MAFG expression in astrocytes promotes astrocyte pathogenic activities and CNS inflammation by downregulating NRF2 signalling. Interestingly, MAFG–MAT2α signalling in astrocytes is induced by GM-CSF, a cytokine produced by encephalitogenic T cells[177,178]. These observations highlight new mechanisms involved in the control of astrocyte responses in the context of CNS pathology, pointing to new therapeutic targets and challenges, as they suggest that epigenetic modifications stabilize disease-promoting astrocyte subsets.

Astrocytes in Alzheimer disease

AD is the most common neurodegenerative disease, characterized by progressive dementia with cognitive decline and impaired long-term memory[179] (BOX 2). The pathological hallmark of AD is the presence of extracellular Aβ plaques and intracellular neurofibrillary tangles (NFTs), comprised of hyperphosphorylated Tau, in the brain. Aβ is a normal by-product of cellular metabolism generated by the cleavage of the transmembrane amyloid precursor protein (APP) by the aspartyl proteases β- and γ-secretase[180]. The accumulation of Aβ in the brain is considered an early event in AD pathogenesis. Aβ interacts with a broad range of receptors expressed by CNS-resident cells, activating signalling pathways that lead to neuroinflammation and neurodegeneration[181].

Microglia and astrocytes cluster around and within Aβ plaques in CNS samples from patients with AD[182]. Astrocytes participate in the degradation of Aβ by secreting proteolytic enzymes such as metalloendopeptidases (NEP, ECE and IDE) and matrix metalloproteinases (MMP2 and MMP9) that cleave Aβ[183]. Indeed, reactive astrocytes surrounding Aβ plaques upregulate MMP2 and MMP9 in AD mouse models[184,185]. However, astrocytes also contribute to Aβ accumulation in the brain because they produce Aβ and release β-secretase 1 (BACE1)[186–189]. Cytokines such as TGFβ, IL-1β, TNF, IL-6 and interferon-γ (IFNγ) boost Aβ production by reactive astrocytes[186,188,189]. Moreover, pro-inflammatory cytokines induce, in astrocytes, the expression of interferon-induced transmembrane protein 3 (IFITM3), which binds to and activates γ-secretase, increasing Aβ production. Of note, IFITM3 expression is upregulated in brain samples from patients with late-onset AD, suggesting that IFITM3 may serve as a biomarker and therapeutic target in AD[190].

scRNA-seq studies have analysed glial subsets in patient samples and preclinical models of AD[29,30]. Indeed, although multiple studies have defined microglial subsets associated with AD[30,191,192], our knowledge of astrocyte heterogeneity in AD is more limited. Disease-associated astrocytes (DAAs) in AD are characterized by the upregulation of genes that encode serine protease inhibitor A3N (*Serpina3n*) and the lysosomal cysteine protease cathepsin B (*Ctsb*), both of which are involved in amyloid processing. DAAs also express pro-inflammatory genes, suggesting that this novel astrocyte subset contributes to the initial stages of AD pathogenesis[10]. In summary, reactive astrocytes exhibit functional diversity in AD pathology, promoting neuroprotection through Aβ degradation and clearance and also contributing to pathological processes triggered by Aβ. These findings highlight the need for a deeper characterization of astrocyte subsets in AD and the mechanisms that control them.

Glutamate homeostasis.

Glutamate is the most abundant excitatory neurotransmitter in the CNS[193]. However, excessive glutamate levels trigger excitotoxicity[194]. Astrocytes express the high-affinity glutamate transporters EAAT1 and EAAT2, which take up extracellular glutamate, thereby playing a pivotal part in glutamate homeostasis, synaptic plasticity and neuron survival[70,71]. Not surprisingly, deficits in glutamate transporter function have been associated with neurodegeneration in AD[195]. Indeed, EAAT2 knock-down in the APP/PS1 AD model exacerbated cognitive decline[196]. In addition, several in vitro studies suggest that Aβ directly modulates glutamate uptake in astrocytes[197,198]. For example, Aβ treatment inhibits

the expression of EAAT2 and GLAST via a mechanism dependent on astrocytic adenosine A2A receptors[197]. Furthermore, human astrocytes derived from patients with AD display decreased glutamate uptake concomitant with reduced EAAT2 and GLAST expression[199]. Evidence that such a mechanism also occurs in vivo during neurodegeneration was recently provided by the analysis of extrasynaptic glutamate dynamics using the fluorescent glutamate indicator iGluSnFR in combination with intravital two-photon laser scanning microscopy[200]. These studies detected decreased EAAT2 expression in reactive astrocytes concomitant with impaired glutamate uptake in association with neuronal dysfunction in the proximity of Aβ plaques in the APP/PS1 AD model. Interestingly, ceftriaxone, an antibiotic shown to upregulate EAAT2 expression[201], increased glutamate uptake via EAAT2 (REF.[200]) (FIG. 2), supporting the targeting of astrocytic glutamate transporters as a therapeutic approach for neurodegenerative diseases.

Calcium homeostasis.

Intracellular Ca^{2+} waves in astrocytes play an important part in synaptic transmission and plasticity[64]. Astrocytes participate in the control of long-term memory in the hippocampus via Ca^{2+} signalling[40], suggesting a link between astrocytic Ca^{2+} homeostasis and AD pathology. Indeed, Aβ enhances Ca^{2+} signalling in astrocytes[202,203], and hyperactive Ca^{2+} transient currents in astrocytes are detected near Aβ plaques in AD mouse models[204]. Conversely, intracerebroventricular injection, or astrocyte-specific overexpression, of the calcineurin–NFAT peptide inhibitor VIVIT restores glutamate dysregulation, synaptic plasticity and neuronal hyperactivity[133,134], providing further support for the role of aberrant astrocyte Ca^{2+} signalling in AD pathogenesis.

Enhanced intracellular Ca^{2+} waves in astrocytes increase the release of glutamate, ATP and GABA[79–84]. Importantly, increased GABA levels are detected in the cerebrospinal fluid of patients with AD[205]. Moreover, selective blockade of GABA signalling in the APP/PS1 mouse model of AD rescues the impairment of spatial memory and hippocampal long-term potentiation (LTP)[206], suggesting an important role for GABA-dependent mechanisms in AD memory impairment.

Indeed, reactive astrocytes have been reported to contribute to GABA-mediated memory loss[85]. When compared with homeostatic astrocytes, reactive astrocytes in close proximity to Aβ plaques release higher amounts of GABA. In APP/PS1 mice, increased monoamine oxidase B (MAOB) activity in reactive astrocytes triggers tonic GABA production via the Ca^{2+}-activated anion channel bestrophin 1 (BEST1). The neuronal uptake of GABA via presynaptic GABA receptors results in the impairment of memory and synaptic plasticity. Interestingly, Aβ treatment induces MAOB-mediated GABA production in cultured astrocytes, suggesting that Aβ plaques are responsible for astrocytic GABA-driven memory dysfunction. Of note, the selective MAOB inhibitor selegiline limits tonic GABA release and restores impairments in spike probability, LTP and learning and memory[85] (FIG. 2). These findings highlight the prominent role of astrocytic Ca^{2+} homeostasis in AD pathogenesis and the potential for targeting astrocyte intracellular Ca^{2+} signalling or GABA production as a therapeutic approach to arrest neurodegeneration in AD.

Cholesterol metabolism.

APOE participates in the transport and clearance of lipids, and the expression of certain isoforms is one of the major risk factors for AD[207]. Astrocytes are the main CNS producers of APOE, which transmits cholesterol to neurons via cell-surface APOE receptors. Three common APOE isoforms exist: APOE2, APOE3 and APOE4 (REF.[208]). A large body of evidence suggests that expression of APOE4 is the most prevalent genetic risk factor for AD, whereas APOE2 is associated with a decreased risk compared with the more common APOE3 isoform[207,209,210]. Subsequent studies established that APOE isoforms regulate Aβ accumulation and clearance in the brain[211,212]. Importantly, APOE also controls cerebrovascular integrity during neurodegeneration. For instance, individuals who carry *APOE4* alleles but no signs of dementia have neurovascular dysfunction[213–215]. Moreover, the conditional knockout of *APOE* in mice causes BBB disruption[216,217]. Along these lines, APOE isoforms show disparate effects on BBB permeability. The inactivation of APOE4, but not of APOE2 or APOE3, results in BBB breakdown by activating CypA–NF-κB–MMP9 signalling in pericytes. This APOE4–CypA-mediated BBB breakdown induces neuronal dysfunction and degeneration. It was also shown that APOE3 secretion by astrocytes inhibits the APOE4-mediated pericyte activation responsible for BBB breakdown. Astrocyte-secreted APOE3, but not APOE4, limits CypA–NF-κB–MMP9 signalling in pericytes via lipoprotein receptor-related protein 1 (LRP1)[55], thus suggesting a neuroprotective role of reactive astrocytes in APOE4-associated neurodegenerative diseases (FIG. 2). Remarkably, pathogenic DAAs upregulate *Apoe* expression and genes linked to Aβ metabolism and clearance in an AD mouse model[10]. Collectively, these findings suggest that astrocytes have important roles in APOE-dependent mechanisms of neurodegeneration and highlight the potential role of APOE as a therapeutic target in AD.

Astrocytes in Parkinson disease

PD is the second most common neurodegenerative disease; it is characterized by the loss of dopamine neurons in the substantia nigra pars compacta and abnormal aggregation of misfolded α-synuclein in Lewy bodies[218] (BOX 2). The molecular mechanisms involved in the pathogenesis of PD have not been fully elucidated and there are currently limited disease-modifying strategies available. However, a large body of genome-wide association studies have identified specific genetic factors related to PD pathogenesis[219]. Although it is unclear whether inflammation is an initiating factor for PD, several lines of evidence suggest that pro-inflammatory glial responses contribute to PD pathogenesis[32,220]. For example, reactive astrocytes are detected in the substantia nigra pars compacta of patients with PD[221] and preclinical models of PD[222,223]. In addition, nuclear receptor subfamily 4 group A member 2 (NR4A2, also known as NURR1), one of the major genetic risk factors for PD, has essential roles in the control of microglia and astrocyte neurotoxicity. NURR1 is an orphan ligand-activated transcription factor that is crucial for the development and maintenance of dopaminergic neurons. Selective downregulation of NURR1 in astrocytes results in the increased production of neurotoxic factors, including NO and ROS. These anti-inflammatory effects of NURR1 in astrocytes involve the corepressor CoREST, which cooperates with NURR1 to suppress NF-κB-driven transcriptional programmes that promote disease pathology[224]. Moreover, a glucagon-like peptide 1 receptor (GLP1R) agonist, a

potent neuroprotective agent in neurodegenerative diseases, prevents dopaminergic neuron loss and behavioural deficits in preclinical PD mouse models by blocking the microglia-driven differentiation of $C3^+$ neurotoxic astrocytes[31]. Indeed, astrocytes also contribute to PD pathology through their roles in glutamate-mediated excitotoxicity, K^+ buffering and Ca^{2+} homeostasis, which control dopaminergic neuron death[32,73,225]. Collectively, these findings suggest that common mechanisms mediate the pathogenic roles of astrocytes in PD and other neurological diseases including AD and HD (BOX 3).

Astrocytes in Huntington disease

HD is a neurodegenerative disorder characterized by cognitive, motor and psychiatric symptoms that are caused by extended polyglutamine-encoding CAG repeats in the huntingtin gene (*HTT*)[226] (BOX 2). The aggregation of misfolded mHTT is one of the hallmarks of HD and is associated with severe neurodegeneration in the striatum and the cortex[226,227]. Increasing evidence suggests that astrocytes express mHTT in HD and its preclinical model[228–230]. Indeed, selective overexpression of mHTT in mouse astrocytes results in significant motor impairment[230]. Conversely, the selective deletion of reactive astrocytes in HD animal models reduces neurodegeneration, suggesting that reactive astrocyte subsets contribute to HD pathogenesis[231]. Whether astrocytes are central drivers of neurodegeneration in HD or simply amplify it needs further investigation. However, it is now clear that mHTT accumulation leads to astrocyte dysfunction and neurodegeneration via the impairment of glutamate uptake, K^+ homeostasis, Ca^{2+} signalling and metabolic reprogramming, all of which are mechanisms common to the pathogenesis of other neurological diseases[33] (FIG. 3).

$C3^+$ astrocytes have been detected in HD brain samples[145]. High-throughput sequencing studies have further analysed reactive astrocyte diversity in HD[36,145,232], identifying additional astrocyte subsets in the cingulate cortex. These astrocyte subsets exhibit low expression of glutamate transporters (*SLC1A2* and *SLC1A3*) and genes related to Ca^{2+} signalling[232]. Moreover, a recent study identified at least 62 differentially expressed signature genes in striatum DAAs in preclinical HD mouse models and patient samples. These DAA-associated genes were mostly related to Ca^{2+}, glutamate and G protein-coupled receptor (GPCR) signalling, which were downregulated in HD samples. This study further identified five upstream transcriptional regulator genes (*Htt*, *Adora2a*, *Mapt*, *Hdac4* and *App*), which provide candidate therapeutic targets for the control of DAAs in HD. Indeed, the selective inhibition of mHTT expression in astrocytes using zinc finger protein (ZFP) transcriptional repressors reversed the transcriptional perturbations detected in HD DAAs, highlighting the importance of mHTT in driving astrocyte responses that contribute to HD pathology[36]. Finally, recent scRNA-seq studies highlighted a central role for astrocyte GPCR signalling in HD pathology, as they showed that impaired synaptic plasticity, Ca^{2+} and GPCR signalling in striatum astrocytes could be reversed by the selective activation of G_i–GPCR signalling in astrocytes[37] using designer receptors exclusively activated by designer drugs (DREADDs)[233] (FIG. 3). These studies identify astrocyte GPCR signalling as a promising target to control neurodegeneration in HD. Moreover, taken together, these results point to aspects of regional astrocyte heterogeneity in HD, but also to common

mechanisms of astrocyte-driven pathology across multiple neurological disorders, such as dysfunctional Ca^{2+} and GPCR signalling and the impairment of glutamate uptake.

Designer receptors exclusively activated by designer drugs

(DREADDs). Widely used tool for selectively manipulating neuronal activity indirectly through g protein-coupled receptor (GPCR)-dependent signalling pathways.

Glutamate and ion homeostasis.

The glutamate transporter EAAT2 is usually downregulated in HD[33], and increasing evidence suggests that this leads to astrocytic dysfunction[33,230,234]. For instance, mHTT expressed in astrocytes impairs EAAT2 expression by inhibiting the binding of the transcription factor SP1 to the promoter of the gene encoding EAAT2 (REF.[230]). Further evidence in support of dysfunctional glutamate signalling in HD astrocytes was recently provided by a study that visualized glutamate release with an intensity-based glutamate-sensing fluorescent reporter (iGluSnFR). In the R6/2 preclinical HD mouse model, striatal astrocytes exhibited reduced spontaneous Ca^{2+} signalling and glutamate clearance. Interestingly, EAAT2 blockade in wild-type mice induced astrocytic dysfunction similar to that detected in R6/2 mice (for example, prolonged iGluSnFR signals and enhanced mGluR2/3-mediated evoked Ca^{2+} signals)[234], suggesting that the impairment of glutamate uptake contributes to astrocytic dysfunction in HD pathogenesis.

Furthermore, mHTT inclusions in astrocytes are associated with decreased expression of $K_{ir}4.1$ in the early stages of disease in the R6/2 and Q175 HD mouse models. $K_{ir}4.1$ channels control the membrane potential and excitability of neurons by promoting extracellular K^+ clearance. Impaired $K_{ir}4.1$ channels elevate extracellular K^+ levels, leading to neuronal hyperexcitability[33,34]. Indeed, selective expression of $K_{ir}4.1$ channels in striatal astrocytes normalizes extracellular K^+ levels and HD-like symptoms, including medium spiny neuron (MSN) depolarization and abnormal motor behaviours, in preclinical models[34]. Further evidence to support the importance of astrocyte-mediated K^+ homeostasis in HD was recently provided in a study in which restoration of $K_{ir}4.1$ in striatal astrocytes partially recovered dysfunctional Ca^{2+} and glutamate signalling in R6/2 mice[234] (FIG. 3). Collectively, these studies suggest that restoring astrocyte K^+ homeostatic mechanisms may provide a therapeutic approach to control neurodegeneration in HD.

Medium spiny neuron

(MSN). Class of inhibitory GABAergic neurons that represents ~95% of the neuronal population in the mammalian striatum.

Energy metabolism

The neuropathological hallmarks of HD include impairment of energy metabolism and oxidative stress[235–237]. Brain metabolism impairment in patients with HD has been detected in the striatum and cerebral cortex via positron emission tomography (PET) studies[238,239],

and emerging evidence suggests that dysfunctional astrocyte–neuron metabolic interactions contribute to neurodegeneration in HD[91,92]. For example, deficits in ascorbic acid astrocyte–neuron transport have been linked to HD symptoms in preclinical models[92]. Ascorbic acid is a vital antioxidant molecule in the brain[240], which is taken up by neurons to inhibit glucose transport and stimulate lactate uptake. In the R6/2 mouse HD model, abnormal neuronal ascorbic acid uptake is detected in the dorsolateral striatum[92,241]. Moreover, in a mouse cellular model of HD, accumulation of mHTT in striatal neurons impairs ascorbic acid transporter 2 (SVCT2) translocation[92], and treatment with ascorbate rescues neuronal activity and motor behaviour in R6/2 mice[242,243]. Thus, the impairment of neuronal ascorbic acid uptake via SVCT2 might promote neuronal metabolic failure and neurodegeneration in HD.

In addition, new evidence suggests that metabolic reprogramming in striatal astrocytes promotes neuronal death in HD. Fluorescence lifetime imaging microscopy (FLIM) revealed abnormal striatal mitochondrial dysfunction in an HdhQ(150/150) HD mouse model. In the striatum, glucose levels were low, and levels of fatty acid metabolites were elevated. Notably, this low glucose environment promotes astrocyte metabolic reprogramming, causing astrocytes to switch from glycolysis to fatty acid oxidation (FAO), which is tightly regulated to minimize the generation of ROS and neuronal hypoxia[244,245]. However, the accumulation of oxidized lipid bodies in the striatum of HD-like HdhQ(150/150) mice results in ROS production and neuronal toxicity. Moreover, the mitochondria-targeted electron scavenger, XJB-5-131, prevents the accumulation of lipid bodies in the brain[91], providing a potential explanation for the results of a previous study in which XJB-5-131 treatment attenuated ROS production, reduced neuronal damage and recovered motor behaviours in an HD mouse model[246] (FIG. 3). Taken together, these findings suggest that focusing on the link between glucose availability and striatal astrocyte metabolism may offer novel therapeutic approaches for HD.

Astrocytes in psychiatric disorders

The mechanisms described above highlight the broad contributions of astrocytes to the pathogenesis of neurodegenerative diseases. In addition, the dysregulation of astrocyte functions, such as the control of neuronal activity, release of neurotransmitters and processes associated with synaptic pruning, have all been associated with neuropsychiatric diseases. Through these and additional mechanisms, astrocytes control multiple aspects of neural circuits and behaviour[42].

Synaptic pruning

Neurodevelopmental process of eliminating neurons and synaptic connections in the brain.

The nucleus accumbens is a small forebrain area that exerts an outsized influence as a central component of the basal ganglia[247]. The basal ganglia consists of several GABAergic neuronal subtypes, including dopamine-responsive MSNs, which express dopamine receptors of the type I (D_1R^+) and type II (D_2R^+) classes; these receptors

have opposing effects on basal ganglia outputs[248]. The dysfunction of dopaminergic neurotransmission in the nucleus accumbens is associated with neurodegenerative and neuropsychiatric disorders, including depression, schizophrenia and behaviours associated with fear and anxiety[249–251]. Hence, targeting MSNs in the nucleus accumbens is considered a potential therapeutic approach for neurological diseases.

Pioneering work from the Araque lab demonstrated that astrocytes differentially influence D_1R^+ and D_2R^+ MSN circuits in the nucleus accumbens[60]. Using photoactivatable Ca^{2+} uncaging, the authors demonstrated that astrocytes participate only in the control of homotypic MSN circuits (for example, D_1R to D_1R or D_2R to D_2R), but not heterotypic circuits (D_1R to D_2R). Interestingly, although astrocyte-derived Ca^{2+} is not crucial for the regulation of heterotypic interactions, astrocytes also participate in heterotypic MSN circuits, suggesting that additional mechanisms of astrocyte-dependent neural circuit regulation remain to be defined.

Photoactivatable Ca^{2+} uncaging

Covalent attachment of a photochemical group to a biomolecule to render it inert until light irradiation releases the bond. in the case of $Ca2^+$ uncaging, the photochemical group is attached to a $Ca2^+$ chelator, such as EGTA.

Astrocyte Ca^{2+} signalling is a central mechanism in the control of neuronal function and behaviour. Khakh and collaborators[38] recently demonstrated that homeostatic astrocyte Ca^{2+} signalling in the nucleus accumbens prevents repetitive behaviours in mice. Using an elegant combination of intravital imaging, electrophysiology and behaviour, the authors demonstrated that depletion of astrocyte Ca^{2+} signalling alleviates tonic inhibition of MSNs through increased activation of sodium- and chloride-dependent GABA transporter 3 (GAT3). Loss of astrocyte Ca^{2+} signalling led to D_1R^+ neuron activation via GAT3 expression, which promoted the excessive grooming commonly associated with obsessive–compulsive disorder owing to loss of GABAergic tone. Astrocyte-specific Ribotag RNA profiling[252] identified *Rab11a* as an upstream negative regulator of GAT3 activity[38]. *Rab11a* has been reported to control GAT3 trafficking downstream of astrocyte Ca^{2+} influx[253]. Thus, a GABA-induced imbalance of astrocyte Ca^{2+} signalling can lead to the elevation of GAT3, mediated by the downregulation of *Rab11a*.

Neurons also signal to astrocytes to control behaviours associated with psychiatric diseases. Nagai et al.[41] recently reported that MSN GABA release upregulates the synaptogenic cue, thrombospondin 1, in a Ca^{2+}-dependent manner. Thrombospondin 1 induction of synapse formation potentiated corticostriatal glutamate signalling. Similar observations have been made in the context of learning and memory, during which astrocyte activation leads to the formation of hippocampal synapses, which are required for the stabilization of fear learning programmes[40]. A recent study proposed that defective astrocyte synapse elimination in adults leads to impaired memory formation and long-term plasticity[254]. These studies point to important mechanisms involved in the neuronal regulation of astrocyte synaptogenic programmes that contribute to the development of behaviours associated with anxiety, obsessive–compulsive disorder and other neuropsychiatric symptoms.

Along these lines, recent studies point to the importance of astrocyte regulation of synaptic pruning via microglia during development[255,256]. For instance, astrocytes promote synaptic pruning in the developing visual system via a mechanism mediated by IL-33. Microglia-dependent synaptic pruning is associated with neurodegenerative diseases such as AD, and also neuropsychiatric disorders such as schizophrenia. Pioneering work by the Barres lab demonstrated that the complement cascade participates in synaptic pruning during development[257]. Specifically, complement production by astrocytes was shown to trigger microglia-dependent pruning to sculpt neural circuits. Later work from Stevens and coworkers[258] showed that microglial synaptic engulfment is modified by neural activity[258]. These insights are especially intriguing considering that the overexpression of specific complement isoforms associated with schizophrenia[259] leads to dysregulated behaviour as well as dysfunctional synaptic pruning in the prefrontal cortex[260]. Hence, targeting dysregulated IL-33 and complement signalling may provide therapeutic avenues for disorders involving altered synapse elimination.

Astrocyte cytokine production is associated with depressive and anxiety-like behaviours[261,262]. For example, amygdalar adenosine signalling in astrocytes contributes to the induction of anxiety-associated phenotypes, in a region- and synapse-specific manner[39]. Similarly, the induction of anxiety-associated behaviours has also recently been attributed to pro-inflammatory CNS-infiltrating T cells through a metabolic programme that consists of xanthine production, which promotes adrenaline production by $CD4^+$ T cells; adrenaline affects behaviour through direct neuronal stimulation[263]. These findings suggest that signalling through astrocyte-expressed GPCRs can also promote anxiety-like phenotypes. Moreover, additional Ca^{2+}-dependent mechanisms associated with fear learning and memory[40,264] may provide therapeutic targets for neuropsychiatric disease.

Beyond GPCR signalling, pro-inflammatory signals, such as those derived from pro-inflammatory T cells, can affect depressive phenotypes by acting on astrocytes. The induction of pro-inflammatory signalling pathways associated with depressive behaviours, such as the UPR[26,163,265], are known to be triggered in astrocytes. These pro-inflammatory pathways can be therapeutically targeted. Indeed, NF-κB-driven pro-inflammatory signalling in astrocytes contributes to the induction of depressive behaviours[266]. For example, the loss of signalling by menin, a negative regulator of NF-κB[267], results in increased astrocyte production of IL-1β, which promotes depressive behaviour by inducing pro-inflammatory signals in neurons[268]. Hence, targeting astrocyte cytokine production may offer novel therapeutic options for circuits that affect depression and related disorders.

Outlook on therapeutic strategies

Given the substantial biological insights made over the past decade, astrocytes constitute attractive therapeutic targets for neurological disorders. However, therapeutic approaches that target astrocytes, as well as other CNS-resident cells, are faced with the challenge of delivering drugs across the BBB. New developments in drug delivery suggest that this important challenge can now be properly addressed. For example, several studies have described synthetic nanoparticles that can be used for astrocyte-specific targeting[269]. Intraspinally administered poly(lactic-*co*-glycolic acid) nanoparticles are taken up by

astrocytes, and persist for long periods of time in the SCI rat model[270]. In addition, systemically administered polyamidoamine dendrimers colocalize with astrocytes that are involved in the early progression of ischaemic injury[271]. Additional non-invasive molecular delivery strategies that bypass the BBB have also been developed, including receptor-mediated transcytosis, neurotropic viruses, nanoparticles and exosomes[272]. These exciting new approaches may facilitate the therapeutic targeting of astrocytes as described below.

Poly(lactic-*co*-glycolic acid) nanoparticles

(PLGA nanoparticles). FDA-approved biodegradable polymeric nanoparticle extensively used in drug delivery systems owing to its biocompatibility and low toxicity.

Polyamidoamine dendrimers

(PAMAM dendrimers). A class of dendrimers, hyperbranched macromolecules with numerous functional amine groups on the surface.

Metabolism.

Metabolic pathways modulate astrocyte reactivity in multiple neurological diseases and therefore may serve as viable targets for therapeutic intervention[91,93,246]. For example, miglustat, a FDA-approved glucosylceramide synthase (GCS) inhibitor used to treat type 1 Gaucher disease and Niemann–Pick disease type C[273], ameliorates chronic progressive EAE in the NOD model by arresting immunometabolic pathways in pathogenic astrocytes[93]. These therapeutic effects of miglustat involve the suppression of cPLA2–MAVS signalling in astrocytes, which promotes CNS inflammation and interferes with the production of lactate involved in neuron metabolic support[93]. These findings also implicate other GCS inhibitors as promising candidates to modulate astrocyte responses that promote CNS inflammation and neurodegeneration. For example, venglustat, a novel CNS-penetrant oral inhibitor of GCS under investigation for the treatment of lysosomal storage diseases, may provide a useful tool to modulate astrocyte responses[274].

Another metabolism-based approach to modulate astrocyte responses could be to target mitochondrial dysfunction, which has been linked with neurodegenerative diseases including MS, AD, PD and HD[275,276]. In HD, for example, low brain glucose levels trigger the metabolic reprogramming of striatal astrocytes, increasing ROS production and neuronal toxicity. XJB-5-131, a mitochondria-targeted antioxidant, limits ROS-induced neuronal damage mediated by astrocytes[91,246], highlighting the potential of targeting astrocyte metabolism for the treatment of neurological diseases.

Physical interactions.

Cell–cell interactions play a key part in brain physiology and pathology[22]. For instance, astrocyte interactions with microglia control synaptic pruning, CNS inflammation and neurodegeneration[15,20,145,256]. Newly developed techniques allow the identification of the pathways and molecules governing CNS cell–cell interactions to systematically uncover novel therapeutic targets[15,277–279]. For instance, using RABID-seq, a method

that combines barcoded viral tracing with scRNA-seq, we identified novel roles for axon guidance molecules (EPHB3–ephrinB3, plexinB1/2–semaphorin4D) in astrocyte–microglia interactions that promote CNS pathology in EAE and, potentially, MS. In this context, a CNS-penetrant inhibitor of EPHB3 signalling suppressed the pathogenic activities of human and mouse astrocytes in vitro and ameliorated EAE pathogenesis in acute and chronic progressive models[15]. These findings identify ephrinB3–EPHB3 signalling as a promising therapeutic candidate for modulating astrocyte and microglial pathogenic functions in MS, and potentially other neurological disorders as suggested by previous reports on the role of EPH signalling in the pathology of neurodegenerative diseases including AD[280] and PD[281].

Targeting transporters and receptors.

The glutamate transporters EAAT1 and EAAT2, which are expressed by glial cells (predominantly astrocytes), are important for neuronal survival and function[70,71]. Numerous studies have defined important roles for astrocytic EAAT2 in neurodegenerative diseases including AD[197–200], HD[33,230,234] and PD[282–284]. Indeed, treatment with the antibiotic ceftriaxone[201], which elevates EAAT2 expression in astrocytes, restores glutamate neurotransmission and shows beneficial effects in a preclinical model of AD[200], identifying EAAT2 as a promising pharmacological target for various neurodegenerative disorders.

Astrocytes also express a wide range of GPCRs, some of which can trigger intracellular Ca^{2+} signalling and stimulate neurotransmitter release, leading to the control of synaptic transmission[285]. In this context, selective activation of G_i–GPCR signalling in striatal astrocytes is reported to rescue HD-associated synaptic and behavioural phenotypes in preclinical models[37]. In addition, S1P receptors (which are GPCRs) promote astrocyte pathogenic responses that contribute to CNS pathology. For example, fingolimod, the first FDA-approved S1P receptor modulator, interferes with the activation of astrocytes, microglia and inflammatory monocytes, limiting disease progression in the NOD EAE model of SPMS[167]. Although S1P receptor modulation by fingolimod failed in the INFORMS phase III trials in primary progressive MS[286]; a more selective S1P receptor modulator (which targets $S1P_1$ and $S1P_5$), siponimod (BAF312), was recently approved for the treatment of SPMS[287]. Based on the emerging roles of S1P signalling and metabolism in the pathology of other neurodegenerative diseases including AD, PD and HD[288], the S1P–S1P receptor axis in astrocytes constitutes an attractive candidate for therapeutic intervention in neurodegeneration.

Glia-to-neuron conversion therapy.

Astrocytes can potentially be genetically reprogrammed into functional neurons[289]. As astrocytes are abundant in the CNS, astrocyte reprogramming might be useful to treat neurodegeneration. Indeed, studies report promising therapeutic effects of in vivo glia-to-neuron conversion in preclinical models of major neurodegenerative diseases including AD[290], PD[291,292] and HD[35]. In HD, for example, selective inactivation of the RNA binding poly-pyrimidine tract-binding protein 1 (PTB, also known as PTBP1 (REFS[293,294])) in astrocytes located in the substantia nigra and striatum resulted in the conversion of astrocytes into dopaminergic neurons, restoring dopamine levels and ameliorating motor behaviour in an animal model of PD[291,292]. Similarly, selective co-expression of

the neuronal transcription factors neurogenic differentiation factor 1 (NEUROD1) and homeobox protein DLX2 in striatal astrocytes resulted in their conversion into GABAergic neurons and improved motor function and survival in an HD mouse model[35]. However, it should be noted that glia-to-neuron conversion is controversial. Using lineage tracing methods, it has recently been suggested that glia do not become neurons, but rather that endogenous neurons are labelled[295,296]. Overall, these studies may underscore the potential of novel regenerative medicine therapeutic interventions that target astrocytes for the treatment of neurodegenerative diseases.

Engineered probiotics.

The gut microbiota and its metabolites modulate CNS function and have been linked to several neurodegenerative diseases and neuropsychiatric disorders[158,159,266,297–300]. For example, in α-synuclein-overexpressing mice, a model of PD, short-chain fatty acids promote aspects of disease pathology[298]. Recent studies revealed that the GBA also controls astrocyte function in CNS inflammation[8,20,21]. For instance, the microbial tryptophan metabolite 3-indoxyl sulfate activates AHR signalling in astrocytes[21] and microglia[20], limiting CNS inflammation and neurodegeneration. The microbiome also educates peripheral immune cells, which then reach the CNS to control resident astrocytes, as we recently reported for the control of anti-inflammatory astrocytes by microbiome-modulated natural killer cells[8]. Collectively, these findings suggest that probiotics may be used to manipulate astrocyte and other CNS-resident cells in neurological diseases. In this context, recent advances in synthetic biology have led to the development of engineered probiotics that target specific molecular pathways for the treatment of inflammation, metabolic dysfunction, infection and cancer. For example, we recently developed self-tunable engineered yeast probiotics that target purinergic signalling to suppress intestinal inflammation[301]. Although there are no currently FDA-approved therapeutic probiotics, several engineered bacterial strains are now being evaluated in clinical trials[302,303]. Therefore, engineered probiotics may provide a novel approach for the therapeutic targeting of the GBA.

Conclusions and future perspectives

Recent technological developments have enabled the identification of novel astrocyte functions in health and disease, highlighting their potential as therapeutic targets. These new technologies, which include specific transgenic lines, intravital imaging, optogenetic and chemogenetic actuators, in situ sequencing, scRNA-seq and methods for the study of cell–cell interactions, have identified local, microbial and environmental factors that control diverse astrocyte subsets and hence have prominent roles in neurodegeneration. Some of these factors also offer well-defined molecular targets for therapeutic intervention in neurological diseases. However, linking transcriptionally defined astrocyte subsets in real time with neuronal activity, behaviour and disease hallmarks remains one of the great challenges in the field. Indeed, deciphering cell interactions between astrocytes and other cells may yield a greater understanding of astrocyte regulation in homeostasis, dysregulation in disease and new therapeutic targets[15,277–279].

One central challenge for the therapeutic targeting of astrocytes is the existence of functional subsets with well-defined roles in health and disease that display marked differences between CNS regions, diseases or disease states (BOX 1). Interestingly, although disease-specific astrocyte triggers and responses have been identified, some astrocyte-related mechanisms of disease pathogenesis are common to multiple neurological disorders. Cross-disease mechanisms include neurotoxicity and deficits in the control of extracellular glutamate levels, recycling of K^+ ions or lactate shuttling (BOX 3). The pathways regulating these and other common dysregulated astrocyte activities may offer targets to manage astrocyte-driven pathology across multiple neurological diseases. However, several fundamental questions should be addressed to enable the therapeutic targeting of astrocytes. How plastic and/or developmentally defined are astrocyte subsets? Moreover, which astrocyte subsets are shared between neurological diseases? How are they spatially distributed in the CNS? How can we compare astrocyte subsets across neurological disorders to identify common mechanisms of pathogenesis and therapeutic targets? Which experimental models are most appropriate for the functional interrogation of these subsets? And, most importantly, how do we therapeutically target specific astrocyte subsets of interest? These and other challenges emphasize the key roles of astrocytes, and their interactions, in health and disease, as well as their potential as viable targets for the treatment of neurological and neuropsychiatric disorders.

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Box 1 |

Defining astrocyte subsets and plasticity

Astrocytes are heterogeneous. Novel molecular techniques have identified astrocyte subsets as defined by their molecular signatures (based on single-cell RNA sequencing (scRNA-seq) studies) and/or function (astrocytes that promote or limit central nervous system (CNS) inflammation or neurodegeneration). These subsets likely reflect at least two sources of astrocyte heterogeneity: astrocyte subsets driven by developmental programmes (developmentally induced astrocyte (DIA) subsets); and astrocyte subsets induced in response to stimulation (stimulus-induced astrocyte (SIA) subsets).

DIAs.

Astrocyte heterogeneity emerges during neurodevelopment. As an example, regional heterogeneity of astrocytes in the spinal cord is linked to developmental transcriptional programmes driven by expression of *Pax6*, *Nkx6.1*, *Reelin*, *Slit1* and *Sema3a*[304–307]. Similar observations have been made when studying astrocytes across cortical layers by in situ RNA profiling[14]. Likewise, the functional properties of astrocytes differ across brain regions, such as the dorsolateral striatum and hippocampus, when focused on electrophysiological, morphological and transcriptional attributes[308]. These and other data indicate that developmental programmes establish defined DIA subsets (Figure, part a). In this sense, DIA groups are similar to neuron subtypes defined by regional, electrophysiological and secretory properties.

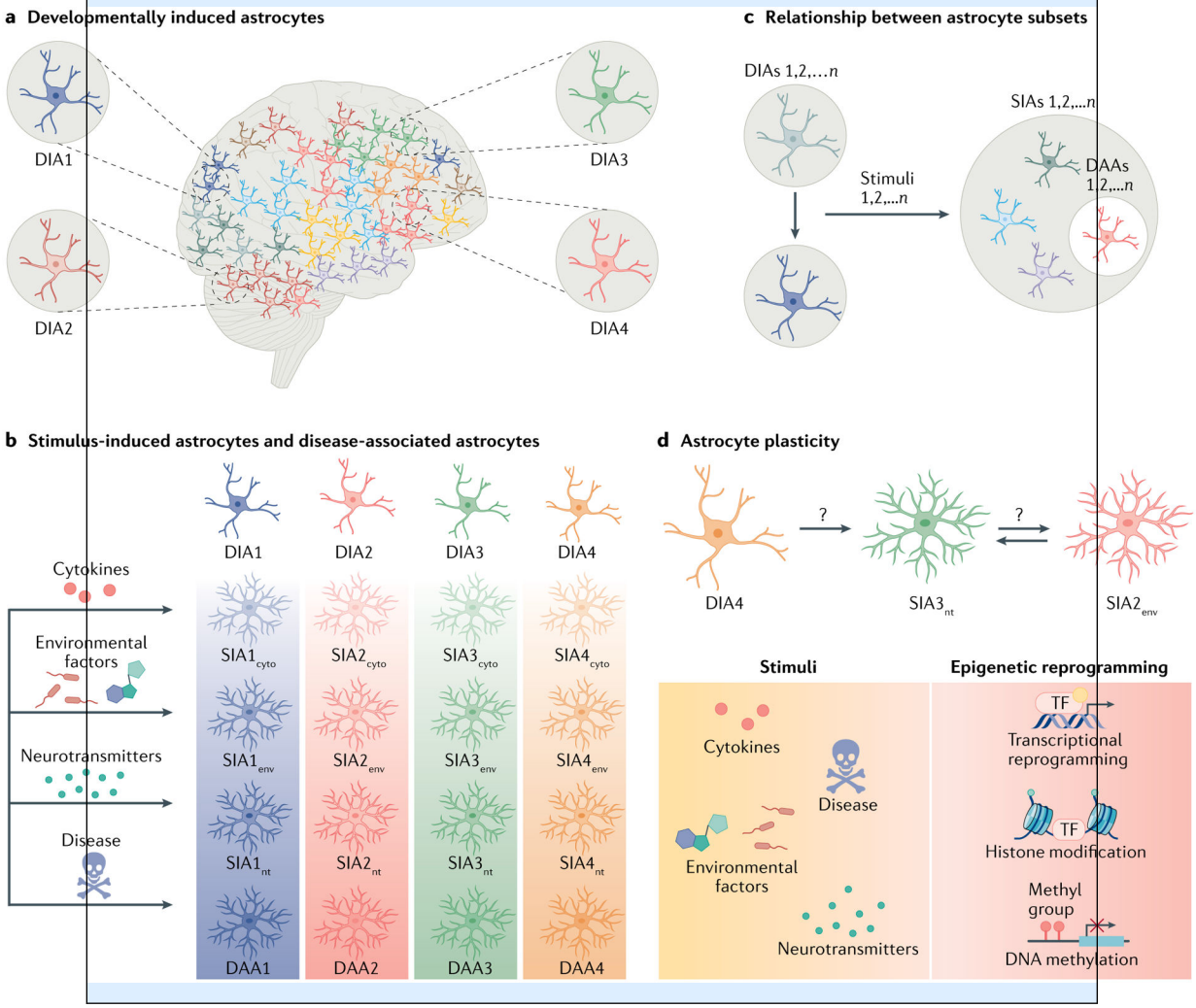
SIAs.

Once matured, astrocytes respond to various stimuli such as neurotransmitters, cytokines, environmental chemicals, extracellular ions and microbial metabolites[22,159,309]. Each stimulus has the potential to induce distinct SIA subsets detectable in single-cell transcriptomic, epigenomic, metabolomic and proteomic analyses. When combined with astrocyte developmental heterogeneity, the same stimulus may induce multiple SIA subsets (Figure, parts b,c). Thus, cytokines, environmental factors and neurotransmitters can induce SIAs from various DIAs, shown here as SIA1–4_{cyto}, SIA1–4_{env} and SIA1–4_{nt}, respectively, in which the number indicates the DIA subtype. In this context, disease-associated astrocytes (DAAs), which have been recently identified by single-cell/nucleus RNA-seq[9,10] in CNS samples from patients affected by neurological diseases and/or preclinical models, are one example of SIAs. DAAs may result from different DIA subsets that converge on a single molecular phenotype induced by disease-related stimuli, or alternatively are the result of the expansion or activation of a single DIA subset. However, SIAs identified as DAAs may contribute to disease pathogenesis and/or participate in mechanisms of tissue repair in a manner dependent on the location and disease phase; astrocyte subsets pathogenic in one neurological disorder may limit disease pathogenesis in another. Hence, we favour the use of SIA and not DAA.

Astrocyte plasticity.

We speculate that astrocyte subsets may be interconvertible, but that their plasticity is limited by epigenetic modifications similar to those associated with the long-term

modification of neuronal[310] or microglial[311,312] responses (Figure, part d). understanding the mechanisms that regulate astrocyte plasticity is likely to have important implications for the therapeutic targeting of astrocyte subsets that contribute to the pathogenesis of neurological disorders.



Box 2 |

Neurodegenerative diseases

Multiple sclerosis

This chronic inflammatory disease of the central nervous system (CNS) is thought to be driven, at least during its initial phases, by an autoimmune response to myelin[139]. Multiple populations of immune cells, most notably t and B lymphocytes, are involved in the pathogenesis of multiple sclerosis (MS). In the late phases of MS, chronic inflammation of the CNS is thought to be driven by activation of resident glial cells, including astrocytes and microglia[22,313]. Current therapies target immune cell extravasation into the CNS, antibody production and B cell development[314].

Alzheimer disease

Alzheimer disease (AD) is a late-onset neurodegenerative disease associated with cognitive and memory impairments. The brain in patients with AD is characterized by the presence of extracellular amyloid-β (aβ) plaques and intracellular neurofibrillary tangles (NFTs), which are composed of hyperphosphorylated tau proteins[315]. The first disease-modifying therapy for AD has recently been approved and promotes the clearance of aβ plaques, although it may work only in a subset of patients[316,317].

Parkinson disease

This neurodegenerative disease is characterized by loss of dopaminergic neurons in the substantia nigra, which is thought to be caused by misfolded α-synuclein in Lewy bodies[218]. Parkinson disease (PD) is marked by motor impairments and other non-motor impairments, such as cognitive and sleep disturbances. several treatments are currently available, such as L-DOPA administration and deep brain stimulation, which help disease management, although neither cures the disease.

Huntington disease

Huntington disease (HD) is a progressive neurodegenerative disease caused by polyglutamine repeats in the huntingtin (*HTT*) gene, which results in misfolding of the HTT protein. HD is characterized by neurodegeneration of the striatum and cortex, as well as motor impairments. No treatments exist that alter the course of the disease, although some reduce motor symptoms.

Box 3 |

Common contributions of astrocytes to neurodegenerative diseases

Glutamate homeostasis

Glutamate is the most prevalent excitatory neurotransmitter in the central nervous system (CNS); however, excessive glutamate levels can trigger neuronal death, a process called excitotoxicity[73,193]. in this context, astrocytes remove extracellular glutamate from the synaptic cleft through the high-affinity glutamate transporters excitatory amino acid transporter 1 (EAAT1) and EAAT2, which play a pivotal part in glutamate homeostasis, synaptic plasticity and neuron survival[70,71]. Therefore, impaired astrocytic glutamate uptake can lead to neuronal excitotoxicity, which is commonly associated with neurodegeneration[73]. For example, previous studies suggest that protein misfolding and aggregation (β-amyloid in alzheimer disease (AD), α-synuclein accumulation in Parkinson disease (PD) and misfolded mutant huntingtin (mHTT) in Huntington disease (HD)), hallmarks of neurodegenerative diseases, inhibit glutamate uptake in astrocytes[197,198,230,318]. In addition, astrocytes in experimental animal models of AD, PD and HD exhibited decreased EAAT2 expression, linked with neuronal dysfunction[200,234,282,318]. indeed, human astrocytes derived from patients with AD display decreased glutamate uptake concomitant with reduced EAAT2 and EAAT1 expression[199]. Furthermore, downregulation of EAAT2 expression correlates with disease severity in postmortem brains of patients with HD[319]. Overall, these studies highlight the importance and potent therapeutic value of glutamate excitotoxicity in many neurodegenerative diseases.

Ion homeostasis

Astrocytes regulate the excitability of neurons by contributing to K^+ uptake and buffering in the brain. In this context, astrocytes express a wide variety of K^+ channels that efficiently clear K^+ ions from the extracellular fluid, a process called K^+ spatial buffering[320]. thus, K^+ channel dysfunction in astrocytes can contribute to neuronal damage, leading to neurodegeneration. For example, mHTT inclusions in astrocytes in a mouse model of HD have decreased expression of the $K_{ir}4.1$ K^+ channel. Selective restoration of $K_{ir}4.1$ in striatal astrocytes reverts HD-like symptoms including extracellular K^+ levels, abnormal motor behaviours and dysfunctional Ca^{2+} and glutamate signalling[34,234]. in preclinical PD mouse models, impairment of $K_{ir}6.1$ in astrocytes aggravates neurodegeneration by increasing dopaminergic neuron damage and motor deficits[68,69]. Collectively, these studies demonstrate that astrocyte K^+ homeostasis has a key role in neurodegeneration in both PD and HD.

Energy metabolism

Astrocytes fuel the energetic needs of neurons by supporting lactate transfer (termed the astrocyte–neuron lactate shuttle)[87,88]. Metabolic dysfunction of astrocytes is associated with neurodegenerative diseases including Ms[93], AD[90], PD[89] and HD[36,91,92]. For instance, lactosylceramide (LacCer)-mediated sphingolipid metabolism in astrocytes contributes to experimental autoimmune encephalomyelitis (EAE) and MS pathogenesis

by controlling the metabolic interactions between astrocytes and neurons[93]. In HD, impairment of astrocyte ascorbic acid shuttling to neurons has been linked to neurodegeneration[92]. Furthermore, the low level of glucose in the brain in HD promotes astrocyte metabolic reprogramming, switching from glycolysis to fatty acid oxidation, which generates reactive oxygen species and causes neuronal death[246]. Taken together, these findings highlight the importance of astrocyte–neuron metabolic crosstalk in neurodegeneration.

Neurotoxicity

The neurotoxic activity of astrocytes has been reported in multiple studies and is likely to involve multiple triggers, astrocyte subsets and effector mechanisms. $C3^+$ neurotoxic astrocyte subsets induced by stimulation with the complement factor C1q, tumour necrosis factor (TNF) and IL-1α, which are produced by microglia, induce neuronal death[145]. Long-chain saturated lipids, synthesized by elongation of very long chain fatty acids protein 1 (ELOVL1) and secreted in lipoparticles, are the neurotoxic factors that these astrocytes secrete[321]. Identification of the molecular mechanisms that regulate and mediate the neurotoxic activity of these and other astrocyte subsets is likely to open novel therapeutic approaches for neurological diseases.

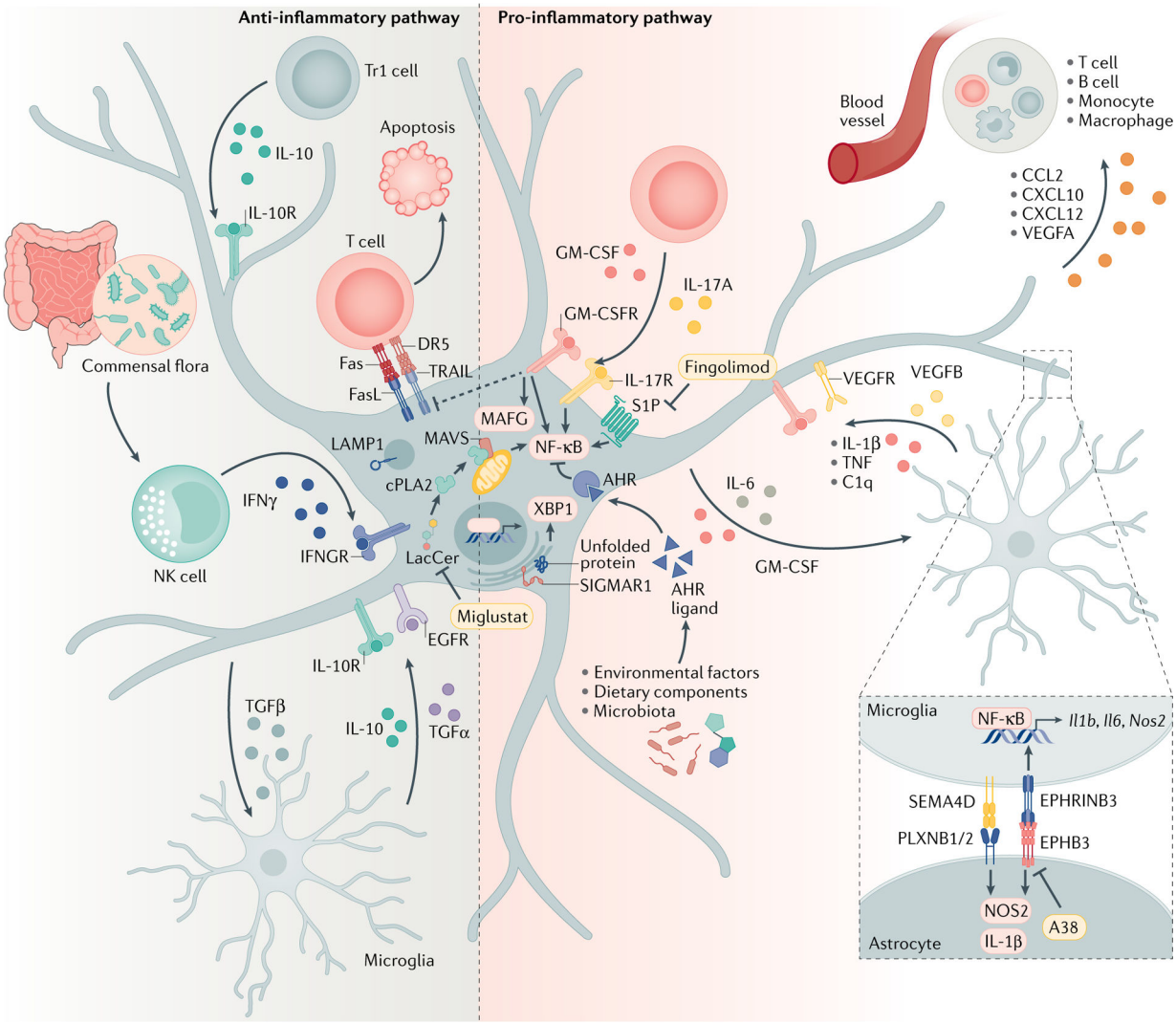


Fig. 1 |. Astrocyte roles in CNS inflammation.

Astrocytes are active players in central nervous system (CNS) inflammation, where they have both pro-inflammatory and anti-inflammatory activities. As a result of their interactions with other cells and molecules in the CNS, astrocytes secrete various cytokines, chemokines and neuromodulatory molecules. AHR, aryl hydrocarbon receptor; CCL2, C-C motif chemokine 2; cPLA2, cytosolic phospholipase A2; CXCL10, C-X-C motif chemokine ligand 10; DR5, death receptor 5; EGFR, epidermal growth factor receptor; EPHB3, ephrin type B receptor 3; EPHNB3, ephrinB3; GM-CSF, granulocyte–macrophage colony-stimulating factor; IFNγ, interferon-γ; LacCer, lactosylceramide; LAMP1, lysosome-associated membrane glycoprotein 1; MAFG, MAF bZIP transcription factor; MAVS, mitochondrial antiviral signalling protein; NF-κB, nuclear factor-κB; NK, natural killer; NOS2, nitric oxide synthase 2; PLXNB, plexin B; SEMA4D, semaphorin4D; S1P, sphingosine 1-phosphate receptor; SIGMAR1, sigma receptor 1; TGF, transforming growth factor; TNF, tumour necrosis factor; Tr1, type 1 regulatory T cell; TRAIL, tumour necrosis factor-related apoptosis-inducing ligand; VEGF, vascular endothelial growth factor; XBP1, X-box binding protein 1.

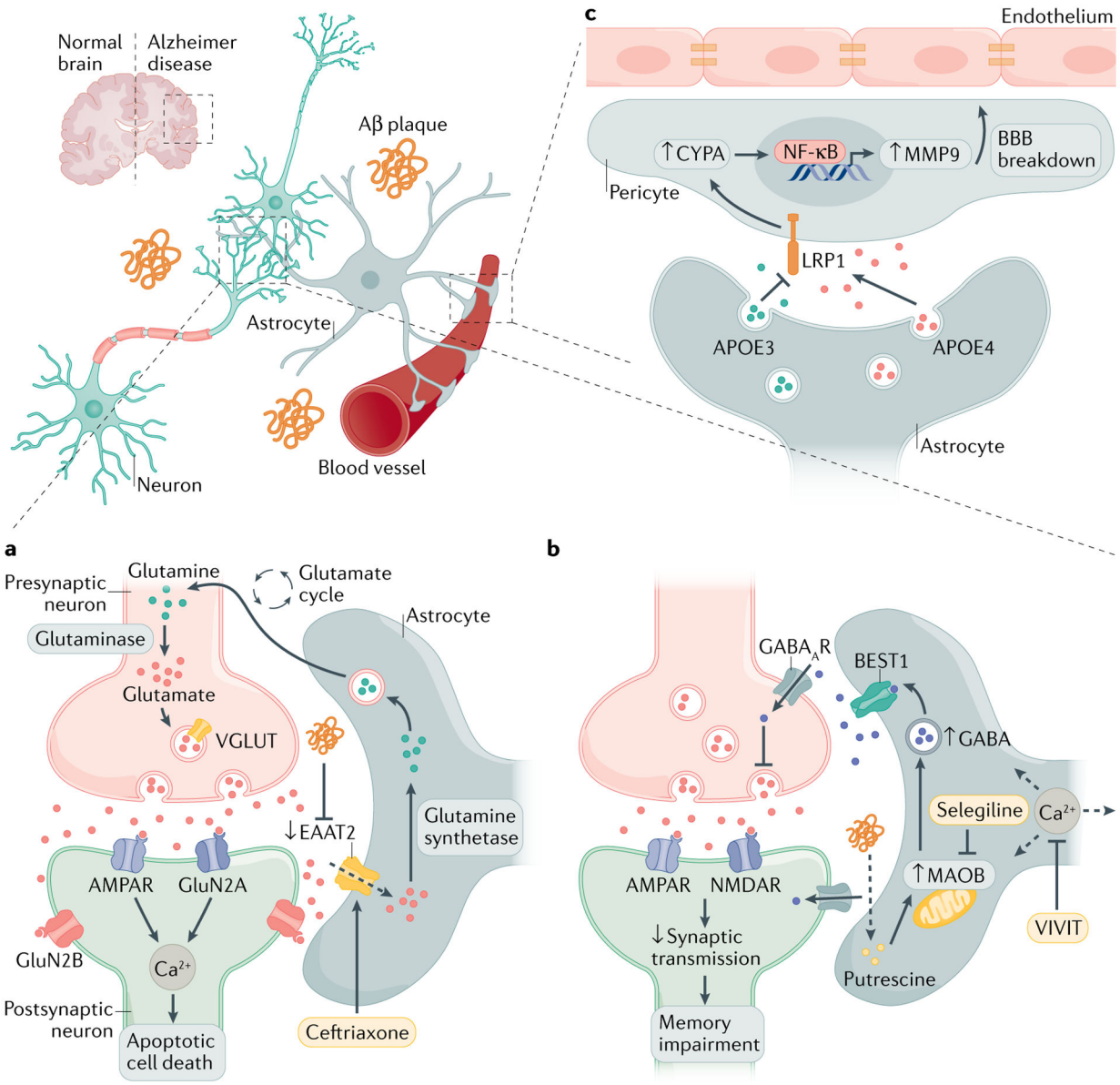


Fig. 2 |. Targeting astrocyte signalling in Alzheimer disease.

a | The accumulation of amyloid-β (Aβ) in the brain modulates glutamate uptake in astrocytes by inhibiting the glutamate transporter excitatory amino acid transporter 2 (EAAT2). This causes excessive activation of neuronally expressed glutamate receptors, which increases intracellular Ca^{2+} and promotes neuronal dysfunction. **b** | Enhanced intracellular Ca^{2+} waves in astrocytes increase the release of γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain. Aβ plaques and putrescine trigger monoamine oxidase B (MAOB)-mediated GABA release via the Ca^{2+}-activated anion channel bestrophin 1 (BEST1). Increased GABA uptake by neurons impairs memory and synaptic plasticity. **c** | Astrocytes are the main producers of apolipoprotein E (APOE), which modulates blood–brain barrier (BBB) permeability. APOE4 secretion induces cyclophilin A (CYPA)–nuclear factor-κB (NF-κB)–metalloproteinase 9 (MMP9) signalling in pericytes,

which leads to BBB breakdown via the lipoprotein receptor-related protein 1 (LRP1). This APOE4-mediated pericyte activation can be negatively regulated by the production of APOE3. Strategies to rescue neuronal dysfunction mediated by glutamate dysregulation and synaptic plasticity include controlling astrocyte glutamate uptake, Ca^{2+} homeostasis and GABA production. AMPAR, AMPA receptor; NMDAR, *N*-methyl-D-aspartate receptor; VGLUT, vesicular glutamate transporter.

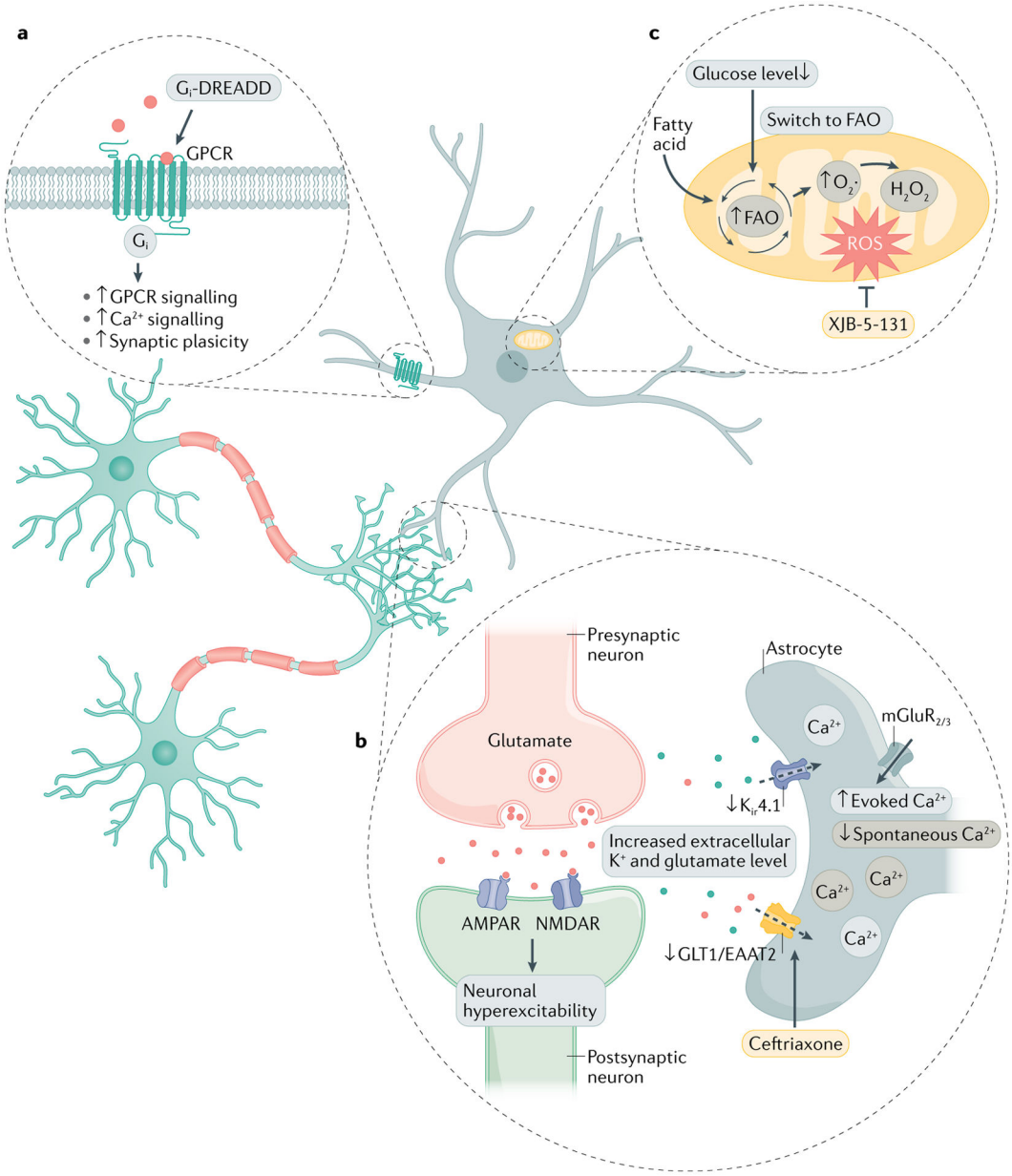


Fig. 3 |. Targeting astrocyte signalling in Huntington disease.

a | Selective activation of G_i–G protein-coupled receptor (GPCR) signalling pathway can recover astrocyte functional impairments and correct synaptic dysfunction. **b** | Mutant huntingtin protein (mHTT) inclusions in astrocytes impair the expression of excitatory amino acid transporter 2 (EAAT2) and K^+ ion channel $K_{ir}4.1$. Reduced glutamate transporter levels lead to robust $mGlu_{2/3}$-mediated Ca^{2+} signalling. This gain of evoked astrocyte Ca^{2+} signals is followed by the loss of spontaneous Ca^{2+} signalling. The elevation of extracellular K^+ and glutamate levels leads to neuronal hyperexcitability and the development of neurodegeneration. **c** | Low glucose levels in the striatum of individuals with Huntington disease (HD) triggers metabolic reprogramming in astrocytes, which switch from using glucose to fatty acids. Fatty acid oxidation (FAO) sustains

energy production but also elevates levels of reactive oxygen species (ROS), which induce damage. In HD, synaptic plasticity, Ca^{2+} signalling and GPCR signalling is impaired in striatal astrocytes. Strategies to rescue neurodegeneration in HD include targeting astrocyte glutamate uptake, metabolism and GPCR signalling. AMPAR, AMPA receptor; NMDAR, *N*-methyl-D-aspartate receptor; mGluR2/3, metabotropic glutamate receptor 2/3; DREADD, designer receptor exclusively activated by designer drugs.